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LPS-responsive chs1/beige-like anchor gene and therapeutic applications thereof

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(54) **LPS-RESPONSIVE *CHS1/BEIGE*-LIKE ANCHOR GENE AND THERAPEUTIC APPLICATIONS THEREOF**

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(2), (4) Date: **Mar. 18, 2004**

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PCT Pub. Date: **Oct. 10, 2002**

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Related U.S. Application Data

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(51) **Int. Cl.**

A01N 43/04	(2006.01)
C12Q 1/68	(2006.01)
C12P 19/34	(2006.01)
C07H 21/02	(2006.01)
C07H 21/04	(2006.01)

(52) **U.S. Cl.** **514/44**; 435/6; 435/91.31; 435/455; 536/23.1; 536/24.31; 536/24.5

(58) **Field of Classification Search** 435/6, 435/91.1, 91.31, 455, 375; 514/1, 2, 44; 536/23.1, 24.5, 24.31

See application file for complete search history.

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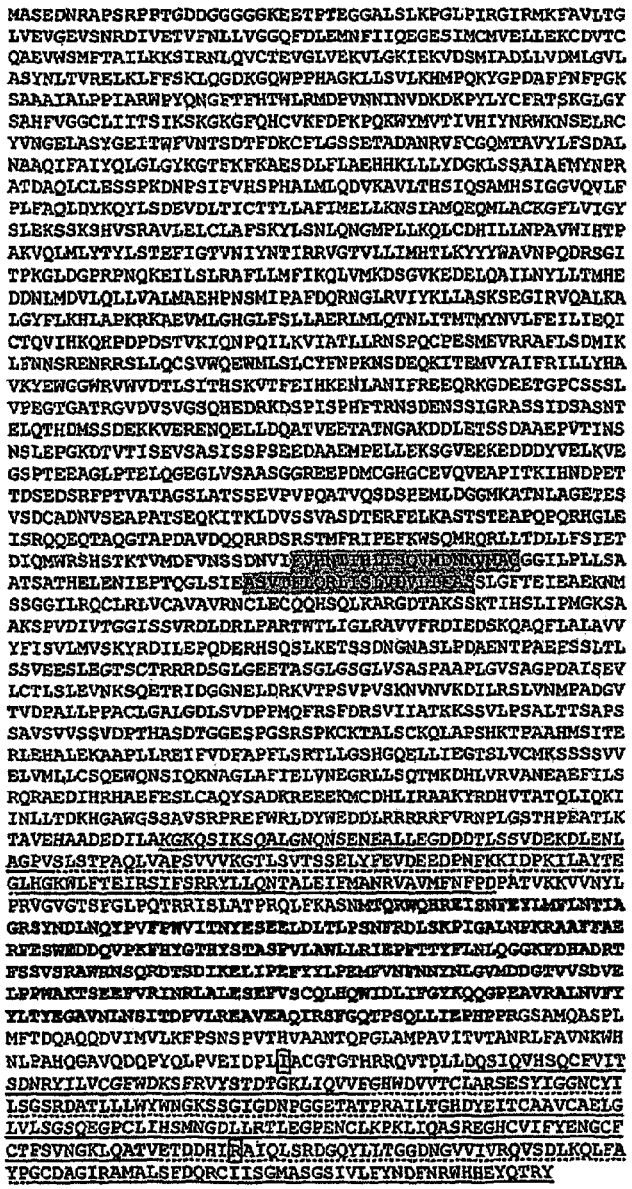
(74) *Attorney, Agent, or Firm*—Saliwanchik, Lloyd & Saliwanchik

(57) **ABSTRACT**

The present invention relates to a novel LPS-responsive and Beige-like Anchor gene (lrba), variants of the lrba gene, fragments of the lrba gene, and polypeptides encoded thereby. The subject invention also pertains to lrba interfering RNA, and uses thereof. In another aspect, the present invention also includes methods of inhibiting tumor growth in a patient by suppressing lrba function.

11 Claims, 21 Drawing Sheets

FIG. 1A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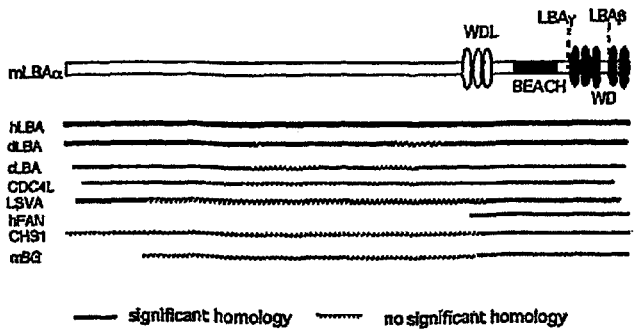
LVEVGEVSNRDIVETVFNLLVGGQFDLEMNFIIQEGESIMCMVELLEKCDVTC
QAEVWSMFTAILKKSIRNLQVCTEVGLVEKVLGKIEKVDSMIADLLVDMLGVL
ASYNLTVRELKLFFSKLQGDKGQWPPHAGKLLSVLKHMPQKYGPDAFFNFPGK
SAAAIALPPIARWPYQNGFTFHTWLRMDFVNNINVDKDKPYLYCFRTSKGLGY
SAHFVGGCLIITSIKSKGKGFQHCVKFDFKPQKWYMVTIVHIYNRWKNSELRC
YVNGELASYGEITWFVNTSDTFDKCFLGSSETADANRVFCGQMTAVYLFSDAL
NAAQIFAIYQLGLGYKGTFKFKAESDLFLAEHHKLLLYDGKLSSAIAFMYNPR
ATDAQLCLESSPKDNPSIFVHSPHALMLQDVKAVLTHSIQSAMHSIGGVQVLF
PLFAQLDYKQYLSDEVDLTICTTLLAFIMELLKNSIAMQEQMLACKGFLVIGY
SLEKSSKSHVSRAVLELCLAPSKYLSNLQNGMPLLKQLCDHILLNPAVWIHTP
AKVQLMLYTYLSTEFIGTVNIYNTIRRVGTVLLIMHTLKYYYWAVNPQDRSGI
TPKGLDGPRPNQKEILSLRAFLLMFIKQLVMKDSGVKEDELQAILNYLLTMHE
DDNLMDVLQLLVALMAEHPNSMIPAFDQRNGLRVIYKLLASKSEGIRVQALKA
LGYFLKHLAPKRKAEVMLGHGLFSLLAERLMLQTNLITMTMYNVLFEILIEQI
CTQVIHKQRPDPDSTVKIQNPQILKVIATLLRNSPQCPESMEVRRAFLSDMIK
LFNNSRENRRSLLQCSVWQEWMLSLCYFNPKNSDEQKITEMVYAIFRILLYHA
VKYEWGGWRVWVDTLSITHSKVTFEIHKENLANIFREEQRKGDEETGPCSSSL
VPEGTGATRGVDVSVGSQHEDRKDSPISPHFTRNSDENSSIGRASSIDSASNT
ELQTHDMSSDEKKVERENQELLDQATVEETATNGAKDDLETSSDAAEPVTINS
NSLEPGKDTVTISEVSASISSPSEEDAAEMPELLEKSGVEEKEDDDYVELKVE
GSPTEEAGLPTELQGEGLVSAASGGREEPDMCGHGCEVQVEAPITKIHNDPET
TDSEDSRFPTVATAGSLATSSEVPVPQATVQSDSPEMLDGGMKATNLAGETES
VSDCADNVSEAPATSEQKITKLDVSSVASDTERFELKASTSTEAPQPQRHGLE
ISRQQEQTAQGTAPDAVDQQRRDSRSTMFRIPEFKWSQMKQRLLTDLLFSIET
DIQMWRSHSTKTVMDEVNSSDNVLEYHWTHIFSQVMDNQHDAGGILPLLSA
ATSATHELENIEPTQGLSIEASVTELQRTSTDVMPSAASSLGFTEIEAEKNM
SSGGILRQCLRLVCAVAVRNCLECQQHSQLKARGDTAKSSKTIHSLIPMGKSA
AKSPVDIVTGGISSVRDLDRLPARTWTLIGLRAVVFRDIEDSKQAQFLALAVV
YFISVLMVSKYRDILEPQDERHSQSLKETSSDNGNASLPDAENTPAEESSLTL
SSVEESLEGTSCTRRRDSGLGEETASGLGSGLVSASPAAPLGVSAGPDAISEV
LCTLSLEVNKSQETRIDGGNELDRKVTPSVPVSKNVNVKDILRSLVNMPADGV
TVDPALLPPACLGRLGDLSVDPPMQFRSFDRSVIIATKKSSVLPSALTTSAPS
SAVSVVSSVDPTHASDTGGESPGSRSPKCKTALSCKQLAPSHKTPAAHMSITE
RLEHALEKAAPLLREIFVDFAPFLSRTLLGSHGQELLIEGTSLVCMKSSSSVV
ELVMLLCSQEWQNSIQKNAGLAFIELVNEGRLLSQTMKDHLVRVANEAEFILS
RQRAEDIHRHAEFESLCAQYSADKREEEKMCDHLIRAAKYRDHVTATQLIQKI
INLLTDKHGAWGSSAVSRPREFWRLDYWEDDLRRRRRFVRNPLGSTHPEATLK
TAVEHAADEDILAKGKQSIKSQALGNQNSENERLLEGDDDTLSSVDEKDLENL
AGPVSLSTPAQLVAPSVVVKGTLSVTSSELYFEVDEEDPNFKKIDPKILAYTE
GLHGKWLFTEIRSIFSRRYLLQNTALEIFMANRVAVMFNFPDPATVKKVVNYL
PRVGVGTSFGLPQTRRISLATPRQLFKASNMTQRWQHRRISNTEYILMFLNTIA
GRSYNDLNQIPVFPWVITNYESEELDLTLPSNFRDLSKPIGALNPKRAAFTAE
RFESWEDDQVPKFHYGTHYSTASPVLANLLRIEPFTTYFLNLQGGKFDHADRT
FSSVSRAWRNSQRDTSDIKELIPEFYILPEMFVNFNNYNLGVMDDGTVVSDVE
LPPWAKTSEEFVRINRLALESEFVSCQLHQWIDLIFGYKQQGPEAVRALNVFT
YLTYEGAVNLNSITDPVLREAVEAQIRSFGQTPSQLLIEPHPPRGSAMQASPL
MFTDQAQQDVIMVLKFPSNSPVTHVAANTQPGLAMPAVITVTANRLFAVNKWH
NLPAHQGAVQDQPYQLPVEIDPLNACGTGTHRRQVTDLLDQSIQVHSQCFVIT
SDNRYILVCGFWDKSFRVYSTDTGKLIQVVEGHWDVVTCLARSESYIGGNCYI
LSGSRDATLLLWYWNGKSSGIGDNPGGETATPRAILTGHDYEITCAAVCAELG
LVLSGSQEGPCLIHSMNGDLLRTLEGPENCLKPKLIQASREGHCVIFYENGCF
CTFSVNGKLQATVETDDHIFAIQLSRDGQYLLTGGDNGVVIVRQVSDLKQLFA
YPGCDAGIRAMALSFDQRCIISGMASGSIVLFYNDFNRWHHEYQTRY

FIG. 1B


WDL
LBAγ
LBAβ
mLBAα
BEACH
WD
hLBA
dLBA
dLBA
CDC4L
LSVA
hFAN
CHS1
αBG
significant homology
no significant homology

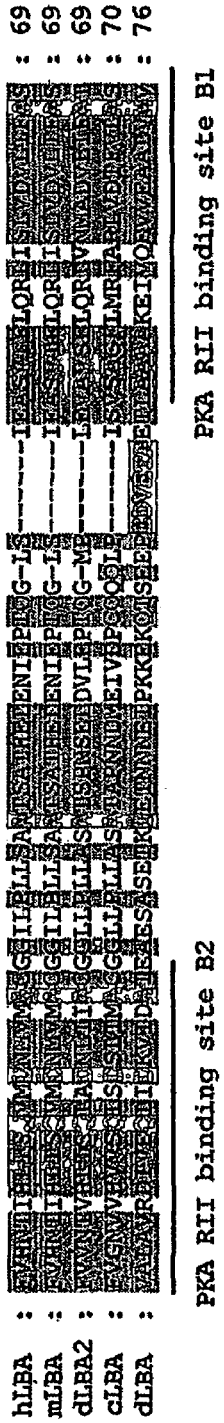

hLBA
mLBA
dLBA2
cLBA
dLBA
PKA RII binding site B2
PKA RII binding site B1

FIG. 2A

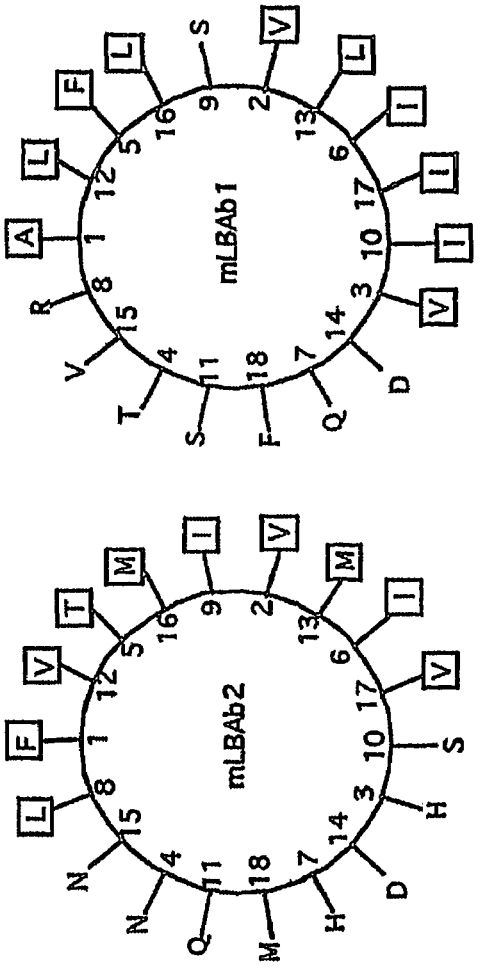

mLBAb1
mLBAb2

FIG. 2B

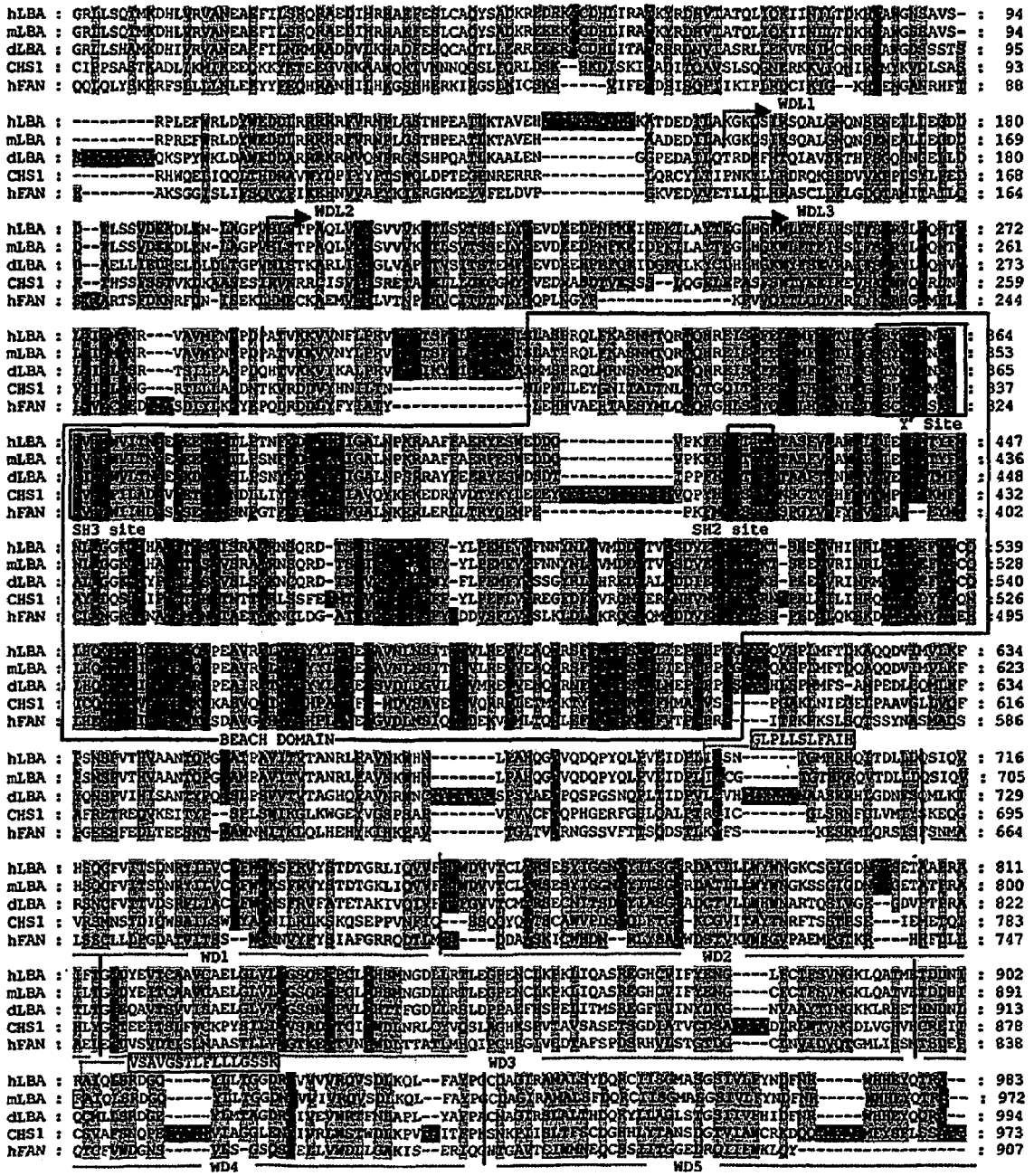

WDL1
WDL2
WDL3
Y Site
SH3 site
SH2 site
BEACH DOMAIN
GLPLLSLFAIH
WD1
WD2
WD3
VSAVGSTLFLLLGSSR
WD4
WD5

FIG. 3

FIG. 4A

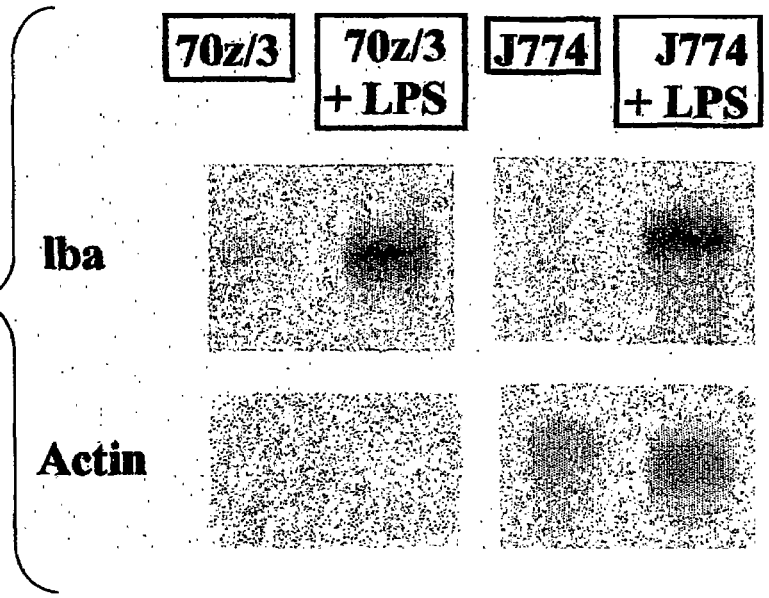


FIG. 4B

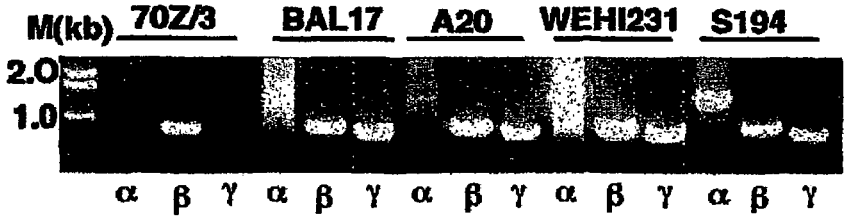
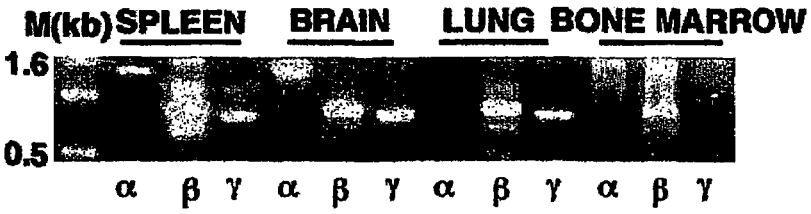


FIG. 4C



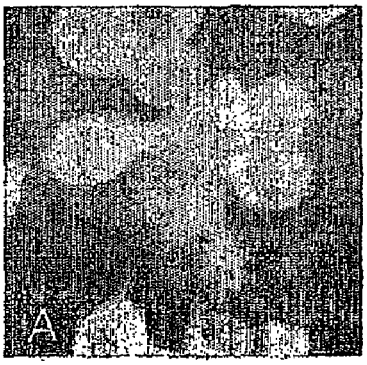


FIG. 5A

FIG. 5B

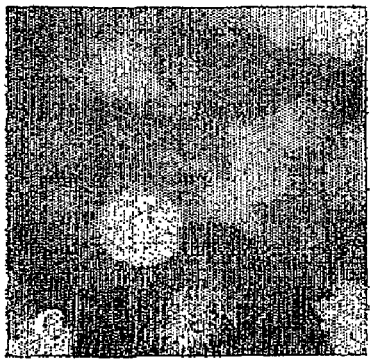


FIG. 5C

FIG. 5D

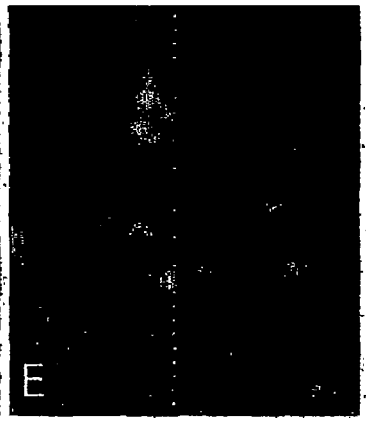


FIG. 5E

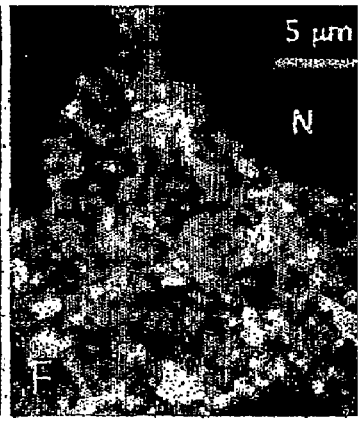


FIG. 5F

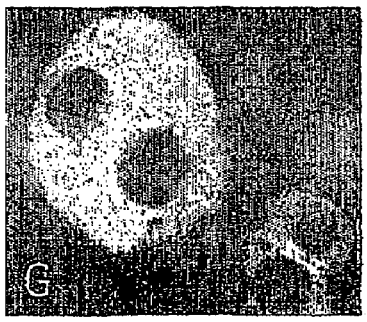


FIG. 5G

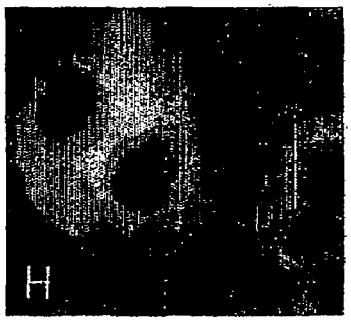


FIG. 5H

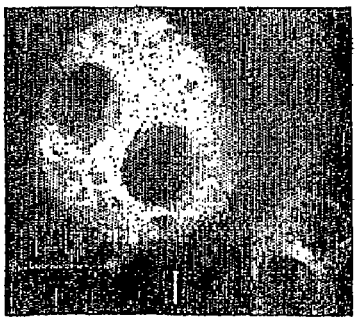


FIG. 5I

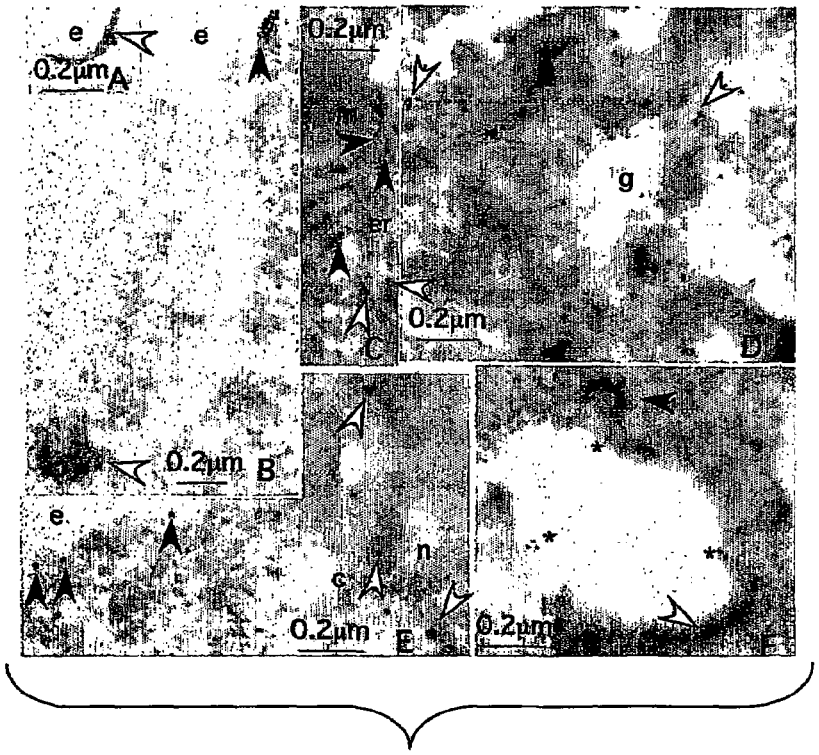

0.2μm
A
B
C
D
E
F
e
g
n

FIG. 6

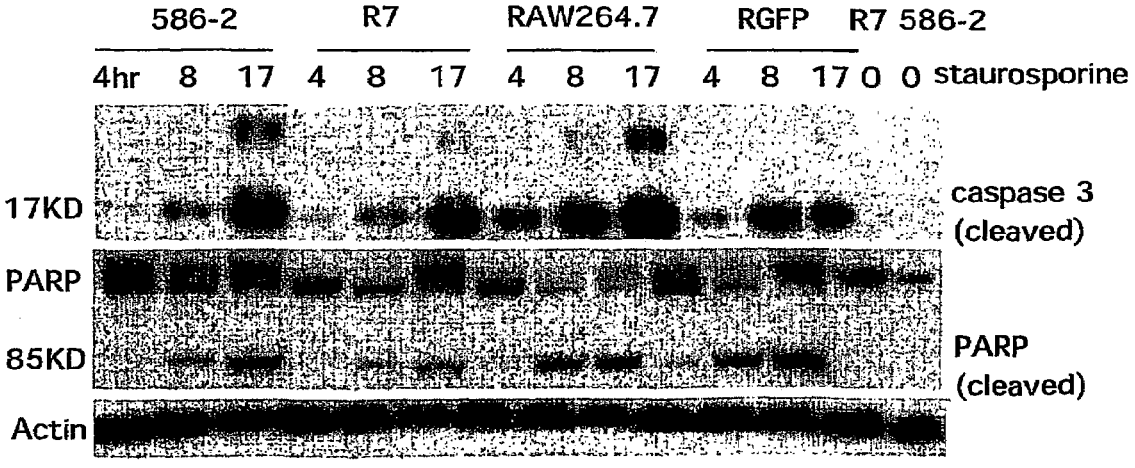

586-2
R7
RAW264.7
RGFP
R7 586-2
4hr 8 17 4 8 17 4 8 17 4 8 17 0 0 staurosporine
17KD
caspase 3
(cleaved)
PARP
85KD
PARP
(cleaved)
Actin

FIG. 8

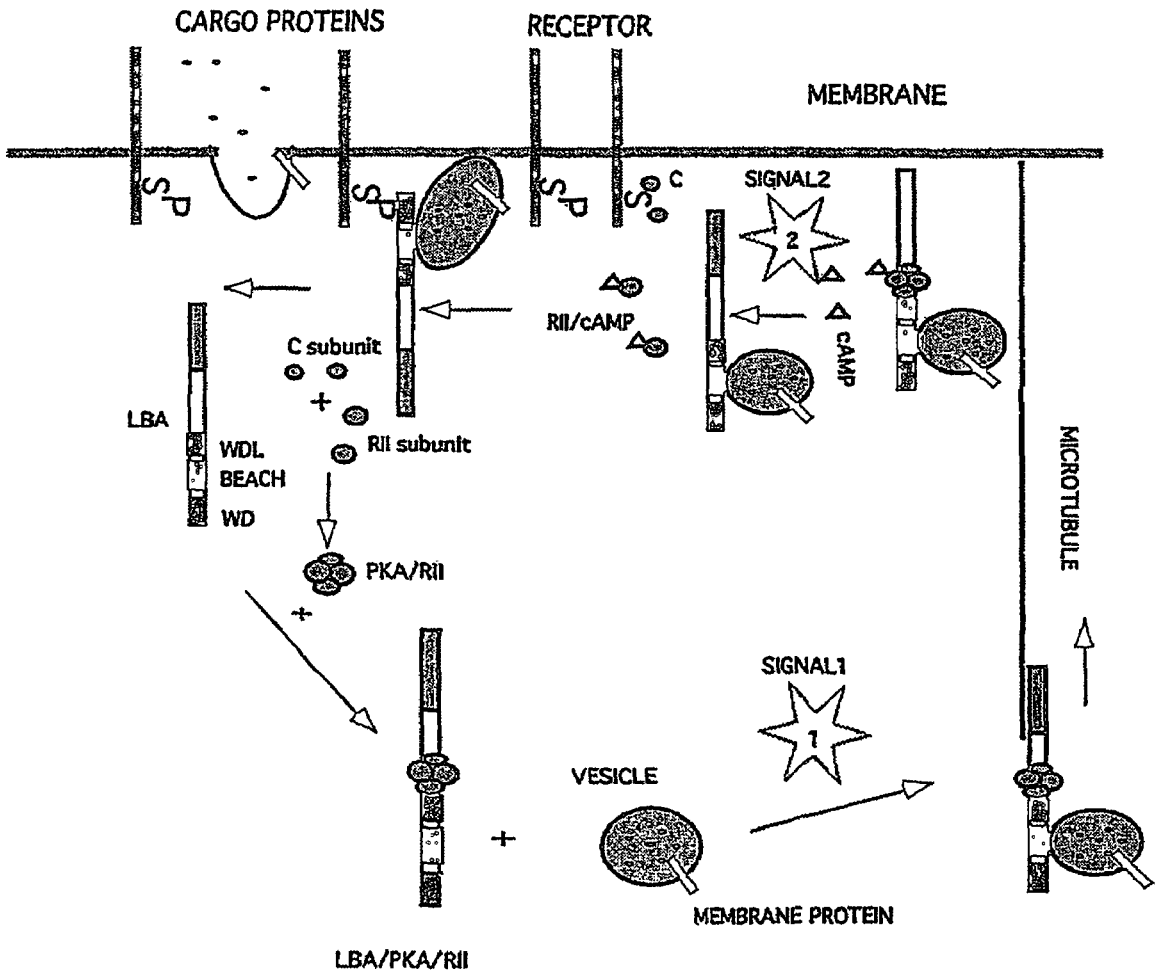

CARGO PROTEINS
RECEPTOR
MEMBRANE
SP
C
SIGNAL2
2
RII/cAMP
cAMP
C subunit
LBA
WDL
BEACH
WD
RII subunit
PKA/RII
MICROTUBULE
SIGNAL1
1
VESICLE
MEMBRANE PROTEIN
LBA/PKA/RII

FIG. 7

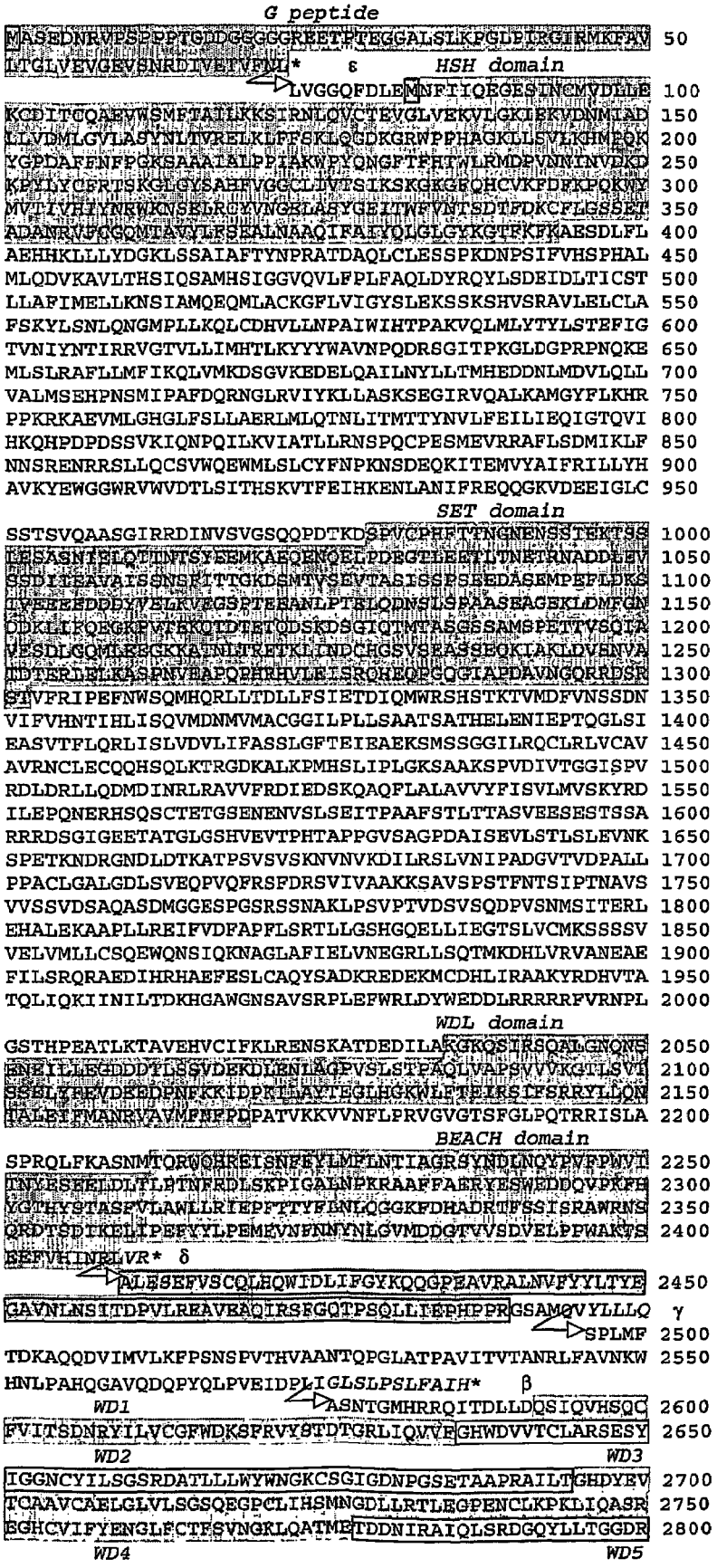

G peptide
HSH domain
SET domain
WDL domain
BEACH domain
WD1
WD2
WD3
WD4
WD5

FIG. 9

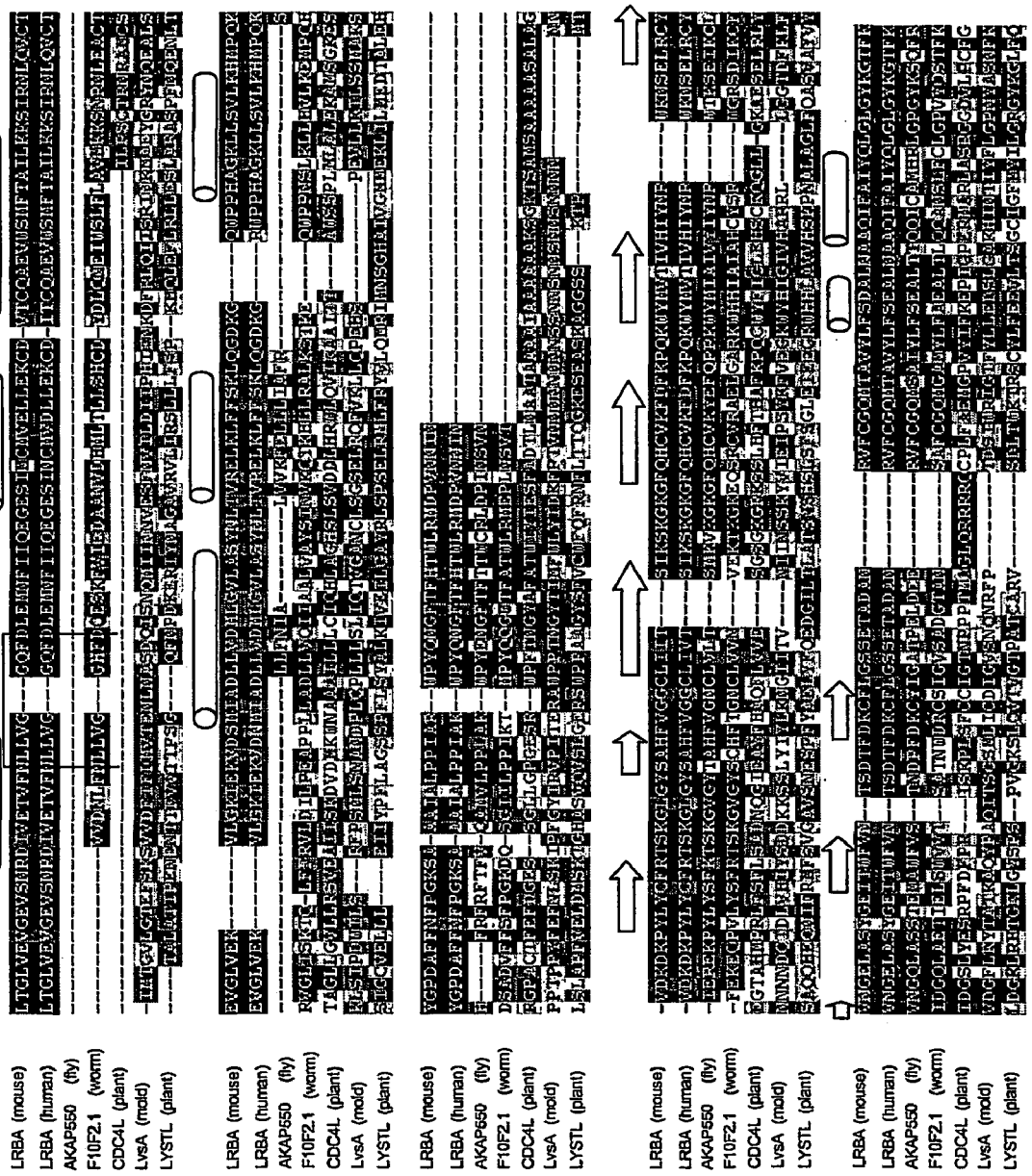

LRBA (mouse)
LRBA (human)
AKAP550 (fly)
F10F2.1 (worm)
CDC4L (plant)
LvsA (mold)
LYSTL (plant)

FIG. 10

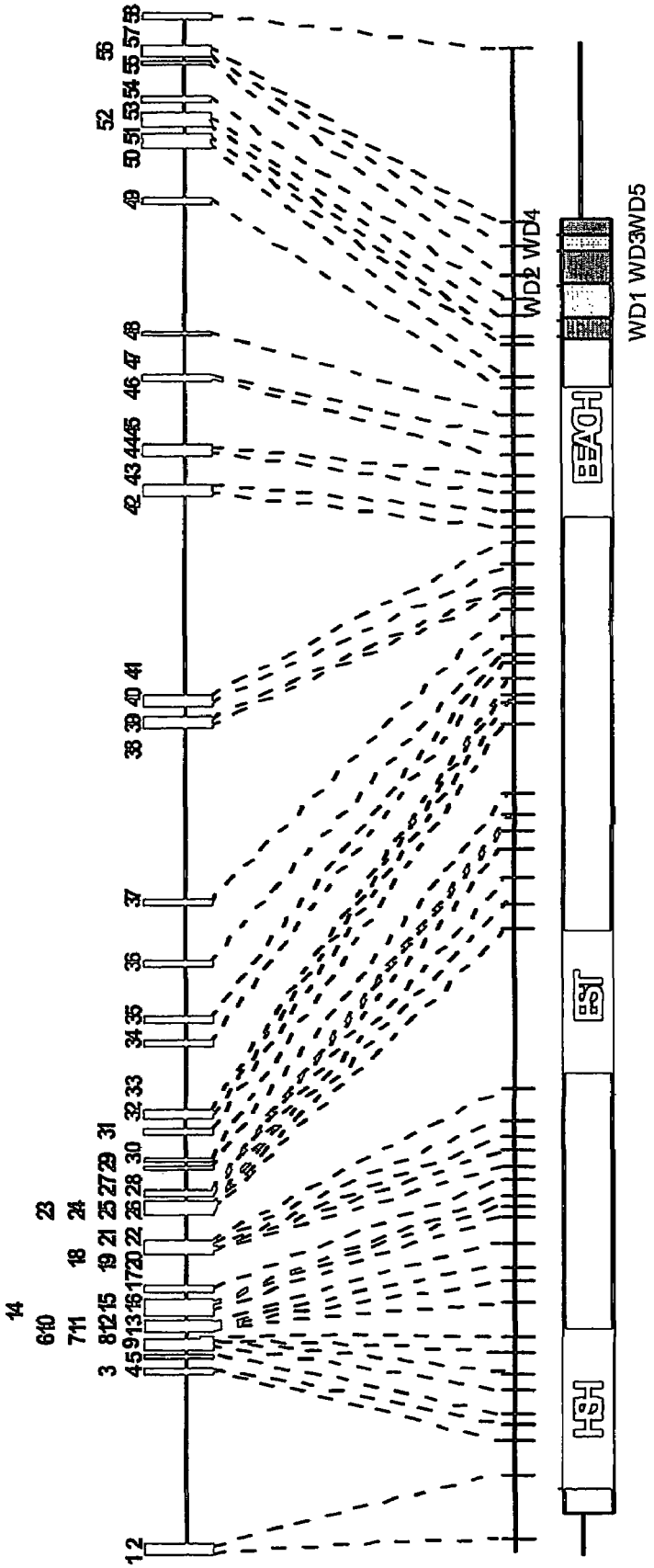


FIG. 11

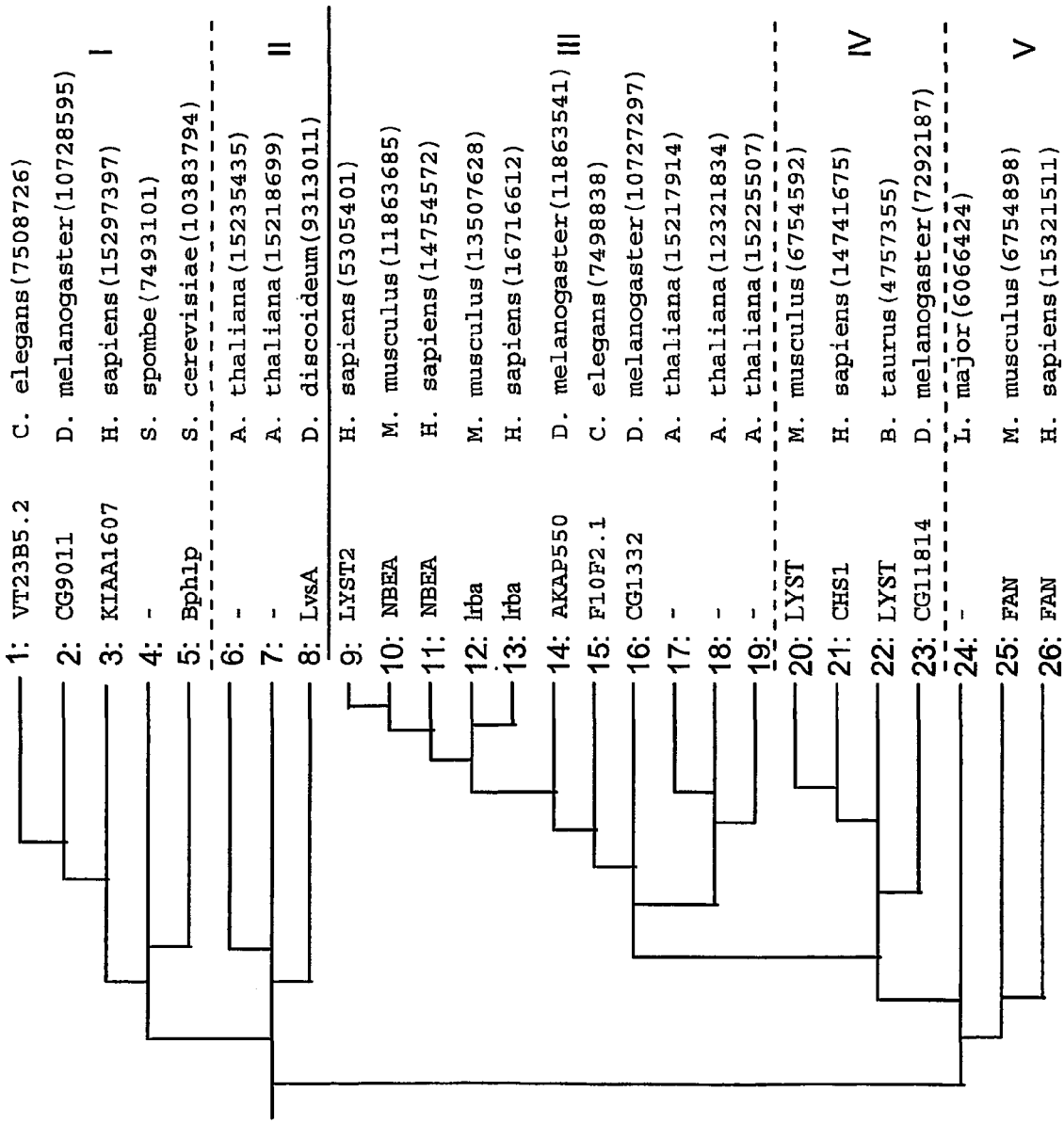

1: VT23B5.2 C. elegans(7508726)
2: CG9011 D. melanogaster(10728595)
3: KIAA1607 H. sapiens(15297397)
4: - S. spombe(7493101)
5: Bph1p S. cerevisiae(10383794)
6: - A. thaliana(15235435)
7: - A. thaliana(15218699)
8: LvsA D. discoideum(9313011)
9: LYST2 H. sapiens(5305401)
10: NBEA M. musculus(11863685)
11: NBEA H. sapiens(14754572)
12: Irba M. musculus(13507628)
13: Irba H. sapiens(16716612)
14: AKAP550 D. melanogaster(11863541)
15: F10F2.1 C. elegans(7498838)
16: CG1332 D. melanogaster(10727297)
17: - A. thaliana(15217914)
18: - A. thaliana(12321834)
19: - A. thaliana(15225507)
20: LYST M. musculus(6754592)
21: CHS1 H. sapiens(14741675)
22: LYST B. taurus(4757355)
23: CG11814 D. melanogaster(7292187)
24: - L. major(6066424)
25: FAN M. musculus(6754898)
26: FAN H. sapiens(15321511)
I
II
III
IV
V

FIG. 12

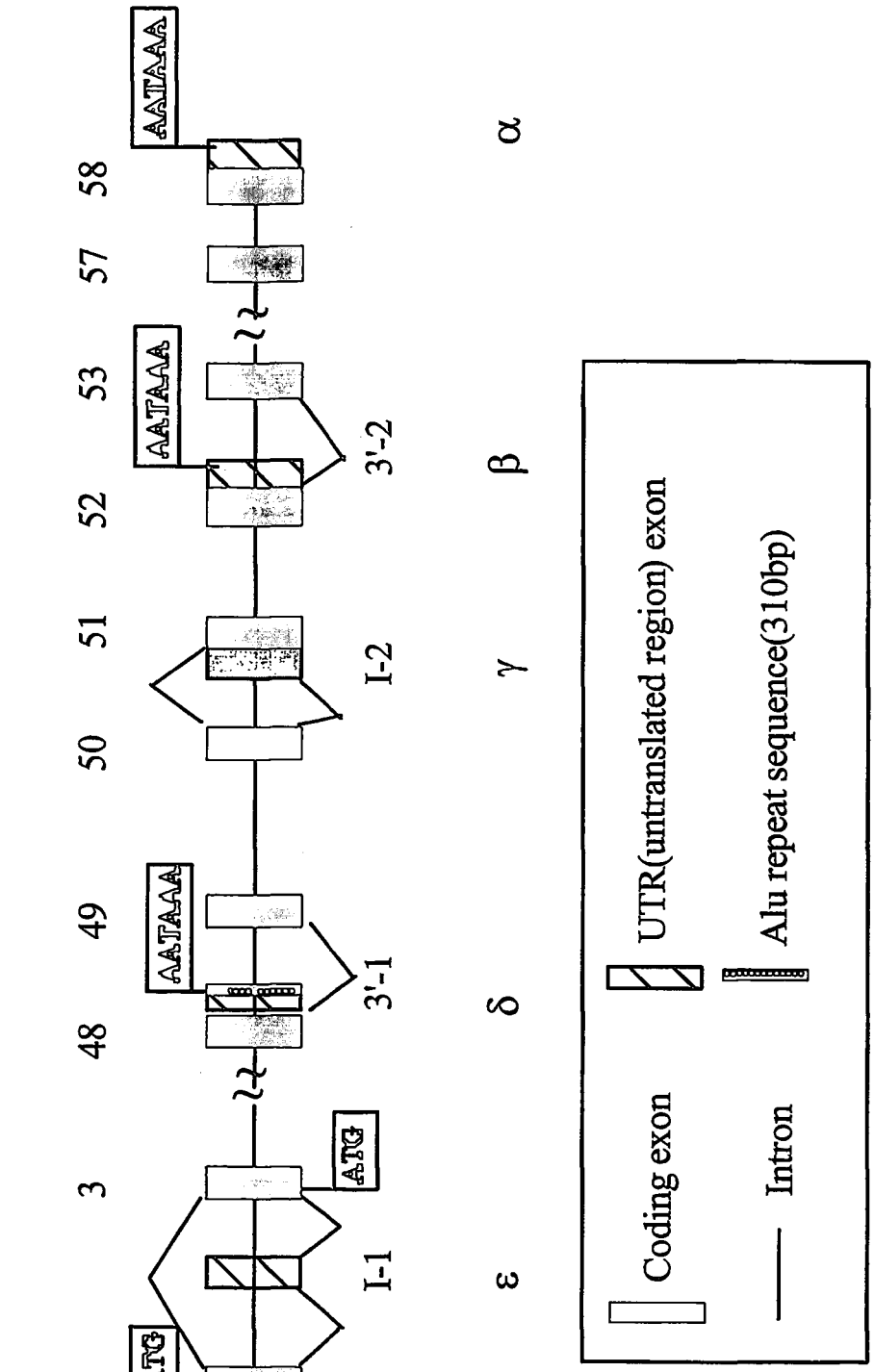

main exons
1
2
3
48
49
50
51
52
53
57
58
ATG
AATAAA
AATAAA
ATG
5'-1
I-1
3'-1
I-2
3'-2
alternative exons
Isoforms
ε
δ
γ
β
α
Coding exon
UTR(untranslated region) exon
Intron
Alu repeat sequence(310bp)

FIG. 13

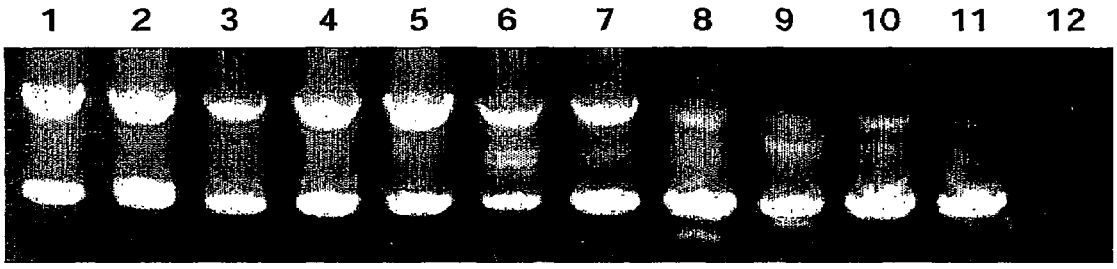
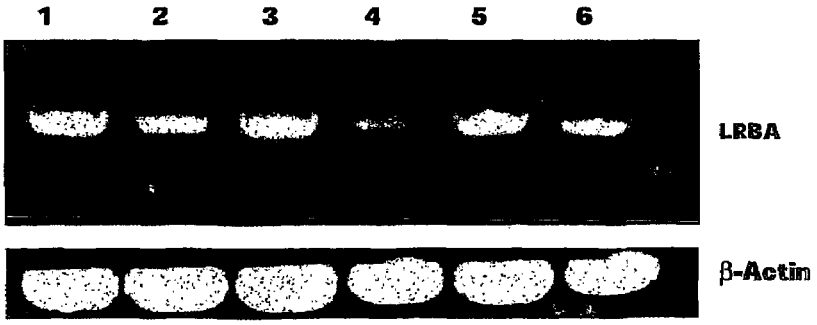


FIG. 14

FIG. 18A

FIG. 18B



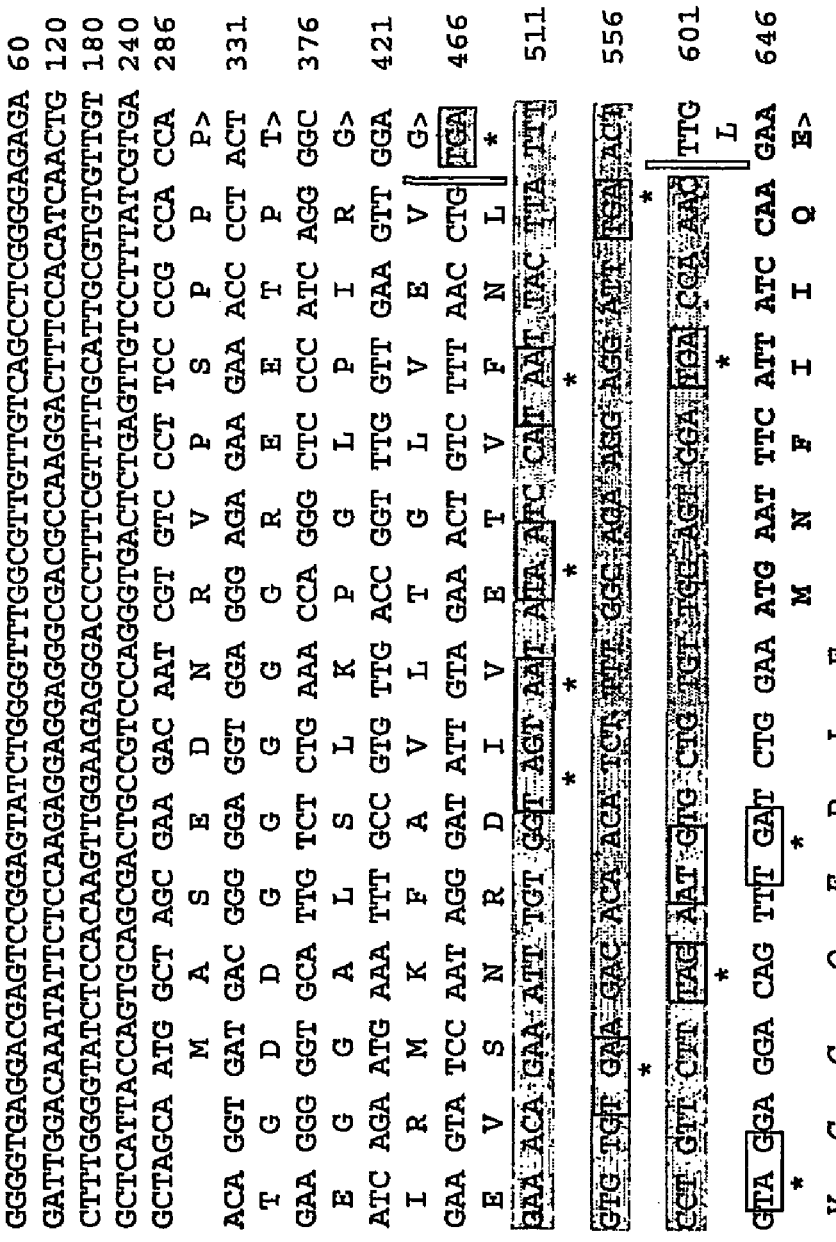

GGGGTGAGGACGAGTCCGGAGTATCTGGGGTTTGGCGTTGTTGTCAGCCTCGGGAGAGA 60
GATTGGACAAATATTCTCCAAGAGGAGGAGGGCGACGCCAAGGACTTTCCACATCAACTG 120
CTTTGGGGTATCTCCACAAGTTGGAAGAGGGACCCTTTCGTTTTGCATTGCGTGTGTTGT 180
GCTCATTACCAGTGCAGCGACTGCCGTCCCAGGGTGACTCTGAGTTGTCCTTTATCGTGA 240
GCTAGCA ATG GCT AGC GAC AAT CGT GTC CCT TCC CCG CCA CCA 286
M A S E D N R V P S P P P>
ACA GGT GAT GAC GGG GGA GGT GGA GGG AGA GAA GAA ACC CCT ACT 331
T G D D G G G G R E E T P T>
GAA GGG GGT GCA TTG TCT CTG AAA CCA GGG CTC CCC ATC AGG GGC 376
E G G A L S L K P G G L P I R G>
ATC AGA ATG AAA TTT GCC GTG TTG ACC GGT TTG GTT GAA GTT GGA 421
I R M K F A V L T G L V E V G>
GAA GTA TCC AAT AGG GAT ATT GTA GAA ACT GTC TTT AAC CTG TGA 466
E V S N R D I V E T V F N L *
GAA ACA GAA ATT TGT GGT AGT AAT ATA ATC CAT AAT TAC TTA TTT 511
GTG TGT GAA GAC ACA ACA TCN TTT GGC AGA AGG AGG ATT TGA ACT 556
CCT GTT CTT TAG AAT GTG CTG TGT TGC AGT GGA TGA CGA AAC TTG 601
L
GTA GGA GGA CAG TTT GAT CTG GAA ATG AAT TTC ATT ATC CAA GAA 646
V G G Q F D L E M N F I I Q E>

FIG. 15

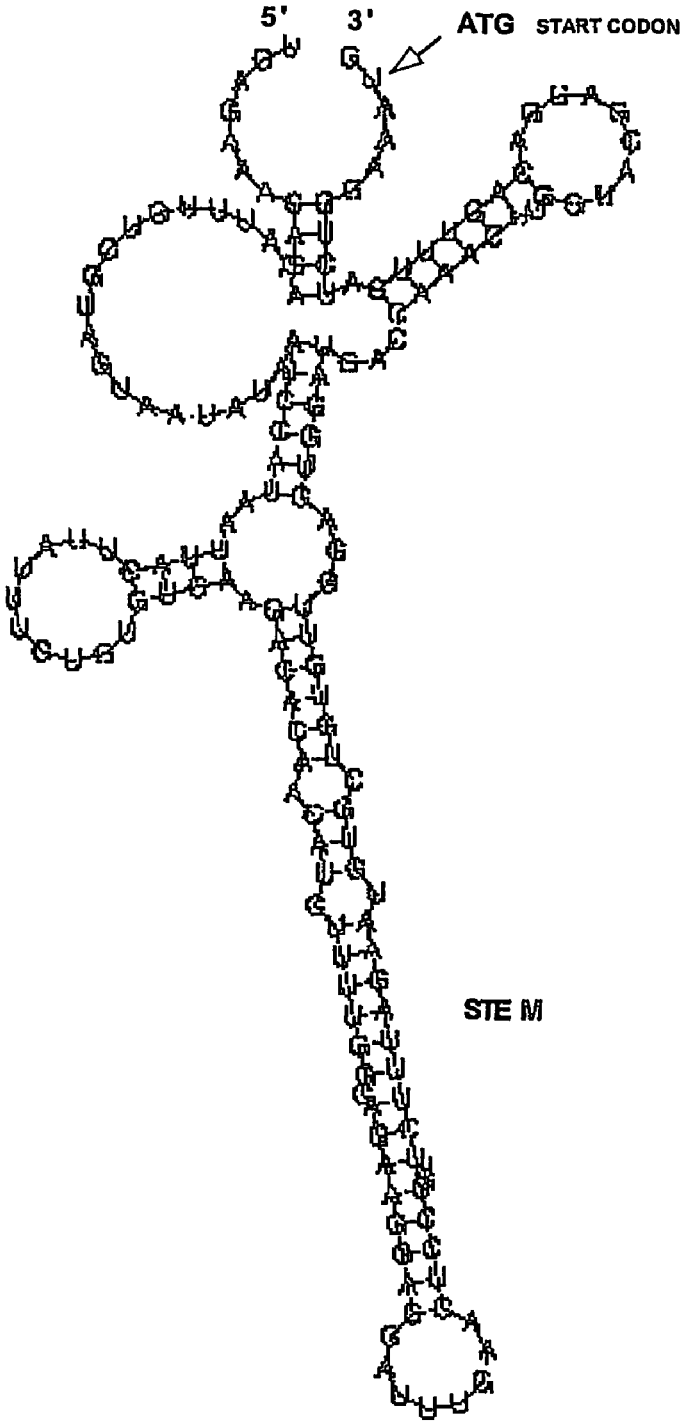


FIG. 16


CCCGGCTTCTGTCCACTTCTCAAGGCCATCTCAAATAACTTTTTCTTCAGGAAACTATTT -1561
CTCAAACCACTATAATTTTTTCCTAAGTTCTCTAGAATTCTTCCTTTGTTTAATCCCACT -1501
TTTTGCTTCACTTTCATTTTAGGAGCTAGGCGTATTTTTAAAAAGGCCCTTTGACCTCAA -1441
AGGATACACGTGGGTGAAAAACCACCTTCCTCTAAATTTATTTTTCACTCACTAGGAAGA -1381
ATGGTTTACTGTTAATAGCGGGTGGAAAGAAGGGACACTGAGTATGAGGACCTATCTGTA -1321
CTACCTAATATAATTTATCTTTTGATCTACTCTGAGAATGACGCGAGCCTAATCTTCACA -1261
TTGGAAAATCACGAGAGGAAAAAACCCTTCGGAGGTCTACAGGCACAAGGAACCCTGTCT -1201
CCACGCTGTTTATAGCAGCTGTCTCAGGAATCCTCTGCCTAGAATGAATGTGGGAGAGGT -1141
TTCGTGGCGCGGCAGCTGCAAAGCAAGGAATCTTTCCCATTCCTCGTCGACTCGGTCCCC -1081
TCCCCTCCCCTCCCGAATGGCGGCAGCTGCCGAGGTATCCCAGTGGAAATCTCCAAGTCT -1021
CCGCCGAGAGCGGCGGGCGGGCAACAGCTGAAAGCAGCCAGGGGTGGGGACTCCTCGCTC -961
CCATTGGGCAGGGACAGCAGCCTCACTGGCTCCAGCGCCGTCACCTCTCTGGCTCGTAGA -901
GGTGCCTCAGGTGTTCTTCTCCAAGTCCAATGAGACACCTAGGCAACGCAGCGCGTGTTC -841
E2F E2F
CCTCCGGCGCCAAGAGACCCTACGGTAACTTAACAACAGCAGGAGCGCCAAAATCCCCGCC -781
TCAGGACTTGGCAGAAGCACCTCCCGAGGTCCGAGAGTGGGAGAGGGGAAAGTGTAGGCC -721
CTCGGACGGAAGGGTCTCTCCTCGCCGGGCCGGGTACACACCTGGTGCTACCAGAGCAGC -661
GCGCCTAGTGCAGCCGGAAGCCCCAGCCCAGCACTCCGGCTGGCTCGGGGCCCCCTTGGC -601
E2F
TGTCCGCGCGTGTAACCGCGCCCCCGGCCGCGCGGGTGGCTCCGCTTTGGCGCCTCCCC -541
GCCCGCGCACTCGCGCTCGCGCACGCGCACGCCGCGCCCGGCAGCACTCGGCGCTGTCAT -481
Sp1
GGCGGCCGGGAGCAGCTTCAGTGGGCACACGACAGCCGCGCGACCCGTGGCGGGGCGAGC -421
TGTGGCAGTAGCATCCTCACCACTCGCAGCAGCCTCAGCCGCGGCGCCCGTAGCGCCAGC -361
Sp1 Sp1 c-Ets-
AGCGGCTGCTTTTGCAAAGGCTGAGCGCAGGGGGCGGGGCGGGCCAGGAAGCCATGGAGTT -301
Exon Intron
CTGTGCAGCCGCGGACTCCCGGGGAGCGGACTAGGGAAACTTGGAGGCTGCGACCAGGTG -241
AML-1a
CACTGACCTCTCTGTCCTCCCTTCTCTCCCTGCGGTGGCCGCTGGGTTTCTCTGGCCGCT -181
CCCCTCCCTTCCTGCCACCACACACACCTCCCCACCCCTTCCCGTCGAATCTCAGGTGCC -121
Tst-1 HSF2
TGAGAGAGGTGCTTCACTCCTCCCACTGGGCCGAGCATTTAGAATAATCACCGCCCCCTT -61
CdxA CdxA
Sp1
CCCCCGCCTTTTCCTGCCCTGGATCTCCGCCGCCACCTCGGTCTCGCTGCTCCTGGGCGG -1
+1 Exon1 Exon2
AML-1a E2F C/EBPa
GGGGTGAGGACGAGTCCGGAGTATCTGCGGTTTGGGGTGTTGTCAGCCTCGGGGAGAGA +60
GATA-3,
GATTGGACAATATTCTCCAAGAGGAGGAGGGCGACGCCAAGGACTTTCCACATCAACTG +120
CTTTGGGGTATCTCCACAAGTTGGAAGAGGGACCCTTTCGTTTTGCATTGCGTGTGTTGT +180
GCTCATTACCAGTGCAGCGACTGCCGTCCCAGGGTGACTCTGAGTTGTCCTTTATCGTGA +240
GCTAGCAATGGCTAGCGAAGACAATCGTGTCCCTTCCCCGCCACCAACAGGTGATGACGG +300

FIG. 17

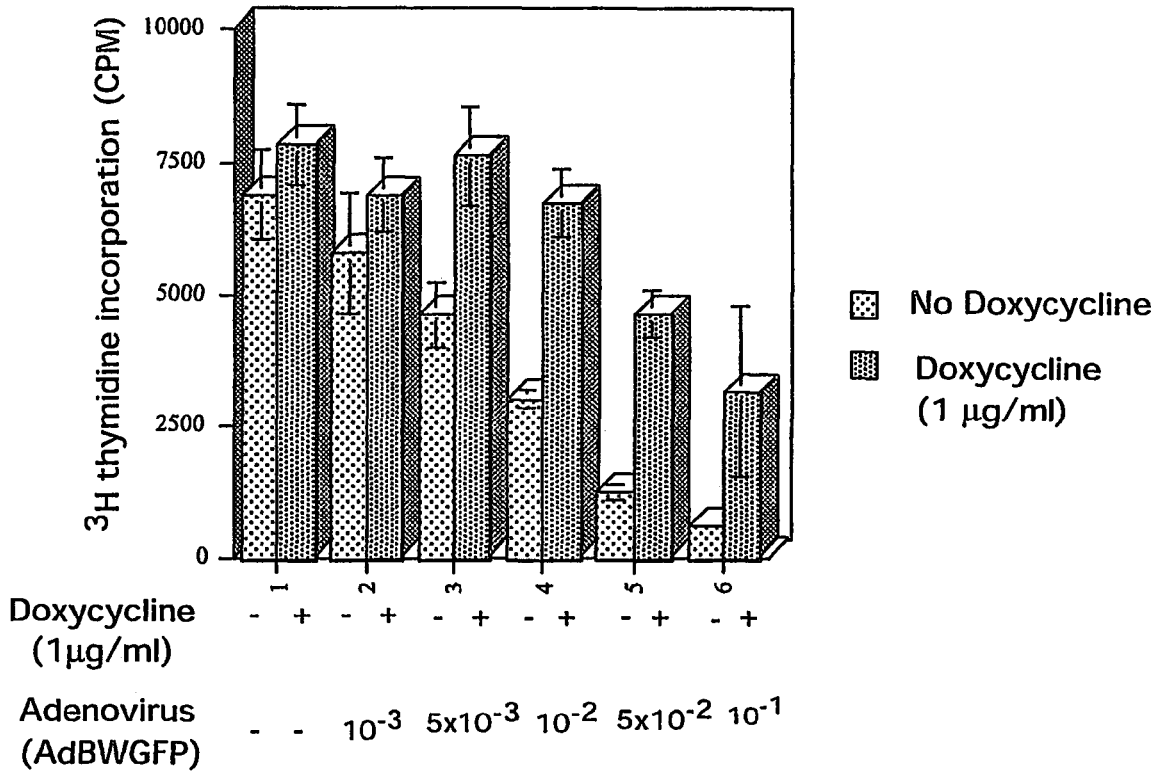

^{3}H thymidine incorporation (CPM)
10000
7500
5000
2500
0
1
2
3
4
5
6
Doxycycline (1µg/ml)
- + - + - + - + - + - +
Adenovirus (AdBWGFP)
- - 10^{-3} $5x10^{-3}$ 10^{-2} $5x10^{-2}$ 10^{-1}
No Doxycycline
Doxycycline (1 µg/ml)

FIG. 19

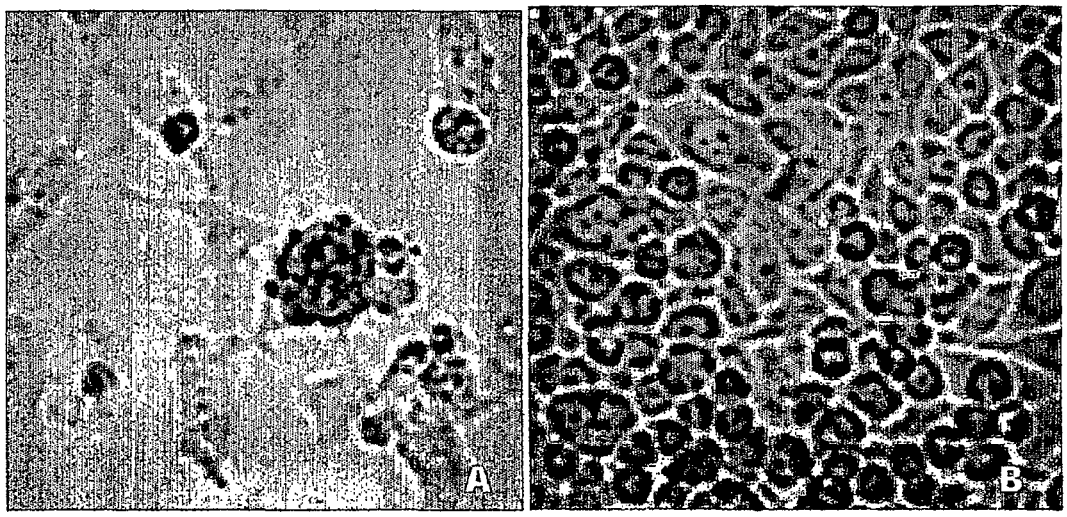


FIG. 20A FIG. 20B

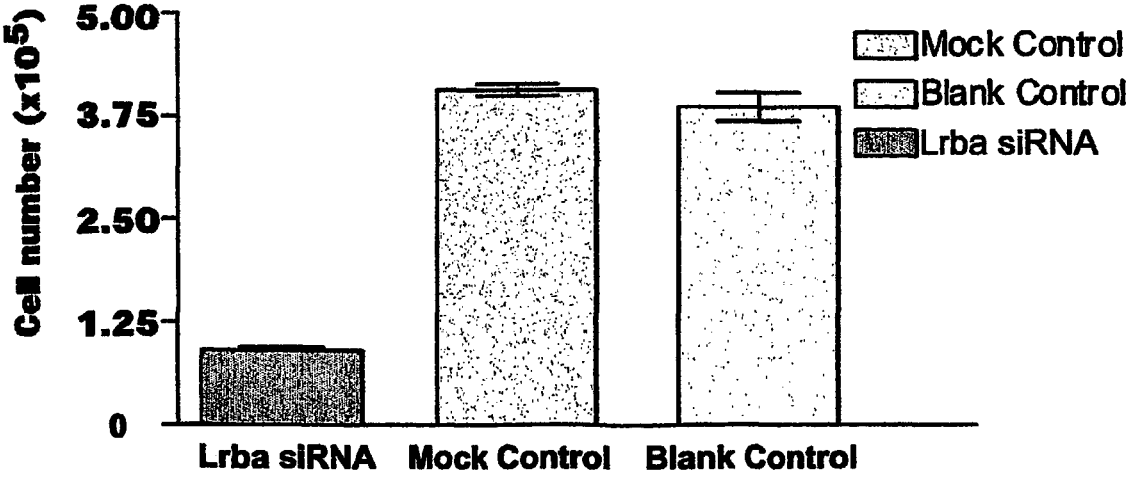


FIG. 20C

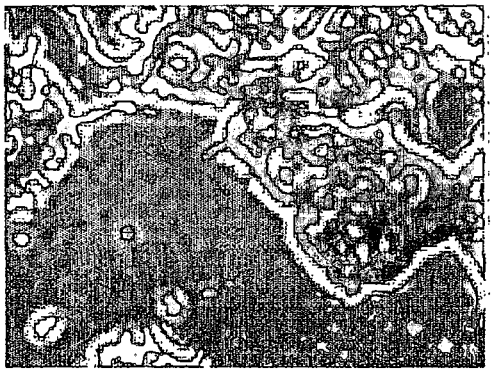


FIG. 21A

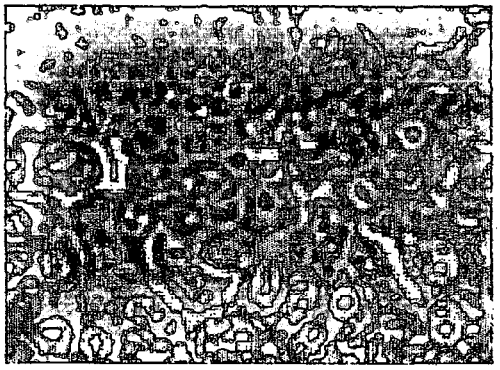


FIG. 21B

FIG. 21C

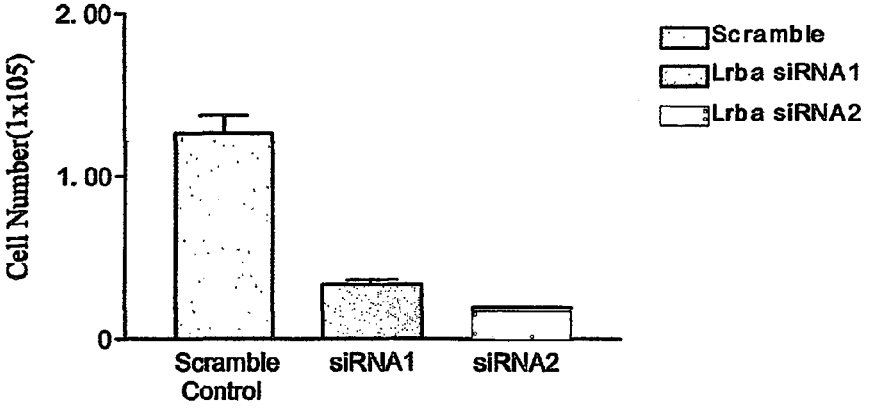
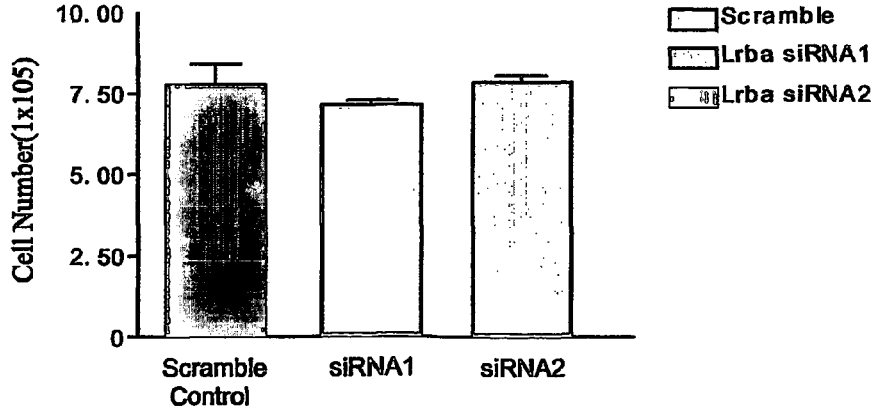


FIG. 21D



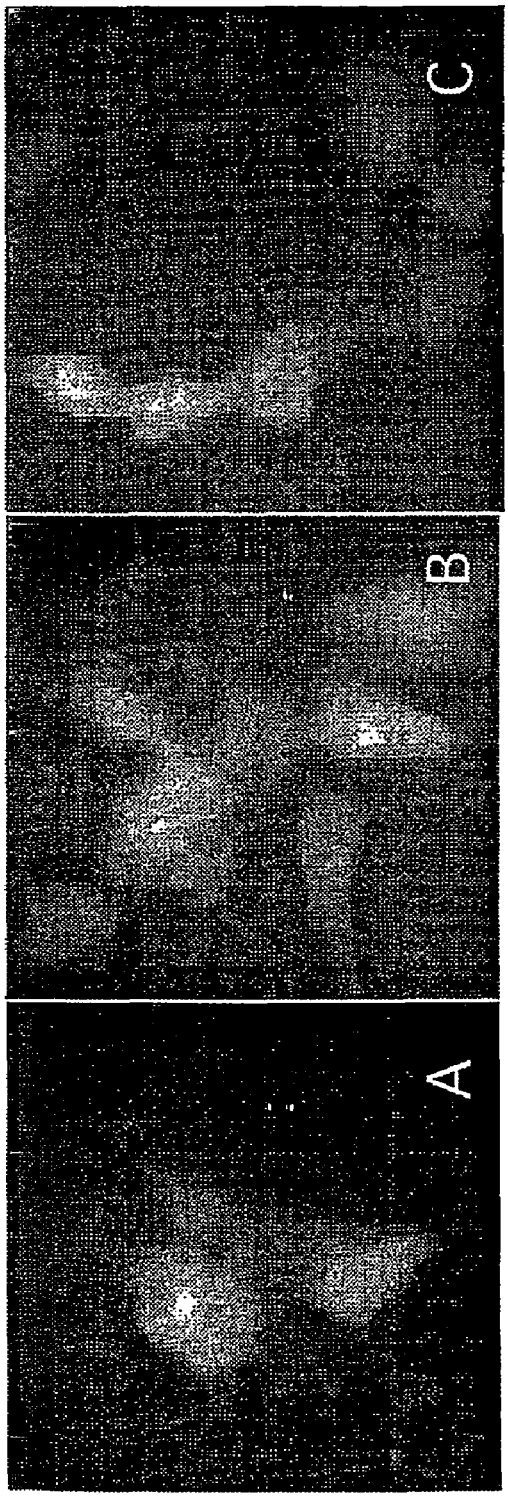


FIG. 22C

FIG. 22B

FIG. 22A

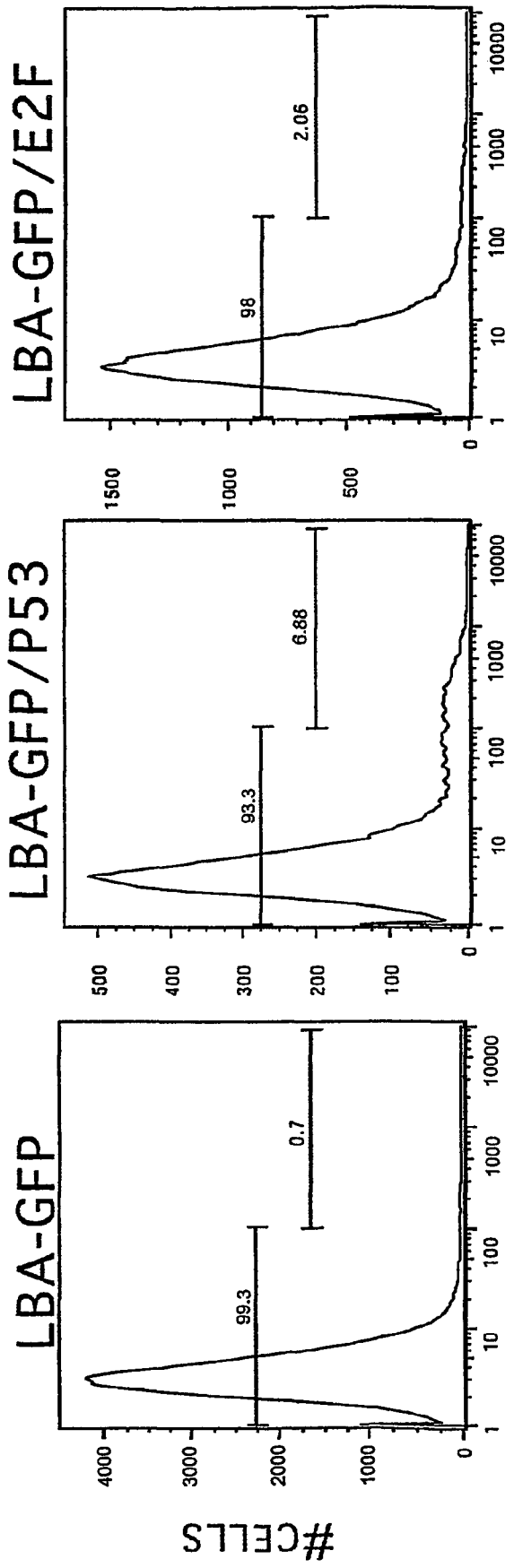


FIG. 22D

FIG. 22E

FIG. 22F

LPS-RESPONSIVE *CHS1/BEIGE*-LIKE ANCHOR GENE AND THERAPEUTIC APPLICATIONS THEREOF

CROSS-REFERENCE TO RELATED APPLICATION(S)

This application is a National Stage filing of International Application No. PCT/US02/10350, filed Apr. 2, 2002, which claims the benefit of provisional patent application Ser. No. 60/280,107, filed Apr. 2, 2001, which is hereby incorporated by reference in its entirety, including all nucleic acid sequences, amino acid sequences, figures, tables, and drawings.

The subject invention was made with government support under a research project supported by the National Institutes of Health Grant Nos. RO1 DK54767, R21 AI44333, and PO1 NS27405. The government may have certain rights in this invention.

BACKGROUND OF THE INVENTION

Mutations in chs1/beige result in a deficiency in intracellular transport of vesicles that leads to a generalized immune deficiency in mouse and man. The function of NK cells, CTL, and granulocytes is impaired by these mutations indicating that polarized trafficking of vesicles is controlled by chs1/beige proteins. However, a molecular explanation for this defect has not been identified.

Lipopolysaccharide (LPS) is a potent inducer of maturation in B cells, monocytes, and dendritic cells that facilitates production of inflammatory cytokines, nitric oxide, and antigen presentation so that these cells can participate in the immune response to bacterial pathogens (Harris, M. R. et al. *Journal of Immunology,* 1984, 133:1202; Tobias, P.S. et al. *Progress in Clinical & Biol. Res.,* 1994, 388:31; Inazawa, M. et al. *Lymphokine Res.,* 1985, 4:343). In an attempt to identify genes involved in the maturation of immune cells, a gene-trapping strategy was developed to identify mammalian genes whose expression is altered by cellular stimuli (Kerr, W. G. et al. *Cold Spring Harbor Symposia on Quantitative Biology,* 1989, 54:767). Several novel LPS-responsive genes were successfully trapped (Kerr, W. G. et al. *Proc. Natl. Acad. of Sci. USA,* 1996, 93:3947), including the SHIP gene that plays a role in controlling the maturation and proliferation of B cells and monocytes/macrophages in vivo (Huber, M. et al. *Prog. in Biophysics and Molecular Biol.,* 1999, 71:423; Ono, M. et al. *Nature,* 1996, 383:263; Ono, M. et al. *Cell,* 1997, 90:293).

Chediak-Higashi Syndrome (CHS^3) patients suffer from a systematic immune deficiency characterized by a severe immune defect, hypopigmentation, progressive neurologic dysfunction and a bleeding diathesis (Spritz, R. A. *Jour. of Clinical Immun.,* 1998, 18:97). Specific defects in immune cells include defects in T cell cytotoxicity (Abo, T. et al. *Jour. of Clinical Investigation,* 1982, 70:193; Baetz, K. et al. *Jour. of Immun.,* 1995, 154:6122), killing by NK cells (Haliotis, T. et al. *Jour. of Exper. Med.,* 1980, 151:1039), defective bactericidal activity and chemotaxis by granulocytes and monocytes (Clark, R. A. and H. R. Kimball *Jour. of Clinical Investigation,* 1971, 50:2645). CHS and beige lysosomes also exhibit compartmental missorting of proteins (Takeuchi, K. et al. *Jour. of Exper. Med.,* 1986, 163:665). Other studies have found that beige macrophages are defective for class II surface presentation (Faigle, W. et al. *J. Cell Biol.,* 1998, 141: 1121; Lem, L. et al. *Jour. of Immun.,* 1999, 162:523) and that T cells in CHS patients are defective for CTLA4 surface expression (Barrat, F. J. et al. *Proc. Natl. Acad. of Sci. USA,* 1999, 96:8645). All cells in beige mice and CHS patients bear giant vesicles that cluster around the nucleus. Affected vesicles include lysosomes, platelet dense granules, endosomes, and cytolytic granules. These giant vesicles seem normal in several aspects except for their failure to release their contents, probably resulting from inability of the giant granules to mobilize and/or fuse with the membrane upon stimulation (Baetz, K. et al. *Jour. of Immun.,* 1995, 154:6122). However, despite these very provocative findings there still remains no direct evidence that BG(beige)/CHS1 proteins associate with intracellular vesicles and thus a molecular explanation for defective vesicle trafficking and protein missorting in these diseases is still sought.

BRIEF SUMMARY OF THE INVENTION

The present invention relates to a novel LPS-responsive and Beige-like Anchor gene (lrba), its transcriptional/translational products, and the targeting of the lrba gene for the treatment of cancer. Thus, the present application is directed to the lrba gene, variants of the lrba gene, fragments of the lrba gene, corresponding polypeptides encoding by such nucleotides, and uses thereof. The mouse lrba gene product is disclosed herein in FIG. **1** and the human lrba gene product is disclosed herein in FIG. **9**. The lrba gene is associated with the vesicular system, such as the Golgi complex, lysosomes, endoplasmic reticulum, plasma membrane and perinuclear ER, and plays an important role in coupling signal transduction and vesicle trafficking to enable polarized secretion and/or membrane deposition of immune effector molecules. In one aspect, the lrba variants of the subject invention include five isoforms of the lrba gene, including lrba-α, lrba-β, lrba-δ, lrba-γ, and lrba-ϵ. The sequences of the mouse lrba cDNAs have been deposited in GENBANK with the following GENBANK accession numbers: lrba-α: AF187731, lrba-β: AF188506, lrba-γ AF188507.

The subject invention also relates to cloning and expression vectors containing the lrba gene, and fragments and variants thereof, and cells transformed with such vectors.

In one aspect, the subject invention concerns lrba small interfering RNA (siRNA) sequences useful for the treatment of cancer. Preferably, the siRNA duplex is formed by annealing single-stranded RNA sequences (ssRNA) of 5'CCAGCAAAGGUCUUGGCUAdTdT3' (SEQ ID NO. 1) and 5'CAGUCGGGUUUGCGACUGGdTdT3' (SEQ ID NO. 2) from the lrba gene.

In a further aspect, the subject invention concerns methods of inhibiting the growth of tumors in a patient by suppressing lrba function. According to the method of the subject invention, suppression of lrba function can be carried out at various levels, including the levels of gene transcription, translation, expression, or post-expression. For example, suppression of lrba gene expression can be carried out using a variety of modalities known in the art for interfering with the production of a functional product of a target gene. For example, siRNA sequences, such as those described above, can be administered to a patient in need thereof. The siRNA can be produced and administered exogenously, or the siRNA can be inserted into an appropriate vector and the vector can be administered to the patient for production of the siRNA in vivo, for example.

The subject invention also provides methods of detecting the presence of lrba nucleic acids, transcriptional products, or polypeptides in samples suspected of containing lrba genes, transcriptional products, or polypeptides.

Another aspect of the subject invention provides kits for detecting the presence of lrba genes, lrba variants, lrba polypeptides, or lrba transcriptional products obtained from the polynucleotide sequences.

BRIEF DESCRIPTION OF DRAWINGS

FIGS. **1**A and **1**B show the sequence and structure of the mouse lrba gene. FIG. **1**A shows the predicted full-length amino acid sequence of the lrba-α (SEQ ID NO. 3) and lrba-β (SEQ ID NO. 4) (stopped at the boxed "R" with the additional sequence VSAVGSTLFLLLGSSK (SEQ ID NO. 5)) and lrba-γ (SEQ ID NO. 6) cDNAs (stopped at the boxed "I" with the additional sequence GLPLLSLFAIH (SEQ ID NO. 7)). Bold amino acids indicate the BEACH domain (2204-2482) based on alignment with 20 other BEACH domains. Eight WD repeats predicted by an algorithm available at http://bmerc-www.bu.edu/psa/request.htm, are underlined or dotted-underlined. The first three WD repeats are not predicted by other programs but resemble WD repeats and thus are referred to herein as WDL (WD-like) repeats. Two putative protein kinase A RII binding sites are shaded. The sequences of the mouse lrba cDNAs have been deposited in GENBANK with the following GENBANK accession numbers: lrba-α: AF187731, lrba-β: AF188506, lrba-γ. AF188507. FIG. **1**B shows a schematic diagram of mLRBA protein and alignment of the predicted mLRBA protein with its orthologues and some paralogues. The stop sites for the lrba-β and lrba-γ are indicated by dashed lines. The human LRBA protein (SEQ ID NO. 8) was predicted from a 9.9 kb "hybrid" cDNA sequence with the first 5' 2577 nucleotides from this work (GENBANK accession numbers AF216648) and the rest from the CDC4L partial cDNA sequence (GENBANK accession numbers M83822) (Feuchter, A. E. et al. (1992) *Genomics* 13:1237) except one G was added after position 5696 for two reasons: (i) the G base is present in the cDNA sequence (GENBANK accession numbers AF217149); and (ii) this addition extended the CDC4L ORF by an additional 165 AA that had high homology with mLRBA and other proteins shown in this figure. The dLRBA was predicted from the *drosophila melanogaster* genomic sequence (GENBANK accession number AE003433). cLRBA (GENBANK accession number T20719, *Caenorhabditis elegans*), aCDC4L (GENBANK accession number T00867, *Arabidopsis thaliana*), LSVA (GENBANK accession number AAD52096, *Dictyostelium discoideum*), hFAN (GENBANK accession number NP_0035711, *Homo sapiens*), CHS1 (Chediak-Higashi Syndrome 1, GENBANK accession number NP_000072, *Homo sapiens*), mBG (GENBANK accession number AAB60778, *Mus musculus*).

FIGS. **2**A and **2**B show the PKA binding sites in LRBA. In FIG. **2**A, the conservation of hydrophobic amino acids of putative PKA binging sites in mLRBA (SEQ ID NO. 9), hLRBA (SEQ ID NO. 10), dLRBA (SEQ ID NOs. 11-12), and cLRBA (SEQ ID NO. 13) are shown by aligning with the known B1 and B2 PKA RII tethering sites (underlined) in DAKAP550 (a partial cDNA sequence for dLRBA) along with other sequences in these regions. FIG. **2**B shows the predicted secondary structure of the putative PKA binding sites in mLRBA (mLRBAb1, mLRBAb2). The hydrophobic amino acids on the hydrophobic side of the predicted amphipathic helices are boxed.

FIG. **3** shows the alignment of the C-terminal sequences of mLRBA (SEQ ID NO. 14), hLRBA (SEQ ID NO. 15), dLRBA (SEQ ID NO. 16), CHS1 (SEQ ID NO. 17), and hFAN (SEQ ID NO. 18), which include the BEACH domains (in the middle, boxed), 5 WD repeats and the 3 WDL repeats predicted in mLRBA and hLRBA. The predicted SH3, SH2 binding sites and tyrosine kinase recognition sites are also boxed. The C-terminal difference of the three isoforms of the mLRBA, α (SEQ ID NO. 14), β (SEQ ID NO. 19), and γ (SEQ ID NO. 20), are shown here (and FIG. **1**B in more detail).

FIGS. **4**A and **4**B show that expression of lrba is inducible in B cells and macrophages. FIG. **4**A shows Northern blot hybridization of mRNA from B cell line 70Z/3 and the macrophage cell line J774. Both cell lines were cultured with or without LPS for 20 hours. The poly A^+RNA was purified from these cells, run on a denaturing formaldehyde agarose gell, and transferred to a Hybond-N+ filter. The filter was hybridized with the 2.5 kb probe that corresponds to the coding region of the lrba gene including the BEACH and WD domains, as described in the Materials and Methods section. The hybridized filter was exposed to X-ray film for 24 hours. Similar amounts of β-actin mRNA were found in all mRNA tested (Actin panels). FIGS. **4**B and **4**C show expression of mRNA of three lrba isoforms (α, β, and γ) in B cell lines (FIG. **4**B) and tissues (FIG. **4**C). Three isoform-specific primer pairs were used to detect the expression of the three isoforms by RT-PCR, the expected product size of the RT-PCR product for the α form is 1344 bp, for the β form 836 bp, and for the γ form 787 bp. Total RNA is analyzed. Aliquots (10 μl) of the PCR products were resolved on 0.8% agarose gels. Three independent experiments were performed and yielded similar results.

FIGS. **5**A-**5**I show subcellular localization of GFP-LRBA fusion proteins revealed by UV-fluorescence microscopy and laser-scan confocal microscopy. FIG. **5**A shows the RAW 267.4 macrophage cell line (R7) stably transfected with a BEACH-WD-GFP fusion construct. Most cells have diffuse, cytosolic GFP fluorescence, but some cells show vesicle association of the GFP fusion protein. In FIG. **5**B, the same cell line from FIG. **5**A was plated on glass-covered plates and stimulated with LPS (100 ng/ml) for 24 hours. Extensive vesicle association of the fusion protein was observed. FIG. **5**C shows RAW 267.4 macrophages stably transfected with the control vector pEGFP-N2 that were cultured with 100 ng/ml LPS stimulation. No obvious vesicle association of native GFP was observed. Magnification: 400×. FIG. **5**D shows part of an R7 macrophage cell, showing GFP fluorescence. FIG. **5**E shows the same part of an R7 macrophage cell as in FIG. **5**D, showing acidic lysosomes specifically labeled by LysoTracker Red in living cells. FIG. **5**F shows lysosome co-localization (white part) of GFP fusion protein by overlapping pictures of FIGS. **5**D and **5**E; N=nucleus. FIG. **5**G shows R7 macrophage cells, showing GFP fluorescence. FIG. **5**H shows the same R7 macrophage cells as in FIG. **5**G, showing prominent labeling of the Golgi complex (between the two nuclei) specifically labeled by BODIPY TR ceramide. Other intracellular membranes are weakly labeled. FIG. **5**I shows Golgi co-localization (white part) of GFP fusion protein by overlapping pictures shown in FIGS. **5**G and **5**H. Co-localization was determined by Zeiss LSM 510 software, which allows for a reliability of 99% for actual pixels with both fluorophores. Co-localization mask pixels are converted to white color for clarity. All cells were stimulated with LPS (100 ng/ml) for 24 hours except for FIG. **5**A.

FIGS. **6**A-**6**F show immunoelectron microscopy of LRBA-GFP fusion protein. The LPS-stimulated R7 macrophage cells were fixed and processed for postembedding immunocytochemistry. The cells were dehydrated and embedded in gelatin capsules in LR White resin. Ultrathin sections of LR White embedded cells were collected on nickel grids and immunolabeled with rabbit-anti-GFP followed by labeling with anti-rabbit IgG-gold secondary anti-

body, and finally stained with uranyl acetate and lead citrate before examination with EM. FIG. **6**A shows a clathrin-coated pit (endocytic, or coated vesicle) labeled with gold particles (open arrow). This is a vesicle forming on the cell surface. The fact that there is clathrin around this vacuole indicates that it is involved in endocytosis and not exocytosis. FIG. **6**B shows intense labeling of a primary lysosome (open arrow) and a vesicle on the cell surface (closed arrow). In FIG. **6**C, the black arrows show ribosomes lining a profile of endoplasmic reticulum (er). There are three gold particles labeling the ER (open arrow). The gray structure next to the ER is a mitochondrion (m), which is not labeled. FIG. **6**D shows a Golgi region of a cell labeled for GFP. The open arrows show gold particles on a Golgi cisterna. FIG. **6**E shows labeling of endoplasmic reticulum comprising the perinuclear cisterna (open arrows), and labeling of the plasma membrane of the cell (closed arrows). FIG. **6**F shows gold particles surrounding a secondary lysosome in a cell (*). At the top of the lysosome is a coated vesicle (closed arrow) fusing with the lysosome. A portion of ER surrounds the bottom of the lysosome, which is also labeled with gold particles (open arrow). Labeling of the perimeter of the secondary lysosome shows routing of GFP from the cell surface to the lysosome limiting membrane. In FIGS. **6**A-**6**F, e=extracellular space; n=nucleus; er=endoplasmic reticulum; g=Golgi; m=mitochondrion; c=cytoplasm. The size of gold particles is 10 nm.

FIG. **7** shows a model of vesicle secretion for WBW protein family using the lrba gene as a prototype. Following immune cell activation, the BEACH domain binds to vesicles containing cargo proteins and membrane proteins for secretion or deposition in the plasma membrane. The anchor domain binds to microtubules to move the vesicles to the membrane where the WD domain binds to phosphorylated sequences of membrane receptor complexes to mediate the fusion of the vesicles with the membrane, thus releasing the cargo proteins or depositing membrane proteins on the plasma membrane of immune cells.

FIG. **8** shows a Western blot of a Raw 264.7 macrophage cell line and stably transfected Raw 264.7 cell lines, demonstrating inhibition of apoptosis by LRBA fusion proteins. 586-2 cells were transfected with BEACH-GFP construct; R7 cells were transfected with BEACH-WD-GFP construct; and RGFP cells were transfected with pEGFP vector. The level of both cleaved PARP (poly(ADP-ribose) polymerase and cleaved caspase 3 are higher in control cell lines (Raw 264.7 and RGFP) than in LRBA transfected Raw 264.7 cell lines (586-2 and R7), suggesting LRBA constructs can prevent cells from apoptosis induced by staursporine.

FIG. **9** shows the predicted full-length amino acid sequence and structure of the human LRBA gene and its five isoforms (SEQ ID NO:182). Each isoform is shown by α (SEQ ID NO. 8), β (SEQ ID NO. 21), γ (SEQ ID NO. 22), δ (SEQ ID NO. 23), ϵ (SEQ ID NO. 24) at the right of each C-terminus or the five amino acid insertion(γ). Residues in italic letters indicate isoform-specific sequences. Asterisk *=stop codon. Sequences are connected by arrows. The numbers at the right are for the α form. The domains are shaded and named above each domain. Five WD repeats predicted by an algorithm available on the protein sequence analysis (PSA) server at the Boston University website are also shaded or boxed. HSH (helix-sheet-helix); SET: Rich in Serine(S), Glutamic acid(E) and Threonine(T). G peptide has five consecutive glycine. The two potential start codons are boxed. The sequences of the LRBA cDNAs have been deposited in GenBank (accession number NM_006726).

FIG. **10** shows secondary structure prediction and alignment of the HSH domain in several WBW proteins (SEQ ID NOs. 25-31). Sequence positions highlighted in magenta and yellow correspond, respectively, to helices and strands. Sequence positions highlighted in blue are potential glycosylation sites. Squared positions correspond to conserved residues found in the three WBW protein. The positions of the predicted helical regions of the HSH structure are indicated as tubes at the top of the sequences. Sequences having homologues in FIG. **9** were analyzed as multiple sequence alignments using the Jpred[2] method (Cuff, J. A. et al. (1998) *Bioinformatics* 14:892-893; Cuff J. A. and Barton, G. J. (1999) *Proteins: Structure, Function and Genetics* 34:508-519; Cuff, J. A. and Barton, G. J. (1999) *Proteins: Structure, Function and Genetics* 40:502-511). Several sequences that, after a first prediction run, were found to have more than 25% homology in one of the three conserved helical regions were reprocessed together as a multiple sequence alignment using Jpred[2] to refine the prediction of that particular region. Secondary structure predictions were performed by the Jpred[2] method. Rectangles indicate -helices and arrows indicate -strands. HSH (helix-sheet-helix) domain: Several WBW proteins have a high homology and a common predicted protein secondary structure (HSH structure) over an 100 amino acid stretch near their N-terminus, as shown in FIG. **10**. Because the HSH domain exists in evolutionarily very distant species (*Dictyostelium* is a cellular slime mold, more ancient than yeast), it may have important function in a cell's life. SET domain: rich in serine (S, 13.70%), glutamic acid (E, 13.40%) and threonine (T, 9.03%). Its function is still unknown. This domain is very hydrophobic and has a very high antigenic index. PI is 3.96.

FIG. **11** shows the genomic structure of the human LRBA gene. The gene contains 59 exons, which span more than 700 kb. The exon/intron structure of the LRBA gene is mapped to the corresponding cDNA regions encoded by each exon. Location and size of exons and introns are drawn to scale (GenBank accession number NM_006726).

FIG. **12** shows a molecular phylogenic tree of the amino acid sequences of WBW genes from various species. The tree was constructed by the neighbor joining method, based on sequence alignment conducted by CLUSTALX software using either whole length sequence or only the BEACH domain, which gave very similar results. This indicates that the BEACH domain is co-evolving with the rest sequence of the gene and, as the whole sequences of some WBW genes are still unavailable (moreover, the length of the BEACH domain is relatively consistent (around 278 amino acids)), using the BEACH domain seems more reasonable. Thus, FIG. **12** is based on the BEACH domain. All the sequences are from GeneBank. The numbers in parenthesis are GI numbers.

FIG. **13** shows alternative splicing of the human LRBA gene. The solid or gray box indicates coding exon, and the hatched box indicates UTR (untranslated region). The top numbers indicate exons in the main form (constitutive isoform versus alternative isoform) of human lrba, while the bottom numbers indicate alternative splicing isoforms of the human LRBA gene. The single Greek letters denote the five isoforms. The LRBAδ has a 310 bp Alu sequence at its poly (A) tail. 5'-1, 3'-1 and 3'-2 indicate 5' end and 3' end splicing, while I-1 and I-2 represent internal splicing. 5'-1 splicing gives alternative transcription start site and suggests alternative promoter for human LRBA gene. The internal splicing I-1 interrupts the coding sequence of LRBA, splitting LRBA into two open reading frames (ORF), and thus alternative potential start codon ATG (the meaning of this splicing is further described and discussed later). Another internal alter-

native splicing I-2 is a 15 bp sequence in frame with the main ORF, inserting a YLLLQ (SEQ ID NO. 32) insertion into the human LRBA protein (noting that the l and w are hydrophobic amino acids). AATAAA indicate a polyadenine signal. 3'-1 and 3'-2 splicing generate two additional different 3' UTR tails for human LRBA gene. The isoform identification was conducted by using the following cultured cells and tissues: (1.) human pre-B (6417) cells; (2.) human Raji B cells; (3.) 293 cells; (4.) human MCF7 breast cancer cells; (5.) human HTB4 lung cancer; (6.) human H322 human lung cancer; (7.) human A539 human lung cancer; (8.) human lung carcinoma; (9.) human lung carcinoma adjacent tissue; (10.) human B-cell lymphoma; (11.) human B-cell lymphoma; and (12.) normal adjacent tissue (3 pairs of tumor tissue and adjacent tissue of human prostate).

FIG. **14** shows results of a 5'RACE (rapid amplification of cDNA end) procedure and 3'RACE procedure, respectively, conducted on the human lrba gene. In FIG. **14**, the lower band contains an AluSx repeat sequence 312 bp long. RNAs were from: (1.) pre-B (6417); (2.) Raji B cells; (3.) 293 cells; (4.) MCF7 breast cells; (5.) HTB4 lung cancer; (6.) H322 human lung cancer; (7.) A539 human lung cancer; (8.) human lung carcinoma; (9.) human lung carcinoma adjacent tissue; (10.) B-cell lymphoma; (11.) B-cell lymphoma; and (12.) normal adjacent tissue.

FIG. **15** shows the 5' end of the human lrbaϵ isoform with a long 5' UTR (SEQ ID NO. 33). There are four small ORFs before the major ORF of the human lrba gene. The longest small ORF encodes the first 73 amino acids of the hlrba protein (SEQ ID NO. 34) and is in frame with the major ORF, though there are four in-frame stop codons and 6 out-of-frame stop codons, in between which would prevent potential read-through that makes a fusion protein. The other three ORFs encode 20 amino acids, 18 amino acids, and 15 amino acids, respectively. The partial major coding sequence is in bold (SEQ ID NO. 35). The amino acid sequence in italics is present in the main form of the LRBA gene but absent in the delta form of the LRBA gene (SEQ ID NO. 36). The grey shaded sequence is the extra exon that has interrupted the LRBA sequence.

FIG. **16** shows the predicted secondary structure of RNA sequence between the two ORF of human lrbaδ (SEQ ID NO:181). The free energy for the structure is −40.29 kcal/mol. This suggests a potential IRES (internal ribosome entry signal). There is no homologous sequence between IRES, however they all have complex secondary structure like long stem structure.

FIG. **17** shows the promoter and part of the 5' cDNA sequence of the human lrba gene (SEQ ID NO. 37). Transcription start sites as determined by 5'RACE procedure are indicated by arrows. Sequence for a CpG island is in bold. The DNA consensus binding motifs for various transcription factors shown in the region −1561 to +1 were identified using the TFSEARCH (version 1.3) software (Yukata Akiyama (Kyoto Univ.)), the first nucleotide of the most 5' cDNA denoted as 1. The initiator methionine is in bold. The transcription binding sites are shaded, boxed, or underlined. The genomic sequences have GenBank accession number AC104796.

FIGS. **18**A and **18**B show RT-PCR of human prostate tumor tissue and adjacent normal tissue, demonstrating that LRBA expression is increased in human prostate cancer relative to matched normal tissue controls. FIG. **18**A shows RT-PCR detection of human LRBA mRNA. FIG. **18**B shows RT-PCR detection of human β-Actin mRNA to control for the amounts of mRNA present. The PCR cycle parameters were as follows: 94° C. for 30 seconds, 68° C. for 30 seconds, 72° C. for 1 minute, 25 cycles. The sources from the matched samples are (from left to right) 1, 3, and 5: prostate adenocarcinoma tissue; 2, 4, and 6: normal prostate tissue. Samples 1 & 2, 3 & 4, and 5 & 6, are matched pairs from three different prostate cancer patients.

FIG. **19** shows growth inhibition of human breast cancer cells by expression of a dominant negative human LRBA mutant. MCF7 human breast cancer cells were seeded (1×10^4/well) into a 96-well plate. On the second day, cells were infected with various titers of a recombinant adenovirus that contains a dominant negative LRBA mutant, in the presence or absence of doxycycline. The BW-GFP mutant comprises the BEACH and WD domains of LRBA fused to GFP. The adenoviral vector has a tetracycline-responsive promoter that is repressed in the presence of doxycycline and, thus, the BW-GFP mutant is expressed in the absence of doxycycline. Three days post-infection, the cells were labeled with ^{3}H-thymidine, the cells harvested and CPM incorporated into high molecular weight DNA counted as a measure of cell proliferation (DNA synthesis).

FIGS. **20**A-**20**C show the knock-down of Lrba expression by LRBA siRNA treatment and death of cancer cells. HeLa cells were plated 2×10^4 cells/well of a 24-well dish. The next day, cells were transfected as indicated or were left untreated (Blank). The cells were photographed 72 hours after transfected and the wells harvested for cell counting. HeLa cells (human adenocarcinoma) transfected with Lrba siRNA and lipofectamine (FIG. **20**A) or mock transfected with H_2O and lipofectamine (FIG. **20**B). Magnification is 400×. Note the presence of apoptotic or necrotic cell bodies as well as the spindly, stressed morphology of the remaining adherent cells in the siRNA Lrba-treated well. FIG. **20**C shows absolute cell numbers recovered as determined by Coulter Counter. Students' T-test: $P<0.0006$ for mock versus Lrba siRNA; $P<0.0036$ for Blank versus Lrba siRNA; $P<0.2271$ for mock versus blank. The siRNA treated cultures show a statistically significant decrease in cell number as compared to either mock or blank cultures, but there is no significant difference in the number of cells recovered from the mock and blank cultures. The RNA sequences that were annealed to make the Lrba siRNA were: Lrba sense-strand: 5'CCAGCAAAGGUCUUGGCUAdTdT3' (SEQ ID NO. 1); Lrba antisense-strand: 5'UAGCCAAGACCUUUGCUGGdTdT3' (SEQ ID NO. 38).

FIGS. **21**A-**21**D show silencing of the Lrba gene in MCF7 human breast cancer cells and MCF10A human breast normal cells by two pairs of Lrba siRNA (siRNA1 and siRNA2), demonstrating that Lrba siRNAs selectively kill human breast cancer cells but not normal cells. MCF7 cells (FIG. **21**A-**21**C) and MCF10A cells (FIG. **21**D) were seeded at 2×10^4 cells per well in 24-well plates. One day later, the cells were transfected with Lrba siRNAs or with scramble siRNA as a negative control using oligofectamine. After 72 hours of siRNA treatment, the photos (FIG. **21**A, MCF7 transfected with siRNA1; FIG. **21**B, MCF7 transfected with scramble siRNA negative control; magnification 400×) were taken and the cell numbers were counted by a Coulter counter. T-test: FIG. **21**C (MCF7), $P=0.0009$ for scramble negative control versus siRNA1; $P=0.0005$ for scramble negative control 1 versus Lrba siRNA2; $P=0.004$ for siRNA1 versus siRNA2. FIG. **21**D (MCF10A), $P=0.4070$ for scramble negative control versus siRNA1; $P=0.9456$ for scramble negative control 1 versus Lrba siRNA2; $P=0.0514$ for siRNA1 versus siRNA2. The siRNA sequences: siRNA1: CCAGCAAAGGUCUUGGCUAdTdT (SEQ ID NO. 1); siRNA2: GGGCACUCUUUCUGUCACCdTdT (SEQ ID NO. 39); scramble negative control: CAGUCGGGUUUGCGACUGGdTdT (SEQ ID NO. 2).

FIGS. **22**A-**22**F show upregulation of lrba promoter activity by p53 and E2F transcription factors. The GFP reporter (GFP gene is placed downstream of the lrba gene promoter, designated pLP-GFP) construct was transfected into 293T cells with or without p53 or E2F wild type vector. The pictures were taken one day after transfection. FACS analysis was carried out 60 hours after transfection. The results show that there is 0.7% GFP positive cells in pLP-GFP only (FIGS. **22**A and **22**D), 6.88% in pLP-GFP+p53 vector (FIGS. **22**B and **22**E), 2.06% in pLP-GFP+pE2F1 vector (FIGS. **22**C and **22**F), suggesting that only a small fraction of cells have detectable lrba promoter activity, p53 and E2F can induce the lrba promoter activity to 9.8, 3-fold respectively. p53 and E2F are important cell cycle and apoptosis mediators. All or most tumors can be characterized as being defective in p53 function.

BRIEF DESCRIPTION OF THE SEQUENCES

SEQ ID NO. 1 is the human lrba siRNA (siRNA1), including 3' two-dT overhang.

SEQ ID NO. 2 is the human lrba siRNA, including 3' two-dT overhang.

SEQ ID NO. 3 is the murine LRBA-α amino acid sequence (FIG. **1**A).

SEQ ID NO. 4 is the murine LRBA-β amino acid sequence (FIG. **1**A).

SEQ ID NO. 5 is the additional amino acid sequence at end of LRBA-β protein sequence (FIG. **1**A).

SEQ ID NO. 6 is the murine LRBA-γ amino acid sequence (FIG. **1**A).

SEQ ID NO. 7 is the additional amino acid sequence at end of LRBA-γ protein sequence (FIG. **1**A).

SEQ ID NO. 8 is the human LRBA amino acid sequence also termed LRBA-α (FIGS. **9** and **3**).

SEQ ID NO. 9 is the amino acid sequence of murine LRBA putative PKA binding sites (FIG. **2**A).

SEQ ID NO. 10 is the amino acid sequence of human LRBA putative PKA binding sites (FIG. **2**A).

SEQ ID NO. 11 is the amino acid sequence of *drosophila* LRBA putative PKA binding sites (FIG. **2**A).

SEQ ID NO. 12 is the amino acid sequence of *drosophila* LRBA2 putative PKA binding sites (FIG. **2**A).

SEQ ID NO. 13 is the amino acid sequence of *C. elegans* LRBA putative PKA binding sites (FIG. **2**A).

SEQ ID NO. 14 is the C-terminal amino acid sequence of murine LRBA also termed LRBA-α (FIG. **3**).

SEQ ID NO. 15 is the C-terminal amino acid sequence of human LRBA (FIG. **3**).

SEQ ID NO. 16 is the C-terminal amino acid sequence of *drosophila* LRBA (FIG. **3**).

SEQ ID NO. 17 is the C-terminal amino acid sequence of human CHS1 (FIG. **3**).

SEQ ID NO. 18 is the C-terminal amino acid sequence of human FAN (FIG. **3**).

SEQ ID NO. 19 is the C-terminal amino acid sequence of murine LRBA-β (FIG. **3**).

SEQ ID NO. 20 is the C-terminal amino acid sequence of murine LRBA-γ (FIG. **3**).

SEQ ID NO. 21 is the human LRBA-β amino acid sequence (FIG. **9**).

SEQ ID NO. 22 is the human LRBA-γ amino acid sequence (FIG. **9**).

SEQ ID NO. 23 is the human LRBA-δ amino acid sequence (FIG. **9**).

SEQ ID NO. 24 is the human LRBA-ϵ amino acid sequence (FIG. **9**).

SEQ ID NO. 25 is the amino acid sequence of HSH domain of murine LRBA (FIG. **10**).

SEQ ID NO. 26 is the amino acid sequence of HSH domain of human LRBA (FIG. **10**).

SEQ ID NO. 27 is the amino acid sequence of HSH domain of *drosophila* AKAP550 (FIG. **10**).

SEQ ID NO. 28 is the amino acid sequence of HSH domain of *C. elegans* F10F2.1 (FIG. **10**).

SEQ ID NO. 29 is the amino acid sequence of HSH domain of arabidopsis CDC4L (FIG. **10**).

SEQ ID NO. 30 is the amino acid sequence of HSH domain of dictyostelium LysA (FIG. **10**).

SEQ ID NO. 31 is the amino acid sequence of HSH domain of arabidopsis LYSTL.

SEQ ID NO. 32 is the inserted amino acid sequence in human LRBA-γ.

SEQ ID NO. 33 is the 5' end of human lrba-ϵ isoform with a long 5' UTR (FIG. **15**).

SEQ ID NO. 34 is the first 73 amino acids of the human LRBA (FIG. **15**).

SEQ ID NO. 35 is the partial major coding sequence of human LRBA (FIG. **15**).

SEQ ID NO. 36 is the amino acids encoded by the extra exon interrupting the lrba gene (FIG. **15**).

SEQ ID NO. 37 is the promoter and part of the 5' cDNA sequence of the human lrba gene (FIG. **17**).

SEQ ID NO. 38 is the human lrba siRNA antisense strand, including 3' two-dT overhang.

SEQ ID NO. 39 is the human lrba siRNA (siRNA2), including 3' two-dT overhang.

SEQ ID NOs. 40-46 are the primers used in cloning and sequencing of murine lrba cDNA.

SEQ ID NOs. 47-50 are the primers used in cloning and sequencing of human lrba cDNA.

SEQ ID NOs. 51-56 are the primers used in RT-PCR analysis of murine lrba expression.

SEQ ID NOs. 48, 57-61 are the primers used for amplification of human lrba.

SEQ ID NOs. 62-118 are the human lrba 5' splice donor sites (exons 1-57) (Table 2).

SEQ ID NOs. 119-175 are the human lrba 3' splice acceptor sites (introns 1-57) (Table 2).

SEQ ID NO. 176 is the amino acid sequence of p21 RAS motif.

SEQ ID NO. 177 is the human lrba siRNA (siRNA1).

SEQ ID NO. 178 is the human lrba siRNA.

SEQ ID NO. 179 is the human lrba siRNA antisense strand.

SEQ ID NO. 180 is the human lrba siRNA (siRNA2).

SEQ ID NO:181 is the RNA sequence between the two open reading frames of human lrbaδ (FIG. **16**).

SEQ ID NO:182 is the predicted full-length amino acid sequence of human LRBA (all five isoforms) (FIG. **9**).

DETAILED DISCLOSURE OF THE INVENTION

The subject invention concerns a method of inhibiting cancerous tumor growth in a patient by suppressing lrba function. Preferably, the method comprises suppressing the functional expression of the lrba gene. Various methods known in the art for suppressing the functional expression of a gene can be utilized to carry out this method of the subject invention. The lrba gene can be disrupted partially (e.g., a leaky mutation), resulting, for example, in reduced expression, or the lrba gene can be fully disrupted (e.g., complete gene ablation). Such mutations can include, for example, point mutations, such as transitions or transversions, or insertions and/or deletions, and the mutation can occur in the coding region encoding lrba

or merely in its regulatory sequences. According to the method of the subject invention, functional expression of the lrba gene can be suppressed at any level. In another aspect, the subject invention includes methods of disrupting expression of the lrba gene in vivo or in vitro.

Using the method of the subject invention, lrba function is suppressed, which causes inhibition of tumor growth. Preferably, the suppression of lrba function results in death of tumor cells. More preferably, lrba function is suppressed to an extent that normal (non-cancerous) cells are not killed.

Various means for suppression of lrba function can be utilized according to the method of the subject invention. For example, suppression of lrba function can be carried by administration of an agent that directly or indirectly causes suppression of lrba function. Agents suitable for the method of the subject invention include nucleic acids, such as a genetic construct or other genetic means for directing expression of an antagonist of lrba function. Nucleic acid molecules suitable for the method of the invention include, for example, anti-sense polynucleotides, or other polynucleotides that bind to lrba mRNA, for example. Preferably, the nucleic acid molecules administered to the patient are those disclosed herein. Other agents that can be utilized to carry out suppression of lrba function include, for example, peptidomimetics, ribozymes, and RNA aptamers.

According to the method of the subject invention, polypeptides can be administered to a patient in order to suppress lrba function and inhibit tumor growth. Preferably, the polypeptides utilized are those disclosed herein. More preferably, the polypeptides comprise fragments of the full-length lrba amino acid sequence (including fragments of full-length amino acid sequences of lrba orthologs). Most preferably, the polypeptides comprise amino acid sequences corresponding to the BEACH domain, WD domain, or BEACH and WD domains, of the lrba gene (including lrba gene orthologs). Various means for delivering polypeptides to a cell can be utilized to carry out the method of the subject invention. For example, protein transduction domains (PTDs) can be fused to the polypeptide, producing a fusion polypeptide, in which the PTDs are capable of transducing the polypeptide cargo across the plasma membrane (Wadia, J. S. and Dowdy, S. F., *Curr. Opin. Biotechnol.,* 2002, 13(1)52-56). Examples of PTDs include the *Drosophila* homeotic transcription protein antennapedia (Antp), the herpes simples virus structural protein VP22, and the human immuno-deficiency virus 1 (HIV-1) transcriptional activator Tat protein.

According to the method of tumor inhibition of the subject invention, recombinant cells can be administered to a patient, wherein the recombinant cells have been genetically modified to express an lrba gene product, such as a portion of the amino acid sequences set forth in FIG. **1** (SEQ ID NOs. 3-7) or FIG. **9** (SEQ ID NOs. 8 and 21-24), or variants thereof.

The method of tumor inhibition of the subject invention can be used to treat patient suffering from cancer or as a cancer preventative. The method of tumor inhibition of the subject invention can be used to treat patients suffering from a variety of cancers including, but not limited, to cancer of the breast, prostate, melanoma, chronic myelogenous leukemia, cervical cancer, adenocarcinoma, lymphoblastic leukemia, colorectal cancer, and lung carcinoma.

In another aspect, the subject invention provides isolated and/or purified nucleotide sequences comprising: (i) a polynucleotide sequence encoding the amino acid sequence set forth in FIG. **1** (SEQ ID NOs. 3-7) or FIG. **9** (SEQ ID NOs. 8 and 21-24), or a complement thereof; (ii) a polynucleotide sequence having at least about 20% to 99.99% identity to the polynucleotide sequence of (i); (iii) a polynucleotide encoding a fragment of the amino acid sequence shown in FIG. **1** (SEQ ID NOs 3-7) or FIG. **9** (SEQ ID NOs. 8 and 21-24); or (iv) an interfering RNA sequence corresponding to the transcript of the polynucleotide set forth in FIG. **1** (SEQ ID NOs. 3-7) or FIG. **9** (SEQ ID NOs. 8 and 21-24), or a fragment of the transcript.

Nucleotide, polynucleotide, or nucleic acid sequences(s) are understood to mean, according to the present invention, either a double-stranded DNA, a single-stranded DNA, or products of transcription of the said DNAs (e.g., RNA molecules). It should also be understood that the present invention does not relate to the genomic nucleotide sequences encoding lrba in their natural/native environment or natural/native state. The nucleic acid, polynucleotide, or nucleotide sequences of the invention have been isolated, purified (or partially purified), by separation methods including, but not limited to, ion-exchange chromatography, molecular size exclusion chromatography, affinity chromatography, or by genetic engineering methods such as amplification, cloning or subcloning.

Optionally, the polynucleotide sequences of the instant invention can also contain one or more polynucleotides encoding heterologous polypeptide sequences (e.g., tags that facilitate purification of the polypeptides of the invention (see, for example, U.S. Pat. No. 6,342,362, hereby incorporated by reference in its entirety; Altendorf et al. [1999-WWW, 2000] "Structure and Function of the F_o Complex of the ATP Synthase from *Escherichia Coli," J. of Experimental Biology* 203:19-28, The Co. of Biologists, Ltd., G.B.; Baneyx [1999] "Recombinant Protein Expression in *Escherichia coli,"* Biotechnology 10:411-21, Elsevier Science Ltd.; Eihauer et al. [2001] "The FLAG™ Peptide, a Versatile Fusion Tag for the Purification of Recombinant Proteins," *J. Biochem Biophys Methods* 49:455-65; Jones et al. [1995] *J. Chromatography* 707:3-22; Jones et al. [1995] "Current Trends in Molecular Recognition and Bioseparation," *J. of Chromatography A.* 707:3-22, Elsevier Science B.V.; Margolin [2000] "Green Fluorescent Protein as a Reporter for Macromolecular Localization in Bacterial Cells," *Methods* 20:62-72, Academic Press; Puig et al. [2001] "The Tandem Affinity Purification (TAP) Method: A General Procedure of Protein Complex Purification," *Methods* 24:218-29, Academic Press; Sassenfeld [1990] "Engineering Proteins for Purification," TibTech 8:88-93; Sheibani [1999] "Prokaryotic Gene Fusion Expression Systems and Their Use in Structural and Functional Studies of Proteins," *Prep. Biochem. & Biotechnol.* 29(1):77-90, Marcel Dekker, Inc.; Skerra et al. [1999] "Applications of a Peptide Ligand for Streptavidin: the Strep-tag", *Biomolecular Engineering* 16:79-86, Elsevier Science, B.V.; Smith [1998] "Cookbook for Eukaryotic Protein Expression: Yeast, Insect, and Plant Expression Systems," *The Scientist* 12(22):20; Smyth et al. [2000] "Eukaryotic Expression and Purification of Recombinant Extracellular Matrix Proteins Carrying the Strep II Tag", *Methods in Molecular Biology,* 139:49-57; Unger [1997] "Show Me the Money: Prokaryotic Expression Vectors and Purification Systems," *The Scientist* 11(17):20, each of which is hereby incorporated by reference in their entireties), or commercially available tags from vendors such as such as STRATAGENE (La Jolla, Calif.), NOVAGEN (Madison, Wis.), QIAGEN, Inc., (Valencia, Calif.), or INVITROGEN (San Diego, Calif.).

Other aspects of the invention provide vectors containing one or more of the polynucleotides of the invention. The vectors can be vaccine, replication, or amplification vectors. In some embodiments of this aspect of the invention, the polynucleotides are operably associated with regulatory ele-

ments capable of causing the expression of the polynucleotide sequences. Such vectors include, among others, chromosomal, episomal and virus-derived vectors, e.g., vectors derived from bacterial plasmids, from bacteriophage, from transposons, from yeast episomes, from insertion elements, from yeast chromosomal elements, from viruses such as baculoviruses, papova viruses, such as SV40, vaccinia viruses, adenoviruses, fowl pox viruses, pseudorabies viruses and retroviruses, and vectors derived from combinations of the aforementioned vector sources, such as those derived from plasmid and bacteriophage genetic elements (e.g., cosmids and phagemids).

As indicated above, vectors of this invention can also comprise elements necessary to provide for the expression and/or the secretion of a polypeptide encoded by the nucleotide sequences of the invention in a given host cell. The vector can contain one or more elements selected from the group consisting of a promoter, signals for initiation of translation, signals for termination of translation, and appropriate regions for regulation of transcription. In certain embodiments, the vectors can be stably maintained in the host cell and can, optionally, contain signal sequences directing the secretion of translated protein. Other embodiments provide vectors that are not stable in transformed host cells. Vectors can integrate into the host genome or be autonomously-replicating vectors.

In a specific embodiment, a vector comprises a promoter operably linked to a protein or peptide-encoding nucleic acid sequence, one or more origins of replication, and, optionally, one or more selectable markers (e.g., an antibiotic resistance gene). Non-limiting exemplary vectors for the expression of the polypeptides of the invention include pBr-type vectors, pET-type plasmid vectors (Promega), pBAD plasmid vectors (Invitrogen) or those provided in the examples below. Furthermore, vectors according to the invention are useful for transforming host cells for the cloning or expression of the nucleotide sequences of the invention.

Promoters which may be used to control expression include, but are not limited to, the CMV promoter, the SV40 early promoter region (Bemoist and Chambon [1981] *Nature* 290:304-310), the promoter contained in the 3' long terminal repeat of *Rous sarcoma* virus (Yamamoto, et al. [1980] Cell 22:787-797), the herpes thymidine kinase promoter (Wagner et al. [1981] *Proc. Natl. Acad. Sci. USA* 78:1441-1445), the regulatory sequences of the metallothionein gene (Brinster et al. [1982] *Nature* 296:39-42); prokaryotic vectors containing promoters such as the β-lactamase promoter (Villa-Kamaroff, et al. [1978] *Proc. Natl. Acad. Sci. USA* 75:3727-3731), or the tac promoter (DeBoer, et al. [1983] *Proc. Natl. Acad. Sci. USA* 80:21-25); see also, "Useful Proteins from Recombinant Bacteria" in *Scientific American,* 1980, 242:74-94; plant expression vectors comprising the nopaline synthetase promoter region (Herrera-Estrella et al. [1983] *Nature* 303: 209-213) or the cauliflower mosaic virus 35S RNA promoter (Gardner, et al. [1981] *Nucl. Acids Res.* 9:2871), and the promoter of the photosynthetic enzyme ribulose biphosphate carboxylase (Herrera-Estrella et al. [1984] *Nature* 310:115-120); promoter elements from yeast or fungi such as the Gal 4 promoter, the ADC (alcohol dehydrogenase) promoter, PGK (phosphoglycerol kinase) promoter, and/or the alkaline phosphatase promoter.

The subject invention also provides for "homologous" or "modified" nucleotide sequences. Modified nucleic acid sequences will be understood to mean any nucleotide sequence obtained by mutagenesis according to techniques well known to persons skilled in the art, and exhibiting modifications in relation to the normal sequences. For example, mutations in the regulatory and/or promoter sequences for the expression of a polypeptide that result in a modification of the level of expression of a polypeptide according to the invention provide for a "modified nucleotide sequence". Likewise, substitutions, deletions, or additions of nucleic acid to the polynucleotides of the invention provide for "homologous" or "modified" nucleotide sequences. In various embodiments, "homologous" or "modified" nucleic acid sequences have substantially the same biological or serological activity as the native (naturally occurring) LRBA polypeptides. A "homologous" or "modified" nucleotide sequence will also be understood to mean a splice variant of the polynucleotides of the instant invention or any nucleotide sequence encoding a "modified polypeptide" as defined below.

A homologous nucleotide sequence, for the purposes of the present invention, encompasses a nucleotide sequence having a percentage identity with the bases of the nucleotide sequences of between at least (or at least about) 20.00% to 99.99% (inclusive). The aforementioned range of percent identity is to be taken as including, and providing written description and support for, any fractional percentage, in intervals of 0.01%, between 20.00% and 99.99%. These percentages are purely statistical and differences between two nucleic acid sequences can be distributed randomly and over the entire sequence length.

In various embodiments, homologous sequences exhibiting a percentage identity with the bases of the nucleotide sequences of the present invention can have 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 percent identity with the polynucleotide sequences of the instant invention.

Both protein and nucleic acid sequence homologies may be evaluated using any of the variety of sequence comparison algorithms and programs known in the art. Such algorithms and programs include, but are by no means limited to, TBLASTN, BLASTP, FASTA, TFASTA, and CLUSTALW (Pearson and Lipman [1988] *Proc. Natl. Acad. Sci. USA* 85(8):2444-2448; Altschul et al. [1990] *J. Mol. Biol.* 215(3): 403-410; Thompson et al. [1994] *Nucleic Acids Res.* 22(2): 4673-4680; Higgins et al. [1996] *Methods Enzymol.* 266:383-402; Altschul et al. [1990] *J. Mol. Biol.* 215(3):403-410; Altschul et al. [1993] *Nature Genetics* 3:266-272).

The subject invention also provides nucleotide sequences complementary to any of the polynucleotide sequences disclosed herein. Thus, the invention is understood to include any DNA whose nucleotides are complementary to those of the sequence of the invention, and whose orientation is reversed (e.g., an antisense sequence).

The present invention further provides fragments of the polynucleotide sequences provided herein. Representative fragments of the polynucleotide sequences according to the invention will be understood to mean any nucleotide fragment having at least 8 or 9 successive nucleotides, preferably at least 12 successive nucleotides, and still more preferably at least 15 or at least 20 successive nucleotides of the sequence from which it is derived. The upper limit for such fragments is the total number of polynucleotides found in the full-length sequence (or, in certain embodiments, of the full length open reading frame (ORF) identified herein). It is understood that such fragments refer only to portions of the disclosed polynucleotide sequences that are not listed in a publicly available database or prior art references. However, it should be understood that with respect to the method for inhibiting tumor growth of the subject invention, disclosed nucleotides (and polypeptides encoded by such nucleotides) that are listed in a

publicly available database or prior art reference can also be utilized. For example, nucleotide sequences that are lrba orthologs, or fragments thereof, which have been previously identified, can be utilized to carry out the method for inhibiting tumor growth of the subject invention. Thus sequences from the *drosophila melanogaster* genomic sequence (GENBANK accession number AE003433), cLRBA (GENBANK accession number T20719, *Caenorhabditis elegans*), aCDC4L (GENBANK accession number T00867, *Arabidopsis thaliana*), LSVA (GENBANK accession number AAD52096, *Dictyostelium discoideum*), hFAN (GENBANK accession number NP_0035711, *Homo sapiens*), CHS1 (Chediak-Higashi Syndrome 1, GENBANK accession number NP_000072, *Homo sapiens*), or mBG (GENBANK accession number AAB60778, *Mus musculus*) can be utilized to carry out the method of tumor growth inhibition of the subject invention.

In other embodiments, fragments contain from one nucleotide less than the full length polynucleotide sequence (1249 nucleotides) to fragments comprising up to, and including 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, . . . and up to, for example, 1,245 consecutive nucleotides of a particular sequence disclosed herein.

Yet other embodiments provide fragments (or detection probes) comprising nucleotides within the lrba cDNA sequence, such as the human lrba cDNA sequence (GenBank accession number NM_006726), including 245 to 458 (G-peptide), 488 to 1424 (HSH domain), 2573-2627 (siRNA1) (SEQ ID NO. 5), 3179 to 4148 (SET domain), 4301 to 4505 (PKA RII binding sites), 6347 to 6749 (WDL repeats), 6878 to 7709 (BEACH domain), 8018 to 8831 (WD repeats).

Among these representative fragments, those capable of hybridizing under stringent conditions with a nucleotide sequence according to the invention are preferred. Conditions of high or intermediate stringency are provided infra and are chosen to allow for hybridization between two complementary DNA fragments. Hybridization conditions for a polynucleotide of about 300 bases in size will be adapted by persons skilled in the art for larger- or smaller-sized oligonucleotides, according to methods well known in the art (see, for example, Sambrook et al. [1989]).

The subject invention also provides detection probes (e.g., fragments of the disclosed polynucleotide sequences) for hybridization with a target sequence or an amplicon generated from the target sequence. Such a detection probe will advantageously have as sequence a sequence of at least 9, 12, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 nucleotides. Alternatively, detection probes can comprise 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, . . . and up to, for example, 1245 consecutive nucleotides of the disclosed nucleic acids. The detection probes can also be used as labeled probe or primer in the subject invention. Labeled probes or primers are labeled with a radioactive compound or with another type of label. Alternatively, non-labeled nucleotide sequences may be used directly as probes or primers; however, the sequences are generally labeled with a radioactive element (^{32}P, ^{35}S, ^{3}H, ^{125}I) or with a molecule such as biotin, acetylaminofluorene, digoxigenin, 5-bromodeoxyuridine, or fluorescein to provide probes that can be used in numerous applications.

The nucleotide sequences according to the invention may also be used in analytical systems, such as DNA chips. DNA chips and their uses are well known in the art and (see for example, U.S. Pat. Nos. 5,561,071; 5,753,439; 6,214,545; Schena et al. [1996] *BioEssays* 18:427-431; Bianchi et al. [1997] *Clin. Diagn. Virol.* 8:199-208; each of which is hereby incorporated by reference in their entireties) and/or are provided by commercial vendors such as AFFYMETRIX, Inc. (Santa Clara, Calif.).

Various degrees of stringency of hybridization can be employed. The more severe the conditions, the greater the complementarity that is required for duplex formation. Severity of conditions can be controlled by temperature, probe concentration, probe length, ionic strength, time, and the like. Preferably, hybridization is conducted under moderate to high stringency conditions by techniques well known in the art, as described, for example, in Keller, G. H., M. M. Manak [1987] *DNA Probes*, Stockton Press, New York, N.Y., pp. 169-170.

By way of example, hybridization of immobilized DNA on Southern blots with ^{32}P-labeled gene-specific probes can be performed by standard methods (Maniatis et al. [1982] *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory, New York). In general, hybridization and subsequent washes can be carried out under moderate to high stringency conditions that allow for detection of target sequences with homology to the exemplified polynucleotide sequence. For double-stranded DNA gene probes, hybridization can be carried out overnight at 20-25° C. below the melting temperature (Tm) of the DNA hybrid in 6× SSPE, 5× Denhardt's solution, 0.1% SDS, 0.1 mg/ml denatured DNA. The melting temperature is described by the following formula (Beltz et al. [1983] *Methods of Enzymology*, R. Wu, L. Grossman and K. Moldave [eds.] Academic Press, New York 100:266-285).

$$T_m = 81.5° \text{ C.} + 16.6 \log[Na+] + 0.41(\% G+C) - 0.61(\% \text{ formamide}) - 600/\text{length of duplex in base pairs.}$$

Washes are typically carried out as follows:

(1) twice at room temperature for 15 minutes in 1× SSPE, 0.1% SDS (low stringency wash);

(2) once at T_m-20° C. for 15 minutes in 0.2× SSPE, 0.1% SDS (moderate stringency wash).

For oligonucleotide probes, hybridization can be carried out overnight at 10-20° C. below the melting temperature (T_m) of the hybrid in 6× SSPE, 5× Denhardt's solution, 0.1% SDS, 0.1 mg/ml denatured DNA. T_m for oligonucleotide probes can be determined by the following formula:

T_m (° C.)=2(number T/A base pairs)+4(number G/C base pairs) (Suggs et al. [1981] *ICN-UCLA Symp. Dev. Biol. Using Purified Genes*, D. D. Brown [ed.], Academic Press, New York, 23:683-693).

Washes can be carried out as follows:

(1) twice at room temperature for 15 minutes 1× SSPE, 0.1% SDS (low stringency wash;

2) once at the hybridization temperature for 15 minutes in 1× SSPE, 0.1% SDS (moderate stringency wash).

In general, salt and/or temperature can be altered to change stringency. With a labeled DNA fragment >70 or so bases in length, the following conditions can be used:

Low:	1 or 2X SSPE, room temperature
Low:	1 or 2X SSPE, 42° C.
Moderate:	0.2X or 1X SSPE, 65° C.
High:	0.1X SSPE, 65° C.

By way of another non-limiting example, procedures using conditions of high stringency can also be performed as follows: Pre-hybridization of filters containing DNA is carried out for 8 h to overnight at 65° C. in buffer composed of 6× SSC, 50 mM Tris-HCl (pH 7.5), 1 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.02% BSA, and 500 μg/ml denatured salmon sperm DNA. Filters are hybridized for 48 h at 65° C., the preferred hybridization temperature, in pre-hybridization mixture containing 100 μg/ml denatured salmon sperm DNA and 5-20×10^6 cpm of ^{32}P-labeled probe. Alternatively, the hybridization step can be performed at 65° C. in the presence of SSC buffer, 1× SSC corresponding to 0.15M NaCl and 0.05 M Na citrate. Subsequently, filter washes can be done at 37° C. for 1 h in a solution containing 2× SSC, 0.01% PVP, 0.01% Ficoll, and 0.01% BSA, followed by a wash in 0.1× SSC at 50° C. for 45 min. Alternatively, filter washes can be performed in a solution containing 2× SSC and 0.1% SDS, or 0.5× SSC and 0.1% SDS, or 0.1× SSC and 0.1% SDS at 68° C. for 15 minute intervals. Following the wash steps, the hybridized probes are detectable by autoradiography. Other conditions of high stringency which may be used are well known in the art (see, for example, Sambrook et al. [1989] *Molecular Cloning, A Laboratory Manual, Second Edition*, Cold Spring Harbor Press, N.Y., pp. 9.47-9.57; and Ausubel et al. [1989] *Current Protocols in Molecular Biology*, Green Publishing Associates and Wiley Interscience, N.Y., each incorporated herein in its entirety).

A further non-limiting example of procedures using conditions of intermediate stringency are as follows: Filters containing DNA are pre-hybridized, and then hybridized at a temperature of 60° C. in the presence of a 5× SSC buffer and labeled probe. Subsequently, filters washes are performed in a solution containing 2× SSC at 50° C. and the hybridized probes are detectable by autoradiography. Other conditions of intermediate stringency which may be used are well known in the art (see, for example, Sambrook et al. [1989] *Molecular Cloning, A Laboratory Manual, Second Edition*, Cold Spring Harbor Press, N.Y., pp. 9.47-9.57; and Ausubel et al. [1989] *Current Protocols in Molecular Biology,* Green Publishing Associates and Wiley Interscience, N.Y., each of which is incorporated herein in its entirety).

Duplex formation and stability depend on substantial complementarity between the two strands of a hybrid and, as noted above, a certain degree of mismatch can be tolerated. Therefore, the probe sequences of the subject invention include mutations (both single and multiple), deletions, insertions of the described sequences, and combinations thereof, wherein said mutations, insertions and deletions permit formation of stable hybrids with the target polynucleotide of interest. Mutations, insertions and deletions can be produced in a given polynucleotide sequence in many ways, and these methods are known to an ordinarily skilled artisan. Other methods may become known in the future.

It is also well known in the art that restriction enzymes can be used to obtain functional fragments of the subject DNA sequences. For example, Bal31 exonuclease can be conveniently used for time-controlled limited digestion of DNA (commonly referred to as "erase-a-base" procedures). See, for example, Maniatis et al. [1982] *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory, New York; Wei et al. [1983] *J. Biol. Chem.* 258:13006-13512. The nucleic acid sequences of the subject invention can also be used as molecular weight markers in nucleic acid analysis procedures.

The invention also provides host cells transformed by a polynucleotide according to the invention and the production of LRBA (or LRBA ortholog) polypeptides by the transformed host cells. In some embodiments, transformed cells comprise an expression vector containing LRBA, or LRBA ortholog, polynucleotide sequences. Other embodiments provide for host cells transformed with nucleic acids. Yet other embodiments provide transformed cells comprising an expression vector containing fragments of lrba, or lrba ortholog, polynucleotide sequences. Transformed host cells according to the invention are cultured under conditions allowing the replication and/or the expression of the nucleotide sequences of the invention. Expressed polypeptides are recovered from culture media and purified, for further use, according to methods known in the art.

The host cell may be chosen from eukaryotic or prokaryotic systems, for example bacterial cells (Gram negative or Gram positive), yeast cells, animal cells, plant cells, and/or insect cells using baculovirus vectors. In some embodiments, the host cell for expression of the polypeptides include, and are not limited to, those taught in U.S. Pat. Nos. 6,319,691; 6,277,375; 5,643,570; 5,565,335; Unger [1997] *The Scientist* 11(17):20; or Smith [1998] *The Scientist* 12(22):20, each of which is incorporated by reference in its entirety, including all references cited within each respective patent or reference. Other exemplary, and non-limiting, host cells include *Staphylococcus* spp., *Enterococcus* spp., *E. coli*, and *Bacillus subtilis*; fungal cells, such as *Streptomyces* spp., *Aspergillus* spp., *S. cerevisiae, Schizosaccharomyces pombe, Pichia pastoris, Hansela polymorpha, Kluveromyces lactis*, and *Yarrowia lipolytica*; insect cells such as *Drosophila* S2 and *Spodoptera* Sf9 cells; animal cells such as CHO, COS, HeLa, C127, 3T3, BHK, 293 and Bowes melanoma cells; and plant cells. A great variety of expression systems can be used to produce the polypeptides of the invention and polynucleotides can be modified according to methods known in the art to provide optimal codon usage for expression in a particular expression system.

Furthermore, a host cell strain may be chosen that modulates the expression of the inserted sequences, modifies the gene product, and/or processes the gene product in the specific fashion. Expression from certain promoters can be elevated in the presence of certain inducers; thus, expression of the genetically engineered polypeptide may be controlled. Furthermore, different host cells have characteristic and specific mechanisms for the translational and post-translational processing and modification (e.g., glycosylation, phosphorylation) of proteins. Appropriate cell lines or host systems can be chosen to ensure the desired modification and processing of the foreign protein expressed. For example, expression in a bacterial system can be used to produce an unglycosylated core protein product whereas expression in yeast will produce a glycosylated product. Expression in mammalian cells can be used to provide "native" glycosylation of a heterologous protein. Furthermore, different vector/host expression systems may effect processing reactions to different extents.

Nucleic acids and/or vectors can be introduced into host cells by well-known methods, such as, calcium phosphate transfection, DEAE-dextran mediated transfection, transfection, microinjection, cationic lipid-mediated transfection, electroporation, transduction, scrape loading, ballistic introduction and infection (see, for example, Sambrook et al.

[1989] *Molecular Cloning: A Laboratory Manual,* 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.).

The subject invention also provides for the expression of a polypeptide, derivative, or a variant (e.g., a splice variant) encoded by a polynucleotide sequence disclosed herein. Alternatively, the invention provides for the expression of a polypeptide fragment obtained from a polypeptide, derivative, or a variant encoded by a polynucleotide fragment derived from the polynucleotide sequences disclosed herein. In either embodiment, the disclosed sequences can be regulated by a second nucleic acid sequence so that the polypeptide or fragment is expressed in a host transformed with a recombinant DNA molecule according to the subject invention. For example, expression of a protein or peptide may be controlled by any promoter/enhancer element known in the art.

The subject invention also provides nucleic acid based methods for the identification of the presence of the lrba gene, or orthologs thereof, in a sample. These methods can utilize the nucleic acids of the subject invention and are well known to those skilled in the art (see, for example, Sambrook et al. [1989] or Abbaszadega [2001] "Advanced Detection of Viruses and Protozoan Parasites in Water," *Reviews in Biology and Biotechnology,* 1(2):21-26). Among the techniques useful in such methods are enzymatic gene amplification (or PCR), Southern blots, Northern blots, or other techniques utilizing nucleic acid hybridization for the identification of polynucleotide sequences in a sample. The nucleic acids can be used to screen individuals for cancers, tumors, or malignancies associated with dysregulation of the lrba gene or its transcriptional products.

The subject invention also provides polypeptides encoded by nucleotide sequences of the invention. The subject invention also provides fragments of at least 5 amino acids of a polypeptide encoded by the polynucleotides of the instant invention.

In the context of the instant invention, the terms polypeptide, peptide and protein are used interchangeably. Likewise, the terms variant and homologous are also used interchangeably. It should be understood that the invention does not relate to the polypeptides in natural form or native environment. Peptides and polypeptides according to the invention have been isolated or obtained by purification from natural sources (or their native environment), chemically synthesized, or obtained from host cells prepared by genetic manipulation (e.g., the polypeptides, or fragments thereof, are recombinantly produced by host cells). Polypeptides according to the instant invention may also contain non-natural amino acids, as will be described below.

"Variant" or "homologous" polypeptides will be understood to designate the polypeptides containing, in relation to the native polypeptide, modifications such as deletion, addition, or substitution of at least one amino acid, truncation, extension, or the addition of chimeric heterologous polypeptides. Optionally, "variant" or "homologous" polypeptides can contain a mutation or post-translational modifications. Among the "variant" or "homologous" polypeptides, those whose amino acid sequence exhibits 20.00% to 99.99% (inclusive) identity to the native polypeptide sequence are preferred. The aforementioned range of percent identity is to be taken as including, and providing written description and support for, any fractional percentage, in intervals of 0.01%, between 50.00% and, up to, including 99.99%. These percentages are purely statistical and differences between two polypeptide sequences can be distributed randomly and over the entire sequence length.

"Variant" or "homologous" polypeptide sequences exhibiting a percentage identity with the polypeptides of the present invention can, alternatively, have 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 91, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 percent identity with the polypeptide sequences of the instant invention. The expression equivalent amino acid is intended here to designate any amino acid capable of being substituted for one of the amino acids in the basic structure without, however, essentially modifying the biological activities of the corresponding peptides and as provided below.

By way of example, amino acid substitutions can be carried out without resulting in a substantial modification of the biological activity of the corresponding modified polypeptides; for example, the replacement of leucine with valine or isoleucine; aspartic acid with glutamic acid; glutamine with asparagine; arginine with lysine; and the reverse substitutions can be performed without substantial modification of the biological activity of the polypeptides.

In other embodiments, homologous polypeptides according to the subject invention also include various splice variants identified within the lrba coding sequence.

The subject invention also provides biologically active fragments of a polypeptide according to the invention and includes those peptides capable of eliciting an immune response. The immune response can provide components (either antibodies or components of the cellular immune response (e.g., B-cells, helper, cytotoxic, and/or suppressor T-cells) reactive with the biologically active fragment of a polypeptide, the intact, full length, unmodified polypeptide disclosed herein, or both the biologically active fragment of a polypeptide and the intact, full length, unmodified polypeptides disclosed herein. Biologically active fragments according to the invention comprise from five (5) amino acids to one amino acid less than the full length of any polypeptide sequence provided herein. Alternatively, fragments comprising 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, . . . and up to 2845 consecutive amino acids of a disclosed polypeptide sequence are provided herein.

Fragments, as described herein, can be obtained by cleaving the polypeptides of the invention with a proteolytic enzyme (such as trypsin, chymotrypsin, or collagenase) or with a chemical reagent, such as cyanogen bromide (CNBr). Alternatively, polypeptide fragments can be generated in a highly acidic environment, for example at pH 2.5. Such polypeptide fragments may be equally well prepared by chemical synthesis or using hosts transformed with an expression vector containing nucleic acids encoding polypeptide fragments according to the invention. The transformed host cells contain a nucleic acid and are cultured according to well-known methods; thus, the invention allows for the expression of these fragments, under the control of appropriate elements for regulation and/or expression of the polypeptide fragments.

Modified polypeptides according to the invention are understood to designate a polypeptide obtained by variation in the splicing of transcriptional products of the lrba gene, genetic recombination, or by chemical synthesis as described below. Modified polypeptides contain at least one modification in relation to the normal polypeptide sequence. These

modifications can include the addition, substitution, deletion of amino acids contained within the polypeptides of the invention.

Conservative substitutions whereby an amino acid of one class is replaced with another amino acid of the same type fall within the scope of the subject invention so long as the substitution does not materially alter the biological activity of the polypeptide. For example, the class of nonpolar amino acids include Ala, Val, Leu, Ile, Pro, Met, Phe, and Trp; the class of uncharged polar amino acids includes Gly, Ser, Thr, Cys, Tyr, Asn, and Gln; the class of acidic amino acids includes Asp and Glu; and the class of basic amino acids includes Lys, Arg, and His. In some instances, non-conservative substitutions can be made where these substitutions do not significantly detract from the biological activity of the polypeptide.

In order to extend the life of the polypeptides of the invention, it may be advantageous to use non-natural amino acids, for example in the D form, or alternatively amino acid analogs, such as sulfur-containing forms of amino acids. Alternative means for increasing the life of polypeptides can also be used in the practice of the instant invention. For example, polypeptides of the invention, and fragments thereof, can be recombinantly modified to include elements that increase the plasma, or serum half-life of the polypeptides of the invention. These elements include, and are not limited to, antibody constant regions (see for example, U.S. Pat. No. 5,565,335, hereby incorporated by reference in its entirety, including all references cited therein), or other elements such as those disclosed in U.S. Pat. Nos. 6,319,691; 6,277,375; or 5,643,570, each of which is incorporated by reference in its entirety, including all references cited within each respective patent. Alternatively, the polynucleotides and genes of the instant invention can be recombinantly fused to elements that are useful in the preparation of immunogenic constructs for the purposes of vaccine formulation or elements useful for the isolation of the polypeptides of the invention.

The polypeptides, fragments, and immunogenic fragments of the invention may further contain linkers that facilitate the attachment of the fragments to a carrier molecule for the stimulation of an immune response or diagnostic purposes. The linkers can also be used to attach fragments according to the invention to solid support matrices for use in affinity purification protocols. In this aspect of the invention, the linkers specifically exclude, and are not to be considered anticipated, where the fragment is a subsequence of another peptide, polypeptide, or protein as identified in a search of protein sequence databases as indicated in the preceding paragraph. In other words, the non-identical portions of the other peptide, polypeptide, of protein is not considered to be a "linker" in this aspect of the invention. Non-limiting examples of "linkers" suitable for the practice of the invention include chemical linkers (such as those sold by Pierce, Rockford, Ill.), peptides that allow for the connection of the immunogenic fragment to a carrier molecule (see, for example, linkers disclosed in U.S. Pat. Nos. 6,121,424; 5,843,464; 5,750,352; and 5,990,275, hereby incorporated by reference in their entirety). In various embodiments, the linkers can be up to 50 amino acids in length, up to 40 amino acids in length, up to 30 amino acids in length, up to 20 amino acids in length, up to 10 amino acids in length, or up to 5 amino acids in length.

In other specific embodiments, the polypeptides, peptides, derivatives, or analogs thereof may be expressed as a fusion, or chimeric protein product (comprising the protein, fragment, analog, or derivative joined via a peptide bond to a heterologous protein sequence (e.g., a different protein)). Such a chimeric product can be made by ligating the appropriate nucleic acid sequences encoding the desired amino acid sequences to each other by methods known in the art, in the proper coding frame, and expressing the chimeric product by methods commonly known in the art (see, for example, U.S. Pat. No. 6,342,362, hereby incorporated by reference in its entirety; Altendorf et al. [1999-WWW, 2000] "Structure and Function of the F_o Complex of the ATP Synthase from *Escherichia Coli*," *J. of Experimental Biology* 203:19-28, The Co. of Biologists, Ltd., G.B.; Baneyx [1999] "Recombinant Protein Expression in *Escherichia coli*," *Biotechnology* 10:411-21, Elsevier Science Ltd.; Eihauer et al. [2001] "The FLAG™ Peptide, a Versatile Fusion Tag for the Purification of Recombinant Proteins," *J. Biochem Biophys Methods* 49:455-65; Jones et al. [1995] *J. Chromatography* 707:3-22; Jones et al. [1995] "Current Trends in Molecular Recognition and Bioseparation," *J. Chromatography A.* 707:3-22, Elsevier Science B.V.; Margolin [2000] "Green Fluorescent Protein as a Reporter for Macromolecular Localization in Bacterial Cells," *Methods* 20:62-72, Academic Press; Puig et al. [2001] "The Tandem Affinity Purification (TAP) Method: A General Procedure of Protein Complex Purification," *Methods* 24:218-29, Academic Press; Sassenfeld [1990] "Engineering Proteins for Purification," *TibTech* 8:88-93; Sheibani [1999] "Prokaryotic Gene Fusion Expression Systems and Their Use in Structural and Functional Studies of Proteins," *Prep. Biochem. & Biotechnol.* 29(1):77-90, Marcel Dekker, Inc.; Skerra et al. [1999] "Applications of a Peptide Ligand for Streptavidin: The Strep-tag", *Biomolecular Engineering* 16:79-86, Elsevier Science, B.V.; Smith [1998] "Cookbook for Eukaryotic Protein Expression: Yeast, Insect, and Plant Expression Systems," *The Scientist* 12(22):20; Smyth et al. [2000] "Eukaryotic Expression and Purification of Recombinant Extracellular Matrix Proteins Carrying the Strep II Tag", *Methods in Molecular Biology,* 139:49-57; Unger [1997] "Show Me the Money: Prokaryotic Expression Vectors and Purification Systems," *The Scientist* 11(17):20, each of which is hereby incorporated by reference in their entireties). Alternatively, such a chimeric product may be made by protein synthetic techniques, e.g., by use of a peptide synthesizer. Fusion peptides can comprise polypeptides of the subject invention and one or more protein transduction domains, as described above. Such fusion peptides are particularly useful for delivering the cargo polypeptide through the cell membrane.

The expression of the lrba gene or lrba gene product (e.g., DNA, RNA, or polypeptide) is disregulated in a variety of cancers, tumors, and/or malignancies. Non-limiting examples of such cancers, tumors, and/or malignancies include prostate cancer, breast cancer, melanoma, chronic myelogenous leukemia, cervical cancer, adenocarcinomas, lymphoblastic leukemia, colorectal cancer, and lung carcinoma. Accordingly, the present invention provides a method for screening, or aiding in the diagnosis of, an individual suspected of having a malignancy or cancer. The subject invention provides methods comprising the steps of determining the amount of lrba in a biological sample obtained from said individual and comparing the measured amount of lrba to the amount of lrba found in the normal population. The presence of a significantly increased amount of lrba is associated with an indication of a malignancy or cancer. Lrba gene product can be detected by well-known methodologies including, and not limited to, Western blots, enzyme linked immunoassays (ELISAs), radioimmunoassays (RIAs), Northern blots, Southern blots, PCR-based assays, or other assays for the quantification of gene product known to the

skilled artisan. This information, in conjunction with other information available to the skilled practitioner, assists in making a diagnosis.

Antisense technology can also be used to interfere with expression of the disclosed polynucleotides. For example, the transformation of a cell or organism with the reverse complement of a gene encoded by a polynucleotide exemplified herein can result in strand co-suppression and silencing or inhibition of a target gene, e.g., one involved in the infection process.

Polynucleotides disclosed herein are useful as target genes for the synthesis of antisense RNA or dsRNA useful for RNA-mediated gene interference. The ability to specifically inhibit gene function in a variety of organisms utilizing antisense RNA or ds RNA-mediated interference is well known in the fields of molecular biology (see for example C. P. Hunter, Current Biology [1999] 9:R440-442; Hamilton et al., [1999] Science, 286:950-952; and S. W. Ding, Current Opinions in Biotechnology [2000] 11:152-156, hereby incorporated by reference in their entireties). dsRNA (RNAi) typically comprises a polynucleotide sequence identical or homologous to a target gene (or fragment thereof) linked directly, or indirectly, to a polynucleotide sequence complementary to the sequence of the target gene (or fragment thereof). The dsRNA may comprise a polynucleotide linker sequence of sufficient length to allow for the two polynucleotide sequences to fold over and hybridize to each other; however, a linker sequence is not necessary. The linker sequence is designed to separate the antisense and sense strands of RNAi significantly enough to limit the effects of steric hindrances and allow for the formation of dsRNA molecules and should not hybridize with sequences within the hybridizing portions of the dsRNA molecule. The specificity of this gene silencing mechanism appears to be extremely high, blocking expression only of targeted genes, while leaving other genes unaffected. Accordingly, one method for controlling gene expression according to the subject invention provides materials and methods using double-stranded interfering RNA (dsRNAi), or RNA-mediated interference (RNAi). The terms "dsRNAi", "RNAi", "iRNA", and "siRNA" are used interchangeably herein unless otherwise noted.

RNA containing a nucleotide sequence identical to a fragment of the target gene is preferred for inhibition; however, RNA sequences with insertions, deletions, and point mutations relative to the target sequence can also be used for inhibition. Sequence identity may optimized by sequence comparison and alignment algorithms known in the art (see Gribskov and Devereux, *Sequence Analysis Primer*, Stockton Press, 1991, and references cited therein) and calculating the percent difference between the nucleotide sequences by, for example, the Smith-Waterman algorithm as implemented in the BESTFIT software program using default parameters (e.g., University of Wisconsin Genetic Computing Group). Alternatively, the duplex region of the RNA may be defined functionally as a nucleotide sequence that is capable of hybridizing with a fragment of the target gene transcript.

RNA may be synthesized either in vivo or in vitro. Endogenous RNA polymerase of the cell may mediate transcription in vivo, or cloned RNA polymerase can be used for transcription in vivo or in vitro. For transcription from a transgene in vivo or an expression construct, a regulatory region (e.g., promoter, enhancer, silencer, splice donor and acceptor, polyadenylation) may be used to transcribe the RNA strand (or strands); the promoters may be known inducible promoters such as baculovirus. Inhibition may be targeted by specific transcription in an organ, tissue, or cell type. The RNA strands may or may not be polyadenylated; the RNA strands may or may not be capable of being translated into a polypeptide by a cell's translational apparatus. RNA may be chemically or enzymatically synthesized by manual or automated reactions. The RNA may be synthesized by a cellular RNA polymerase or a bacteriophage RNA polymerase (e.g., T3, T7, SP6). The use and production of an expression construct are known in the art (see, for example, WO 97/32016; U.S. Pat. Nos. 5,593,874; 5,698,425; 5,712,135; 5,789,214; and 5,804,693; and the references cited therein). If synthesized chemically or by in vitro enzymatic synthesis, the RNA may be purified prior to introduction into the cell. For example, RNA can be purified from a mixture by extraction with a solvent or resin, precipitation, electrophoresis, chromatography, or a combination thereof. Alternatively, the RNA may be used with no, or a minimum of, purification to avoid losses due to sample processing. The RNA may be dried for storage or dissolved in an aqueous solution. The solution may contain buffers or salts to promote annealing, and/or stabilization of the duplex strands.

Preferably and most conveniently, dsRNAi can be targeted to an entire polynucleotide sequence set forth herein. Preferred RNAi molecules of the instant invention are highly homologous or identical to the polynucleotides of the sequence listing. The homology may be greater than 70%, preferably greater than 80%, more preferably greater than 90% and is most preferably greater than 95%.

Fragments of genes can also be utilized for targeted suppression of gene expression. These fragments are typically in the approximate size range of about 20 nucleotides. Thus, targeted fragments are preferably at least about 15 nucleotides. In certain embodiments, the gene fragment targeted by the RNAi molecule is about 20-25 nucleotides in length. In a more preferred embodiment, the gene fragments are at least about 25 nucleotides in length. In an even more preferred embodiment, the gene fragments are at least 50 nucleotides in length.

Thus, RNAi molecules of the subject invention are not limited to those that are targeted to the full-length polynucleotide or gene. Gene product can be inhibited with an RNAi molecule that is targeted to a portion or fragment of the exemplified polynucleotides; high homology (90-95%) or greater identity is also preferred, but not necessarily essential, for such applications.

In another aspect of the invention, the dsRNA molecules of the invention may be introduced into cells with single stranded (ss) RNA molecules which are sense or anti-sense RNA derived from the nucleotide sequences disclosed herein. Methods of introducing ssRNA and dsRNA molecules into cells are well-known to the skilled artisan and includes transcription of plasmids, vectors, or genetic constructs encoding the ssRNA or dsRNA molecules according to this aspect of the invention; electroporation, biolistics, or other well-known methods of introducing nucleic acids into cells may also be used to introduce the ssRNA and dsRNA molecules of this invention into cells.

As used herein, the term "administration" or "administering" refers to the process of delivering an agent to a patient, wherein the agent directly or indirectly suppresses lrba function and inhibits the growth of tumors. The process of administration can be varied, depending on the agent, or agents, and the desired effect. Administration can be accomplished by any means appropriate for the therapeutic agent, for example, by parenteral, mucosal, pulmonary, topical, catheter-based, or oral means of delivery. Parenteral delivery can include for example, subcutaneous intravenous, intramuscular, intra-arterial, and injection into the tissue of an organ, particularly tumor tissue. Mucosal delivery can include, for example,

intranasal delivery. Oral or intranasal delivery can include the administration of a propellant. Pulmonary delivery can include inhalation of the agent. Catheter-based delivery can include delivery by iontropheretic catheter-based delivery. Oral delivery can include delivery of a coated pill, or administration of a liquid by mouth. Administration can generally also include delivery with a pharmaceutically acceptable carrier, such as, for example, a buffer, a polypeptide, a peptide, a polysaccharide conjugate, a liposome, and/or a lipid. Gene therapy protocol is also considered an administration in which the therapeutic agent is a polynucleotide capable of accomplishing a therapeutic goal when expressed as a transcript or a polypeptide into the patient.

As used herein, the term "biological activity" with respect to the nucleotides and polypeptides of the subject invention refers to the inhibition of tumor cell growth or proliferation. Thus, cell-based assays can be utilized to determine whether an agent, such as nucleotide or polypeptide, can be utilized to carry out the method of tumor growth inhibition of the subject invention, as shown in FIGS. **18**A-**21**D.

The term "means for inhibiting or suppressing lrba function" comprises genetic and non-genetic means for inhibiting or suppressing lrba function. Among the genetic constructs inhibiting lrba function are various "gene delivery vehicles" known to those of ordinary skill in the art, that facilitate delivery to a cell of, for example, a coding sequence for expression of a polypeptide, such as an lrba inhibitor, an anti-sense oligonucleotide, an RNA aptamer capable of inhibiting lrba function, or other genetic construct capable of inhibiting lrba function at the transciption, translation, or post-translation level. Methods of gene silencing and/or knock-down, as described herein, and as known to those of ordinary skill in the art, can be utilized to suppress lrba function, for example. For example, gene therapy comprising administration of a dominant negative lrba mutant can be utilized to carry out the method of tumor inhibition of the subject invention.

Among the non-genetic means for inhibiting lrba function are pharmaceutical agents, or pharmaceutically acceptable salts thereof, which are preferably administered in a pharmaceutically acceptable carrier.

The term "patient", as used herein, refers to any vertebrate species. Preferably, the patient is of a mammalian species. Mammalian species which benefit from the disclosed methods of treatment include, and are not limited to, apes, chimpanzees, orangutans, humans, monkeys; domesticated animals (e.g., pets) such as dogs, cats, guinea pigs, hamsters, Vietnamese pot-bellied pigs, rabbits, and ferrets; domesticated farm animals such as cows, buffalo, bison, horses, donkey, swine, sheep, and goats; exotic animals typically found in zoos, such as bear, lions, tigers, panthers, elephants, hippopotamus, rhinoceros, giraffes, antelopes, sloth, gazelles, zebras, wildebeests, prairie dogs, koala bears, kangaroo, opossums, raccoons, pandas, hyena, seals, sea lions, elephant seals, otters, porpoises, dolphins, and whales.

The terms "lrba", "LRBA", and "Lrba" (italicized and unitalicized) are used herein interchangeably to refer to the LPS-responsive CHS1/beige-like gene or its polypeptide product, and includes lrba homologs (such as human and mouse orthologs), unless otherwise noted.

The terms "comprising", "consisting of", and "consisting essentially of" are defined according to their standard meaning and may be substituted for one another throughout the instant application in order to attach the specific meaning associated with each term.

Materials and Methods

Murine RNA Isolation and cDNA Synthesis. Total RNA was prepared using the RNEASY kit (QIAGEN, Valencia, Calif.). Poly(A)$^+$ RNA was prepared using the FAST TRACK mRNA isolation kit (INVITROGEN, Calsbad, Calif.). RNA was prepared from murine cell lines as well as liver and thymus of C57BL6/J mice per the manufacturers' instructions. RNAs were treated with Rnase-free Dnase I (AMERSHAM PHARMACIA BIOTECH, Piscataway, N.J.) at 10 U/μg of RNA for 30 minutes at 37° C. to destroy genomic DNA. First-strand cDNA synthesis was primed with random DNA hexamers or oligo(dT) primers at 42° C. for 1 hour using the SUPERSCRIPT II RNase H Reverse Transcriptase cDNA Synthesis System (Life Technologies, Inc., Rockville, Md.).

Cloning and Sequencing of Murine lrba Gene cDNAs. Primers (5'AGAGAAGAGGAGAAGATGTGTGATC3' (SEQ ID NO. 40); and 5'CCAGGCTCCATGCTTGTCTGTGAG3' (SEQ ID NO. 41) forward and reverse, respectively) were designed from a 143 bp cDNA fragment obtained from previous gene-trap experiments (Kerr, W. G. et al. *Proc. Natl. Acad. of Sci. USA,* 1996, 93:3947) and combined with Lambda GT10 forward and reverse primers (5'AGCAAGTTCAGCCTGGTTAAGT3' (SEQ ID NO. 42) and 5'TTATGAGTATTTCTTCCAGGG3' (SEQ ID NO. 43), respectively) to amplify the lrba gene cDNA from a mouse B lymphocyte cDNA library (Mouse lymphocyte 5' stretch cDNA library, CLONTECH, Palo Alto, Calif.). These PCR products were then cloned and sequenced. New primers were then designed from these sequences and further RT-PCR reactions were carried out to extend the cDNA sequence to the 5' or 3' direction. The SMART RACE amplification kit (CLONTECH, Palo Alto, Calif.) was used to amplify 5' cDNA ends using the following lrba-specific primers: 5'ACTGCAGCAAGCTCCTCCTGTTTTCTC3' (SEQ ID NO. 44) and a nested primer: 5'TGGGCGAAGAGCGGAAACAGAAC3' (SEQ ID NO. 45), while for 3' cDNA clones the following primers were used: 5'AGAGAAGAGGAGAAGATGTGTGATC3' (SEQ ID NO. 40) and a nested primer: 5'GAGTGATGGATGATGGGACAGTGGTG3' (SEQ ID NO. 46). PCR conditions for the 5'-RACE and 3'-RACE were as follows using the ADVANTAGE polymerase mix (CLONTECH, Palo Alto, Calif.): 94° C. for 30 seconds, followed by 5 cycles at 94° C. for 30 seconds, 70° C. for 30 seconds, and 72° C. for 3-5 minutes; 5 cycles at 94° C. for 30 seconds, 68° C. for 30 seconds, and 72° C. for 3-5 minutes; 20 cycles at 94° C. for 30 seconds, 65° C. for 30 seconds, and 72° C. for 3-5 minutes; and a final extension at 72° C. for 30 minutes. After the full-length cDNA sequence of the lrba gene was obtained, several primers were designed to amplify the region of the lrba gene cDNA containing its major open reading frame (ORF). The region containing the major ORF of the lrba gene was then amplified from a single source of C57BL6/J liver mRNA and resequenced to confirm that the lrba cDNAs obtained from liver cells were identical to that amplified from the aligned cDNA fragments amplified from primary and transformed B lymphocytes, indicating that these represent the major mRNAs expressed from the lrba locus. All RT-PCR and RACE products were isolated and purified from agarose gels using the QIAEX II Gel Extraction Kit (QIAGEN; Valencia, Calif.). The purified products were sequenced directly to avoid detecting the mutations introduced during PCT. Both

strands of each template were sequenced and the sequence was confirmed by sequence analysis of at least two independent PCR products. PCR products and RACE products were cloned into PCRII vector (TA cloning kit; INVITROGEN, Carlsbad, Calif.) and multiple clones were sequenced. Plasmids were purified from liquid cultures using the QIAGEN plasmid Maxi preparation kit (QIAGEN; Valencia, Calif.).

Human lrba cDNA Cloning and Sequencing. A search of GENBANK indicated that the murine lrba gene has a high degree of homology to a 7.3 kb human partial cDNA sequence (GENBANK accession numbers M83822) called BGL (Feuchter, A. E. et al. *Genomics,* 1992, 13:1237), which was thereby tentatively identified as possibly a small fragment of a human lrba gene. The 5' end of the human lrba gene was obtained by using a 5' primer (5'GCCACCTCCGTCTCGCTGC3' (SEQ ID NO. 47)) from the mouse lrba gene cDNA sequence and a 3' primer (5'GGGCACTGGGGAGAATTTCGAAGTAGG3' (SEQ ID NO. 48)) from the human BGL sequence. Human lung, brain, and kidney cDNA libraries (MARATHON cDNA Libraries, CLONTECH, Palo Alto, Calif.) were used as templates for the amplification of the 5' and 3' ends of the human cDNA under the following PCR conditions: 35 cycles at 95° C. for 45 seconds; 60° C. for 15 seconds; 72° C. for 3 minutes. The PCR products were cloned into a TA cloning vector and multiple clones were sequenced. Additional PCRs were carried out with the primers from the 3' cDNA clones obtained as described above to complete the sequence of the human lrba cDNA. The primer pairs used for these additional 3' cDNA clones were 5'TTCAGGCAGTTTTCAGGACCCTCCAAG3' (SEQ ID NO. 49) and 5'TAGTGTCTGATGTTGAACTTCCTCCTG3' (SEQ ID NO. 50). Overlapping regions of the 5' and 3' human lrba cDNAs were compared and merged with the human BGL cDNA in GENBANK to construct, for the first time, a complete sequence for the human lrba gene (GenBank accession number AF216648). The human lrba gene encodes a 319KD protein that has 2863 amino acids. The amino acid homology between the human and murine lrba gene is 93% (identity 89%, similarity 4%). Like the murine lrba gene, the human lrba gene contains BEACH domain, five WD40 repeats and two novel domains that are defined as followed (FIGS. **9** and **10**).

Northern Blot Analysis. 70Z/3 B lymphoma cells were maintained in RPMI1640 supplemented with 10^{-5}M 2-mercaptoethanol and 10% fetal bovine serum (FBS). J774 cells were maintained in DMEM supplemented with 10% FBS. 70Z/3 cells were stimulated with 10 ng/ml LPS (Sigma, St. Louis, Mo.) and J774 cells were stimulated with 1 ng/ml LPS for 20 hours. Poly(A)$^+$ RNA was prepared from 10^8 stimulated or unstimulated cells using the FASTRACK isolation kit (INVITROGEN, Carlsbad, Calif.). Poly(A)$^+$ RNA (5 μg/lane) was size-fractionated by electrophoresis on a 6% formaldehyde/1% agarose gel buffered with MOPS, transferred to a nylon membrane (STRATAGENE, La Jolla, Calif.) by capillary action in 20× SSC and immobilized by UV cross-linking. The filter was probed with a uniformly labeled ^{32}P probe using the READY-TO-GO DNA labeling kit (AMERSHAM PHARMACIA BIOTECH, Piscataway, N.J.). The probe corresponds to a 2.5 kb PCR product that spans nucleotides 3545-6040 of the murine lrba cDNA. The filter was hybridized with the probe in 2× SSC, 0.5% SDS, 5× Denhardt's containing 100 μg/ml heat denatured salmon sperm DNA at 68° C. overnight. Filters were washed 2 times for 5 minutes at room temperature in 2× SSC/0.5% SDS and 2 times for 30 minutes at 68° C. in 0.1× SSC/0.1% SDS. Hybridization signals were detected and quantitated using a Molecular Dynamics PHOSPHORIMAGER and IMAGEQUANT software.

RT-PCR Analysis of lrba Expression. The cell lines (70Z/3, BAL17, A20, WEHI231, and S194) used for the RT-PCR were obtained from ATCC (Rockville, Md.). Spleen, brain, lung, and bone marrow were obtained from C57BL6/J mice. The preparation of total RNA and cDNA synthesis were carried out as described above. First strand cDNA reaction products (2 μl) were amplified in a 25 μl PCR reaction using primers that detect three of the lrba isoforms ("5'GGCACAACCTTCCTGCTCAC3'" (SEQ ID NO. 51) and "5'CCTGTCCCCCATTTGAACCC3'" (SEQ ID NO. 52) for the α form: "5'ACGGCTGCTTCTGCACCTTC3'" (SEQ ID NO. 53) and "5'TTTTGGGACAGGGCTTCTCTG3'" (SEQ ID NO. 54) for the β form; "5'GGCACAACCTTCCTGCTCAC3'" (SEQ ID NO. 55) and "5'GCAGATGCTCTCCTCGCTCC3'" (SEQ ID NO. 56) for the γ form). The cycling program was: 94° C. for 30 seconds, followed by 5 cycles at 94° C. for 30 seconds, 70° C. for 30 seconds, and 72° C. for 4 minutes; 5 cycles at 94° C. for 30 seconds, 68° C. for 30 seconds, and 72° C. for 4 minutes; 30 cycles at 94° C. for 30 seconds, 62° C. for 30 seconds, and 72° C. for 4 minutes; and a final extension at 72° C. for 10 minutes.

Gene and Protein Structure Prediction. Analyses of the nucleotide and amino acid sequences for the murine and human lrba gene were performed using MACVECTOR (Oxford Molecular Group Inc., Oxford, UK). Nucleotide sequence alignments and other analyses were carried out using BLAST (Altschul, S. F. and E. V. Koonin *Trends in Biochemical Sciences,* 1998, 23:444). SMART (Schultz, J. et al. *Nucleic Acids Res.,* 2000, 28:231), and CLUSTLX (Thompson, J. D. et al. *Clinical Orthopaedics & Related Res.,* 1997, 241) were used for protein secondary structure predictions. For WD repeat prediction, an algorithm developed by Neer et al (Neer, E. J. and T. F. Smith *Cell,* 1996, 84:175; Garcia-Higuera, I. et al. *Biochemistry,* 1996, 35:13985; Neer, E. J. et al. *Nature, October* 1994, 371(6500):812; Smith, T. F. et al. *Trends Biochem.,* 1999, 24:181; Neer, E. J. and T. F. Smith *Proc. Natl. Acad. Sci. USA,* 2000, 97:960) is used.

Construction, Expression, and Fluorescence Microscopy of the Lrba-GFP Fusion Protein. A region from the murine lrba cDNA that includes the BEACH and the WD domains 3' to the BEACH domain was inserted "in-frame" and upstream of the coding region of a modified GFP gene cloned in a mammalian expression vector pEGFP-N2 (CLONTECH, Palo Alto, Calif.). Recombinant clones (called pBWEGFP) were picked, plasmid DNAs prepared and sequenced to confirm that no mutations were introduced during these manipulations. Murine 3T3 cells, the macrophage RAW264.7 cells, and human 293 cells were transfected by the FUGEN transfection kit (ROCHE Molecular Biochemicals, Indianapolis, Ind.) or by electroporation (Gene Pulser; BIO-RAD Laboratories, Hercules, Calif.) with 20 μg of linearized recombinant plasmid pBWEGFP DNA as well as the control vector pEGFP at 250V, 500 μF. One day later, cells were cultured in DMEM containing 0.8 μg/ml of G418 (LIFE TECHNOLOGIES, Inc., Rockville, Md.). This medium was changed every day for the first four days. The surviving G418 resistant colonies were isolated and used for further experimentation. For subcellular localization, cells were plated in glass-covered plates at 2.5×10^5 cells/ml in 2 ml DMEM media with or without LPS at 100 ng/ml. After 12 hours, cells were directly examined by fluorescence microscopy using a fluorescein isothiocyanate filter to detect expression of GFP fusion proteins. Fluorescent photomicrography was performed using

Nikon photomicrographic equipment model H-III and image software (NIKON, Tokyo, Japan).

Confocal Laser Scanning Microscopy. The RAW 264.7 cells stably transfected with the pBWEGFP construct were grown on glass coverslips and stimulated with 100 ng/ml LPS for 24 hours. Golgi and lysosomes were specifically labeled with BODIPY TR ceramide and LysoTracker Red DND-99 (MOLECULAR PROBE, Eugene, Oreg.), respectively, following the manufacturer's protocols. Briefly, for Golgi labeling, cells were washed with PBS three times and incubated for 30 minutes at 4° C. with 5 μM BODIPY TR ceramide, rinsed several times with ice-cold medium, and then incubated in fresh medium at 37° C. for another 30 minutes. For lysosome labeling, medium was changed with pre-warmed fresh medium containing 60-75 nM lysosome probe and the cell sample was incubated for 30 minutes. Finally, the medium was removed, washed with PBS three times, fixed with 3.7% formaldehyde for 10-20 minutes, washed again, and the slides were mounted with DAPI-containing VECTASHIELD medium (VECTOR LABORATORIES, Burlingame, Calif.). Cells were observed on a Zeiss inverted Axiovert 100 M laser scanning confocal microscope. Fluorescence of GFP was excited using a 458/488 nm argon/krypton laser, and emitted fluorescence was detected with 505-530 nm band pass filter. For LysoTracker Red and BODIPY TR, a 633-nm helium/neon laser was used for excitation, and fluorescence was detected with a 585 nm band pass filter, using a 100× oil immersion lens. The co-localization function of LSM510 software (EMBO Laboratory) allows for a reliability of 99% for actual pixels with both fluorophores. The co-localization mask pixels were converted to white color for clarity.

Immunoelectron Microscopy. The RAW 264.7 cells stably transfected with the pBWEGFP construct were grown in the presence of 100 ng/ml LPS for 24 hours, washed with PBS three times, fixed with 2% paraformaldehyde in phosphate buffer for 1 hour and 4° C., and processed for postembedding immunocytochemistry. The cells were scraped from the dishes they were grown in and pelleted by low speed centrifugation. The pellets were dehydrated in a graded series of ethanol dilutions and embedded in gelatin capsules in LR White resin. The resin was polymerized for 48 hours at 50° C. Ultrathin sections of LR White embedded cells were collected on nickel grids and immunolabeled according to the technique of Haller et al. (Haller, E. M. et al. *J. Histochem Cytochem,* 1992, 40:1491) with rabbit-anti-GFP (CLONTECH, Palo Alto, Calif.) at 1:20 ration for 1 hour at room temperature, followed by extensive rinsing and then labeling with 10 nm goat-anti-rabbit IgG-gold (AURION, Wageningen, The Netherlands) for 1 hour at room temperature. Control grids were labeled by replacing the primary antibody with normal rabbit serum. After extensive washing, thin sections were stained with uranyl acetate and lead citrate before examination with EM.

Primers. The gene-specific primers were designed from the partial sequences of the human lrba that were obtained and from BGL sequence in the GenBank (GenBank accession numbers M83822). The sequences of synthetic oligonucleotides used for PCR amplification were as follows: cdc415mar2: CACACAGAGCATTGTAGCAAGCTCCTC (SEQ ID NO. 57); h65-56153: TGCAGACTTGAAGATTCCG (SEQ ID NO. 58); 3CDS: 5'-AAGCAGTGGTATCAACGCAGAGTACTTTTTTTTTTTTTTTTTTTTTT-TTTTTTVN-3' (SEQ ID NO. 59); h6439: GAGTGATGGATGATGGGACAGTAGTG (SEQ ID NO. 60); cdc415mar1: GGGCACTGGGGAGAATTTCGAAGTAGG (SEQ ID NO. 48); and h5end65': CGAGAAGATGAGAAGATGTGTGATC (SEQ ID NO. 61).

Human RNA isolation and cDNA synthesis. Total RNA was prepared using the RNeasy kit (QIAGEN, Valencia, Calif.). RNA was prepared from cell lines as well as human prostate tumor tissues and normal adjacent tissue per the manufacturers' instructions. First-strand cDNA synthesis was primed with gene-specific primers or oligo(dT) primers at 42° C. for 1 h-2 h using the SUPERSCRIPT II RNase H Reverse Transcriptase cDNA Synthesis System (Life TECHNOLOGIES, Inc., Rockville, Md.) or PowerScript Reverse Transcriptase (CLONTECH, Palo Alto, Calif.).

5'-RACE, 3'-RACE and the Cloning of human lrba Gene cDNAs. 5'-RACE, 3'-RACE of hlrba gene were carried out by using the SMART RACE amplification kit (CLONTECH, Palo Alto, Calif.) and the following condition: 5'-RACE: cdc415mar2 as reverse transcription primer, 1-2.5 μg RNAs were used. cdc415mar1 was used for first PCR reaction, h65-56153 ( ) was used for nested primer; 3'-RACE: 3CDS from the kit was used as reverse transcription primer. h5end65' was used for first PCR reaction and h6439 was used for nested PCR primer. The PCR parameters are: 94° C. for 30 seconds, followed by 5 cycles at 94° C. for 30 s, 70° C. for 30 s, and 72° C. for 3-5 min; 5 cycles at 94° C. for 30 s, 68° C. for 30 s, and 72° C. for 3-5 min; 25 cycles at 94° C. for 30 s, 65° C. for 30 s, and 72° C. for 3-5 min; and a final extension at 72° C. for 10 min. All RT-PCR and RACE products were isolated and purified from agarose gels using the QIAEX II Gel Extraction Kit (QIAGEN; Valencia, Calif.). The purified products were sequenced directly to avoid detecting the mutations introduced during PCR. Both strands of each template were sequenced and the sequence was confirmed by sequence analysis of at least two independent PCR products. PCR products and RACE products were cloned into PCRII vector (TA cloning kit; INVITROGEN, Carlsbad, Calif.) and multiple clones were sequenced.

Mapping of the 5' end of the human lrba gene. The 5' end of the human lrba gene were determined by SMART 5' RACE (Clontech, Palo Alto, Calif.) in tumor tissues and adjacent tissues from prostate, human lung carcinoma, B-cell lymphoma and B-cell lymphoma (AMBION, Austin, Tex.). cdc415mar1 as reverse transcription primer were used. The lrba gene-specific primer cdc415mar2 was used to prime reverse transcription using 1-2.5 μg RNAs. Then first PCR reaction was performed using gene-specific primer cdc415mar2, h65-56153 was used for nested primer. Products were sequenced both directly and indirectly by first cloning into pCR2.1 vector (TA cloning kit; INVITROGEN, Carlsbad, Calif.).

Multiple Sequence Alignment. All amino acid sequences were obtained from the SWISS-PROT/TrEMBL database at the Expasy web site (www.expasy.ch). Homologous sequences were searched for using the BLAST server of Expasy. To gather tetraspanin and tetraspanin-like sequences from the data base, BLAST searches were performed using a number of sequences from well established members of the tetraspanin superfamily (i.e. CD81, CD82, CD9, CD53, CD63, UPK, RDS, and ROM). A multiple sequence alignment was initially achieved with the CLUSTAL1X software. The alignment was then improved manually using the GENEDOC software.

Secondary Structure Prediction. To predict the secondary structure of the HSH domain, two methods (available on the World Wide Web) based on a consensus assignment were used. The first method, Jpred[2], takes a multiple sequence alignment as input and performs a consensus average of nine

different alignment-based secondary structure prediction methods. Alignment-based prediction methods have been demonstrated to have a significantly better accuracy than those using single sequences, and consensus averaging by Jpred[2] has been shown to increase the accuracy to 72.9%. The use of alignment-based secondary structure prediction methods requires the sequences to have a degree of homology of at least ~25%.

RT-PCR Analysis of hlrba Expression. The cell lines MCF7 breast cancer cell line, 293 cell line, pre-B (6417); Raji B cells; HTB4 lung cancer; H322 human lung cancer; A539 human lung cancer used for the RT-PCR were obtained from ATCC (Rockville, Md.). The preparation of total RNA and cDNA synthesis were carried out as described above. First strand cDNA reaction products (2 μl) were amplified in a 25 μl PCR reaction using primers.

Following examples illustrate procedures for practicing the invention. These examples should not be construed as limiting. All percentages are by weight and all solvent mixture proportions are by volume unless otherwise noted.

EXAMPLE 1

Cloning and Sequencing of the Murine lrba cDNA

An LPS-inducible gene was identified by integration of Gensr1 gene-trap retrovirus (Kerr, W. G. et al. *Proc. Natl. Acad. of Sci. USA,* 1996, 93:3947). A partial cDNA sequence of the LPS-inducible gene-trap cell clone, 7a65, was used to design PCR primers to amplify the upstream and downstream regions of cDNA from a mouse B lymphocyte library. Initially, a 1.6 Kb cDNA sequence was obtained by this strategy. Sequence analysis confirmed that this 1.6 Kb cDNA sequence contains the original 142 bp sequence obtained by gene-trapping (Kerr, W. G. et al. *Proc. Natl. Acad. of Sci. USA,* 1996, 93:3947). 5' RACE reactions using anti-sense primers from the 5' end of this 1.6 Kb region yield additional 5' cDNA sequences including the 5' UTS of the lrba gene as well as the ATG of its major ORF. Sense strand primers were also designed from the 1.6 Kb cDNA sequence and three 3' RACE fragments of 2.5 Kb, 2 Kb, and 1.4 Kb were obtained that have identical 5' end sequence; however, their 3' ends differ substantially. The amino acid sequence of the major ORF in the murine lrba cDNA is shown in FIG. **1**A. The human lrba orthologue is obtained as described in the Experimental Procedures section.

Sequence analysis of the lrba cDNAs indicated the existence of three isoforms with identical 5' ends that differ at their 3' termini. These isoforms include a 9903 bp form (lrba-α), a 9396 bp form (lrba-β) and 8854 bp form (lrba-γ) encoding proteins of 2856, 2792, and 2779aa, respectively. All three ORFs begin with the same Kozak consensus ATG at nucleotide 308. The first 2776aa of the β form are identical to the first 2776aa of the α form, while the 16aa at its C-terminus are unique to it. The first 2769aa of the γ form are identical to the first 2769aa of the α and β forms with its C-terminal 10aa unique to it; the α form has its C-terminal 80aa unique to it (FIG. **1**). Homology search indicates that all lrba isoforms have a BEACH domain (Nagle, D. L. et al *Nature Genetics,* 1996, 14:307); however, the lrba-α isoform has 5 WD repeats, lrba-β has 3 WD repeats while lrba-γ lacks WD repeats (FIG. **1**B). The isoform specific unique coding sequences and the associated 3' untranslated sequence (totally 1267 bp for α form, 761 bp for β form, and 845 bp for γ form) show no significant homology with each other. Interestingly, only the α form has an AATAAA sequence for polyA recognition and a TGA stop codon, while the β and γ forms have TAA stop codons.

EXAMPLE 2

Lrba Orthologues Exist in Diverse Organisms and Belong to a Novel Gene Family

Homology analysis revealed that lrba has significant homology with the partial protein sequence DAKAP550 (Han, J. D. et al. *Jour. Biol. Chem.,* 1997, 272:26611), which is an AKAP, and with AKAP550 (GENBANK accession number AAF46011) predicted from the *Drosophila* genomic sequence (GENBANK accession number AE003433). A longer sequence for this gene is predicted from the genomic sequence and is designated dLRBA, which is identical to AKAP550 except that it has an additional 160aa at its N-terminus. As used herein, the first letter of the genus is placed before the gene's name to distinguish the lrba genes of different species. Thus, DAKAP550 is a partial sequence of dLRBA and AKAP550. Amino acid alignment analysis shows that the murine LRBA protein has 85% aa identity with human LRBA, 51% aa identity with dLRBA and 35% aa identity with the *C. elegans* CDC4L gene (GENBANK accession number T20719) (designated cLRBA for clarity) (FIG. **1**B). This homology analysis shows that the lrba and DAKAP550 genes are othologues based on their high homology that extends from their N terminus to the C terminus (FIGS. **1**-**3** and Table 1). Furthermore, two putative PKA binding sites are found in all lrba orthologues (FIGS. **2**A and **2**B) and are structurally similar to the B1 and B2 RII binding sites of DAKAP550, a protein that has been demonstrated to bind PKA in vitro and in vivo (Han, J. D. et al. *Jour. Biol. Chem.,* 1997, 272:26611). This region is highly conserved in lrba orthologues in mice, man, *Drosophila,* and *C. elegans* (FIG. **2**A) and potentially provides another two PKA binding sites for DAKAP550. Unexpectedly, the B1 and B2 sites of DAKAP550 are not found in other LRBA proteins; they may be species-specific and these potential RII binding sites need to be confirmed by biochemical studies.

TABLE 1

	Identities	Positives		Length (aa)
mLBA dLBA				
92-405	47-394	51%	73%	314
405-959	601-1160	55%	75%	555
998-1576	1542-2127	36%	53%	579
1793-2856	2642-3727	56%	74%	1064
mLBA cLBA				
65-946	164-1057	42%	61%	882
1300-1571	1065-1333	39%	59%	271
1787-2856	1436-22512	47%	64%	1070
mLBA hLBA				
1-2856	1-2863	85%	88%	2856
mLBA mBG				
1934-2839	1460-2335	27%	43%	906
mLBA hFAN				
2038-2841	163-913	29%	45%	803

Table 1 shows the protein homology between LRBA and dLRBA, mBG, and HFAN, showing the percentage of identity, and positive gaps. The positions of each fragment are also indicated.

These lrba orthologues also have a highly conserved long C-terminal region (around 1000 amino acids) shared with a

group of proteins including CHS1/BG (Perou, C. M. et al. *Nature Genetics,* 1996, 13:303; Kingsmore, S. F. et al. *Jour. Invest. Med.,* 1996, 44:454), FAN (Adam-Klages, S. et al. *Cell,* 1996, 86:937), LVSA (Kwak, E. et al. *Cell,* 1999, 10:4429) proteins (FIGS. **2**A and **2**B), and a number of anonymous ORFs. They constitute a new gene family. The conserved region contains an unidentified region followed by one BEACH domain and several WD repeats. Several WD repeats are found in the unidentified region of homology in these genes when about 1000 aa of C-terminal sequence is searched for WD repeats; however, no WD repeat is predicted when this region is analyzed alone (data not shown). Thus, this region is designated herein as WD repeat-like domain (WDL). In aggregate, and not to be limited by theory, the entire WDL-BEACH-WD (WBW) structure may have a precise functional role since the WD repeats found in the WBW structures of different beige-like genes have a higher degree of homology with each other than with other WD repeats in proteins that lack a BEACH domain (FIG. **3**). This homology analysis suggests the evolutionary conservation of the WBW structure in a gene family that includes lrba, chs1/beige, FAN, lvsA, and other unidentified ORFs in GENBANK. However, the BEACH domain can exist without WD motifs as in the case of lrba-γ (FIGS. **1**A, **1**B and **3**). It is shown herein that all BEACH domains have an SH3 binding site (consensus sequence PXXP), an SH2 binding site (consensus sequence YXXhy) (Pawson, T. and J. D. Scott *Science,* 1997, 278: 2075), and a tyrosine kinase phosphorylation site (consensus sequence: (RK)-x(2,3)-(DE)-x(2,3)-Y) (Patschinsky, T. et al. *Proc. Natl. Acad. Sci. USA,* 1982, 79:973; Hunter, T. *J. Biol. Chem.,* 1982, 257:4843; Cooper, J. A. et al. *J. Biol. Chem.,* 1984, 259:7835), as shown in FIG. **3**. These putative binding sites show that WBW proteins may interact with multiple signal transduction components.

EXAMPLE 3

Analysis of lrba mRNA Expression

Northern blot analysis indicates a single mRNA of about 10 Kb encoding the lrba gene is present in LPS-induced J774 macrophages and 70Z/3 B cells (FIG. **4**A), as well as in other B cell lines (WEHI231, BCL1) and the macrophage cell line, RAW264.7 [RAW267.4]. The size (~10 Kb) of the transcript is consistent with the cDNA sequence analysis described herein (9903 bp for lrba-α). The expression of the lrba gene is significantly up-regulated in LPS-induced J774 macrophage cells as the lrba mRNA is nearly undetectable in J774 cells in the absence of LPS stimulation. The level of lrba mRNA is increased by 3 fold in 70Z/3 B cells (FIG. **4**A) using β-actin mRNA as an internal standard. The upregulation of lrba expression in the B cell lines is consistent with the FACS analysis of lacZ induction in the 7a65 gene-trap cell clone (Kerr, W. G. et al. *Proc. Natl. Acad. of Sci. USA,* 1996, 93:3947).

A multiplex RT-PCR assay was also developed that can simultaneously detect the expression of the lrba mRNA isoforms. RT-PCR analysis of lrba mRNA (FIGS. **4**B and **4**C) shows that lrba-β mRNA is expressed in all cell lines and tissues analyzed; however, lrba-α mRNA is absent in 70Z/3, lung and bone marrow and is less abundant in spleen and lung, suggesting that these different isoforms may have discrete functions in different tissues.

EXAMPLE 4

Subcellular Localization of LRBA-GFP Fusion Protein Shifts Upon LPS Stimulation

All mutations in beige or chs1 genes result in truncated proteins that lack the BEACH and COOH terminal WD repeats (Certain, S. et al. *Blood,* 2000, 95:979). This region may contain sequences critical to the function of chs1/beige and lrba genes. In particular, the ability of their gene products to associate with intracellular vesicles to influence their trafficking may be lost in these truncated mutants. Therefore, a GFP fusion with the BEACH-WD region of lrba called BW-GFP was created. As shown in FIGS. **5**A-**5**I, fluorescence microscopy of RAW 267.4 cells stably transfected with an expression vector encoding the BW-GFP fusion shows that the BW-GFP protein is present in the cytosol with rare cells showing a vesicular staining pattern in the absence of LPS stimulation (FIG. **5**A). However, this vesicular staining pattern is dramatically increased in these cells following LPS stimulation (FIG. **5**B). Both the percentage of cells and the degree of vesicular staining in each cell are increased following LPS stimulation. RAW267.4 cells stably transfected with a GFP control construct show no change in their GFP fluorescence pattern upon LPS stimulation (FIG. **5**C).

To determine which vesicular compartments the BW-GFP fusion localizes to, the RAW264.7 cells stably transfected with the pBWEGFP construct stained with a lysosome specific dye (FIG. **5**E) and trans-Golgi specific dye (FIG. **5**H) were analyzed with confocal microscopy. The merged pictures show that some LRBA-GFP proteins are co-localized with lysosomes (FIG. **5**F, white area) and co-localization with the trans-Golgi complex (FIG. **5**I, white peri-nucleus area).

Immunogold labeling experiments were also performed that show the LRBA-GFP fusion protein can be found in association with the Golgi complex (FIG. **6**D), lysosomes (FIGS. **6**B and **6**F), endoplasmic reticulum (FIG. **6**C), plasma membrane (FIG. **6**E), perinuclear ER (FIG. **6**E), and endocytic vacuole (FIG. **6**A, as the gold particles are labeling a clathrin coated endocytic vacuole, which indicates that it is involved in endocytosis and not exocytosis). The immunoelectron microscopy results agree well with the observations made by fluorescence microscopy and confocal fluorescence microscopy.

EXAMPLE 5

Exon/Intron Structure of the Human lrba Gene

The genomic locus of lrba gene is composed of 58 exons and 57 introns, spinning over a 700 K bps genomic sequence. Exon 1 and exon 2 contain the first part of the 5' UTR, exon 2 contains the rest of the 5'UTR and the start methione, while exon 58, the final exon, contains part of the WD5 and the whole 3'UTR. There are two considerably large exons—exon 24 (1059 bps) and exon 58 (1148 bps). The entire SET domain is encoded by one exon—exon 24, while other domains are econded by multiple exons. The remaining exons range in size from 33 to 435 bps, most are below 200 bps. All exon/intron junctions conform to the GT-donor/AG-acceptor rule (Breathnach and Chambon, 1981)(Table 1). The function of the lrba gene is defined by its domain structure consisting of BEACH domain, WD repeats, HSH domain and SET domain and potential RII binding sites. The BEACH domain is encoded by exons 45 to 51. The 5-WD repeat domain is encoded by exons 54 to 58. Isoforms are formed by splicing with splicing site inside the exons of the other isoforms.

Table 2 shows the exon/intron organization of the human lrba gene.

TABLE 2

Exon/Intron Organization of the Human lrba Gene

Exon No	Exon size (bp)	5'Splice donor	SEQ ID NO.	Intron No	Intron size (kb)	3'Splice acceptor	SEQ ID NO.
1	~67	AGT ATC TGG gtgaggaag	62	I	0.340	tccaataag GGT TTG GCG	119
2	435	TTT AAC CTG gtaagtcca	63	II	85.572	ccttgtaag TTG GTA GGA	120
3	232	TGA TAG CAG gtatgattt	64	III	0.217	tgtttccag ATC TTT TGG	121
4	101	GGA CGA TCG gtaaaaaaa	65	IV	7.224	tcttcatag CCT CCA CAT	122
5	96	AGT GCT GCA gtaagtaa	66	V	4.458	ttcctttag GCT ATT GCA	123
6	122	TTT GTA TTG gtatgtatt	67	VI	0.089	tctttatag TTT CAG AAC	124
7	127	CCA CAA AAG gtacatgat	68	VII	0.674	cttctgcag TGG TAT ATG	125
8	120	ACT AGC GAT gtaagtagt	69	VIII	1.266	cttttacag ACC TTT GAC	126
9	147	GGA TAC AAG gtagtttgc	70	IX	5.537	ttcttagag GGT ACA TTT	127
10	198	ATG CTC CAG gtactaact	71	X	0.192	tcttacaag GAT GTA AAG	128
11	134	GAC TAT ATG gtgagtgcc	72	XI	1.971	aaattctag TTC AAC CTT	129
12	109	CTT GAA AAG gtaaagtat	73	XII	0.306	tttttgcag TCT TCC AAA	130
13	153	CCA GCC AAG gtaatatat	74	XIII	5.619	attctgtag GTT CAA CTG	131
14	169	AAG GAT TAG gtatataat	75	XIV	2.233	ttttaaaag ATG GAC CGC	132
15	80	GTG ATG AAG gtaggttca	76	XV	1.282	tttttgaag GAT TCT GGA	133
16	63	ATG CAT GAG gtaatatat	77	XVI	3.245	tgattatag GAT GAC AAT	134
17	98	TGG GTT ACG gtaagagtt	78	XVII	20.299	ttcattcag TGT TAT CTA	135
18	93	GGC CCC AAA gtaagtatg	79	XVIII	1.209	taattgcag GAG GAA AGC	136
19	109	CTG TTT GAG gtaggaatg	80	XIX	0.738	cttctgtag ATT CTT ATA	137
20	82	AAA CCC CTC gtatgtatg	81	XX	2.220	agattacag AGA TAC TAA	138
21	124	AAA CAG GAG gtaagctga	82	XXI	0.318	aattttcag GAG CTT GCT	139
22	193	CAT TCA AAG gtaagtttc	83	XXII	14.688	ttcacctag GTC ACT TTT	140
23	1059	GTG CTT GAG gtgatttta	84	XIII	0.982	tgtattaag ATA TCA AGG	141
24	179	GTG GAG AAG gtttgtcta	85	XXIV	1.148	tttggacag CCA TTC AAC	142
25	154	TCG GCT ACA gtaaggact	86	XXV	0.423	tctttacag CAT GAA CTG	143
26	181	TCC GAC TAG gtgagctgc	87	XXVI	4.039	aaattacag TTT GTG CAG	144
27	122	GCA GCG AAG gtaagtata	88	XXVII	0.450	cttaaatag AGC CCA GTG	145
28	108	AGA GAC ATA gtaagttac	89	XXVIII	12.124	ttttcccag GAG GAT AGC	146
29	160	CAC TCT CTG gtaagtttg	90	XXIX	3.193	atgatatag AAA TCA CAC	147
30	442	TTT TGA CAG gtactgata	91	XXX	10.928	ttattacag AAG TGT CAT	148
31	134	AAT CAC CAG gtgagttag	92	XXXI	8.713	cttttatag GCA GTA GAT	149
32	79	AAA TAT GAG gtatttaag	93	XXXII	1.909	tttccttag TAT TAC AGA	150
33	134	AAG GAA CAA gtaagtggt	94	XXXIII	7.964	ttaaaatag GTC TGG TTT	151
34	62	TGT TCT CAG gtgagtggc	95	XXXIV	35.939	tttttatag GAG TGG CAA	152
35	65	ATG AGG AAG gtaatttat	96	XXXV	26.429	ttcttacag GTT GCT TAG	153
36	109	GAA TTT GAG gtaggttac	97	XXXVI	>28.963	ctctccaag TCA CTG TGT	154
37	167	TGC AGT GAG gtaaaggga	98	XXXVII	83.886	cattgtag TCG TCC TCT	155

TABLE 2-continued

Exon/Intron Organization of the Human lrba Gene

Exon No	Exon size (bp)	5'Splice donor	SEQ ID NO.	Intron No	Intron size (kb)	3'Splice acceptor	SEQ ID NO.
38	125	TGG AAC ATG gtcagtgg	99	XXXVIII	1.891	atgttttag TGT GCA TTT	156
39	33	ACA GCA AAG gtaagcatt	100	XXXIX	6.179	tcatttcag CCA CAG ATG	157
40	147	ATC TTG CCG gtaaatttg	101	XXXX	2.515	ttttggcag GTC CTG TTA	158
41	137	GAC CCC AAG gt	102	XXXXI	96.572	cctcattag ATC TTG GCA	159
42	118	CAA ACA GAG gtaatgtgt	103	XXXXII	3.088	ctgttgtag TTG CTG TGA	160
43	103	TCA AAC CAG gtactgttt	104	XXXXIII	15.997	ttcttgcag ACG TAT TTC	161
44	116	CGA TAG CAG gtaacctaa	105	XXXXIV	3.840	ccctatcag GAC GGA GTT	162
45	113	TTG TCC AAG gtaatttct	106	XXXXV	30.846	tattggcag CCA ATA GGA	163
46	141	CTA AGA ATA gtaagttca	107	XXXXVI	1.015	attttttag GAA CCC TTT	164
47	120	GAT ATT AAG gtacagaaa	108	XXXXVII	19.536	tttatatag GAG TTG ATC	165
48	153	AAC AGA TTG gtaagataa	109	XXXXVIII	65.358	ttttttcag GCC CTG GAG	166
49	169	TTG AGA GAG gtaa9ttat	110	XXXXIX	24.093	ccttttcag GCT GTT GAA	167
50	90	ATG CAA GTG gtaagtgct	111	XXXXX	4.443	ctcctgcag AGT CCA TTG	168
51	178	ACC TTC CTG gtaagtaaa	112	XXXXXI	5.563	gaattccag CTC ATC AAG	169
52	63	CTC TCA TAG gtctgtcac	113	XXXXXII	5.176	ttcttacag CCA GCA ATA	170
53	156	CAG ACA CAG gtaattttc	114	XXXXXIII	7.441	gcattacag GAA GAT TGA	171
54	168	ACC CAG GCA gtaagtatg	115	XXXXXIV	16.043	ttcctaaag GTG AGA CTG	172
55	102	GTT CAC AAG gtaaacctg	116	XXXXXV	3.286	tcttctcag AAG GAC CAT	173
56	197	AAC ATA AGA gtgagtgcc	117	XXXXXVI	4.444	gtctcacag GCC ATC CAG	174
57	152	CGA CCA GAG gtaacactg	118	XXXXXVII	12.028	ttctcctag GTG CAT CAT	175
58	1148						
Total	9936				>716.138		

EXAMPLE 6

Molecular Phylogenic Relationship of hlrba Proteins with Other WBWs

Phylogenic analysis of the WBW family reveals that the members can be grouped into two major families, as shown in FIG. **12**. One family is composed of proteins from *C. elegans, D. melanogaster, H. sapiens, S. pombe, S. cerevisiae, A. thaliana, D. discoideum*, and the other family contains proteins from *H. sapiens, M. musculus, Dr. melanogaster, C. elegans, A. thaliana, B. taurus, L. major*. These can be further sub-grouped into five distinct subfamilies, each of which may contains every species from the very ancient unicellular eukaryote to human. Lrba in human and murine, AKAP550 in fruit fly, F10F2.1 in *C. elegans* are orthologs as indicated previously, while NBEA and CG1332 are very close to lrba gene. Lrba, CHS1/beige and FAN belong to the same family. Despite the divergence of these species over several hundred million years, there is a high degree of sequence conservation in the BEACH domain, which may suggest an important role in the life of the cell concerning the BEACH domain.

EXAMPLE 7

The Human lrbaϵ Alternative Transcript has Two In-frame ORF

The ORF prediction shows there are two in frame ORFs in the human lrbaϵ alternative transcript. One ORF encodes a 72 amino acid protein, another encodes a 2782 amino acid protein. A very conserved motif (p21 RAS motif IV(LLGVGGFD (SEQ ID NO. 176))) is missing from both proteins as a result of the disruption. Both ATGs are in the Kozak sequence and thus could serve as translation initiation sites. According to the translation scanning theory, the translation of the first ORF should not be a problem. There are three possibilities for the translation of the second ORF. The first possibility is leaking scanning, meaning that some ribosomes do not recognize the first ATG, but recognize the later ATG. However, there are four ATGs before the main ATG, and there is a long stem secondary structure between the two ORFs. Therefore, it is unlikely that the leaking model is the mechanism of trans-

lation. The second possibility is reading through translation, meaning that the translation machinery ignores the stop codon and reads through it. However, there are 10 stop codons between the two ORFs. Likewise, this is unlikely. A third possibility is that IRES (internal ribosome entry signal) translation is cap-independent. There is no homologous sequence between IRES, but they have complex secondary structure, such as long stem secondary structure. The RNA sequence between the two ORFs of human lrbaε can form a long stem structure, which could further make the leaking scanning or reading through impossible. Some mRNAs encoding pro-apoptic proteins, including Apaf-1 and DAP5 are also translated via an IRES element. IRES-independent initiation is sometimes utilized during mitosis. The numberous mRNAs whose 5' UTR structures likely interfere with the 5' cap-dependent ribosome are good candidates for the presence of an IRES. However, the prediction of an IRES from only looking at the 5' UTR could be strengthened by a better understanding of the structural components that comprise these IRES elements.

(SEQ ID NO. 32) additional sequence between BEACH domain and WD repeats. This insertion isoform also exists in murine LRBA gene, and the 15 bp nucleotide sequence insertion remains unchanged. All the isoforms are summarized as shown in FIG. **13**.

TABLE 3

Isoforms	Positions	Features	Implications	Pattern of alternative splicing*
1α	There is one extra exon between Exon2 and Exon 3	Disrrupt the coding sequence of the lrba gene at the N-terminus	Bicistron may exist in eukaryotes. Ribosome Internal entry sequence.	Cassette
2β	Poly(A) alternative splicing after Exon 48	There is a 312 bp Alu repeat sequence at the 5'UTR, splitting the BEACH domain at two third into two potential domains	1. The BEACH domain is not a minimum domain, could be actually composed of two domains. 2. The Alu sequence may regulate the translation of LRBA gene or other gene.	Multiple Polyadenylation Site
3γ	15 bp insertion before Exon 51, just after BEACH domain and before WD repeats	The insertion encodes a YLLLQ peptide insertion into the LRBA protein.	Leucine (L) is a hydrophobic amino acid and may be involved in protein-protein interaction(as Leucine Zipper structure). That there are three consecutive Ls in a short sequence is unusual and Y could be a potential target for phosphorilation.	Retained intron
4δ	Poly(A) alternative splicing after Exon 52	The isoform doesn't have WD repeats but BEACH domain	Although BEACH domain and WD repeats often stay together, they are separate domain and can exist and function separately.	Multiple Polyadenylation Site
5ε	An additional exon at 5' end (Exon 5'-1) before Exon 1	Alternative promoter and transcription start site	LRBA may use different promoters to regulate the expression of LRBA.	Multiple Promoters

EXAMPLE 8

Identification of the Five Isoforms of the Human lrba Gene

Four isoforms that encode four different proteins are present in human lrba gene, among which three isoforms differ at C-terminal: h-lrbaα has five WD repeats, h-lrbaβ lacks WD repeats, h-lrbaδ lacks WD repeats and part of BEACH domain. The fourth isoform h-lrbaγ has a YLLLQ

The LRBA gene and five isoforms of the LRBA gene are disclosed and characterized herein. Northern blot experiments show that expression of lrba is upregulated 2-4 fold following LPS stimulation of B cells and macrophages. A homology search of GENBANK reveals that lrba gene has othologues in *C. elegans, Drosophila*, mice and humans and paralogues in diverse species ranging from yeast to human. These genes define a new protein family that are designated the WBW gene family herein because the members share an evolutionarily conserved structure over a long protein sequence (around 1000 aa). The analysis of subcellular localization with a BEACH-WD-GFP fusion protein described herein provides the first direct evidence that the lrba member of the WBW family can physically associate with various vesicular compartments in cells. Furthermore, it is proposed that the lrba gene is also an AKAP, suggesting that WBW family proteins may have microtubule and PKA binding properties like AKAPs (Colledge, M. and J. D. Scott *Trends in Cell Biology,* 1999, 9:216). Studies of FAN suggest that WBW proteins can bind to cytoplasmic tails of activated receptors via their WE repeats (Adam-Klages, S. et al. *Cell,* 1996, 86:937).

The evidence suggests that WBW proteins are involved in intracellular vesicle trafficking. For example, the strikingly enlarged vesicles in beige/CHS cells occur in membrane-

bound organelles. The CHS1/BG protein has a similar modular architecture to the VPS15 and Huntington proteins that are associated with the membrane fraction (Nagle, D. L. et al. *Nature Genetics,* 1996, 14:307) and the lvsA gene that is essential for cytokinesis (Kwak, E. et al. *Cell,* 1999, 10:4429)-a process that also involves fusion of intracellular vesicles (Jantsch-Plunger, V. and M. Glotzer *Curr. Biol.,* 1999, 9:738; Heese, M. et al. *Curr. Opin. Plant Biol.,* 1998, 1:486). FAN may also be involved in vesicle trafficking since FAN-deficient mice, after cutaneous barrier disruption, have delayed kinetics of skin recovery that requires secretion of vesicles (Kreder, D. et al. *EMBO Journal,* 1999, 18:2472; Elias, P. M. *J. Invest. Dermatol.,* 1983, 80:44s). However, there is no direct evidence that these WBW proteins directly associate with vesicles. In contrast, others found unexpectedly by Western blot that the BG, LVSA, and DAKAP550 proteins are present in the cytosolic fraction of cells and not in the membrane fraction (Kwak, E. et al. *Cell,* 1999, 10:4429; Perou, C. M. et al. *Jour. Biol. Chem.,* 1997, 272:29790) or cytoskeleton (Han, J. D. et al. *Jour. Biol. Chem.,* 1997, 272: 26611). This paradox can be explained by hypothesizing (without being limited by theory) that these proteins are not constitutively associated with vesicles, but rather associate with vesicles under certain conditions like LPS stimulation. This hypothesis agrees well with the observation that an LRBA-GFP fusion protein is located in the cytosol; however, it becomes associated with vesicles following activation of the cells by LPS stimulation. Confocal microscopy also shows this fusion protein co-localizes with the trans-Golgi and lysosomes. Immunoelectron microscopy further demonstrates that it is also localized to endoplasmic reticulum and the plasma membrane as well as the trans-Golgi complex and lysosomes. Therefore, it is established herein that the BEACH-WD-GFP fusion protein is associated with the vesicular system. This may be true for the intact LRBA protein as well as for other WBW proteins like CHS1/BG, LVSA, and FAN, since they share high homology with the region in mouse lrba that was used for the GFP fusion experiment. The activation-triggered vesicle trafficking hypothesis is further supported by the following: (1) BEACH domain contains a tyrosine phosphorylation site, (2) the WD repeats binding site of FAN contains a serine residue (Adam-Klages, S. et al. *Cell,* 1996, 86:937), it is possible that this serine is a target of serine kinases, as some experiments suggest that the WD repeats binding requires phosphorylation of the WD binding sites (Skowyra, D. et al. *Cell,* 1997, 91:209) and (3) MAPK was suggested to control the movement of lytic granules of NK cells (Wei, S. et al. *Jour. Exper. Med.,* 1998, 187:1753). Potentially, WBW protein functions are activated by tyrosine and/or serine/threonine kinases following stimulation by agents like LPS. Although the GFP fusion experiment previously described does not demonstrate that the BEACH domain and/or the WD repeats in LRBA directly associate with intracellular vesicles, it is proposed that the BEACH domain binds to vesicles while the WD repeat domains bind to a membrane-associated protein. It is proposed that because BEACH domains and WD repeats exist separately in some proteins, they have separate functions. For instance, the WD repeats of the FAN protein bind to the cytoplasmic tail of the TNFR55 receptor independent of the BEACH domain (Adam-Klages, S. et al. *Cell,* 1996, 86:937). It is worth noting that the FAN gene is made up almost entirely of the sequence in the highly conserved WBW structure (FIG. **3**), therefore other WBW-containing proteins may act like FAN and bind the cytoplasmic tails of TNFR55 or TNFR55-like receptors.

As indicated above, the lrba gene is a potential AKAP. The recently completed genomic sequence of *Drosophila* indicates that lrba has an orthologue in *Drosophila* (DAKAP550) that is capable of binding to protein kinase A (Han, J. D. et al. *Jour. Biol. Chem.,* 1997, 272:26611). The DAKAP550 gene is expressed in all tissues throughout development and is the principal A-kinase anchor protein in adult flies; it is enriched in secretory tissues such as neurons and salivary glands, and is found concentrated in the apical cytoplasm of some cells (Han, J. D. et al. *Jour. Biol. Chem.,* 1997, 272:26611), in agreement with the proposed function in secretion of lrba. Although the B1 and B2 RII binding sites of DAKAP550 are not present in mLRBA, hLRBA, and cLRBA, two sequences are disclosed that are very similar to the B1 and B2 RII binding sites in all lrba orthologues. The two sequences are predicted to form two adjacent amphipathic helices characteristic of PKA binding sites, satisfying the requirement of the hydrophobic interaction mechanism of RII peptide binding to the RII subunits of PKA revealed recently (Newlon, M. G. et al. *Nat. Struct. Biol.,* 1999, 6:222). Thus, lrba may serve as an AKAP that is involved in cAMP-mediated signaling secretory processes by translocating PKA to specific membrane sites. This translocation may require microtubule binding as suggested by the recent finding that another WBW protein, human CHS1, can associate with microtubules (Faigle, W. et al. *J. Cell Biol.,* 1998, 141:1121). Based on these findings, it is proposed a two-signal model for the function of the WBW protein family using the lrba gene as a protoype: LRBA is constitutively associated with PKA like other AKAPs and following LPS stimulation (signal one) the BEACH domain is phosphorylated. This enables the LRBA/PKA complex to bind to intracellular vesicles and tether vesicles to microtubules for transport to the plasma membrane. At the membrane, a second signal is required that generates cAMP. Binding of locally generated cAMP to the LRBA/PKA complex releases PKA, allowing it to phosphorylate cytoplasmic tails of activated receptors to enable binding of LRBA via its WD repeats. This final step would result in vesicle fusion with the plasma membrane (FIG. **7**). Many immune processes need a second signal such as in the case of co-stimulators. Without being bound by theory, it proposed that a first signal activates an immune cell to transport enough vesicles to the plasma membrane area that contact another cell. A second signal generated by the contact with the target cell produces cAMP that stimulates PKA activity resulting in membrane fusion of vesicles. Thus, LRBA and other WBW proteins may provide a means for eukaryotic cells to direct the fusion of membrane-bound vesicles in a polarized fashion, in coordination with signal transduction complexes at the plasma membrane as is required of many different effector cell types in the immune system (Stinchcombe, J. C. and G. M. Griffiths *Jour. Cell Biol.,* 1999, 147:1).

Increasing evidence suggests that all clinical symptoms of CHS/beige patients could be explained by a secretion malfunction. The cytolytic proteins (granzymes A/B and perforin) in CHS CTL are expressed normally, but are not secreted upon stimulation (Baetz, K. et al. *Jour. of Immun.,* 1995, 154:6122). Secretion of other enzymes are also defective in macrophages and neutrophils (Barak, Y. and E. Nir *American Journal of Pediatric Hematology-Oncology,* 1987, 9:42) as are the membrane deposition of class II molecules (Faigle, W. et al. *J. Cell Biol.,* 1998, 141:1121) and CTL-4 (Barrat, F. J. et al. *Proc. Natl. Acad. of Sci. USA,* 1999, 96:8645). However, there is a dispute over whether giant lysosomes in beige/CHS disease are a result of abnormalities in the fusion or fission of lysosomes (Baetz, K. et al. *Jour. of Immun.,* 1995, 154:6122; Barrat, F. J. et al. *Proc. Natl. Acad. of Sci. USA,* 1999, 96:8645; Perou, C. M. et al. *Jour. Biol. Chem.,* 1997, 272:29790; Cervero, C. et al. *Sangre,* 1994,

39:135; Barbosa, M. D. et al. *Nature,* 1996, 382:262; Menard, M. and K. M. Meyers *Blood,* 1988, 72:1726). How the secretion pathway is impaired is unclear. The characterization of the lrba gene and the model for its function, described herein, may provide a molecular explanation for these two major cellular dysfunctions of CHS/beige: giant vesicles and secretion malfunction. Vesicles may require association with the BEACH domain of CHS1 for fission and/or movement to the plasma membrane. After reaching the plasma membrane, they then require recognition of certain membrane proteins by the WD repeats to mediate fusion with the plasma membrane. This requires CHS1 proteins to be full-length for proper function since the WD repeats are at the COOH terminus. Thus, truncated beige/CHS protein molecules (or perhaps LRBA proteins) that lack the COOH terminal WD repeats would be expected to cause disease (Certain, S. et al. *Blood,* 2000, 95:979). The giant lysosomes in the affected cells may come from the failure of vesicle movement and/or fusion with the membrane. Similar disorders of beige/CHS have also been described in mink, cattle, cats, and killer whales. Given the structural similarity of the WBW gene family, it is proposed that the genetic mutations in these species also involve other WBW genes. There are also other lysosomal trafficking mutants in mice with similar phenotypes to beige that may also involve mutation of other WBW gene family members.

In summary, the existence of a novel gene family, the WBW family, is demonstrated herein, which includes the lrba gene that: (1) is associated with the vesicular system, including the Golgi complex, lysosomes, endoplasmic reticulum, plasma membrane, and perinuclear ER, (2) is LPS inducible, (3) is an A kinase anchor protein (AKAP), and (4) has 5 different isoforms that differ in WD repeat number. These findings suggest an important role for lrba in coupling signal transduction and vesicle trafficking to enable polarized secretion and/or membrane deposition of immune effector molecules. This disclosure provides novel tools and methods that can be used to further the understanding of the mechanism of CHS and other related diseases as well as general immune cell function.

The cell membrane system not only delimits and protects cell and intracellular organelles, maintaining the essential differences between the cell interior and the environment, but also transports various molecules back and forth between the membrane-bound compartments in the cell, and between the cell and the environment through vesicle trafficking processes. These processes are critical for the correct biological functioning of a eukaryotic cell. A novel gene family, WBW, may play an essential role in vesicle trafficking has been identified in eukaryotic organisms from the very ancient unicellular organism Dictyostelium to human, but not in prokaryotes, which have no vesicle system (Wang, J. W. et al. *Journal of Immunology,* 2001, 166(7):4586-4595; Kwak, E. et al. *Mol. Biol. Cell,* 1999, 10(12):4429-4439; Adam-Klages, S. et al. *Cell,* 1996, 86(6):937-947; Barbosa, M. D. et al *Nature,* 1996, 382(6588):262-265; Nagle, D. L. et al. *Nat. Genet.,* 1996, 14(3):307-311). The WBW proteins all have a highly conserved long WBW(WDL-BEACH-WD) structure composed of three domains at their C-termini (Wang, J. W. et al. *Journal of Immunology,* 2001, 166(7):4586-4595). WD domain is present in over two thousand proteins and is thought to be involved in protein-protein interaction (Smith, T. F. et al. *Trends Biochem. Sci.,* 1999, 24(5):181-185). The WD repeats of FAN bind to NSD motif of TNFR55 to mediate the activation of the plasma membrane-bound neutral sphingomyelinase, producing the secondary messenger ceramide to activate raf-1 and MAP kinases, leading to cell growth and inflammation responses (Adam-Klages, S. et al. *Cell,* 1996, 86(6):937-947). The function of the BEACH domain is unclear, it potentially has SH3 and SH2 binding sites and a tyrosine kinase phosphorylation site, and those sites may interact with multiple signal transduction proteins (Wang, J. W. et al. *Journal of Immunology,* 2001, 166(7):4586-4595). The WDL domain was first described in a previous publication, and its function also remains unknown (Wang, J. W. et al. *Journal of Immunology,* 2001, 166(7):4586-4595). However, the WBW structure is very conserved and the WBW structure of FAN represents most of its ORF, and thus it is reasonable to propose that the WBW structure has a similar function to that of FAN. Another interesting question is if WBW proteins are also AKAPs (A kinase anchor protein), as DAKAP550 and Neurobeachin have been experimentally proved to be AKAPs, which can direct protein kinase A to discrete intracellular locations, where PKA may be activated by the secondary messenger cAMP (Han, J. D. et al. *J. Biol. Chem.,* 1997, 272(42):26611-26619; Wang, X. et al *J. Neurosci.,* 2000, 20(23):8551-8565). The subcellular localizations of the WBW proteins are not restricted to the plasma membrane, but are found in the Golgi complex, lysosomes, ER, perinuclear ER and clathrin-coated endocytosis pits (Wang, J. W. et al. *Journal of Immunology,* 2001, 166(7):4586-4595; Wang, X. et al. *J. Neurosci.,* 2000, 20(23):8551-8565), moreover are associated with microtubules (Faigle, W. et al. *J. Cell Biol.,* 1998, 141(5):1121-1134).

In the WBW family chs1/beige gene is the most extensively studied. The mutations of the gene can cause a generalized immunodeficiency in mice and humans with the impairment of NK cells, CTL, and granulocytes and often cause premature death in humans due to a second disease phase characterized by a lymphoproliferative syndrome, probably as a result of defective intracellular trafficking of vesicles (Spritz, R. A. et al. *J. Clin. Immunol.,* 1998, 18(2): 97-105). For example, the deposition of some membrane proteins (HLA-DR) and antigen presentation are affected (Faigle, W. et al. *J. Cell Biol.,* 1998, 141(5):1121-1134). FAN has a role in TNF pathway by binding to a cytoplasmic motif upstream of the death domain of some TNF family receptors (TNFR55 and CD40) (Adam-Klages, S. et al. *Cell,* 1996, 86(6):937-947; Segui, B. et al. *J. Biol. Chem.,* 1999, 274(52): 37251-37258). FAN knockout or FAN dominant-negative form can protect cell from apoptosis mediated by CD40 or TNF receptor (Segui, B. et al. *J. Clin. Invest.,* 2001, 108(1): 143-151; Segui, B. et al. *J. Biol. Chem.,* 1999, 274(52): 37251-37258). LvsA gene is essential for cytokinesis by possibly playing an important role in a membrane-processing pathway (Kwak, E. et al. *Mol. Biol. Cell,* 1999, 10(12):4429-4439). These studies suggest that the WBW proteins may play a role not only in vesicle trafficking, but also in some important cell processes like apoptosis and cell cycle.

However, the exact molecular mechanism of vesicle trafficking for the WBW proteins remains largely unclear. The mouse lrba (LPS-responsive beige-like PKA anchor gene) has its three isoforms, which differ at C-termini and have tissue-specific and development stage-specific expression pattern. LRBA gene is LPS inducible and can physically associate with various vesicular compartments in cells (Wang, J. W. et al. *Journal of Immunology,* 2001, 166(7): 4586-4695). Described herein is the cloning, genomic structure and promoter analysis of the human lrba gene and its five isoforms. Its genomic locus consists of 58 exons and 57 introns, spinning over 700 K bps. Three isoforms (α, β, δ) differ at BEACH domain and WD repeats at their C-termini. The fourth isoform(γ) has a YLLLQ insertion sequence. The mRNA of the fifth isoform (δ) has two ORFs and a potential IRES for the translation of the second ORF. In the promoter region, there are four E2F binding sites and a CpG island, and surprisingly a potential p53 binding site was found in the promoter, suggesting that lrba gene may be involved in p53

mediated apoptosis or cell arrest, and E2F regulated cell cycle progress, and is regulated developmentally by CpG island. These results show that the Lrba gene is highly regulated at both the transcriptional and translational level, indicating that lrba gene may have a critical role in the life of the cell.

All patents, patent applications, provisional applications, publications, and nucleic acid and amino acid sequences associated with the GenBank accession numbers referred to or cited herein are incorporated by reference in their entirety, including all figures and tables, to the extent they are not inconsistent with the explicit teachings of this specification.

It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application.

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Lys Asn  Met Ser Ser Gly Gly  Ile Leu Arg Gln Cys  Leu Arg Leu
    1430                1435                1440

Val Cys  Ala Val Ala Val Arg  Asn Cys Leu Glu Cys  Gln Gln His
    1445                1450                1455

Ser Gln  Leu Lys Ala Arg Gly  Asp Thr Ala Lys Ser  Ser Lys Thr
    1460                1465                1470
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Ile His  Ser Leu Ile Pro Met  Gly Lys Ser Ala Ala  Lys Ser Pro
    1475                1480                1485

Val Asp  Ile Val Thr Gly Gly  Ile Ser Ser Val Arg  Asp Leu Asp
    1490                1495                1500

Arg Leu  Pro Ala Arg Thr Trp  Thr Leu Ile Gly Leu  Arg Ala Val
    1505                1510                1515

Val Phe  Arg Asp Ile Glu Asp  Ser Lys Gln Ala Gln  Phe Leu Ala
    1520                1525                1530

Leu Ala  Val Val Tyr Phe Ile  Ser Val Leu Met Val  Ser Lys Tyr
    1535                1540                1545

Arg Asp  Ile Leu Glu Pro Gln  Asp Glu Arg His Ser  Gln Ser Leu
    1550                1555                1560

Lys Glu  Thr Ser Ser Asp Asn  Gly Asn Ala Ser Leu  Pro Asp Ala
    1565                1570                1575

Glu Asn  Thr Pro Ala Glu Phe  Ser Ser Leu Thr Leu  Ser Ser Val
    1580                1585                1590

Glu Glu  Ser Leu Glu Gly Thr  Ser Cys Thr Arg Arg  Arg Asp Ser
    1595                1600                1605

Gly Leu  Gly Glu Glu Thr Ala  Ser Gly Leu Gly Ser  Gly Leu Val
    1610                1615                1620

Ser Ala  Ser Pro Ala Ala Pro  Leu Gly Val Ser Ala  Gly Pro Asp
    1625                1630                1635

Ala Ile  Ser Glu Val Leu Cys  Thr Leu Ser Leu Glu  Val Asn Lys
    1640                1645                1650

Ser Gln  Glu Thr Arg Ile Asp  Gly Gly Asn Glu Leu  Asp Arg Lys
    1655                1660                1665

Val Thr  Pro Ser Val Pro Val  Ser Lys Asn Val Asn  Val Lys Asp
    1670                1675                1680

Ile Leu  Arg Ser Leu Val Asn  Met Pro Ala Asp Gly  Val Thr Val
    1685                1690                1695

Asp Pro  Ala Leu Leu Pro Pro  Ala Cys Leu Gly Ala  Leu Gly Asp
    1700                1705                1710

Leu Ser  Val Asp Pro Pro Met  Gln Phe Arg Ser Phe  Asp Arg Ser
    1715                1720                1725

Val Ile  Ile Ala Thr Lys Lys  Ser Ser Val Leu Pro  Ser Ala Leu
    1730                1735                1740

Thr Thr  Ser Ala Pro Ser Ser  Ala Val Ser Val Val  Ser Ser Val
    1745                1750                1755

Asp Pro  Thr His Ala Ser Asp  Thr Gly Gly Glu Ser  Pro Gly Ser
    1760                1765                1770

Arg Ser  Pro Lys Cys Lys Thr  Ala Leu Ser Cys Lys  Gln Leu Ala
    1775                1780                1785

Pro Ser  His Lys Thr Pro Ala  Ala His Met Ser Ile  Thr Glu Arg
    1790                1795                1800

Leu Glu  His Ala Leu Glu Lys  Ala Ala Pro Leu Leu  Arg Glu Ile
    1805                1810                1815

Phe Val  Asp Phe Ala Pro Phe  Leu Ser Arg Thr Leu  Leu Gly Ser
    1820                1825                1830

His Gly  Gln Glu Leu Leu Ile  Glu Gly Thr Ser Leu  Val Cys Met
    1835                1840                1845

Lys Ser  Ser Ser Ser Val Val  Glu Leu Val Met Leu  Leu Cys Ser
    1850                1855                1860
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Gln Glu  Trp Gln Asn Ser Ile  Gln Lys Asn Ala Gly  Leu Ala Phe
    1865                1870                1875

Ile Glu  Leu Val Asn Glu Gly  Arg Leu Leu Ser Gln  Thr Met Lys
    1880                1885                1890

Asp His  Leu Val Arg Val Ala  Asn Glu Ala Glu Phe  Ile Leu Ser
    1895                1900                1905

Arg Gln  Arg Ala Glu Asp Ile  His Arg His Ala Glu  Phe Glu Ser
    1910                1915                1920

Leu Cys  Ala Gln Tyr Ser Ala  Asp Lys Arg Glu Glu  Glu Lys Met
    1925                1930                1935

Cys Asp  His Leu Ile Arg Ala  Ala Lys Tyr Arg Asp  His Val Thr
    1940                1945                1950

Ala Thr  Gln Leu Ile Gln Lys  Ile Ile Asn Leu Leu  Thr Asp Lys
    1955                1960                1965

His Gly  Ala Trp Gly Ser Ser  Ala Val Ser Arg Pro  Arg Glu Phe
    1970                1975                1980

Trp Arg  Leu Asp Tyr Trp Glu  Asp Asp Leu Arg Arg  Arg Arg Arg
    1985                1990                1995

Phe Val  Arg Asn Pro Leu Gly  Ser Thr His Pro Glu  Ala Thr Leu
    2000                2005                2010

Lys Thr  Ala Val Glu His Ala  Ala Asp Glu Asp Ile  Leu Ala Lys
    2015                2020                2025

Gly Lys  Gln Ser Ile Lys Ser  Gln Ala Leu Gly Asn  Gln Asn Ser
    2030                2035                2040

Glu Asn  Glu Ala Leu Leu Glu  Gly Asp Asp Asp Thr  Leu Ser Ser
    2045                2050                2055

Val Asp  Glu Lys Asp Leu Glu  Asn Leu Ala Gly Pro  Val Ser Leu
    2060                2065                2070

Ser Thr  Pro Ala Gln Leu Val  Ala Pro Ser Val Val  Val Lys Gly
    2075                2080                2085

Thr Leu  Ser Val Thr Ser Ser  Glu Leu Tyr Phe Glu  Val Asp Glu
    2090                2095                2100

Glu Asp  Pro Asn Phe Lys Lys  Ile Asp Pro Lys Ile  Leu Ala Tyr
    2105                2110                2115

Thr Glu  Gly Leu His Gly Lys  Trp Leu Phe Thr Glu  Ile Arg Ser
    2120                2125                2130

Ile Phe  Ser Arg Arg Tyr Leu  Leu Gln Asn Thr Ala  Leu Glu Ile
    2135                2140                2145

Phe Met  Ala Asn Arg Val Ala  Val Met Phe Asn Phe  Pro Asp Pro
    2150                2155                2160

Ala Thr  Val Lys Lys Val Val  Asn Tyr Leu Pro Arg  Val Gly Val
    2165                2170                2175

Gly Thr  Ser Phe Gly Leu Pro  Gln Thr Arg Arg Ile  Ser Leu Ala
    2180                2185                2190

Thr Pro  Arg Gln Leu Phe Lys  Ala Ser Asn Met Thr  Gln Arg Trp
    2195                2200                2205

Gln His  Arg Glu Ile Ser Asn  Phe Glu Tyr Leu Met  Phe Leu Asn
    2210                2215                2220

Thr Ile  Ala Gly Arg Ser Tyr  Asn Asp Leu Asn Gln  Tyr Pro Val
    2225                2230                2235

Phe Pro  Trp Val Ile Thr Asn  Tyr Glu Ser Glu Glu  Leu Asp Leu
    2240                2245                2250
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Thr Leu  Pro Ser Asn Phe Arg  Asp Leu Ser Lys Pro  Ile Gly Ala
    2255                 2260                 2265

Leu Asn  Pro Lys Arg Ala Ala  Phe Phe Ala Glu Arg  Phe Glu Ser
    2270                 2275                 2280

Trp Glu  Asp Asp Gln Val Pro  Lys Phe His Tyr Gly  Thr His Tyr
    2285                 2290                 2295

Ser Thr  Ala Ser Phe Val Leu  Ala Trp Leu Leu Arg  Ile Glu Pro
    2300                 2305                 2310

Phe Thr  Thr Tyr Phe Leu Asn  Leu Gln Gly Gly Lys  Phe Asp His
    2315                 2320                 2325

Ala Asp  Arg Thr Phe Ser Ser  Val Ser Arg Ala Trp  Arg Asn Ser
    2330                 2335                 2340

Gln Arg  Asp Thr Ser Asp Ile  Lys Glu Leu Ile Pro  Glu Phe Tyr
    2345                 2350                 2355

Tyr Leu  Pro Glu Met Phe Val  Asn Phe Asn Asn Tyr  Asn Leu Gly
    2360                 2365                 2370

Val Met  Asp Asp Gly Thr Val  Val Ser Asp Val Glu  Leu Pro Pro
    2375                 2380                 2385

Trp Ala  Lys Thr Ser Glu Glu  Phe Val Arg Ile Asn  Arg Leu Ala
    2390                 2395                 2400

Leu Glu  Ser Glu Phe Val Ser  Cys Gln Leu His Gln  Trp Ile Asp
    2405                 2410                 2415

Leu Ile  Phe Gly Tyr Lys Gln  Gln Gly Pro Glu Ala  Val Arg Ala
    2420                 2425                 2430

Leu Asn  Val Phe Tyr Tyr Leu  Thr Tyr Glu Gly Ala  Val Asn Leu
    2435                 2440                 2445

Asn Ser  Ile Thr Asp Pro Val  Leu Arg Glu Ala Val  Glu Ala Gln
    2450                 2455                 2460

Ile Arg  Ser Phe Gly Gln Thr  Pro Ser Gln Leu Leu  Ile Glu Pro
    2465                 2470                 2475

His Pro  Pro Arg Gly Ser Ala  Met Gln Ala Ser Pro  Leu Met Phe
    2480                 2485                 2490

Thr Asp  Gln Ala Gln Gln Asp  Val Ile Met Val Leu  Lys Phe Pro
    2495                 2500                 2505

Ser Asn  Ser Pro Val Thr His  Val Ala Ala Asn Thr  Gln Pro Gly
    2510                 2515                 2520

Leu Ala  Met Pro Ala Val Ile  Thr Val Thr Ala Asn  Arg Leu Phe
    2525                 2530                 2535

Ala Val  Asn Lys Trp His Asn  Leu Pro Ala His Gln  Gly Ala Val
    2540                 2545                 2550

Gln Asp  Gln Pro Tyr Gln Leu  Pro Val Glu Ile Asp  Pro Leu Ile
    2555                 2560                 2565

Ala Cys  Gly Thr Gly Thr His  Arg Arg Gln Val Thr  Asp Leu Leu
    2570                 2575                 2580

Asp Gln  Ser Ile Gln Val His  Ser Gln Cys Phe Val  Ile Thr Ser
    2585                 2590                 2595

Asp Asn  Arg Tyr Ile Leu Val  Cys Gly Phe Trp Asp  Lys Ser Phe
    2600                 2605                 2610

Arg Val  Tyr Ser Thr Asp Thr  Gly Lys Leu Ile Gln  Val Val Phe
    2615                 2620                 2625

Gly His  Trp Asp Val Val Thr  Cys Leu Ala Arg Ser  Glu Ser Tyr
    2630                 2635                 2640
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Ile Gly  Gly Asn Cys Tyr Ile  Leu Ser Gly Ser Arg  Asp Ala Thr
    2645                 2650                 2655

Leu Leu  Leu Trp Tyr Trp Asn  Gly Lys Ser Ser Gly  Ile Gly Asp
    2660                 2665                 2670

Asn Pro  Gly Gly Glu Thr Ala  Thr Pro Arg Ala Ile  Leu Thr Gly
    2675                 2680                 2685

His Asp  Tyr Glu Ile Thr Cys  Ala Ala Val Cys Ala  Glu Leu Gly
    2690                 2695                 2700

Leu Val  Leu Ser Gly Ser Gln  Glu Gly Pro Cys Leu  Ile His Ser
    2705                 2710                 2715

Met Asn  Gly Asp Leu Leu Arg  Thr Leu Glu Gly Pro  Glu Asn Cys
    2720                 2725                 2730

Leu Lys  Pro Lys Leu Ile Gln  Ala Ser Arg Glu Gly  His Cys Val
    2735                 2740                 2745

Ile Phe  Tyr Glu Asn Gly Cys  Phe Cys Thr Phe Ser  Val Asn Gly
    2750                 2755                 2760

Lys Leu  Gln Ala Thr Val Glu  Thr Asp Asp His Ile  Arg Ala Ile
    2765                 2770                 2775

Gln Leu  Ser Arg Asp Gly Gln  Tyr Leu Leu Thr Gly  Gly Asp Asn
    2780                 2785                 2790

Gly Val  Val Ile Val Arg Gln  Val Ser Asp Leu Lys  Gln Leu Phe
    2795                 2800                 2805

Ala Tyr  Pro Gly Cys Asp Ala  Gly Ile Arg Ala Met  Ala Leu Ser
    2810                 2815                 2820

Phe Asp  Gln Arg Cys Ile Ile  Ser Gly Met Ala Ser  Gly Ser Ile
    2825                 2830                 2835

Val Leu  Phe Tyr Asn Asp Phe  Asn Arg Trp His His  Glu Tyr Gln
    2840                 2845                 2850

Thr Arg  Tyr
    2855


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

Leu Ser Leu Lys Pro Gly Leu Pro Ile Arg Gly Ile Arg Met Lys Phe
35 40 45

Ala Val Leu Thr Gly Leu Val Glu Val Gly Glu Val Ser Asn Arg Asp
50 55 60

Ile Val Glu Thr Val Phe Asn Leu Leu Val Gly Gly Gln Phe Asp Leu
65 70 75 80

Glu Met Asn Phe Ile Ile Gln Glu Gly Glu Ser Ile Met Cys Met Val
85 90 95

Glu Leu Leu Glu Lys Cys Asp Val Thr Cys Gln Ala Glu Val Trp Ser
100 105 110

Met Phe Thr Ala Ile Leu Lys Lys Ser Ile Arg Asn Leu Gln Val Cys
115 120 125

Thr Glu Val Gly Leu Val Glu Lys Val Leu Gly Lys Ile Glu Lys Val
130 135 140

Asp Ser Met Ile Ala Asp Leu Leu Val Asp Met Leu Gly Val Leu Ala
145 150 155 160

Ser Tyr Asn Leu Thr Val Arg Glu Leu Lys Leu Phe Phe Ser Lys Leu
165 170 175

Gln Gly Asp Lys Gly Gln Trp Pro Pro His Ala Gly Lys Leu Leu Ser
180 185 190

Val Leu Lys His Met Pro Gln Lys Tyr Gly Pro Asp Ala Phe Phe Asn
195 200 205

Phe Pro Gly Lys Ser Ala Ala Ala Ile Ala Leu Pro Pro Ile Ala Arg
210 215 220

Trp Pro Tyr Gln Asn Gly Phe Thr Phe His Thr Trp Leu Arg Met Asp
225 230 235 240

Pro Val Asn Asn Ile Asn Val Asp Lys Asp Lys Pro Tyr Leu Tyr Cys
245 250 255

Phe Arg Thr Ser Lys Gly Leu Gly Tyr Ser Ala His Phe Val Gly Gly
260 265 270

Cys Leu Ile Ile Thr Ser Ile Lys Ser Lys Gly Lys Gly Phe Gln His
275 280 285

Cys Val Lys Phe Asp Phe Lys Pro Gln Lys Trp Tyr Met Val Thr Ile
290 295 300

Val His Ile Tyr Asn Arg Trp Lys Asn Ser Glu Leu Arg Cys Tyr Val
305 310 315 320

Asn Gly Glu Leu Ala Ser Tyr Gly Glu Ile Thr Trp Phe Val Asn Thr
325 330 335

Ser Asp Thr Phe Asp Lys Cys Phe Leu Gly Ser Ser Glu Thr Ala Asp
340 345 350

Ala Asn Arg Val Phe Cys Gly Gln Met Thr Ala Val Tyr Leu Phe Ser
355 360 365

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Asp Ala Leu Asn Ala Ala Gln Ile Phe Ala Ile Tyr Gln Leu Gly Leu
    370                 375                 380

Gly Tyr Lys Gly Thr Phe Lys Phe Lys Ala Glu Ser Asp Leu Phe Leu
385                 390                 395                 400

Ala Glu His His Lys Leu Leu Leu Tyr Asp Gly Lys Leu Ser Ser Ala
                405                 410                 415

Ile Ala Phe Met Tyr Asn Pro Arg Ala Thr Asp Ala Gln Leu Cys Leu
            420                 425                 430

Glu Ser Ser Pro Lys Asp Asn Pro Ser Ile Phe Val His Ser Pro His
        435                 440                 445

Ala Leu Met Leu Gln Asp Val Lys Ala Val Leu Thr His Ser Ile Gln
    450                 455                 460

Ser Ala Met His Ser Ile Gly Gly Val Gln Val Leu Phe Pro Leu Phe
465                 470                 475                 480

Ala Gln Leu Asp Tyr Lys Gln Tyr Leu Ser Asp Glu Val Asp Leu Thr
                485                 490                 495

Ile Cys Thr Thr Leu Leu Ala Phe Ile Met Glu Leu Leu Lys Asn Ser
            500                 505                 510

Ile Ala Met Gln Glu Gln Met Leu Ala Cys Lys Gly Phe Leu Val Ile
        515                 520                 525

Gly Tyr Ser Leu Glu Lys Ser Ser Lys Ser His Val Ser Arg Ala Val
    530                 535                 540

Leu Glu Leu Cys Leu Ala Phe Ser Lys Tyr Leu Ser Asn Leu Gln Asn
545                 550                 555                 560

Gly Met Pro Leu Leu Lys Gln Leu Cys Asp His Ile Leu Leu Asn Pro
                565                 570                 575

Ala Val Trp Ile His Thr Pro Ala Lys Val Gln Leu Met Leu Tyr Thr
            580                 585                 590

Tyr Leu Ser Thr Glu Phe Ile Gly Thr Val Asn Ile Tyr Asn Thr Ile
        595                 600                 605

Arg Arg Val Gly Thr Val Leu Leu Ile Met His Thr Leu Lys Tyr Tyr
    610                 615                 620

Tyr Trp Ala Val Asn Pro Gln Asp Arg Ser Gly Ile Thr Pro Lys Gly
625                 630                 635                 640

Leu Asp Gly Pro Arg Pro Asn Gln Lys Glu Ile Leu Ser Leu Arg Ala
                645                 650                 655

Phe Leu Leu Met Phe Ile Lys Gln Leu Val Met Lys Asp Ser Gly Val
            660                 665                 670

Lys Glu Asp Glu Leu Gln Ala Ile Leu Asn Tyr Leu Leu Thr Met His
        675                 680                 685

Glu Asp Asp Asn Leu Met Asp Val Leu Gln Leu Leu Val Ala Leu Met
    690                 695                 700

Ala Glu His Pro Asn Ser Met Ile Pro Ala Phe Asp Gln Arg Asn Gly
705                 710                 715                 720

Leu Arg Val Ile Tyr Lys Leu Leu Ala Ser Lys Ser Glu Gly Ile Arg
                725                 730                 735

Val Gln Ala Leu Lys Ala Leu Gly Tyr Phe Leu Lys His Leu Ala Pro
            740                 745                 750

Lys Arg Lys Ala Glu Val Met Leu Gly His Gly Leu Phe Ser Leu Leu
        755                 760                 765

Ala Glu Arg Leu Met Leu Gln Thr Asn Leu Ile Thr Met Thr Met Tyr
    770                 775                 780
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Asn Val Leu Phe Glu Ile Leu Ile Glu Gln Ile Cys Thr Gln Val Ile
785                 790                 795                 800

His Lys Gln His Pro Asp Pro Asp Ser Thr Val Lys Ile Gln Asn Pro
                805                 810                 815

Gln Ile Leu Lys Val Ile Ala Thr Leu Leu Arg Asn Ser Pro Gln Cys
            820                 825                 830

Pro Glu Ser Met Glu Val Arg Arg Ala Phe Leu Ser Asp Met Ile Lys
        835                 840                 845

Leu Phe Asn Asn Ser Arg Glu Asn Arg Arg Ser Leu Leu Gln Cys Ser
    850                 855                 860

Val Trp Gln Glu Trp Met Leu Ser Leu Cys Tyr Phe Asn Pro Lys Asn
865                 870                 875                 880

Ser Asp Glu Gln Lys Ile Thr Glu Met Val Tyr Ala Ile Phe Arg Ile
                885                 890                 895

Leu Leu Tyr His Ala Val Lys Tyr Glu Trp Gly Gly Trp Arg Val Trp
            900                 905                 910

Val Asp Thr Leu Ser Ile Thr His Ser Lys Val Thr Phe Glu Ile His
        915                 920                 925

Lys Glu Asn Leu Ala Asn Ile Phe Arg Glu Glu Gln Arg Lys Gly Asp
    930                 935                 940

Glu Glu Thr Gly Pro Cys Ser Ser Ser Leu Val Pro Glu Gly Thr Gly
945                 950                 955                 960

Ala Thr Arg Gly Val Asp Val Ser Val Gly Ser Gln His Glu Asp Arg
                965                 970                 975

Lys Asp Ser Pro Ile Ser Pro His Phe Thr Arg Asn Ser Asp Glu Asn
            980                 985                 990

Ser Ser Ile Gly Arg Ala Ser Ser  Ile Asp Ser Ala Ser  Asn Thr Glu
        995                 1000                1005

Leu Gln  Thr His Asp Met Ser  Ser Asp Glu Lys Lys  Val Glu Arg
    1010                1015                1020

Glu Asn  Gln Glu Leu Leu Asp  Gln Ala Thr Val Glu  Glu Thr Ala
    1025                1030                1035

Thr Asn  Gly Ala Lys Asp Asp  Leu Glu Thr Ser Ser  Asp Ala Ala
    1040                1045                1050

Glu Pro  Val Thr Ile Asn Ser  Asn Ser Leu Glu Pro  Gly Lys Asp
    1055                1060                1065

Thr Val  Thr Ile Ser Glu Val  Ser Ala Ser Ile Ser  Ser Pro Ser
    1070                1075                1080

Glu Glu  Asp Ala Ala Glu Met  Pro Glu Leu Leu Glu  Lys Ser Gly
    1085                1090                1095

Val Glu  Glu Lys Glu Asp Asp  Asp Tyr Val Glu Leu  Lys Val Glu
    1100                1105                1110

Gly Ser  Pro Thr Glu Glu Ala  Gly Leu Pro Thr Glu  Leu Gln Gly
    1115                1120                1125

Glu Gly  Leu Val Ser Ala Ala  Ser Gly Gly Arg Glu  Glu Pro Asp
    1130                1135                1140

Met Cys  Gly His Gly Cys Glu  Val Gln Val Glu Ala  Pro Ile Thr
    1145                1150                1155

Lys Ile  His Asn Asp Pro Glu  Thr Thr Asp Ser Glu  Asp Ser Arg
    1160                1165                1170

Phe Pro  Thr Val Ala Thr Ala  Gly Ser Leu Ala Thr  Ser Ser Glu
    1175                1180                1185
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Val Pro  Val Pro Gln Ala Thr  Val Gln Ser Asp Ser  His Glu Met
    1190                 1195                 1200

Leu Asp  Gly Gly Met Lys Ala  Thr Asn Leu Ala Gly  Glu Thr Glu
    1205                 1210                 1215

Ser Val  Ser Asp Cys Ala Asp  Asn Val Ser Glu Ala  Pro Ala Thr
    1220                 1225                 1230

Ser Glu  Gln Lys Ile Thr Lys  Leu Asp Val Ser Ser  Val Ala Ser
    1235                 1240                 1245

Asp Thr  Glu Arg Phe Glu Leu  Lys Ala Ser Thr Ser  Thr Glu Ala
    1250                 1255                 1260

Pro Gln  Pro Gln Arg His Gly  Leu Glu Ile Ser Arg  Gln Gln Glu
    1265                 1270                 1275

Gln Thr  Ala Gln Gly Thr Ala  Pro Asp Ala Val Asp  Gln Gln Arg
    1280                 1285                 1290

Arg Asp  Ser Arg Ser Thr Met  Phe Arg Ile Pro Glu  Phe Lys Trp
    1295                 1300                 1305

Ser Gln  Met His Gln Arg Leu  Leu Thr Asp Leu Leu  Phe Ser Ile
    1310                 1315                 1320

Glu Thr  Asp Ile Gln Met Trp  Arg Ser His Ser Thr  Lys Thr Val
    1325                 1330                 1335

Met Asp  Phe Val Asn Ser Ser  Asp Asn Val Ile Phe  Val His Asn
    1340                 1345                 1350

Thr Ile  His Leu Ile Ser Gln  Val Met Asp Asn Met  Val Met Ala
    1355                 1360                 1365

Cys Gly  Gly Ile Leu Pro Leu  Leu Ser Ala Ala Thr  Ser Ala Thr
    1370                 1375                 1380

His Glu  Leu Glu Asn Ile Glu  Pro Thr Gln Gly Leu  Ser Ile Glu
    1385                 1390                 1395

Ala Ser  Val Thr Phe Leu Gln  Arg Leu Ile Ser Leu  Val Asp Val
    1400                 1405                 1410

Leu Ile  Phe Ala Ser Ser Leu  Gly Phe Thr Glu Ile  Glu Ala Glu
    1415                 1420                 1425

Lys Asn  Met Ser Ser Gly Gly  Ile Leu Arg Gln Cys  Leu Arg Leu
    1430                 1435                 1440

Val Cys  Ala Val Ala Val Arg  Asn Cys Leu Glu Cys  Gln Gln His
    1445                 1450                 1455

Ser Gln  Leu Lys Ala Arg Gly  Asp Thr Ala Lys Ser  Ser Lys Thr
    1460                 1465                 1470

Ile His  Ser Leu Ile Pro Met  Gly Lys Ser Ala Ala  Lys Ser Pro
    1475                 1480                 1485

Val Asp  Ile Val Thr Gly Gly  Ile Ser Ser Val Arg  Asp Leu Asp
    1490                 1495                 1500

Arg Leu  Pro Ala Arg Thr Trp  Thr Leu Ile Gly Leu  Arg Ala Val
    1505                 1510                 1515

Val Phe  Arg Asp Ile Glu Asp  Ser Lys Gln Ala Gln  Phe Leu Ala
    1520                 1525                 1530

Leu Ala  Val Val Tyr Phe Ile  Ser Val Leu Met Val  Ser Lys Tyr
    1535                 1540                 1545

Arg Asp  Ile Leu Glu Pro Gln  Asp Glu Arg His Ser  Gln Ser Leu
    1550                 1555                 1560

Lys Glu  Thr Ser Ser Asp Asn  Gly Asn Ala Ser Leu  Pro Asp Ala
    1565                 1570                 1575
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Glu Asn  Thr Pro Ala Glu Phe  Ser Ser Leu Thr Leu  Ser Ser Val
    1580                 1585                 1590

Glu Glu  Ser Leu Glu Gly Thr  Ser Cys Thr Arg Arg  Arg Asp Ser
    1595                 1600                 1605

Gly Leu  Gly Glu Glu Thr Ala  Ser Gly Leu Gly Ser  Gly Leu Val
    1610                 1615                 1620

Ser Ala  Ser Pro Ala Ala Pro  Leu Gly Val Ser Ala  Gly Pro Asp
    1625                 1630                 1635

Ala Ile  Ser Glu Val Leu Cys  Thr Leu Ser Leu Glu  Val Asn Lys
    1640                 1645                 1650

Ser Gln  Glu Thr Arg Ile Asp  Gly Gly Asn Glu Leu  Asp Arg Lys
    1655                 1660                 1665

Val Thr  Pro Ser Val Pro Val  Ser Lys Asn Val Asn  Val Lys Asp
    1670                 1675                 1680

Ile Leu  Arg Ser Leu Val Asn  Met Pro Ala Asp Gly  Val Thr Val
    1685                 1690                 1695

Asp Pro  Ala Leu Leu Pro Pro  Ala Cys Leu Gly Ala  Leu Gly Asp
    1700                 1705                 1710

Leu Ser  Val Asp Pro Pro Met  Gln Phe Arg Ser Phe  Asp Arg Ser
    1715                 1720                 1725

Val Ile  Ile Ala Thr Lys Lys  Ser Ser Val Leu Pro  Ser Ala Leu
    1730                 1735                 1740

Thr Thr  Ser Ala Pro Ser Ser  Ala Val Ser Val Val  Ser Ser Val
    1745                 1750                 1755

Asp Pro  Thr His Ala Ser Asp  Thr Gly Gly Glu Ser  Pro Gly Ser
    1760                 1765                 1770

Arg Ser  Pro Lys Cys Lys Thr  Ala Leu Ser Cys Lys  Gln Leu Ala
    1775                 1780                 1785

Pro Ser  His Lys Thr Pro Ala  Ala His Met Ser Ile  Thr Glu Arg
    1790                 1795                 1800

Leu Glu  His Ala Leu Glu Lys  Ala Ala Pro Leu Leu  Arg Glu Ile
    1805                 1810                 1815

Phe Val  Asp Phe Ala Pro Phe  Leu Ser Arg Thr Leu  Leu Gly Ser
    1820                 1825                 1830

His Gly  Gln Glu Leu Leu Ile  Glu Gly Thr Ser Leu  Val Cys Met
    1835                 1840                 1845

Lys Ser  Ser Ser Ser Val Val  Glu Leu Val Met Leu  Leu Cys Ser
    1850                 1855                 1860

Gln Glu  Trp Gln Asn Ser Ile  Gln Lys Asn Ala Gly  Leu Ala Phe
    1865                 1870                 1875

Ile Glu  Leu Val Asn Glu Gly  Arg Leu Leu Ser Gln  Thr Met Lys
    1880                 1885                 1890

Asp His  Leu Val Arg Val Ala  Asn Glu Ala Glu Phe  Ile Leu Ser
    1895                 1900                 1905

Arg Gln  Arg Ala Glu Asp Ile  His Arg His Ala Glu  Phe Glu Ser
    1910                 1915                 1920

Leu Cys  Ala Gln Tyr Ser Ala  Asp Lys Arg Glu Glu  Glu Lys Met
    1925                 1930                 1935

Cys Asp  His Leu Ile Arg Ala  Ala Lys Tyr Arg Asp  His Val Thr
    1940                 1945                 1950

Ala Thr  Gln Leu Ile Gln Lys  Ile Ile Asn Leu Leu  Thr Asp Lys
    1955                 1960                 1965
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His Gly  Ala Trp Gly Ser Ser  Ala Val Ser Arg Pro  Arg Glu Phe
    1970                 1975                 1980

Trp Arg  Leu Asp Tyr Trp Glu  Asp Asp Leu Arg Arg  Arg Arg Arg
    1985                 1990                 1995

Phe Val  Arg Asn Pro Leu Gly  Ser Thr His Pro Glu  Ala Thr Leu
    2000                 2005                 2010

Lys Thr  Ala Val Glu His Ala  Ala Asp Glu Asp Ile  Leu Ala Lys
    2015                 2020                 2025

Gly Lys  Gln Ser Ile Lys Ser  Gln Ala Leu Gly Asn  Gln Asn Ser
    2030                 2035                 2040

Glu Asn  Glu Ala Leu Leu Glu  Gly Asp Asp Asp Thr  Leu Ser Ser
    2045                 2050                 2055

Val Asp  Glu Lys Asp Leu Glu  Asn Leu Ala Gly Pro  Val Ser Leu
    2060                 2065                 2070

Ser Thr  Pro Ala Gln Leu Val  Ala Pro Ser Val Val  Val Lys Gly
    2075                 2080                 2085

Thr Leu  Ser Val Thr Ser Ser  Glu Leu Tyr Phe Glu  Val Asp Glu
    2090                 2095                 2100

Glu Asp  Pro Asn Phe Lys Lys  Ile Asp Pro Lys Ile  Leu Ala Tyr
    2105                 2110                 2115

Thr Glu  Gly Leu His Gly Lys  Trp Leu Phe Thr Glu  Ile Arg Ser
    2120                 2125                 2130

Ile Phe  Ser Arg Arg Tyr Leu  Leu Gln Asn Thr Ala  Leu Glu Ile
    2135                 2140                 2145

Phe Met  Ala Asn Arg Val Ala  Val Met Phe Asn Phe  Pro Asp Pro
    2150                 2155                 2160

Ala Thr  Val Lys Lys Val Val  Asn Tyr Leu Pro Arg  Val Gly Val
    2165                 2170                 2175

Gly Thr  Ser Phe Gly Leu Pro  Gln Thr Arg Arg Ile  Ser Leu Ala
    2180                 2185                 2190

Thr Pro  Arg Gln Leu Phe Lys  Ala Ser Asn Met Thr  Gln Arg Trp
    2195                 2200                 2205

Gln His  Arg Glu Ile Ser Asn  Phe Glu Tyr Leu Met  Phe Leu Asn
    2210                 2215                 2220

Thr Ile  Ala Gly Arg Ser Tyr  Asn Asp Leu Asn Gln  Tyr Pro Val
    2225                 2230                 2235

Phe Pro  Trp Val Ile Thr Asn  Tyr Glu Ser Glu Glu  Leu Asp Leu
    2240                 2245                 2250

Thr Leu  Pro Ser Asn Phe Arg  Asp Leu Ser Lys Pro  Ile Gly Ala
    2255                 2260                 2265

Leu Asn  Pro Lys Arg Ala Ala  Phe Phe Ala Glu Arg  Phe Glu Ser
    2270                 2275                 2280

Trp Glu  Asp Asp Gln Val Pro  Lys Phe His Tyr Gly  Thr His Tyr
    2285                 2290                 2295

Ser Thr  Ala Ser Phe Val Leu  Ala Trp Leu Leu Arg  Ile Glu Pro
    2300                 2305                 2310

Phe Thr  Thr Tyr Phe Leu Asn  Leu Gln Gly Gly Lys  Phe Asp His
    2315                 2320                 2325

Ala Asp  Arg Thr Phe Ser Ser  Val Ser Arg Ala Trp  Arg Asn Ser
    2330                 2335                 2340

Gln Arg  Asp Thr Ser Asp Ile  Lys Glu Leu Ile Pro  Glu Phe Tyr
    2345                 2350                 2355
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Tyr Leu  Pro Glu Met Phe Val  Asn Phe Asn Asn Tyr  Asn Leu Gly
    2360                 2365                 2370

Val Met  Asp Asp Gly Thr Val  Val Ser Asp Val Glu  Leu Pro Pro
    2375                 2380                 2385

Trp Ala  Lys Thr Ser Glu Glu  Phe Val Arg Ile Asn  Arg Leu Ala
    2390                 2395                 2400

Leu Glu  Ser Glu Phe Val Ser  Cys Gln Leu His Gln  Trp Ile Asp
    2405                 2410                 2415

Leu Ile  Phe Gly Tyr Lys Gln  Gln Gly Pro Glu Ala  Val Arg Ala
    2420                 2425                 2430

Leu Asn  Val Phe Tyr Tyr Leu  Thr Tyr Glu Gly Ala  Val Asn Leu
    2435                 2440                 2445

Asn Ser  Ile Thr Asp Pro Val  Leu Arg Glu Ala Val  Glu Ala Gln
    2450                 2455                 2460

Ile Arg  Ser Phe Gly Gln Thr  Pro Ser Gln Leu Leu  Ile Glu Pro
    2465                 2470                 2475

His Pro  Pro Arg Gly Ser Ala  Met Gln Ala Ser Pro  Leu Met Phe
    2480                 2485                 2490

Thr Asp  Gln Ala Gln Gln Asp  Val Ile Met Val Leu  Lys Phe Pro
    2495                 2500                 2505

Ser Asn  Ser Pro Val Thr His  Val Ala Ala Asn Thr  Gln Pro Gly
    2510                 2515                 2520

Leu Ala  Met Pro Ala Val Ile  Thr Val Thr Ala Asn  Arg Leu Phe
    2525                 2530                 2535

Ala Val  Asn Lys Trp His Asn  Leu Pro Ala His Gln  Gly Ala Val
    2540                 2545                 2550

Gln Asp  Gln Pro Tyr Gln Leu  Pro Val Glu Ile Asp  Pro Leu Ile
    2555                 2560                 2565

Ala Cys  Gly Thr Gly Thr His  Arg Arg Gln Val Thr  Asp Leu Leu
    2570                 2575                 2580

Asp Gln  Ser Ile Gln Val His  Ser Gln Cys Phe Val  Ile Thr Ser
    2585                 2590                 2595

Asp Asn  Arg Tyr Ile Leu Val  Cys Gly Phe Trp Asp  Lys Ser Phe
    2600                 2605                 2610

Arg Val  Tyr Ser Thr Asp Thr  Gly Lys Leu Ile Gln  Val Val Phe
    2615                 2620                 2625

Gly His  Trp Asp Val Val Thr  Cys Leu Ala Arg Ser  Glu Ser Tyr
    2630                 2635                 2640

Ile Gly  Gly Asn Cys Tyr Ile  Leu Ser Gly Ser Arg  Asp Ala Thr
    2645                 2650                 2655

Leu Leu  Leu Trp Tyr Trp Asn  Gly Lys Ser Ser Gly  Ile Gly Asp
    2660                 2665                 2670

Asn Pro  Gly Gly Glu Thr Ala  Thr Pro Arg Ala Ile  Leu Thr Gly
    2675                 2680                 2685

His Asp  Tyr Glu Ile Thr Cys  Ala Ala Val Cys Ala  Glu Leu Gly
    2690                 2695                 2700

Leu Val  Leu Ser Gly Ser Gln  Glu Gly Pro Cys Leu  Ile His Ser
    2705                 2710                 2715

Met Asn  Gly Asp Leu Leu Arg  Thr Leu Glu Gly Pro  Glu Asn Cys
    2720                 2725                 2730

Leu Lys  Pro Lys Leu Ile Gln  Ala Ser Arg Glu Gly  His Cys Val
    2735                 2740                 2745
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Ile Phe  Tyr Glu Asn Gly Cys  Phe Cys Thr Phe Ser  Val Asn Gly
    2750                 2755                 2760

Lys Leu  Gln Ala Thr Val Glu  Thr Asp Asp His Ile  Arg Val Ser
    2765                 2770                 2775

Ala Val  Gly Ser Thr Leu Phe  Leu Leu Leu Gly Ser  Ser Lys
    2780                 2785                 2790


<210> SEQ ID NO 5
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 5

Val Ser Ala Val Gly Ser Thr Leu Phe Leu Leu Leu Gly Ser Ser Lys
1               5                   10                  15


<210> SEQ ID NO 6
<211> LENGTH: 2579
<212> TYPE: PRT
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: BINDING
<222> LOCATION: (1350)..(1369)
<223> OTHER INFORMATION: Putative Protein Kinase A RII binding site
<220> FEATURE:
<221> NAME/KEY: BINDING
<222> LOCATION: (1399)..(1418)
<223> OTHER INFORMATION: Putative Protein Kinase A RII binding site
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (2028)..(2071)
<223> OTHER INFORMATION: WDL (WD-like) repeat
<220> FEATURE:
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<222> LOCATION: (2072)..(2121)
<223> OTHER INFORMATION: WDL (WD-like) repeat
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (2122)..(2162)
<223> OTHER INFORMATION: WDL (WD-like) repeat
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (2204)..(2482)
<223> OTHER INFORMATION: BEACH domain

<400> SEQUENCE: 6

Met Ala Ser Glu Asp Asn Arg Ala Pro Ser Arg Pro Pro Thr Gly Asp
1               5                   10                  15

Asp Gly Gly Gly Gly Gly Lys Glu Glu Thr Pro Thr Glu Gly Gly Ala
            20                  25                  30

Leu Ser Leu Lys Pro Gly Leu Pro Ile Arg Gly Ile Arg Met Lys Phe
        35                  40                  45

Ala Val Leu Thr Gly Leu Val Glu Val Gly Glu Val Ser Asn Arg Asp
    50                  55                  60

Ile Val Glu Thr Val Phe Asn Leu Leu Val Gly Gly Gln Phe Asp Leu
65                  70                  75                  80

Glu Met Asn Phe Ile Ile Gln Glu Gly Glu Ser Ile Met Cys Met Val
                85                  90                  95

Glu Leu Leu Glu Lys Cys Asp Val Thr Cys Gln Ala Glu Val Trp Ser
            100                 105                 110

Met Phe Thr Ala Ile Leu Lys Lys Ser Ile Arg Asn Leu Gln Val Cys
        115                 120                 125

Thr Glu Val Gly Leu Val Glu Lys Val Leu Gly Lys Ile Glu Lys Val
    130                 135                 140
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Asp Ser Met Ile Ala Asp Leu Leu Val Asp Met Leu Gly Val Leu Ala
145                 150                 155                 160

Ser Tyr Asn Leu Thr Val Arg Glu Leu Lys Leu Phe Phe Ser Lys Leu
                165                 170                 175

Gln Gly Asp Lys Gly Gln Trp Pro Pro His Ala Gly Lys Leu Leu Ser
            180                 185                 190

Val Leu Lys His Met Pro Gln Lys Tyr Gly Pro Asp Ala Phe Phe Asn
        195                 200                 205

Phe Pro Gly Lys Ser Ala Ala Ala Ile Ala Leu Pro Pro Ile Ala Arg
    210                 215                 220

Trp Pro Tyr Gln Asn Gly Phe Thr Phe His Thr Trp Leu Arg Met Asp
225                 230                 235                 240

Pro Val Asn Asn Ile Asn Val Asp Lys Asp Lys Pro Tyr Leu Tyr Cys
                245                 250                 255

Phe Arg Thr Ser Lys Gly Leu Gly Tyr Ser Ala His Phe Val Gly Gly
            260                 265                 270

Cys Leu Ile Ile Thr Ser Ile Lys Ser Lys Gly Lys Gly Phe Gln His
        275                 280                 285

Cys Val Lys Phe Asp Phe Lys Pro Gln Lys Trp Tyr Met Val Thr Ile
    290                 295                 300

Val His Ile Tyr Asn Arg Trp Lys Asn Ser Glu Leu Arg Cys Tyr Val
305                 310                 315                 320

Asn Gly Glu Leu Ala Ser Tyr Gly Glu Ile Thr Trp Phe Val Asn Thr
                325                 330                 335

Ser Asp Thr Phe Asp Lys Cys Phe Leu Gly Ser Ser Glu Thr Ala Asp
            340                 345                 350

Ala Asn Arg Val Phe Cys Gly Gln Met Thr Ala Val Tyr Leu Phe Ser
        355                 360                 365

Asp Ala Leu Asn Ala Ala Gln Ile Phe Ala Ile Tyr Gln Leu Gly Leu
    370                 375                 380

Gly Tyr Lys Gly Thr Phe Lys Phe Lys Ala Glu Ser Asp Leu Phe Leu
385                 390                 395                 400

Ala Glu His His Lys Leu Leu Leu Tyr Asp Gly Lys Leu Ser Ser Ala
                405                 410                 415

Ile Ala Phe Met Tyr Asn Pro Arg Ala Thr Asp Ala Gln Leu Cys Leu
            420                 425                 430

Glu Ser Ser Pro Lys Asp Asn Pro Ser Ile Phe Val His Ser Pro His
        435                 440                 445

Ala Leu Met Leu Gln Asp Val Lys Ala Val Leu Thr His Ser Ile Gln
    450                 455                 460

Ser Ala Met His Ser Ile Gly Gly Val Gln Val Leu Phe Pro Leu Phe
465                 470                 475                 480

Ala Gln Leu Asp Tyr Lys Gln Tyr Leu Ser Asp Glu Val Asp Leu Thr
                485                 490                 495

Ile Cys Thr Thr Leu Leu Ala Phe Ile Met Glu Leu Leu Lys Asn Ser
            500                 505                 510

Ile Ala Met Gln Glu Gln Met Leu Ala Cys Lys Gly Phe Leu Val Ile
        515                 520                 525

Gly Tyr Ser Leu Glu Lys Ser Ser Lys Ser His Val Ser Arg Ala Val
    530                 535                 540

Leu Glu Leu Cys Leu Ala Phe Ser Lys Tyr Leu Ser Asn Leu Gln Asn
545                 550                 555                 560
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Gly Met Pro Leu Leu Lys Gln Leu Cys Asp His Ile Leu Leu Asn Pro
                565                 570                 575

Ala Val Trp Ile His Thr Pro Ala Lys Val Gln Leu Met Leu Tyr Thr
            580                 585                 590

Tyr Leu Ser Thr Glu Phe Ile Gly Thr Val Asn Ile Tyr Asn Thr Ile
        595                 600                 605

Arg Arg Val Gly Thr Val Leu Leu Ile Met His Thr Leu Lys Tyr Tyr
    610                 615                 620

Tyr Trp Ala Val Asn Pro Gln Asp Arg Ser Gly Ile Thr Pro Lys Gly
625                 630                 635                 640

Leu Asp Gly Pro Arg Pro Asn Gln Lys Glu Ile Leu Ser Leu Arg Ala
                645                 650                 655

Phe Leu Leu Met Phe Ile Lys Gln Leu Val Met Lys Asp Ser Gly Val
            660                 665                 670

Lys Glu Asp Glu Leu Gln Ala Ile Leu Asn Tyr Leu Leu Thr Met His
        675                 680                 685

Glu Asp Asp Asn Leu Met Asp Val Leu Gln Leu Leu Val Ala Leu Met
    690                 695                 700

Ala Glu His Pro Asn Ser Met Ile Pro Ala Phe Asp Gln Arg Asn Gly
705                 710                 715                 720

Leu Arg Val Ile Tyr Lys Leu Leu Ala Ser Lys Ser Glu Gly Ile Arg
                725                 730                 735

Val Gln Ala Leu Lys Ala Leu Gly Tyr Phe Leu Lys His Leu Ala Pro
            740                 745                 750

Lys Arg Lys Ala Glu Val Met Leu Gly His Gly Leu Phe Ser Leu Leu
        755                 760                 765

Ala Glu Arg Leu Met Leu Gln Thr Asn Leu Ile Thr Met Thr Met Tyr
    770                 775                 780

Asn Val Leu Phe Glu Ile Leu Ile Glu Gln Ile Cys Thr Gln Val Ile
785                 790                 795                 800

His Lys Gln His Pro Asp Pro Asp Ser Thr Val Lys Ile Gln Asn Pro
                805                 810                 815

Gln Ile Leu Lys Val Ile Ala Thr Leu Leu Arg Asn Ser Pro Gln Cys
            820                 825                 830

Pro Glu Ser Met Glu Val Arg Arg Ala Phe Leu Ser Asp Met Ile Lys
        835                 840                 845

Leu Phe Asn Asn Ser Arg Glu Asn Arg Arg Ser Leu Leu Gln Cys Ser
    850                 855                 860

Val Trp Gln Glu Trp Met Leu Ser Leu Cys Tyr Phe Asn Pro Lys Asn
865                 870                 875                 880

Ser Asp Glu Gln Lys Ile Thr Glu Met Val Tyr Ala Ile Phe Arg Ile
                885                 890                 895

Leu Leu Tyr His Ala Val Lys Tyr Glu Trp Gly Gly Trp Arg Val Trp
            900                 905                 910

Val Asp Thr Leu Ser Ile Thr His Ser Lys Val Thr Phe Glu Ile His
        915                 920                 925

Lys Glu Asn Leu Ala Asn Ile Phe Arg Glu Glu Gln Arg Lys Gly Asp
    930                 935                 940

Glu Glu Thr Gly Pro Cys Ser Ser Ser Leu Val Pro Glu Gly Thr Gly
945                 950                 955                 960

Ala Thr Arg Gly Val Asp Val Ser Val Gly Ser Gln His Glu Asp Arg
                965                 970                 975
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Lys Asp Ser Pro Ile Ser Pro His Phe Thr Arg Asn Ser Asp Glu Asn
            980                 985                 990

Ser Ser Ile Gly Arg Ala Ser Ser  Ile Asp Ser Ala Ser  Asn Thr Glu
        995                1000                1005

Leu Gln  Thr His Asp Met Ser  Ser Asp Glu Lys Lys  Val Glu Arg
    1010                1015                1020

Glu Asn  Gln Glu Leu Leu Asp  Gln Ala Thr Val Glu  Glu Thr Ala
    1025                1030                1035

Thr Asn  Gly Ala Lys Asp Asp  Leu Glu Thr Ser Ser  Asp Ala Ala
    1040                1045                1050

Glu Pro  Val Thr Ile Asn Ser  Asn Ser Leu Glu Pro  Gly Lys Asp
    1055                1060                1065

Thr Val  Thr Ile Ser Glu Val  Ser Ala Ser Ile Ser  Ser Pro Ser
    1070                1075                1080

Glu Glu  Asp Ala Ala Glu Met  Pro Glu Leu Leu Glu  Lys Ser Gly
    1085                1090                1095

Val Glu  Glu Lys Glu Asp Asp  Asp Tyr Val Glu Leu  Lys Val Glu
    1100                1105                1110

Gly Ser  Pro Thr Glu Glu Ala  Gly Leu Pro Thr Glu  Leu Gln Gly
    1115                1120                1125

Glu Gly  Leu Val Ser Ala Ala  Ser Gly Gly Arg Glu  Glu Pro Asp
    1130                1135                1140

Met Cys  Gly His Gly Cys Glu  Val Gln Val Glu Ala  Pro Ile Thr
    1145                1150                1155

Lys Ile  His Asn Asp Pro Glu  Thr Thr Asp Ser Glu  Asp Ser Arg
    1160                1165                1170

Phe Pro  Thr Val Ala Thr Ala  Gly Ser Leu Ala Thr  Ser Ser Glu
    1175                1180                1185

Val Pro  Val Pro Gln Ala Thr  Val Gln Ser Asp Ser  His Glu Met
    1190                1195                1200

Leu Asp  Gly Gly Met Lys Ala  Thr Asn Leu Ala Gly  Glu Thr Glu
    1205                1210                1215

Ser Val  Ser Asp Cys Ala Asp  Asn Val Ser Glu Ala  Pro Ala Thr
    1220                1225                1230

Ser Glu  Gln Lys Ile Thr Lys  Leu Asp Val Ser Ser  Val Ala Ser
    1235                1240                1245

Asp Thr  Glu Arg Phe Glu Leu  Lys Ala Ser Thr Ser  Thr Glu Ala
    1250                1255                1260

Pro Gln  Pro Gln Arg His Gly  Leu Glu Ile Ser Arg  Gln Gln Glu
    1265                1270                1275

Gln Thr  Ala Gln Gly Thr Ala  Pro Asp Ala Val Asp  Gln Gln Arg
    1280                1285                1290

Arg Asp  Ser Arg Ser Thr Met  Phe Arg Ile Pro Glu  Phe Lys Trp
    1295                1300                1305

Ser Gln  Met His Gln Arg Leu  Leu Thr Asp Leu Leu  Phe Ser Ile
    1310                1315                1320

Glu Thr  Asp Ile Gln Met Trp  Arg Ser His Ser Thr  Lys Thr Val
    1325                1330                1335

Met Asp  Phe Val Asn Ser Ser  Asp Asn Val Ile Phe  Val His Asn
    1340                1345                1350

Thr Ile  His Leu Ile Ser Gln  Val Met Asp Asn Met  Val Met Ala
    1355                1360                1365
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Cys Gly  Gly Ile Leu Pro Leu  Leu Ser Ala Ala Thr  Ser Ala Thr
    1370                1375                1380

His Glu  Leu Glu Asn Ile Glu  Pro Thr Gln Gly Leu  Ser Ile Glu
    1385                1390                1395

Ala Ser  Val Thr Phe Leu Gln  Arg Leu Ile Ser Leu  Val Asp Val
    1400                1405                1410

Leu Ile  Phe Ala Ser Ser Leu  Gly Phe Thr Glu Ile  Glu Ala Glu
    1415                1420                1425

Lys Asn  Met Ser Ser Gly Gly  Ile Leu Arg Gln Cys  Leu Arg Leu
    1430                1435                1440

Val Cys  Ala Val Ala Val Arg  Asn Cys Leu Glu Cys  Gln Gln His
    1445                1450                1455

Ser Gln  Leu Lys Ala Arg Gly  Asp Thr Ala Lys Ser  Ser Lys Thr
    1460                1465                1470

Ile His  Ser Leu Ile Pro Met  Gly Lys Ser Ala Ala  Lys Ser Pro
    1475                1480                1485

Val Asp  Ile Val Thr Gly Gly  Ile Ser Ser Val Arg  Asp Leu Asp
    1490                1495                1500

Arg Leu  Pro Ala Arg Thr Trp  Thr Leu Ile Gly Leu  Arg Ala Val
    1505                1510                1515

Val Phe  Arg Asp Ile Glu Asp  Ser Lys Gln Ala Gln  Phe Leu Ala
    1520                1525                1530

Leu Ala  Val Val Tyr Phe Ile  Ser Val Leu Met Val  Ser Lys Tyr
    1535                1540                1545

Arg Asp  Ile Leu Glu Pro Gln  Asp Glu Arg His Ser  Gln Ser Leu
    1550                1555                1560

Lys Glu  Thr Ser Ser Asp Asn  Gly Asn Ala Ser Leu  Pro Asp Ala
    1565                1570                1575

Glu Asn  Thr Pro Ala Glu Phe  Ser Ser Leu Thr Leu  Ser Ser Val
    1580                1585                1590

Glu Glu  Ser Leu Glu Gly Thr  Ser Cys Thr Arg Arg  Arg Asp Ser
    1595                1600                1605

Gly Leu  Gly Glu Glu Thr Ala  Ser Gly Leu Gly Ser  Gly Leu Val
    1610                1615                1620

Ser Ala  Ser Pro Ala Ala Pro  Leu Gly Val Ser Ala  Gly Pro Asp
    1625                1630                1635

Ala Ile  Ser Glu Val Leu Cys  Thr Leu Ser Leu Glu  Val Asn Lys
    1640                1645                1650

Ser Gln  Glu Thr Arg Ile Asp  Gly Gly Asn Glu Leu  Asp Arg Lys
    1655                1660                1665

Val Thr  Pro Ser Val Pro Val  Ser Lys Asn Val Asn  Val Lys Asp
    1670                1675                1680

Ile Leu  Arg Ser Leu Val Asn  Met Pro Ala Asp Gly  Val Thr Val
    1685                1690                1695

Asp Pro  Ala Leu Leu Pro Pro  Ala Cys Leu Gly Ala  Leu Gly Asp
    1700                1705                1710

Leu Ser  Val Asp Pro Pro Met  Gln Phe Arg Ser Phe  Asp Arg Ser
    1715                1720                1725

Val Ile  Ile Ala Thr Lys Lys  Ser Ser Val Leu Pro  Ser Ala Leu
    1730                1735                1740

Thr Thr  Ser Ala Pro Ser Ser  Ala Val Ser Val Val  Ser Ser Val
    1745                1750                1755
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Asp Pro  Thr His Ala Ser Asp  Thr Gly Gly Glu Ser  Pro Gly Ser
    1760                 1765                 1770

Arg Ser  Pro Lys Cys Lys Thr  Ala Leu Ser Cys Lys  Gln Leu Ala
    1775                 1780                 1785

Pro Ser  His Lys Thr Pro Ala  Ala His Met Ser Ile  Thr Glu Arg
    1790                 1795                 1800

Leu Glu  His Ala Leu Glu Lys  Ala Ala Pro Leu Leu  Arg Glu Ile
    1805                 1810                 1815

Phe Val  Asp Phe Ala Pro Phe  Leu Ser Arg Thr Leu  Leu Gly Ser
    1820                 1825                 1830

His Gly  Gln Glu Leu Leu Ile  Glu Gly Thr Ser Leu  Val Cys Met
    1835                 1840                 1845

Lys Ser  Ser Ser Ser Val Val  Glu Leu Val Met Leu  Leu Cys Ser
    1850                 1855                 1860

Gln Glu  Trp Gln Asn Ser Ile  Gln Lys Asn Ala Gly  Leu Ala Phe
    1865                 1870                 1875

Ile Glu  Leu Val Asn Glu Gly  Arg Leu Leu Ser Gln  Thr Met Lys
    1880                 1885                 1890

Asp His  Leu Val Arg Val Ala  Asn Glu Ala Glu Phe  Ile Leu Ser
    1895                 1900                 1905

Arg Gln  Arg Ala Glu Asp Ile  His Arg His Ala Glu  Phe Glu Ser
    1910                 1915                 1920

Leu Cys  Ala Gln Tyr Ser Ala  Asp Lys Arg Glu Glu  Glu Lys Met
    1925                 1930                 1935

Cys Asp  His Leu Ile Arg Ala  Ala Lys Tyr Arg Asp  His Val Thr
    1940                 1945                 1950

Ala Thr  Gln Leu Ile Gln Lys  Ile Ile Asn Leu Leu  Thr Asp Lys
    1955                 1960                 1965

His Gly  Ala Trp Gly Ser Ser  Ala Val Ser Arg Pro  Arg Glu Phe
    1970                 1975                 1980

Trp Arg  Leu Asp Tyr Trp Glu  Asp Asp Leu Arg Arg  Arg Arg Arg
    1985                 1990                 1995

Phe Val  Arg Asn Pro Leu Gly  Ser Thr His Pro Glu  Ala Thr Leu
    2000                 2005                 2010

Lys Thr  Ala Val Glu His Ala  Ala Asp Glu Asp Ile  Leu Ala Lys
    2015                 2020                 2025

Gly Lys  Gln Ser Ile Lys Ser  Gln Ala Leu Gly Asn  Gln Asn Ser
    2030                 2035                 2040

Glu Asn  Glu Ala Leu Leu Glu  Gly Asp Asp Asp Thr  Leu Ser Ser
    2045                 2050                 2055

Val Asp  Glu Lys Asp Leu Glu  Asn Leu Ala Gly Pro  Val Ser Leu
    2060                 2065                 2070

Ser Thr  Pro Ala Gln Leu Val  Ala Pro Ser Val Val  Val Lys Gly
    2075                 2080                 2085

Thr Leu  Ser Val Thr Ser Ser  Glu Leu Tyr Phe Glu  Val Asp Glu
    2090                 2095                 2100

Glu Asp  Pro Asn Phe Lys Lys  Ile Asp Pro Lys Ile  Leu Ala Tyr
    2105                 2110                 2115

Thr Glu  Gly Leu His Gly Lys  Trp Leu Phe Thr Glu  Ile Arg Ser
    2120                 2125                 2130

Ile Phe  Ser Arg Arg Tyr Leu  Leu Gln Asn Thr Ala  Leu Glu Ile
    2135                 2140                 2145
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Phe Met  Ala Asn Arg Val Ala  Val Met Phe Asn Phe  Pro Asp Pro
    2150                 2155                 2160

Ala Thr  Val Lys Lys Val Val  Asn Tyr Leu Pro Arg  Val Gly Val
    2165                 2170                 2175

Gly Thr  Ser Phe Gly Leu Pro  Gln Thr Arg Arg Ile  Ser Leu Ala
    2180                 2185                 2190

Thr Pro  Arg Gln Leu Phe Lys  Ala Ser Asn Met Thr  Gln Arg Trp
    2195                 2200                 2205

Gln His  Arg Glu Ile Ser Asn  Phe Glu Tyr Leu Met  Phe Leu Asn
    2210                 2215                 2220

Thr Ile  Ala Gly Arg Ser Tyr  Asn Asp Leu Asn Gln  Tyr Pro Val
    2225                 2230                 2235

Phe Pro  Trp Val Ile Thr Asn  Tyr Glu Ser Glu Glu  Leu Asp Leu
    2240                 2245                 2250

Thr Leu  Pro Ser Asn Phe Arg  Asp Leu Ser Lys Pro  Ile Gly Ala
    2255                 2260                 2265

Leu Asn  Pro Lys Arg Ala Ala  Phe Phe Ala Glu Arg  Phe Glu Ser
    2270                 2275                 2280

Trp Glu  Asp Asp Gln Val Pro  Lys Phe His Tyr Gly  Thr His Tyr
    2285                 2290                 2295

Ser Thr  Ala Ser Phe Val Leu  Ala Trp Leu Leu Arg  Ile Glu Pro
    2300                 2305                 2310

Phe Thr  Thr Tyr Phe Leu Asn  Leu Gln Gly Gly Lys  Phe Asp His
    2315                 2320                 2325

Ala Asp  Arg Thr Phe Ser Ser  Val Ser Arg Ala Trp  Arg Asn Ser
    2330                 2335                 2340

Gln Arg  Asp Thr Ser Asp Ile  Lys Glu Leu Ile Pro  Glu Phe Tyr
    2345                 2350                 2355

Tyr Leu  Pro Glu Met Phe Val  Asn Phe Asn Asn Tyr  Asn Leu Gly
    2360                 2365                 2370

Val Met  Asp Asp Gly Thr Val  Val Ser Asp Val Glu  Leu Pro Pro
    2375                 2380                 2385

Trp Ala  Lys Thr Ser Glu Glu  Phe Val Arg Ile Asn  Arg Leu Ala
    2390                 2395                 2400

Leu Glu  Ser Glu Phe Val Ser  Cys Gln Leu His Gln  Trp Ile Asp
    2405                 2410                 2415

Leu Ile  Phe Gly Tyr Lys Gln  Gln Gly Pro Glu Ala  Val Arg Ala
    2420                 2425                 2430

Leu Asn  Val Phe Tyr Tyr Leu  Thr Tyr Glu Gly Ala  Val Asn Leu
    2435                 2440                 2445

Asn Ser  Ile Thr Asp Pro Val  Leu Arg Glu Ala Val  Glu Ala Gln
    2450                 2455                 2460

Ile Arg  Ser Phe Gly Gln Thr  Pro Ser Gln Leu Leu  Ile Glu Pro
    2465                 2470                 2475

His Pro  Pro Arg Gly Ser Ala  Met Gln Ala Ser Pro  Leu Met Phe
    2480                 2485                 2490

Thr Asp  Gln Ala Gln Gln Asp  Val Ile Met Val Leu  Lys Phe Pro
    2495                 2500                 2505

Ser Asn  Ser Pro Val Thr His  Val Ala Ala Asn Thr  Gln Pro Gly
    2510                 2515                 2520

Leu Ala  Met Pro Ala Val Ile  Thr Val Thr Ala Asn  Arg Leu Phe
    2525                 2530                 2535
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Ala Val  Asn Lys Trp His Asn  Leu Pro Ala His Gln  Gly Ala Val
    2540                2545                2550

Gln Asp  Gln Pro Tyr Gln Leu  Pro Val Glu Ile Asp  Pro Leu Ile
    2555                2560                2565

Gly Leu  Pro Leu Leu Ser Leu  Phe Ala Ile His
    2570                2575


<210> SEQ ID NO 7
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 7

Gly Leu Pro Leu Leu Ser Leu Phe Ala Ile His
1               5                   10


<210> SEQ ID NO 8
<211> LENGTH: 2863
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (1)..(72)
<223> OTHER INFORMATION: G peptide
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (82)..(393)
<223> OTHER INFORMATION: HSH (helix-sheet-helix) domain
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (979)..(1302)
<223> OTHER INFORMATION: SET Domain (Rich in Serine, Glutamic acid and
      Threonine)
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (2035)..(2169)
<223> OTHER INFORMATION: WDL (WD-like) domain
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (2212)..(2489)
<223> OTHER INFORMATION: BEACH domain
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (2592)..(2635)
<223> OTHER INFORMATION: WD repeat
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (2636)..(2694)
<223> OTHER INFORMATION: WD repeat
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (2695)..(2778)
<223> OTHER INFORMATION: WD repeat
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (2779)..(2819)
<223> OTHER INFORMATION: WD repeat
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (2820)..(2863)
<223> OTHER INFORMATION: WD repeat

<400> SEQUENCE: 8

Met Ala Ser Glu Asp Asn Arg Val Pro Ser Pro Pro Pro Thr Gly Asp
1               5                   10                  15

Asp Gly Gly Gly Gly Gly Arg Glu Glu Thr Pro Thr Glu Gly Gly Ala
            20                  25                  30

Leu Ser Leu Lys Pro Gly Leu Pro Ile Arg Gly Ile Arg Met Lys Phe
        35                  40                  45
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Ala Val Leu Thr Gly Leu Val Glu Val Gly Glu Val Ser Asn Arg Asp
    50                  55                  60

Ile Val Glu Thr Val Phe Asn Leu Leu Val Gly Gly Gln Phe Asp Leu
65                  70                  75                  80

Glu Met Asn Phe Ile Ile Gln Glu Gly Glu Ser Ile Asn Cys Met Val
                85                  90                  95

Asp Leu Leu Glu Lys Cys Asp Ile Thr Cys Gln Ala Glu Val Trp Ser
            100                 105                 110

Met Phe Thr Ala Ile Leu Lys Lys Ser Ile Arg Asn Leu Gln Val Cys
        115                 120                 125

Thr Glu Val Gly Leu Val Glu Lys Val Leu Gly Lys Ile Glu Lys Val
    130                 135                 140

Asp Asn Met Ile Ala Asp Leu Leu Val Asp Met Leu Gly Val Leu Ala
145                 150                 155                 160

Ser Tyr Asn Leu Thr Val Arg Glu Leu Lys Leu Phe Phe Ser Lys Leu
                165                 170                 175

Gln Gly Asp Lys Gly Arg Trp Pro Pro His Ala Gly Lys Leu Leu Ser
            180                 185                 190

Val Leu Lys His Met Pro Gln Lys Tyr Gly Pro Asp Ala Phe Phe Asn
        195                 200                 205

Phe Pro Gly Lys Ser Ala Ala Ala Ile Ala Leu Pro Pro Ile Ala Lys
    210                 215                 220

Trp Pro Tyr Gln Asn Gly Phe Thr Phe His Thr Trp Leu Arg Met Asp
225                 230                 235                 240

Pro Val Asn Asn Ile Asn Val Asp Lys Asp Lys Pro Tyr Leu Tyr Cys
                245                 250                 255

Phe Arg Thr Ser Lys Gly Leu Gly Tyr Ser Ala His Phe Val Gly Gly
            260                 265                 270

Cys Leu Ile Val Thr Ser Ile Lys Ser Lys Gly Lys Gly Phe Gln His
        275                 280                 285

Cys Val Lys Phe Asp Phe Lys Pro Gln Lys Trp Tyr Met Val Thr Ile
    290                 295                 300

Val His Ile Tyr Asn Arg Trp Lys Asn Ser Glu Leu Arg Cys Tyr Val
305                 310                 315                 320

Asn Gly Glu Leu Ala Ser Tyr Gly Glu Ile Thr Trp Phe Val Asn Thr
                325                 330                 335

Ser Asp Thr Phe Asp Lys Cys Phe Leu Gly Ser Ser Glu Thr Ala Asp
            340                 345                 350

Ala Asn Arg Val Phe Cys Gly Gln Met Thr Ala Val Tyr Leu Phe Ser
        355                 360                 365

Glu Ala Leu Asn Ala Ala Gln Ile Phe Ala Ile Tyr Gln Leu Gly Leu
    370                 375                 380

Gly Tyr Lys Gly Thr Phe Lys Phe Lys Ala Glu Ser Asp Leu Phe Leu
385                 390                 395                 400

Ala Glu His His Lys Leu Leu Leu Tyr Asp Gly Lys Leu Ser Ser Ala
                405                 410                 415

Ile Ala Phe Thr Tyr Asn Pro Arg Ala Thr Asp Ala Gln Leu Cys Leu
            420                 425                 430

Glu Ser Ser Pro Lys Asp Asn Pro Ser Ile Phe Val His Ser Pro His
        435                 440                 445

Ala Leu Met Leu Gln Asp Val Lys Ala Val Leu Thr His Ser Ile Gln
    450                 455                 460
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Ser Ala Met His Ser Ile Gly Gly Val Gln Val Leu Phe Pro Leu Phe
465                 470                 475                 480

Ala Gln Leu Asp Tyr Arg Gln Tyr Leu Ser Asp Glu Ile Asp Leu Thr
                485                 490                 495

Ile Cys Ser Thr Leu Leu Ala Phe Ile Met Glu Leu Leu Lys Asn Ser
            500                 505                 510

Ile Ala Met Gln Glu Gln Met Leu Ala Cys Lys Gly Phe Leu Val Ile
        515                 520                 525

Gly Tyr Ser Leu Glu Lys Ser Ser Lys Ser His Val Ser Arg Ala Val
    530                 535                 540

Leu Glu Leu Cys Leu Ala Phe Ser Lys Tyr Leu Ser Asn Leu Gln Asn
545                 550                 555                 560

Gly Met Pro Leu Leu Lys Gln Leu Cys Asp His Val Leu Leu Asn Pro
                565                 570                 575

Ala Ile Trp Ile His Thr Pro Ala Lys Val Gln Leu Met Leu Tyr Thr
            580                 585                 590

Tyr Leu Ser Thr Glu Phe Ile Gly Thr Val Asn Ile Tyr Asn Thr Ile
        595                 600                 605

Arg Arg Val Gly Thr Val Leu Leu Ile Met His Thr Leu Lys Tyr Tyr
    610                 615                 620

Tyr Trp Ala Val Asn Pro Gln Asp Arg Ser Gly Ile Thr Pro Lys Gly
625                 630                 635                 640

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

Phe Leu Leu Met Phe Ile Lys Gln Leu Val Met Lys Asp Ser Gly Val
            660                 665                 670

Lys Glu Asp Glu Leu Gln Ala Ile Leu Asn Tyr Leu Leu Thr Met His
        675                 680                 685

Glu Asp Asp Asn Leu Met Asp Val Leu Gln Leu Leu Val Ala Leu Met
    690                 695                 700

Ser Glu His Pro Asn Ser Met Ile Pro Ala Phe Asp Gln Arg Asn Gly
705                 710                 715                 720

Leu Arg Val Ile Tyr Lys Leu Leu Ala Ser Lys Ser Glu Gly Ile Arg
                725                 730                 735

Val Gln Ala Leu Lys Ala Met Gly Tyr Phe Leu Lys His Arg Pro Pro
            740                 745                 750

Lys Arg Lys Ala Glu Val Met Leu Gly His Gly Leu Phe Ser Leu Leu
        755                 760                 765

Ala Glu Arg Leu Met Leu Gln Thr Asn Leu Ile Thr Met Thr Thr Tyr
    770                 775                 780

Asn Val Leu Phe Glu Ile Leu Ile Glu Gln Ile Gly Thr Gln Val Ile
785                 790                 795                 800

His Lys Gln His Pro Asp Pro Asp Ser Ser Val Lys Ile Gln Asn Pro
                805                 810                 815

Gln Ile Leu Lys Val Ile Ala Thr Leu Leu Arg Asn Ser Pro Gln Cys
            820                 825                 830

Pro Glu Ser Met Glu Val Arg Arg Ala Phe Leu Ser Asp Met Ile Lys
        835                 840                 845

Leu Phe Asn Asn Ser Arg Glu Asn Arg Arg Ser Leu Leu Gln Cys Ser
    850                 855                 860

Val Trp Gln Glu Trp Met Leu Ser Leu Cys Tyr Phe Asn Pro Lys Asn
865                 870                 875                 880
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Ser Asp Glu Gln Lys Ile Thr Glu Met Val Tyr Ala Ile Phe Arg Ile
               885                 890                 895

Leu Leu Tyr His Ala Val Lys Tyr Glu Trp Gly Gly Trp Arg Val Trp
           900                 905                 910

Val Asp Thr Leu Ser Ile Thr His Ser Lys Val Thr Phe Glu Ile His
        915                 920                 925

Lys Glu Asn Leu Ala Asn Ile Phe Arg Glu Gln Gln Gly Lys Val Asp
    930                 935                 940

Glu Glu Ile Gly Leu Cys Ser Ser Thr Ser Val Gln Ala Ala Ser Gly
945                 950                 955                 960

Ile Arg Arg Asp Ile Asn Val Ser Val Gly Ser Gln Gln Pro Asp Thr
               965                 970                 975

Lys Asp Ser Pro Val Cys Pro His Phe Thr Thr Asn Gly Asn Glu Asn
           980                 985                 990

Ser Ser Ile Glu Lys Thr Ser Ser  Leu Glu Ser Ala Ser  Asn Ile Glu
        995                 1000                1005

Leu Gln  Thr Thr Asn Thr Ser  Tyr Glu Glu Met Lys  Ala Glu Gln
    1010                1015                1020

Glu Asn  Gln Glu Leu Pro Asp  Glu Gly Thr Leu Glu  Glu Thr Leu
    1025                1030                1035

Thr Asn  Glu Thr Arg Asn Ala  Asp Asp Leu Glu Val  Ser Ser Asp
    1040                1045                1050

Ile Ile  Glu Ala Val Ala Ile  Ser Ser Asn Ser Phe  Ile Thr Thr
    1055                1060                1065

Gly Lys  Asp Ser Met Thr Val  Ser Glu Val Thr Ala  Ser Ile Ser
    1070                1075                1080

Ser Pro  Ser Glu Glu Asp Ala  Ser Glu Met Pro Glu  Phe Leu Asp
    1085                1090                1095

Lys Ser  Ile Val Glu Glu Glu  Glu Asp Asp Asp Tyr  Val Glu Leu
    1100                1105                1110

Lys Val  Glu Gly Ser Pro Thr  Glu Glu Ala Asn Leu  Pro Thr Glu
    1115                1120                1125

Leu Gln  Asp Asn Ser Leu Ser  Pro Ala Ala Ser Glu  Ala Gly Glu
    1130                1135                1140

Lys Leu  Asp Met Phe Gly Asn  Asp Asp Lys Leu Ile  Phe Gln Glu
    1145                1150                1155

Gly Lys  Pro Val Thr Glu Lys  Gln Thr Asp Thr Glu  Thr Gln Asp
    1160                1165                1170

Ser Lys  Asp Ser Gly Ile Gln  Thr Met Thr Ala Ser  Gly Ser Ser
    1175                1180                1185

Ala Met  Ser Pro Glu Thr Thr  Val Ser Gln Ile Ala  Val Glu Ser
    1190                1195                1200

Asp Leu  Gly Gln Met Leu Glu  Glu Gly Lys Lys Ala  Thr Asn Leu
    1205                1210                1215

Thr Arg  Glu Thr Lys Leu Ile  Asn Asp Cys His Gly  Ser Val Ser
    1220                1225                1230

Glu Ala  Ser Ser Glu Gln Lys  Ile Ala Lys Leu Asp  Val Ser Asn
    1235                1240                1245

Val Ala  Thr Asp Thr Glu Arg  Leu Glu Leu Lys Ala  Ser Pro Asn
    1250                1255                1260

Val Glu  Ala Pro Gln Pro His  Arg His Val Leu Glu  Ile Ser Arg
    1265                1270                1275
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Gln His  Glu Gln Pro Gly Gln  Gly Ile Ala Pro Asp  Ala Val Asn
    1280                 1285                 1290

Gly Gln  Arg Arg Asp Ser Arg  Ser Thr Val Phe Arg  Ile Pro Glu
    1295                 1300                 1305

Phe Asn  Trp Ser Gln Met His  Gln Arg Leu Leu Thr  Asp Leu Leu
    1310                 1315                 1320

Phe Ser  Ile Glu Thr Asp Ile  Gln Met Trp Arg Ser  His Ser Thr
    1325                 1330                 1335

Lys Thr  Val Met Asp Phe Val  Asn Ser Ser Asp Asn  Val Ile Phe
    1340                 1345                 1350

Val His  Asn Thr Ile His Leu  Ile Ser Gln Val Met  Asp Asn Met
    1355                 1360                 1365

Val Met  Ala Cys Gly Gly Ile  Leu Pro Leu Leu Ser  Ala Ala Thr
    1370                 1375                 1380

Ser Ala  Thr His Glu Leu Glu  Asn Ile Glu Pro Thr  Gln Gly Leu
    1385                 1390                 1395

Ser Ile  Glu Ala Ser Val Thr  Phe Leu Gln Arg Leu  Ile Ser Leu
    1400                 1405                 1410

Val Asp  Val Leu Ile Phe Ala  Ser Ser Leu Gly Phe  Thr Glu Ile
    1415                 1420                 1425

Glu Ala  Glu Lys Ser Met Ser  Ser Gly Gly Ile Leu  Arg Gln Cys
    1430                 1435                 1440

Leu Arg  Leu Val Cys Ala Val  Ala Val Arg Asn Cys  Leu Glu Cys
    1445                 1450                 1455

Gln Gln  His Ser Gln Leu Lys  Thr Arg Gly Asp Lys  Ala Leu Lys
    1460                 1465                 1470

Pro Met  His Ser Leu Ile Pro  Leu Gly Lys Ser Ala  Ala Lys Ser
    1475                 1480                 1485

Pro Val  Asp Ile Val Thr Gly  Gly Ile Ser Pro Val  Arg Asp Leu
    1490                 1495                 1500

Asp Arg  Leu Leu Gln Asp Met  Asp Ile Asn Arg Leu  Arg Ala Val
    1505                 1510                 1515

Val Phe  Arg Asp Ile Glu Asp  Ser Lys Gln Ala Gln  Phe Leu Ala
    1520                 1525                 1530

Leu Ala  Val Val Tyr Phe Ile  Ser Val Leu Met Val  Ser Lys Tyr
    1535                 1540                 1545

Arg Asp  Ile Leu Glu Pro Gln  Asn Glu Arg His Ser  Gln Ser Cys
    1550                 1555                 1560

Thr Glu  Thr Gly Ser Glu Asn  Glu Asn Val Ser Leu  Ser Glu Ile
    1565                 1570                 1575

Thr Pro  Ala Ala Phe Ser Thr  Leu Thr Thr Ala Ser  Val Glu Glu
    1580                 1585                 1590

Ser Glu  Ser Thr Ser Ser Ala  Arg Arg Arg Asp Ser  Gly Ile Gly
    1595                 1600                 1605

Glu Glu  Thr Ala Thr Gly Leu  Gly Ser His Val Glu  Val Thr Pro
    1610                 1615                 1620

His Thr  Ala Pro Pro Gly Val  Ser Ala Gly Pro Asp  Ala Ile Ser
    1625                 1630                 1635

Glu Val  Leu Ser Thr Leu Ser  Leu Glu Val Asn Lys  Ser Pro Glu
    1640                 1645                 1650

Thr Lys  Asn Asp Arg Gly Asn  Asp Leu Asp Thr Lys  Ala Thr Pro
    1655                 1660                 1665
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Ser Val  Ser Val Ser Lys Asn  Val Asn Val Lys Asp  Ile Leu Arg
    1670                 1675                 1680

Ser Leu  Val Asn Ile Pro Ala  Asp Gly Val Thr Val  Asp Pro Ala
    1685                 1690                 1695

Leu Leu  Pro Pro Ala Cys Leu  Gly Ala Leu Gly Asp  Leu Ser Val
    1700                 1705                 1710

Glu Gln  Pro Val Gln Phe Arg  Ser Phe Asp Arg Ser  Val Ile Val
    1715                 1720                 1725

Ala Ala  Lys Lys Ser Ala Val  Ser Pro Ser Thr Phe  Asn Thr Ser
    1730                 1735                 1740

Ile Pro  Thr Asn Ala Val Ser  Val Val Ser Ser Val  Asp Ser Ala
    1745                 1750                 1755

Gln Ala  Ser Asp Met Gly Gly  Glu Ser Pro Gly Ser  Arg Ser Ser
    1760                 1765                 1770

Asn Ala  Lys Leu Pro Ser Val  Pro Thr Val Asp Ser  Val Ser Gln
    1775                 1780                 1785

Asp Pro  Val Ser Asn Met Ser  Ile Thr Glu Arg Leu  Glu His Ala
    1790                 1795                 1800

Leu Glu  Lys Ala Ala Pro Leu  Leu Arg Glu Ile Phe  Val Asp Phe
    1805                 1810                 1815

Ala Pro  Phe Leu Ser Arg Thr  Leu Leu Gly Ser His  Gly Gln Glu
    1820                 1825                 1830

Leu Leu  Ile Glu Gly Thr Ser  Leu Val Cys Met Lys  Ser Ser Ser
    1835                 1840                 1845

Ser Val  Val Glu Leu Val Met  Leu Leu Cys Ser Gln  Glu Trp Gln
    1850                 1855                 1860

Asn Ser  Ile Gln Lys Asn Ala  Gly Leu Ala Phe Ile  Glu Leu Val
    1865                 1870                 1875

Asn Glu  Gly Arg Leu Leu Ser  Gln Thr Met Lys Asp  His Leu Val
    1880                 1885                 1890

Arg Val  Ala Asn Glu Ala Glu  Phe Ile Leu Ser Arg  Gln Arg Ala
    1895                 1900                 1905

Glu Asp  Ile His Arg His Ala  Glu Phe Glu Ser Leu  Cys Ala Gln
    1910                 1915                 1920

Tyr Ser  Ala Asp Lys Arg Glu  Asp Glu Lys Met Cys  Asp His Leu
    1925                 1930                 1935

Ile Arg  Ala Ala Lys Tyr Arg  Asp His Val Thr Ala  Thr Gln Leu
    1940                 1945                 1950

Ile Gln  Lys Ile Ile Asn Ile  Leu Thr Asp Lys His  Gly Ala Trp
    1955                 1960                 1965

Gly Asn  Ser Ala Val Ser Arg  Pro Leu Glu Phe Trp  Arg Leu Asp
    1970                 1975                 1980

Tyr Trp  Glu Asp Asp Leu Arg  Arg Arg Arg Arg Phe  Val Arg Asn
    1985                 1990                 1995

Pro Leu  Gly Ser Thr His Pro  Glu Ala Thr Leu Lys  Thr Ala Val
    2000                 2005                 2010

Glu His  Val Cys Ile Phe Lys  Leu Arg Glu Asn Ser  Lys Ala Thr
    2015                 2020                 2025

Asp Glu  Asp Ile Leu Ala Lys  Gly Lys Gln Ser Ile  Arg Ser Gln
    2030                 2035                 2040

Ala Leu  Gly Asn Gln Asn Ser  Glu Asn Glu Ile Leu  Leu Glu Gly
    2045                 2050                 2055
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Asp Asp  Asp Thr Leu Ser Ser  Val Asp Glu Lys Asp  Leu Glu Asn
    2060                 2065                 2070

Leu Ala  Gly Pro Val Ser Leu  Ser Thr Pro Ala Gln  Leu Val Ala
    2075                 2080                 2085

Pro Ser  Val Val Val Lys Gly  Thr Leu Ser Val Thr  Ser Ser Glu
    2090                 2095                 2100

Leu Tyr  Phe Glu Val Asp Glu  Glu Asp Pro Asn Phe  Lys Lys Ile
    2105                 2110                 2115

Asp Pro  Lys Ile Leu Ala Tyr  Thr Glu Gly Leu His  Gly Lys Trp
    2120                 2125                 2130

Leu Phe  Thr Glu Ile Arg Ser  Ile Phe Ser Arg Arg  Tyr Leu Leu
    2135                 2140                 2145

Gln Asn  Thr Ala Leu Glu Ile  Phe Met Ala Asn Arg  Val Ala Val
    2150                 2155                 2160

Met Phe  Asn Phe Pro Asp Pro  Ala Thr Val Lys Lys  Val Val Asn
    2165                 2170                 2175

Phe Leu  Pro Arg Val Gly Val  Gly Thr Ser Phe Gly  Leu Pro Gln
    2180                 2185                 2190

Thr Arg  Arg Ile Ser Leu Ala  Ser Pro Arg Gln Leu  Phe Lys Ala
    2195                 2200                 2205

Ser Asn  Met Thr Gln Arg Trp  Gln His Arg Glu Ile  Ser Asn Phe
    2210                 2215                 2220

Glu Tyr  Leu Met Phe Leu Asn  Thr Ile Ala Gly Arg  Ser Tyr Asn
    2225                 2230                 2235

Asp Leu  Asn Gln Tyr Pro Val  Phe Pro Trp Val Ile  Thr Asn Tyr
    2240                 2245                 2250

Glu Ser  Glu Glu Leu Asp Leu  Thr Leu Pro Thr Asn  Phe Arg Asp
    2255                 2260                 2265

Leu Ser  Lys Pro Ile Gly Ala  Leu Asn Pro Lys Arg  Ala Ala Phe
    2270                 2275                 2280

Phe Ala  Glu Arg Tyr Glu Ser  Trp Glu Asp Asp Gln  Val Pro Lys
    2285                 2290                 2295

Phe His  Tyr Gly Thr His Tyr  Ser Thr Ala Ser Phe  Val Leu Ala
    2300                 2305                 2310

Trp Leu  Leu Arg Ile Glu Pro  Phe Thr Thr Tyr Phe  Leu Asn Leu
    2315                 2320                 2325

Gln Gly  Gly Lys Phe Asp His  Ala Asp Arg Thr Phe  Ser Ser Ile
    2330                 2335                 2340

Ser Arg  Ala Trp Arg Asn Ser  Gln Arg Asp Thr Ser  Asp Ile Lys
    2345                 2350                 2355

Glu Leu  Ile Pro Glu Phe Tyr  Tyr Leu Pro Glu Met  Phe Val Asn
    2360                 2365                 2370

Phe Asn  Asn Tyr Asn Leu Gly  Val Met Asp Asp Gly  Thr Val Val
    2375                 2380                 2385

Ser Asp  Val Glu Leu Pro Pro  Trp Ala Lys Thr Ser  Glu Glu Phe
    2390                 2395                 2400

Val His  Ile Asn Arg Leu Ala  Leu Glu Ser Glu Phe  Val Ser Cys
    2405                 2410                 2415

Gln Leu  His Gln Trp Ile Asp  Leu Ile Phe Gly Tyr  Lys Gln Gln
    2420                 2425                 2430

Gly Pro  Glu Ala Val Arg Ala  Leu Asn Val Phe Tyr  Tyr Leu Thr
    2435                 2440                 2445
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Tyr Glu  Gly Ala Val Asn Leu  Asn Ser Ile Thr Asp  Pro Val Leu
    2450                 2455                 2460

Arg Glu  Ala Val Glu Ala Gln  Ile Arg Ser Phe Gly  Gln Thr Pro
    2465                 2470                 2475

Ser Gln  Leu Leu Ile Glu Pro  His Pro Pro Arg Gly  Ser Ala Met
    2480                 2485                 2490

Gln Val  Ser Pro Leu Met Phe  Thr Asp Lys Ala Gln  Gln Asp Val
    2495                 2500                 2505

Ile Met  Val Leu Lys Phe Pro  Ser Asn Ser Pro Val  Thr His Val
    2510                 2515                 2520

Ala Ala  Asn Thr Gln Pro Gly  Leu Ala Thr Pro Ala  Val Ile Thr
    2525                 2530                 2535

Val Thr  Ala Asn Arg Leu Phe  Ala Val Asn Lys Trp  His Asn Leu
    2540                 2545                 2550

Pro Ala  His Gln Gly Ala Val  Gln Asp Gln Pro Tyr  Gln Leu Pro
    2555                 2560                 2565

Val Glu  Ile Asp Pro Leu Ile  Ala Ser Asn Thr Gly  Met His Arg
    2570                 2575                 2580

Arg Gln  Ile Thr Asp Leu Leu  Asp Gln Ser Ile Gln  Val His Ser
    2585                 2590                 2595

Gln Cys  Phe Val Ile Thr Ser  Asp Asn Arg Tyr Ile  Leu Val Cys
    2600                 2605                 2610

Gly Phe  Trp Asp Lys Ser Phe  Arg Val Tyr Ser Thr  Asp Thr Gly
    2615                 2620                 2625

Arg Leu  Ile Gln Val Val Phe  Gly His Trp Asp Val  Val Thr Cys
    2630                 2635                 2640

Leu Ala  Arg Ser Glu Ser Tyr  Ile Gly Gly Asn Cys  Tyr Ile Leu
    2645                 2650                 2655

Ser Gly  Ser Arg Asp Ala Thr  Leu Leu Leu Trp Tyr  Trp Asn Gly
    2660                 2665                 2670

Lys Cys  Ser Gly Ile Gly Asp  Asn Pro Gly Ser Glu  Thr Ala Ala
    2675                 2680                 2685

Pro Arg  Ala Ile Leu Thr Gly  His Asp Tyr Glu Val  Thr Cys Ala
    2690                 2695                 2700

Ala Val  Cys Ala Glu Leu Gly  Leu Val Leu Ser Gly  Ser Gln Glu
    2705                 2710                 2715

Gly Pro  Cys Leu Ile His Ser  Met Asn Gly Asp Leu  Leu Arg Thr
    2720                 2725                 2730

Leu Glu  Gly Pro Glu Asn Cys  Leu Lys Pro Lys Leu  Ile Gln Ala
    2735                 2740                 2745

Ser Arg  Glu Gly His Cys Val  Ile Phe Tyr Glu Asn  Gly Leu Phe
    2750                 2755                 2760

Cys Thr  Phe Ser Val Asn Gly  Lys Leu Gln Ala Thr  Met Glu Thr
    2765                 2770                 2775

Asp Asp  Asn Ile Arg Ala Ile  Gln Leu Ser Arg Asp  Gly Gln Tyr
    2780                 2785                 2790

Leu Leu  Thr Gly Gly Asp Arg  Gly Val Val Val Val  Arg Gln Val
    2795                 2800                 2805

Ser Asp  Leu Lys Gln Leu Phe  Ala Tyr Pro Gly Cys  Asp Ala Gly
    2810                 2815                 2820

Ile Arg  Ala Met Ala Leu Ser  Tyr Asp Gln Arg Cys  Ile Ile Ser
    2825                 2830                 2835
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Gly Met  Ala Ser Gly Ser Ile  Val Leu Phe Tyr Asn  Asp Phe Asn
    2840                2845                2850

Arg Trp  His His Glu Tyr Gln  Thr Arg Tyr
    2855                2860


<210> SEQ ID NO 9
<211> LENGTH: 69
<212> TYPE: PRT
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: BINDING
<222> LOCATION: (1)..(21)
<223> OTHER INFORMATION: Putative Protein Kinase A RII binding site
<220> FEATURE:
<221> NAME/KEY: BINDING
<222> LOCATION: (50)..(69)
<223> OTHER INFORMATION: Putative Protein Kinase A RII binding site

<400> SEQUENCE: 9

Phe Val His Asn Thr Ile His Leu Ile Ser Gln Val Met Asp Asn Met
1               5                   10                  15

Val Met Ala Cys Gly Gly Ile Leu Pro Leu Leu Ser Ala Ala Thr Ser
            20                  25                  30

Ala Thr His Glu Leu Glu Asn Ile Glu Pro Thr Gln Gly Leu Ser Ile
        35                  40                  45

Glu Ala Ser Val Thr Phe Leu Gln Arg Leu Ile Ser Leu Val Asp Val
    50                  55                  60

Leu Ile Phe Ala Ser
65


<210> SEQ ID NO 10
<211> LENGTH: 69
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: BINDING
<222> LOCATION: (1)..(21)
<223> OTHER INFORMATION: Putative Protein Kinase A RII binding site
<220> FEATURE:
<221> NAME/KEY: BINDING
<222> LOCATION: (50)..(69)
<223> OTHER INFORMATION: Putative Protein Kinase A RII binding site

<400> SEQUENCE: 10

Phe Val His Asn Thr Ile His Leu Ile Ser Gln Val Met Asp Asn Met
1               5                   10                  15

Val Met Ala Cys Gly Gly Ile Leu Pro Leu Leu Ser Ala Ala Thr Ser
            20                  25                  30

Ala Thr His Glu Leu Glu Asn Ile Glu Pro Thr Gln Gly Leu Ser Ile
        35                  40                  45

Glu Ala Ser Val Thr Phe Leu Gln Arg Leu Ile Ser Leu Val Asp Val
    50                  55                  60

Leu Ile Phe Ala Ser
65


<210> SEQ ID NO 11
<211> LENGTH: 76
<212> TYPE: PRT
<213> ORGANISM: Drosophila melanogaster
<220> FEATURE:
<221> NAME/KEY: BINDING
<222> LOCATION: (1)..(21)
<223> OTHER INFORMATION: Putative Protein Kinase A RII binding site
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<220> FEATURE:
<221> NAME/KEY: BINDING
<222> LOCATION: (57)..(76)
<223> OTHER INFORMATION: Putative Protein Kinase A RII binding site

<400> SEQUENCE: 11

Val Ala Leu Ala Val Arg Asp Ile Val Glu Gln Leu Ile Asp Lys Val
1 5 10 15

Ile Asp Ala Thr Glu Ala Glu Ser Ala Ser Glu Thr Lys Thr Glu Thr
20 25 30

Asn Asn Asn Glu Ile Pro Lys Lys Glu Lys Gln Thr Ser Glu Glu Pro
35 40 45

Glu Asp Val Glu Thr Ala Glu Thr Leu Ala Ala Ala Ala Lys Glu Ile
50 55 60

Val Gln Glu Val Val Glu Ala Ala Leu Val Val Val
65 70 75

<210> SEQ ID NO 12
<211> LENGTH: 69
<212> TYPE: PRT
<213> ORGANISM: Drosophila melanogaster
<220> FEATURE:
<221> NAME/KEY: BINDING
<222> LOCATION: (1)..(21)
<223> OTHER INFORMATION: Putative Protein Kinase A RII binding site
<220> FEATURE:
<221> NAME/KEY: BINDING
<222> LOCATION: (50)..(69)
<223> OTHER INFORMATION: Putative Protein Kinase A RII binding site

<400> SEQUENCE: 12

Phe Val Val Asn Thr Val His Leu Ile Ser Gln Leu Ala Asp Asn Leu
1 5 10 15

Ile Ile Ala Cys Gly Gly Leu Leu Pro Leu Leu Ala Ser Ala Thr Ser
20 25 30

Pro Asn Ser Glu Leu Asp Val Leu Glu Pro Thr Gln Gly Met Pro Leu
35 40 45

Glu Val Ala Val Ser Phe Leu Gln Arg Leu Val Asn Met Ala Asp Val
50 55 60

Leu Ile Phe Ala Thr
65

<210> SEQ ID NO 13
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Caenorhabditis elegans
<220> FEATURE:
<221> NAME/KEY: BINDING
<222> LOCATION: (1)..(21)
<223> OTHER INFORMATION: Putative Protein Kinase A RII binding site
<220> FEATURE:
<221> NAME/KEY: BINDING
<222> LOCATION: (51)..(70)
<223> OTHER INFORMATION: Putative Protein Kinase A RII binding site

<400> SEQUENCE: 13

Phe Val Gly Asn Val Val His Val Val Ser Gln Leu Ser Asp Ser Leu
1 5 10 15

Ile Met Ala Cys Gly Gly Leu Leu Pro Leu Leu Ala Ser Ala Thr Ala
20 25 30

Pro Asn Asn Asp Met Glu Ile Val Asp Pro Cys Gln Gln Gln Leu Pro
35 40 45

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Ile Ser Val Ser Ala Gly Phe Leu Met Arg Phe Ala Arg Leu Val Asp
    50                  55                  60

Thr Phe Val Leu Ala Ser
65                  70


<210> SEQ ID NO 14
<211> LENGTH: 972
<212> TYPE: PRT
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (144)..(187)
<223> OTHER INFORMATION: WDL (WD-like) repeat
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (188)..(237)
<223> OTHER INFORMATION: WDL (WD-like) repeat
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (238)..(278)
<223> OTHER INFORMATION: WDL (WD-like) repeat
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (308)..(599)
<223> OTHER INFORMATION: BEACH domain
<220> FEATURE:
<221> NAME/KEY: SITE
<222> LOCATION: (345)..(352)
<223> OTHER INFORMATION: Tyrosine kinase recognition site
<220> FEATURE:
<221> NAME/KEY: BINDING
<222> LOCATION: (353)..(356)
<223> OTHER INFORMATION: SH3 binding site
<220> FEATURE:
<221> NAME/KEY: BINDING
<222> LOCATION: (411)..(414)
<223> OTHER INFORMATION: SH2 binding site
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (702)..(744)
<223> OTHER INFORMATION: WD repeat
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (745)..(803)
<223> OTHER INFORMATION: WD repeat
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (804)..(886)
<223> OTHER INFORMATION: WD repeat
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (887)..(928)
<223> OTHER INFORMATION: WD repeat
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (929)..(972)
<223> OTHER INFORMATION: WD repeat

<400> SEQUENCE: 14

Gly Arg Leu Leu Ser Gln Thr Met Lys Asp His Leu Val Arg Val Ala
1               5                   10                  15

Asn Glu Ala Glu Phe Ile Leu Ser Arg Gln Arg Ala Glu Asp Ile His
            20                  25                  30

Arg His Ala Glu Phe Glu Ser Leu Cys Ala Gln Tyr Ser Ala Asp Lys
        35                  40                  45

Arg Glu Glu Glu Lys Met Cys Asp His Leu Ile Arg Ala Ala Lys Tyr
    50                  55                  60

Arg Asp His Val Thr Ala Thr Gln Leu Ile Gln Lys Ile Ile Asn Leu
65                  70                  75                  80

Leu Thr Asp Lys His Gly Ala Trp Gly Ser Ser Ala Val Ser Arg Pro
                85                  90                  95
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Arg Glu Phe Trp Arg Leu Asp Tyr Trp Glu Asp Asp Leu Arg Arg Arg
            100                 105                 110

Arg Arg Phe Val Arg Asn Pro Leu Gly Ser Thr His Pro Glu Ala Thr
        115                 120                 125

Leu Lys Thr Ala Val Glu His Ala Ala Asp Glu Asp Ile Leu Ala Lys
    130                 135                 140

Gly Lys Gln Ser Ile Lys Ser Gln Ala Leu Gly Asn Gln Asn Ser Glu
145                 150                 155                 160

Asn Glu Ala Leu Leu Glu Gly Asp Asp Asp Thr Leu Ser Ser Val Asp
                165                 170                 175

Glu Lys Asp Leu Glu Asn Leu Ala Gly Pro Val Ser Leu Ser Thr Pro
            180                 185                 190

Ala Gln Leu Val Ala Pro Ser Val Val Val Lys Gly Thr Leu Ser Val
        195                 200                 205

Thr Ser Ser Glu Leu Tyr Phe Glu Val Asp Glu Glu Asp Pro Asn Phe
    210                 215                 220

Lys Lys Ile Asp Pro Lys Ile Leu Ala Tyr Thr Glu Gly Leu His Gly
225                 230                 235                 240

Lys Trp Leu Phe Thr Glu Ile Arg Ser Ile Phe Ser Arg Arg Tyr Leu
                245                 250                 255

Leu Gln Asn Thr Ala Leu Glu Ile Phe Met Ala Asn Arg Val Ala Val
            260                 265                 270

Met Phe Asn Phe Pro Asp Pro Ala Thr Val Lys Lys Val Val Asn Tyr
        275                 280                 285

Leu Pro Arg Val Gly Val Gly Thr Ser Phe Gly Leu Pro Gln Thr Arg
    290                 295                 300

Arg Ile Ser Leu Ala Thr Pro Arg Gln Leu Phe Lys Ala Ser Asn Met
305                 310                 315                 320

Thr Gln Arg Trp Gln His Arg Glu Ile Ser Asn Phe Glu Tyr Leu Met
                325                 330                 335

Phe Leu Asn Thr Ile Ala Gly Arg Ser Tyr Asn Asp Leu Asn Gln Tyr
            340                 345                 350

Pro Val Phe Pro Trp Val Ile Thr Asn Tyr Glu Ser Glu Glu Leu Asp
        355                 360                 365

Leu Thr Leu Pro Ser Asn Phe Arg Asp Leu Ser Lys Pro Ile Gly Ala
    370                 375                 380

Leu Asn Pro Lys Arg Ala Ala Phe Phe Ala Glu Arg Phe Glu Ser Trp
385                 390                 395                 400

Glu Asp Asp Gln Val Pro Lys Phe His Tyr Gly Thr His Tyr Ser Thr
                405                 410                 415

Ala Ser Phe Val Leu Ala Trp Leu Leu Arg Ile Glu Pro Phe Thr Thr
            420                 425                 430

Tyr Phe Leu Asn Leu Gln Gly Gly Lys Phe Asp His Ala Asp Arg Thr
        435                 440                 445

Phe Ser Ser Val Ser Arg Ala Trp Arg Asn Ser Gln Arg Asp Thr Ser
    450                 455                 460

Asp Ile Lys Glu Leu Ile Pro Glu Phe Tyr Tyr Leu Pro Glu Met Phe
465                 470                 475                 480

Val Asn Phe Asn Asn Tyr Asn Leu Gly Val Met Asp Asp Gly Thr Val
                485                 490                 495

Val Ser Asp Val Glu Leu Pro Pro Trp Ala Lys Thr Ser Glu Glu Phe
            500                 505                 510
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Val Arg Ile Asn Arg Leu Ala Leu Glu Ser Glu Phe Val Ser Cys Gln
        515                 520                 525

Leu His Gln Trp Ile Asp Leu Ile Phe Gly Tyr Lys Gln Gln Gly Pro
    530                 535                 540

Glu Ala Val Arg Ala Leu Asn Val Phe Tyr Tyr Leu Thr Tyr Glu Gly
545                 550                 555                 560

Ala Val Asn Leu Asn Ser Ile Thr Asp Pro Val Leu Arg Glu Ala Val
                565                 570                 575

Glu Ala Gln Ile Arg Ser Phe Gly Gln Thr Pro Ser Gln Leu Leu Ile
            580                 585                 590

Glu Pro His Pro Pro Arg Gly Ser Ala Met Gln Ala Ser Pro Leu Met
        595                 600                 605

Phe Thr Asp Gln Ala Gln Gln Asp Val Ile Met Val Leu Lys Phe Pro
    610                 615                 620

Ser Asn Ser Pro Val Thr His Val Ala Ala Asn Thr Gln Pro Gly Leu
625                 630                 635                 640

Ala Met Pro Ala Val Ile Thr Val Thr Ala Asn Arg Leu Phe Ala Val
                645                 650                 655

Asn Lys Trp His Asn Leu Pro Ala His Gln Gly Ala Val Gln Asp Gln
            660                 665                 670

Pro Tyr Gln Leu Pro Val Glu Ile Asp Pro Leu Ile Ala Cys Gly Thr
        675                 680                 685

Gly Thr His Arg Arg Gln Val Thr Asp Leu Leu Asp Gln Ser Ile Gln
    690                 695                 700

Val His Ser Gln Cys Phe Val Ile Thr Ser Asp Asn Arg Tyr Ile Leu
705                 710                 715                 720

Val Cys Gly Phe Trp Asp Lys Ser Phe Arg Val Tyr Ser Thr Asp Thr
                725                 730                 735

Gly Lys Leu Ile Gln Val Val Phe Gly His Trp Asp Val Val Thr Cys
            740                 745                 750

Leu Ala Arg Ser Glu Ser Tyr Ile Gly Gly Asn Cys Tyr Ile Leu Ser
        755                 760                 765

Gly Ser Arg Asp Ala Thr Leu Leu Leu Trp Tyr Trp Asn Gly Lys Ser
    770                 775                 780

Ser Gly Ile Gly Asp Asn Pro Gly Gly Glu Thr Ala Thr Pro Arg Ala
785                 790                 795                 800

Ile Leu Thr Gly His Asp Tyr Glu Ile Thr Cys Ala Ala Val Cys Ala
                805                 810                 815

Glu Leu Gly Leu Val Leu Ser Gly Ser Gln Glu Gly Pro Cys Leu Ile
            820                 825                 830

His Ser Met Asn Gly Asp Leu Leu Arg Thr Leu Glu Gly Pro Glu Asn
        835                 840                 845

Cys Leu Lys Pro Lys Leu Ile Gln Ala Ser Arg Glu Gly His Cys Val
    850                 855                 860

Ile Phe Tyr Glu Asn Gly Cys Phe Cys Thr Phe Ser Val Asn Gly Lys
865                 870                 875                 880

Leu Gln Ala Thr Val Glu Thr Asp Asp His Ile Arg Ala Ile Gln Leu
                885                 890                 895

Ser Arg Asp Gly Gln Tyr Leu Leu Thr Gly Gly Asp Asn Gly Val Val
            900                 905                 910

Ile Val Arg Gln Val Ser Asp Leu Lys Gln Leu Phe Ala Tyr Pro Gly
        915                 920                 925
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Cys Asp Ala Gly Ile Arg Ala Met Ala Leu Ser Phe Asp Gln Arg Cys
    930                 935                 940

Ile Ile Ser Gly Met Ala Ser Gly Ser Ile Val Leu Phe Tyr Asn Asp
945                 950                 955                 960

Phe Asn Arg Trp His His Glu Tyr Gln Thr Arg Tyr
                965                 970


<210> SEQ ID NO 15
<211> LENGTH: 983
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (155)..(198)
<223> OTHER INFORMATION: WDL (WD-like) repeat
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (199)..(248)
<223> OTHER INFORMATION: WDL (WD-like) repeat
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (249)..(289)
<223> OTHER INFORMATION: WDL (WD-like) repeat
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (319)..(610)
<223> OTHER INFORMATION: BEACH domain
<220> FEATURE:
<221> NAME/KEY: SITE
<222> LOCATION: (356)..(363)
<223> OTHER INFORMATION: Tyrosine kinase recognition site
<220> FEATURE:
<221> NAME/KEY: BINDING
<222> LOCATION: (364)..(367)
<223> OTHER INFORMATION: SH3 binding site
<220> FEATURE:
<221> NAME/KEY: BINDING
<222> LOCATION: (422)..(425)
<223> OTHER INFORMATION: SH2 binding site
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (713)..(755)
<223> OTHER INFORMATION: WD repeat
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (756)..(814)
<223> OTHER INFORMATION: WD repeat
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (815)..(897)
<223> OTHER INFORMATION: WD repeat
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (898)..(939)
<223> OTHER INFORMATION: WD repeat
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (940)..(983)
<223> OTHER INFORMATION: WD repeat

<400> SEQUENCE: 15

Gly Arg Leu Leu Ser Gln Thr Met Lys Asp His Leu Val Arg Val Ala
1               5                   10                  15

Asn Glu Ala Glu Phe Ile Leu Ser Arg Gln Arg Ala Glu Asp Ile His
            20                  25                  30

Arg His Ala Glu Phe Glu Ser Leu Cys Ala Gln Tyr Ser Ala Asp Lys
        35                  40                  45

Arg Glu Asp Glu Lys Met Cys Asp His Leu Ile Arg Ala Ala Lys Tyr
    50                  55                  60

Arg Asp His Val Thr Ala Thr Gln Leu Ile Gln Lys Ile Ile Asn Ile
65                  70                  75                  80
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Leu Thr Asp Lys His Gly Ala Trp Gly Asn Ser Ala Val Ser Arg Pro
                85                  90                  95

Leu Glu Phe Trp Arg Leu Asp Tyr Trp Glu Asp Asp Leu Arg Arg Arg
            100                 105                 110

Arg Arg Phe Val Arg Asn Pro Leu Gly Ser Thr His Pro Glu Ala Thr
        115                 120                 125

Leu Lys Thr Ala Val Glu His Val Cys Ile Phe Lys Leu Arg Glu Asn
    130                 135                 140

Ser Lys Ala Thr Asp Glu Asp Ile Leu Ala Lys Gly Lys Gln Ser Ile
145                 150                 155                 160

Arg Ser Gln Ala Leu Gly Asn Gln Asn Ser Glu Asn Glu Ile Leu Leu
                165                 170                 175

Glu Gly Asp Asp Asp Thr Leu Ser Ser Val Asp Glu Lys Asp Leu Glu
            180                 185                 190

Asn Leu Ala Gly Pro Val Ser Leu Ser Thr Pro Ala Gln Leu Val Ala
        195                 200                 205

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

Tyr Phe Glu Val Asp Glu Glu Asp Pro Asn Phe Lys Lys Ile Asp Pro
225                 230                 235                 240

Lys Ile Leu Ala Tyr Thr Glu Gly Leu His Gly Lys Trp Leu Phe Thr
                245                 250                 255

Glu Ile Arg Ser Ile Phe Ser Arg Arg Tyr Leu Leu Gln Asn Thr Ala
            260                 265                 270

Leu Glu Ile Phe Met Ala Asn Arg Val Ala Val Met Phe Asn Phe Pro
        275                 280                 285

Asp Pro Ala Thr Val Lys Lys Val Val Asn Phe Leu Pro Arg Val Gly
    290                 295                 300

Val Gly Thr Ser Phe Gly Leu Pro Gln Thr Arg Arg Ile Ser Leu Ala
305                 310                 315                 320

Ser Pro Arg Gln Leu Phe Lys Ala Ser Asn Met Thr Gln Arg Trp Gln
                325                 330                 335

His Arg Glu Ile Ser Asn Phe Glu Tyr Leu Met Phe Leu Asn Thr Ile
            340                 345                 350

Ala Gly Arg Ser Tyr Asn Asp Leu Asn Gln Tyr Pro Val Phe Pro Trp
        355                 360                 365

Val Ile Thr Asn Tyr Glu Ser Glu Glu Leu Asp Leu Thr Leu Pro Thr
    370                 375                 380

Asn Phe Arg Asp Leu Ser Lys Pro Ile Gly Ala Leu Asn Pro Lys Arg
385                 390                 395                 400

Ala Ala Phe Phe Ala Glu Arg Tyr Glu Ser Trp Glu Asp Asp Gln Val
                405                 410                 415

Pro Lys Phe His Tyr Gly Thr His Tyr Ser Thr Ala Ser Phe Val Leu
            420                 425                 430

Ala Trp Leu Leu Arg Ile Glu Pro Phe Thr Thr Tyr Phe Leu Asn Leu
        435                 440                 445

Gln Gly Gly Lys Phe Asp His Ala Asp Arg Thr Phe Ser Ser Ile Ser
    450                 455                 460

Arg Ala Trp Arg Asn Ser Gln Arg Asp Thr Ser Asp Ile Lys Glu Leu
465                 470                 475                 480

Ile Pro Glu Phe Tyr Tyr Leu Pro Glu Met Phe Val Asn Phe Asn Asn
                485                 490                 495
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```
Tyr Asn Leu Gly Val Met Asp Asp Gly Thr Val Val Ser Asp Val Glu
            500                 505                 510

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

Leu Ala Leu Glu Ser Glu Phe Val Ser Cys Gln Leu His Gln Trp Ile
    530                 535                 540

Asp Leu Ile Phe Gly Tyr Lys Gln Gln Gly Pro Glu Ala Val Arg Ala
545                 550                 555                 560

Leu Asn Val Phe Tyr Tyr Leu Thr Tyr Glu Gly Ala Val Asn Leu Asn
                565                 570                 575

Ser Ile Thr Asp Pro Val Leu Arg Glu Ala Val Glu Ala Gln Ile Arg
            580                 585                 590

Ser Phe Gly Gln Thr Pro Ser Gln Leu Leu Ile Glu Pro His Pro Pro
        595                 600                 605

Arg Gly Ser Ala Met Gln Val Ser Pro Leu Met Phe Thr Asp Lys Ala
    610                 615                 620

Gln Gln Asp Val Ile Met Val Leu Lys Phe Pro Ser Asn Ser Pro Val
625                 630                 635                 640

Thr His Val Ala Ala Asn Thr Gln Pro Gly Leu Ala Thr Pro Ala Val
                645                 650                 655

Ile Thr Val Thr Ala Asn Arg Leu Phe Ala Val Asn Lys Trp His Asn
            660                 665                 670

Leu Pro Ala His Gln Gly Ala Val Gln Asp Gln Pro Tyr Gln Leu Pro
        675                 680                 685

Val Glu Ile Asp Pro Leu Ile Ala Ser Asn Thr Gly Met His Arg Arg
    690                 695                 700

Gln Ile Thr Asp Leu Leu Asp Gln Ser Ile Gln Val His Ser Gln Cys
705                 710                 715                 720

Phe Val Ile Thr Ser Asp Asn Arg Tyr Ile Leu Val Cys Gly Phe Trp
                725                 730                 735

Asp Lys Ser Phe Arg Val Tyr Ser Thr Asp Thr Gly Arg Leu Ile Gln
            740                 745                 750

Val Val Phe Gly His Trp Asp Val Val Thr Cys Leu Ala Arg Ser Glu
        755                 760                 765

Ser Tyr Ile Gly Gly Asn Cys Tyr Ile Leu Ser Gly Ser Arg Asp Ala
    770                 775                 780

Thr Leu Leu Leu Trp Tyr Trp Asn Gly Lys Cys Ser Gly Ile Gly Asp
785                 790                 795                 800

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

Asp Tyr Glu Val Thr Cys Ala Ala Val Cys Ala Glu Leu Gly Leu Val
            820                 825                 830

Leu Ser Gly Ser Gln Glu Gly Pro Cys Leu Ile His Ser Met Asn Gly
        835                 840                 845

Asp Leu Leu Arg Thr Leu Glu Gly Pro Glu Asn Cys Leu Lys Pro Lys
    850                 855                 860

Leu Ile Gln Ala Ser Arg Glu Gly His Cys Val Ile Phe Tyr Glu Asn
865                 870                 875                 880

Gly Leu Phe Cys Thr Phe Ser Val Asn Gly Lys Leu Gln Ala Thr Met
                885                 890                 895

Glu Thr Asp Asp Asn Ile Arg Ala Ile Gln Leu Ser Arg Asp Gly Gln
            900                 905                 910
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```
Tyr Leu Leu Thr Gly Gly Asp Arg Gly Val Val Val Val Arg Gln Val
        915                 920                 925

Ser Asp Leu Lys Gln Leu Phe Ala Tyr Pro Gly Cys Asp Ala Gly Ile
    930                 935                 940

Arg Ala Met Ala Leu Ser Tyr Asp Gln Arg Cys Ile Ile Ser Gly Met
945                 950                 955                 960

Ala Ser Gly Ser Ile Val Leu Phe Tyr Asn Asp Phe Asn Arg Trp His
                965                 970                 975

His Glu Tyr Gln Thr Arg Tyr
            980


<210> SEQ ID NO 16
<211> LENGTH: 994
<212> TYPE: PRT
<213> ORGANISM: Drosophila melanogaster
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (320)..(611)
<223> OTHER INFORMATION: BEACH domain
<220> FEATURE:
<221> NAME/KEY: SITE
<222> LOCATION: (357)..(364)
<223> OTHER INFORMATION: Tyrosine kinase recognition site
<220> FEATURE:
<221> NAME/KEY: BINDING
<222> LOCATION: (365)..(368)
<223> OTHER INFORMATION: SH3 binding site
<220> FEATURE:
<221> NAME/KEY: BINDING
<222> LOCATION: (423)..(426)
<223> OTHER INFORMATION: SH2 binding site

<400> SEQUENCE: 16

Gly Arg Leu Leu Ser His Ala Met Lys Asp His Ile Val Arg Val Ala
1               5                   10                  15

Asn Glu Ala Glu Phe Ile Leu Asn Arg Met Arg Ala Asp Asp Val Leu
            20                  25                  30

Lys His Ala Asp Phe Glu Ser Gln Cys Ala Gln Thr Leu Leu Glu Arg
        35                  40                  45

Arg Glu Glu Glu Arg Met Cys Asp His Leu Ile Thr Ala Ala Arg Arg
    50                  55                  60

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

Met Cys Asn Arg His Gly Ala Trp Gly Asp Ser Ser Ser Thr Ser Ser
                85                  90                  95

Gly Gly Ala Ile Val Gly Ala Val Gln Lys Ser Pro Tyr Trp Lys Leu
            100                 105                 110

Asp Ala Trp Glu Asp Asp Ala Arg Arg Arg Lys Arg Met Val Gln Asn
        115                 120                 125

Pro Arg Gly Ser Ser His Pro Gln Ala Thr Leu Lys Ala Ala Leu Glu
    130                 135                 140

Asn Gly Gly Pro Glu Asp Ala Ile Leu Gln Thr Arg Asp Glu Phe His
145                 150                 155                 160

Thr Gln Ile Ala Val Ser Arg Thr His Pro Ser Gly Gln His Asn Gly
                165                 170                 175

Glu Leu Leu Asp Asp Ala Glu Leu Leu Ile Glu Asp Arg Glu Leu Asp
            180                 185                 190

Leu Asp Leu Thr Gly Pro Val Asn Ile Ser Thr Lys Ala Arg Leu Ile
        195                 200                 205
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```
Ala Pro Gly Leu Val Ala Pro Gly Thr Val Ser Ile Thr Ser Thr Glu
    210                 215                 220

Met Phe Phe Glu Val Asp Glu Glu His Pro Glu Phe Gln Lys Ile Asp
225                 230                 235                 240

Gly Glu Val Leu Lys Tyr Cys Asp His Leu His Gly Lys Trp Tyr Phe
                245                 250                 255

Ser Glu Val Arg Ala Ile Phe Ser Arg Arg Tyr Leu Leu Gln Asn Val
            260                 265                 270

Ala Leu Glu Ile Phe Leu Ala Ser Arg Thr Ser Ile Leu Phe Ala Phe
        275                 280                 285

Pro Asp Gln His Thr Val Lys Lys Val Ile Lys Ala Leu Pro Arg Val
    290                 295                 300

Gly Val Gly Ile Lys Tyr Gly Ile Pro Gln Thr Arg Arg Ala Ser Met
305                 310                 315                 320

Met Ser Pro Arg Gln Leu Met Arg Asn Ser Asn Met Thr Gln Lys Trp
                325                 330                 335

Gln Arg Arg Glu Ile Ser Asn Phe Glu Tyr Leu Met Phe Leu Asn Thr
            340                 345                 350

Ile Ala Gly Arg Thr Tyr Asn Asp Leu Asn Gln Tyr Pro Ile Phe Pro
        355                 360                 365

Trp Val Leu Thr Asn Tyr Glu Ser Lys Asp Leu Asp Leu Ser Leu Pro
    370                 375                 380

Ser Asn Tyr Arg Asp Leu Ser Lys Pro Ile Gly Ala Leu Asn Pro Ser
385                 390                 395                 400

Arg Arg Ala Tyr Phe Glu Glu Arg Tyr Glu Ser Trp Asp Ser Asp Thr
                405                 410                 415

Ile Pro Pro Phe His Tyr Gly Thr His Tyr Ser Thr Ala Ala Phe Thr
            420                 425                 430

Leu Asn Trp Leu Val Arg Val Glu Pro Phe Thr Thr Met Phe Leu Ala
        435                 440                 445

Leu Gln Gly Gly Lys Phe Asp Tyr Pro Asp Arg Leu Phe Ser Ser Val
    450                 455                 460

Ser Leu Ser Trp Lys Asn Cys Gln Arg Asp Thr Ser Asp Val Lys Glu
465                 470                 475                 480

Leu Ile Pro Glu Trp Tyr Phe Leu Pro Glu Met Phe Tyr Asn Ser Ser
                485                 490                 495

Gly Tyr Arg Leu Gly His Arg Glu Asp Gly Ala Leu Val Asp Asp Ile
            500                 505                 510

Glu Leu Pro Pro Trp Ala Lys Ser Pro Glu Glu Phe Val Arg Ile Asn
        515                 520                 525

Arg Met Ala Leu Glu Ser Glu Phe Val Ser Cys Gln Leu His Gln Trp
    530                 535                 540

Ile Asp Leu Ile Phe Gly Tyr Lys Gln Arg Gly Pro Glu Ala Ile Arg
545                 550                 555                 560

Ala Thr Asn Val Phe Tyr Tyr Leu Thr Tyr Glu Gly Ser Val Asp Leu
                565                 570                 575

Asp Gly Val Leu Asp Pro Val Met Arg Glu Ala Val Glu Asn Gln Ile
            580                 585                 590

Arg Asn Phe Gly Gln Thr Pro Ser Gln Leu Leu Met Glu Pro His Pro
        595                 600                 605

Pro Arg Ser Ser Ala Met His Leu Ser Pro Met Met Phe Ser Ala Met
    610                 615                 620
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Pro Glu Asp Leu Cys Gln Met Leu Lys Phe Tyr Gln Asn Ser Pro Val
625                 630                 635                 640

Ile His Ile Ser Ala Asn Thr Tyr Pro Gln Leu Ser Leu Pro Ser Val
                645                 650                 655

Val Thr Val Thr Ala Gly His Gln Phe Ala Val Asn Arg Trp Asn Cys
            660                 665                 670

Asn Tyr Thr Ala Ser Val Gln Ser Pro Ser Tyr Ala Glu Ser Pro Gln
        675                 680                 685

Ser Pro Gly Ser Asn Gln Pro Leu Thr Ile Asp Pro Val Leu Ala Val
    690                 695                 700

His Gly Thr Asn Asn Asn Ser Asn Ala Ala Ser Arg Arg His Leu Gly
705                 710                 715                 720

Asp Asn Phe Ser Gln Met Leu Lys Ile Arg Ser Asn Cys Phe Val Thr
                725                 730                 735

Thr Val Asp Ser Arg Phe Leu Ile Ala Cys Gly Phe Trp Asp Asn Ser
            740                 745                 750

Phe Arg Val Phe Ala Thr Glu Thr Ala Lys Ile Val Gln Ile Val Phe
        755                 760                 765

Gly His Phe Gly Val Val Thr Cys Met Ala Arg Ser Glu Cys Asn Ile
    770                 775                 780

Thr Ser Asp Cys Tyr Ile Ala Ser Gly Ser Ala Asp Cys Thr Val Leu
785                 790                 795                 800

Leu Trp His Trp Asn Ala Arg Thr Gln Ser Ile Val Gly Glu Gly Asp
                805                 810                 815

Val Pro Thr Pro Arg Ala Thr Leu Thr Gly His Glu Gln Ala Val Thr
            820                 825                 830

Ser Val Val Ile Ser Ala Glu Leu Gly Leu Val Val Ser Gly Ser Ser
        835                 840                 845

Asn Gly Pro Val Leu Ile His Thr Thr Phe Gly Asp Leu Leu Arg Ser
    850                 855                 860

Leu Asp Pro Pro Ala Glu Phe His Ser Pro Glu Leu Ile Thr Met Ser
865                 870                 875                 880

Arg Glu Gly Phe Ile Val Ile Asn Tyr Asp Lys Gly Asn Val Ala Ala
                885                 890                 895

Tyr Thr Ile Asn Gly Lys Lys Leu Arg His Glu Thr His Asn Asp Asn
            900                 905                 910

Leu Gln Cys Met Leu Leu Ser Arg Asp Gly Glu Tyr Leu Met Thr Ala
        915                 920                 925

Gly Asp Arg Gly Ile Val Glu Val Trp Arg Thr Phe Asn Leu Ala Pro
    930                 935                 940

Leu Tyr Ala Phe Pro Ala Cys Asn Ala Gly Ile Arg Ser Leu Ala Leu
945                 950                 955                 960

Thr His Asp Gln Lys Tyr Leu Leu Ala Gly Leu Ser Thr Gly Ser Ile
                965                 970                 975

Ile Val Phe His Ile Asp Phe Asn Arg Trp His His Glu Tyr Gln Gln
            980                 985                 990

Arg Tyr
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<210> SEQ ID NO 17
<211> LENGTH: 973
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (292)..(595)
<223> OTHER INFORMATION: BEACH domain
<220> FEATURE:
<221> NAME/KEY: SITE
<222> LOCATION: (329)..(336)
<223> OTHER INFORMATION: Tyrosine kinase recognition site
<220> FEATURE:
<221> NAME/KEY: BINDING
<222> LOCATION: (337)..(340)
<223> OTHER INFORMATION: SH3 binding site
<220> FEATURE:
<221> NAME/KEY: BINDING
<222> LOCATION: (407)..(410)
<223> OTHER INFORMATION: SH2 binding site

<400> SEQUENCE: 17

Cys Ile Pro Pro Ser Ala Ser Thr Lys Ala Asp Leu Ile Lys Met Ile
1 5 10 15

Lys Glu Glu Gln Lys Lys Tyr Glu Thr Glu Glu Gly Val Asn Lys Ala
20 25 30

Ala Trp Gln Lys Thr Val Asn Asn Asn Gln Gln Ser Leu Phe Gln Arg
35 40 45

Leu Asp Ser Lys Ser Lys Asp Ile Ser Lys Ile Ala Ala Asp Ile Thr
50 55 60

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

His Ile Arg Gly Met Tyr Lys Val Asp Leu Ser Ala Ser Arg His Trp
85 90 95

Gln Glu Leu Ile Gln Gln Leu Thr His Asp Arg Ala Val Trp Tyr Asp
100 105 110

Pro Ile Tyr Tyr Pro Thr Ser Trp Gln Leu Asp Pro Thr Glu Gly Pro
115 120 125

Asn Arg Glu Arg Arg Arg Leu Gln Arg Cys Tyr Leu Thr Ile Pro Asn
130 135 140

Lys Tyr Leu Leu Arg Asp Arg Gln Lys Ser Glu Asp Val Val Lys Pro
145 150 155 160

Pro Leu Ser Tyr Leu Phe Glu Asp Lys Thr His Ser Ser Phe Ser Ser
165 170 175

Thr Val Lys Asp Lys Ala Ala Ser Glu Ser Ile Arg Val Asn Arg Arg
180 185 190

Cys Ile Ser Val Ala Pro Ser Arg Glu Thr Ala Gly Glu Leu Leu Leu
195 200 205

Gly Lys Cys Gly Met Tyr Phe Val Glu Asp Asn Ala Ser Asp Thr Val
210 215 220

Glu Ser Ser Ser Leu Gln Gly Glu Leu Glu Pro Ala Ser Phe Ser Trp
225 230 235 240

Thr Tyr Glu Glu Ile Lys Glu Val His Lys Arg Trp Trp Gln Leu Arg
245 250 255

Asp Asn Ala Val Glu Ile Phe Leu Thr Asn Gly Arg Thr Leu Leu Leu
260 265 270

Ala Phe Asp Asn Thr Lys Val Arg Asp Asp Val Tyr His Asn Ile Leu
275 280 285

Thr Asn Asn Leu Pro Asn Leu Leu Glu Tyr Gly Asn Ile Thr Ala Leu
290 295 300

Thr Asn Leu Trp Tyr Thr Gly Gln Ile Thr Asn Phe Glu Tyr Leu Thr
305 310 315 320

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His Leu Asn Lys His Ala Gly Arg Ser Phe Asn Asp Leu Met Gln Tyr
                325                 330                 335

Pro Val Phe Pro Phe Ile Leu Ala Asp Tyr Val Ser Glu Thr Leu Asp
            340                 345                 350

Leu Asn Asp Leu Leu Ile Tyr Arg Asn Leu Ser Lys Pro Ile Ala Val
        355                 360                 365

Gln Tyr Lys Glu Lys Glu Asp Arg Tyr Val Asp Thr Tyr Lys Tyr Leu
    370                 375                 380

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

Val Gln Pro Tyr His Tyr Gly Ser His Tyr Ser Asn Ser Gly Thr Val
                405                 410                 415

Leu His Phe Leu Val Arg Met Pro Pro Phe Thr Lys Met Phe Leu Ala
            420                 425                 430

Tyr Gln Asp Gln Ser Phe Asp Ile Pro Asp Arg Thr Phe His Ser Thr
        435                 440                 445

Asn Thr Thr Trp Arg Leu Ser Ser Phe Glu Ser Met Thr Asp Val Lys
    450                 455                 460

Glu Leu Ile Pro Glu Phe Phe Tyr Leu Pro Glu Phe Leu Val Asn Arg
465                 470                 475                 480

Glu Gly Phe Asp Phe Gly Val Arg Gln Asn Gly Glu Arg Val Asn His
                485                 490                 495

Val Asn Leu Pro Pro Trp Ala Arg Asn Asp Pro Arg Leu Phe Ile Leu
            500                 505                 510

Ile His Arg Gln Ala Leu Glu Ser Asp Tyr Val Ser Gln Asn Ile Cys
        515                 520                 525

Gln Trp Ile Asp Leu Val Phe Gly Tyr Lys Gln Lys Gly Lys Ala Ser
    530                 535                 540

Val Gln Ala Ile Asn Val Phe His Pro Ala Thr Tyr Phe Gly Met Asp
545                 550                 555                 560

Val Ser Ala Val Glu Asp Pro Val Gln Arg Arg Ala Leu Glu Thr Met
                565                 570                 575

Ile Lys Thr Tyr Gly Gln Thr Pro Arg Gln Leu Phe His Met Ala His
            580                 585                 590

Val Ser Arg Pro Gly Ala Lys Leu Asn Ile Glu Gly Glu Leu Pro Ala
        595                 600                 605

Ala Val Gly Leu Leu Val Gln Phe Ala Phe Arg Glu Thr Arg Glu Gln
    610                 615                 620

Val Lys Glu Ile Thr Tyr Pro Ser Pro Leu Ser Trp Ile Lys Gly Leu
625                 630                 635                 640

Lys Trp Gly Glu Tyr Val Gly Ser Pro Ser Ala Pro Val Pro Val Val
                645                 650                 655

Cys Phe Ser Gln Pro His Gly Glu Arg Phe Gly Ser Leu Gln Ala Leu
            660                 665                 670

Pro Thr Arg Ala Ile Cys Gly Leu Ser Arg Asn Phe Cys Leu Val Met
        675                 680                 685

Thr Tyr Ser Lys Glu Gln Gly Val Arg Ser Met Asn Ser Thr Asp Ile
    690                 695                 700

Gln Trp Ser Ala Ile Leu Ser Trp Gly Tyr Ala Asp Asn Ile Leu Arg
705                 710                 715                 720

Leu Lys Ser Lys Gln Ser Glu Pro Pro Val Asn Phe Ile Gln Ser Ser
                725                 730                 735
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Gln Gln Tyr Gln Val Thr Ser Cys Ala Trp Val Pro Asp Ser Cys Gln
            740                 745                 750

Leu Phe Thr Gly Ser Lys Cys Gly Val Ile Thr Ala Tyr Thr Asn Arg
        755                 760                 765

Phe Thr Ser Ser Thr Pro Ser Glu Ile Glu Met Glu Thr Gln Ile His
    770                 775                 780

Leu Tyr Gly His Thr Glu Glu Ile Thr Ser Leu Phe Val Cys Lys Pro
785                 790                 795                 800

Tyr Ser Ile Leu Ile Ser Val Ser Arg Asp Gly Thr Cys Ile Ile Trp
                805                 810                 815

Asp Leu Asn Arg Leu Cys Tyr Val Gln Ser Leu Ala Gly His Lys Ser
            820                 825                 830

Pro Val Thr Ala Val Ser Ala Ser Glu Thr Ser Gly Asp Ile Ala Thr
        835                 840                 845

Val Cys Asp Ser Ala Gly Gly Gly Ser Asp Leu Arg Leu Trp Thr Val
    850                 855                 860

Asn Gly Asp Leu Val Gly His Val His Cys Arg Glu Ile Ile Cys Ser
865                 870                 875                 880

Val Ala Phe Ser Asn Gln Pro Glu Gly Val Ser Ile Asn Val Ile Ala
                885                 890                 895

Gly Gly Leu Glu Asn Gly Ile Val Arg Leu Trp Ser Thr Trp Asp Leu
            900                 905                 910

Lys Pro Val Arg Glu Ile Thr Phe Pro Lys Ser Asn Lys Pro Ile Ile
        915                 920                 925

Ser Leu Thr Phe Ser Cys Asp Gly His His Leu Tyr Thr Ala Asn Ser
    930                 935                 940

Asp Gly Thr Val Ile Ala Trp Cys Arg Lys Asp Gln Gln Arg Leu Lys
945                 950                 955                 960

Gln Pro Met Phe Tyr Ser Phe Leu Ser Ser Tyr Ala Ala
                965                 970


<210> SEQ ID NO 18
<211> LENGTH: 907
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (279)..(565)
<223> OTHER INFORMATION: BEACH domain
<220> FEATURE:
<221> NAME/KEY: SITE
<222> LOCATION: (316)..(323)
<223> OTHER INFORMATION: Tyrosine kinase recognition site
<220> FEATURE:
<221> NAME/KEY: BINDING
<222> LOCATION: (324)..(327)
<223> OTHER INFORMATION: SH3 binding site
<220> FEATURE:
<221> NAME/KEY: BINDING
<222> LOCATION: (379)..(382)
<223> OTHER INFORMATION: SH2 binding site

<400> SEQUENCE: 18

Gln Gln Leu Gln Leu Tyr Ser Lys Glu Arg Phe Ser Leu Leu Leu Leu
1               5                   10                  15

Asn Leu Glu Glu Tyr Tyr Phe Glu Gln His Arg Ala Asn His Ile Leu
            20                  25                  30

His Lys Gly Ser His His Glu Arg Lys Ile Arg Gly Ser Leu Lys Ile
        35                  40                  45
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Cys Ser Lys Ser Val Ile Phe Glu Pro Asp Ser Ile Ser Gln Pro Ile
    50                  55                  60

Ile Lys Ile Pro Leu Arg Asp Cys Ile Lys Ile Gly Lys His Gly Glu
65                  70                  75                  80

Asn Gly Ala Asn Arg His Phe Thr Lys Ala Lys Ser Gly Gly Ile Ser
                85                  90                  95

Leu Ile Phe Ser Gln Val Tyr Phe Ile Lys Glu His Asn Val Val Ala
            100                 105                 110

Pro Tyr Lys Ile Glu Arg Gly Lys Met Glu Tyr Val Phe Glu Leu Asp
        115                 120                 125

Val Pro Gly Lys Val Glu Asp Val Val Glu Thr Leu Leu Gln Leu His
    130                 135                 140

Arg Ala Ser Cys Leu Asp Lys Leu Gly Asp Gln Thr Ala Met Ile Thr
145                 150                 155                 160

Ala Ile Leu Gln Ser Arg Leu Ala Arg Thr Ser Phe Asp Lys Asn Arg
                165                 170                 175

Phe Gln Asn Ile Ser Glu Lys Leu His Met Glu Cys Lys Ala Glu Met
            180                 185                 190

Val Thr Pro Leu Val Thr Asn Pro Gly His Val Cys Ile Thr Asp Thr
        195                 200                 205

Asn Leu Tyr Phe Gln Pro Leu Asn Gly Tyr Pro Lys Pro Val Val Gln
    210                 215                 220

Ile Thr Leu Gln Asp Val Arg Arg Ile Tyr Lys Arg Arg His Gly Leu
225                 230                 235                 240

Met Pro Leu Gly Leu Glu Val Phe Cys Thr Glu Asp Asp Leu Cys Ser
                245                 250                 255

Asp Ile Tyr Leu Lys Phe Tyr Glu Pro Gln Asp Arg Asp Asp Leu Tyr
            260                 265                 270

Phe Tyr Ile Ala Thr Tyr Leu Glu His His Val Ala Glu His Thr Ala
        275                 280                 285

Glu Ser Tyr Met Leu Gln Trp Gln Arg Gly His Leu Ser Asn Tyr Gln
    290                 295                 300

Tyr Leu Leu His Leu Asn Asn Leu Ala Asp Arg Ser Cys Asn Asp Leu
305                 310                 315                 320

Ser Gln Tyr Pro Val Phe Pro Trp Ile Ile His Asp Tyr Ser Ser Ser
                325                 330                 335

Glu Leu Asp Leu Ser Asn Pro Gly Thr Phe Arg Asp Leu Ser Lys Pro
            340                 345                 350

Val Gly Ala Leu Asn Lys Glu Arg Leu Glu Arg Leu Leu Thr Arg Tyr
        355                 360                 365

Gln Glu Met Pro Glu Pro Lys Phe Met Tyr Gly Ser His Tyr Ser Ser
    370                 375                 380

Pro Gly Tyr Val Leu Phe Tyr Leu Val Arg Ile Ala Pro Glu Tyr Met
385                 390                 395                 400

Leu Cys Leu Gln Asn Gly Arg Phe Asp Asn Ala Asp Arg Met Phe Asn
                405                 410                 415

Ser Ile Ala Glu Thr Trp Lys Asn Cys Leu Asp Gly Ala Thr Asp Phe
            420                 425                 430

Lys Glu Leu Ile Pro Glu Phe Tyr Gly Asp Asp Val Ser Phe Leu Val
        435                 440                 445

Asn Ser Leu Lys Leu Asp Leu Gly Lys Arg Gln Gly Gly Gln Met Val
    450                 455                 460
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Asp Asp Val Glu Leu Pro Pro Trp Ala Ser Ser Pro Glu Asp Phe Leu
465                 470                 475                 480

Gln Lys Ser Lys Asp Ala Leu Glu Ser Asn Tyr Val Ser Glu His Leu
                485                 490                 495

His Glu Trp Ile Asp Leu Ile Phe Gly Tyr Lys Gln Lys Gly Ser Asp
            500                 505                 510

Ala Val Gly Ala His Asn Val Phe His Pro Leu Thr Tyr Glu Gly Gly
        515                 520                 525

Val Asp Leu Asn Ser Ile Gln Asp Pro Asp Glu Lys Val Ala Met Leu
    530                 535                 540

Thr Gln Ile Leu Glu Phe Gly Gln Thr Pro Lys Gln Leu Phe Val Thr
545                 550                 555                 560

Pro His Pro Arg Arg Ile Thr Pro Lys Phe Lys Ser Leu Ser Gln Thr
                565                 570                 575

Ser Ser Tyr Asn Ala Ser Met Ala Asp Ser Pro Gly Glu Glu Ser Phe
            580                 585                 590

Glu Asp Leu Thr Glu Glu Ser Lys Thr Leu Ala Trp Asn Asn Ile Thr
        595                 600                 605

Lys Leu Gln Leu His Glu His Tyr Lys Ile His Lys Glu Ala Val Thr
    610                 615                 620

Gly Ile Thr Val Ser Arg Asn Gly Ser Ser Val Phe Thr Thr Ser Gln
625                 630                 635                 640

Asp Ser Thr Leu Lys Met Phe Ser Lys Glu Ser Lys Met Leu Gln Arg
                645                 650                 655

Ser Ile Ser Phe Ser Asn Met Ala Leu Ser Ser Cys Leu Leu Leu Pro
            660                 665                 670

Gly Asp Ala Thr Val Ile Thr Ser Ser Trp Asp Asn Asn Val Tyr Phe
        675                 680                 685

Tyr Ser Ile Ala Phe Gly Arg Arg Gln Asp Thr Leu Met Gly His Asp
    690                 695                 700

Asp Ala Val Ser Lys Ile Cys Trp His Asp Asn Arg Leu Tyr Ser Ala
705                 710                 715                 720

Ser Trp Asp Ser Thr Val Lys Val Trp Ser Gly Val Pro Ala Glu Met
                725                 730                 735

Pro Gly Thr Lys Arg His His Phe Asp Leu Leu Ala Glu Leu Glu His
            740                 745                 750

Asp Val Ser Val Asp Thr Ile Ser Leu Asn Ala Ala Ser Thr Leu Leu
        755                 760                 765

Val Ser Gly Thr Lys Glu Gly Thr Val Asn Ile Trp Asp Leu Thr Thr
    770                 775                 780

Ala Thr Leu Met His Gln Ile Pro Cys His Ser Gly Ile Val Cys Asp
785                 790                 795                 800

Thr Ala Phe Ser Pro Asp Ser Arg His Val Leu Ser Thr Gly Thr Asp
                805                 810                 815

Gly Cys Leu Asn Val Ile Asp Val Gln Thr Gly Met Leu Ile Ser Ser
            820                 825                 830

Met Thr Ser Asp Glu Pro Gln Thr Cys Phe Val Trp Asp Gly Asn Ser
        835                 840                 845

Val Leu Ser Gly Ser Gln Ser Gly Glu Leu Leu Val Trp Asp Leu Leu
    850                 855                 860

Gly Ala Lys Ile Ser Glu Arg Ile Gln Gly His Thr Gly Ala Val Thr
865                 870                 875                 880
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Cys Ile Trp Met Asn Glu Gln Cys Ser Ser Ile Ile Thr Gly Gly Glu
                885                 890                 895

Asp Arg Gln Ile Ile Phe Trp Lys Leu Gln Tyr
            900                 905


<210> SEQ ID NO 19
<211> LENGTH: 908
<212> TYPE: PRT
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (144)..(187)
<223> OTHER INFORMATION: WDL (WD-like) repeat
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (188)..(237)
<223> OTHER INFORMATION: WDL (WD-like) repeat
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (238)..(278)
<223> OTHER INFORMATION: WDL (WD-like) repeat
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (308)..(599)
<223> OTHER INFORMATION: BEACH domain
<220> FEATURE:
<221> NAME/KEY: SITE
<222> LOCATION: (345)..(352)
<223> OTHER INFORMATION: Tyrosine kinase recognition site
<220> FEATURE:
<221> NAME/KEY: BINDING
<222> LOCATION: (353)..(356)
<223> OTHER INFORMATION: SH3 binding site
<220> FEATURE:
<221> NAME/KEY: BINDING
<222> LOCATION: (411)..(414)
<223> OTHER INFORMATION: SH2 binding site
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (702)..(744)
<223> OTHER INFORMATION: WD repeat
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (745)..(803)
<223> OTHER INFORMATION: WD repeat
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (804)..(886)
<223> OTHER INFORMATION: WD repeat

<400> SEQUENCE: 19

Gly Arg Leu Leu Ser Gln Thr Met Lys Asp His Leu Val Arg Val Ala
1               5                   10                  15

Asn Glu Ala Glu Phe Ile Leu Ser Arg Gln Arg Ala Glu Asp Ile His
            20                  25                  30

Arg His Ala Glu Phe Glu Ser Leu Cys Ala Gln Tyr Ser Ala Asp Lys
        35                  40                  45

Arg Glu Glu Glu Lys Met Cys Asp His Leu Ile Arg Ala Ala Lys Tyr
    50                  55                  60

Arg Asp His Val Thr Ala Thr Gln Leu Ile Gln Lys Ile Ile Asn Leu
65                  70                  75                  80

Leu Thr Asp Lys His Gly Ala Trp Gly Ser Ser Ala Val Ser Arg Pro
                85                  90                  95

Arg Glu Phe Trp Arg Leu Asp Tyr Trp Glu Asp Asp Leu Arg Arg Arg
            100                 105                 110

Arg Arg Phe Val Arg Asn Pro Leu Gly Ser Thr His Pro Glu Ala Thr
        115                 120                 125
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Leu Lys Thr Ala Val Glu His Ala Ala Asp Glu Asp Ile Leu Ala Lys
    130                 135                 140

Gly Lys Gln Ser Ile Lys Ser Gln Ala Leu Gly Asn Gln Asn Ser Glu
145                 150                 155                 160

Asn Glu Ala Leu Leu Glu Gly Asp Asp Asp Thr Leu Ser Ser Val Asp
                165                 170                 175

Glu Lys Asp Leu Glu Asn Leu Ala Gly Pro Val Ser Leu Ser Thr Pro
            180                 185                 190

Ala Gln Leu Val Ala Pro Ser Val Val Val Lys Gly Thr Leu Ser Val
        195                 200                 205

Thr Ser Ser Glu Leu Tyr Phe Glu Val Asp Glu Glu Asp Pro Asn Phe
    210                 215                 220

Lys Lys Ile Asp Pro Lys Ile Leu Ala Tyr Thr Glu Gly Leu His Gly
225                 230                 235                 240

Lys Trp Leu Phe Thr Glu Ile Arg Ser Ile Phe Ser Arg Arg Tyr Leu
                245                 250                 255

Leu Gln Asn Thr Ala Leu Glu Ile Phe Met Ala Asn Arg Val Ala Val
            260                 265                 270

Met Phe Asn Phe Pro Asp Pro Ala Thr Val Lys Lys Val Val Asn Tyr
        275                 280                 285

Leu Pro Arg Val Gly Val Gly Thr Ser Phe Gly Leu Pro Gln Thr Arg
    290                 295                 300

Arg Ile Ser Leu Ala Thr Pro Arg Gln Leu Phe Lys Ala Ser Asn Met
305                 310                 315                 320

Thr Gln Arg Trp Gln His Arg Glu Ile Ser Asn Phe Glu Tyr Leu Met
                325                 330                 335

Phe Leu Asn Thr Ile Ala Gly Arg Ser Tyr Asn Asp Leu Asn Gln Tyr
            340                 345                 350

Pro Val Phe Pro Trp Val Ile Thr Asn Tyr Glu Ser Glu Glu Leu Asp
        355                 360                 365

Leu Thr Leu Pro Ser Asn Phe Arg Asp Leu Ser Lys Pro Ile Gly Ala
    370                 375                 380

Leu Asn Pro Lys Arg Ala Ala Phe Phe Ala Glu Arg Phe Glu Ser Trp
385                 390                 395                 400

Glu Asp Asp Gln Val Pro Lys Phe His Tyr Gly Thr His Tyr Ser Thr
                405                 410                 415

Ala Ser Phe Val Leu Ala Trp Leu Leu Arg Ile Glu Pro Phe Thr Thr
            420                 425                 430

Tyr Phe Leu Asn Leu Gln Gly Gly Lys Phe Asp His Ala Asp Arg Thr
        435                 440                 445

Phe Ser Ser Val Ser Arg Ala Trp Arg Asn Ser Gln Arg Asp Thr Ser
    450                 455                 460

Asp Ile Lys Glu Leu Ile Pro Glu Phe Tyr Tyr Leu Pro Glu Met Phe
465                 470                 475                 480

Val Asn Phe Asn Asn Tyr Asn Leu Gly Val Met Asp Asp Gly Thr Val
                485                 490                 495

Val Ser Asp Val Glu Leu Pro Pro Trp Ala Lys Thr Ser Glu Glu Phe
            500                 505                 510

Val Arg Ile Asn Arg Leu Ala Leu Glu Ser Glu Phe Val Ser Cys Gln
        515                 520                 525

Leu His Gln Trp Ile Asp Leu Ile Phe Gly Tyr Lys Gln Gln Gly Pro
    530                 535                 540
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Glu Ala Val Arg Ala Leu Asn Val Phe Tyr Tyr Leu Thr Tyr Glu Gly
545                 550                 555                 560

Ala Val Asn Leu Asn Ser Ile Thr Asp Pro Val Leu Arg Glu Ala Val
                565                 570                 575

Glu Ala Gln Ile Arg Ser Phe Gly Gln Thr Pro Ser Gln Leu Leu Ile
            580                 585                 590

Glu Pro His Pro Pro Arg Gly Ser Ala Met Gln Ala Ser Pro Leu Met
        595                 600                 605

Phe Thr Asp Gln Ala Gln Gln Asp Val Ile Met Val Leu Lys Phe Pro
    610                 615                 620

Ser Asn Ser Pro Val Thr His Val Ala Ala Asn Thr Gln Pro Gly Leu
625                 630                 635                 640

Ala Met Pro Ala Val Ile Thr Val Thr Ala Asn Arg Leu Phe Ala Val
                645                 650                 655

Asn Lys Trp His Asn Leu Pro Ala His Gln Gly Ala Val Gln Asp Gln
            660                 665                 670

Pro Tyr Gln Leu Pro Val Glu Ile Asp Pro Leu Ile Ala Cys Gly Thr
        675                 680                 685

Gly Thr His Arg Arg Gln Val Thr Asp Leu Leu Asp Gln Ser Ile Gln
    690                 695                 700

Val His Ser Gln Cys Phe Val Ile Thr Ser Asp Asn Arg Tyr Ile Leu
705                 710                 715                 720

Val Cys Gly Phe Trp Asp Lys Ser Phe Arg Val Tyr Ser Thr Asp Thr
                725                 730                 735

Gly Lys Leu Ile Gln Val Val Phe Gly His Trp Asp Val Val Thr Cys
            740                 745                 750

Leu Ala Arg Ser Glu Ser Tyr Ile Gly Gly Asn Cys Tyr Ile Leu Ser
        755                 760                 765

Gly Ser Arg Asp Ala Thr Leu Leu Leu Trp Tyr Trp Asn Gly Lys Ser
    770                 775                 780

Ser Gly Ile Gly Asp Asn Pro Gly Gly Glu Thr Ala Thr Pro Arg Ala
785                 790                 795                 800

Ile Leu Thr Gly His Asp Tyr Glu Ile Thr Cys Ala Ala Val Cys Ala
                805                 810                 815

Glu Leu Gly Leu Val Leu Ser Gly Ser Gln Glu Gly Pro Cys Leu Ile
            820                 825                 830

His Ser Met Asn Gly Asp Leu Leu Arg Thr Leu Glu Gly Pro Glu Asn
        835                 840                 845

Cys Leu Lys Pro Lys Leu Ile Gln Ala Ser Arg Glu Gly His Cys Val
    850                 855                 860

Ile Phe Tyr Glu Asn Gly Cys Phe Cys Thr Phe Ser Val Asn Gly Lys
865                 870                 875                 880

Leu Gln Ala Thr Val Glu Thr Asp Asp His Ile Arg Val Ser Ala Val
                885                 890                 895

Gly Ser Thr Leu Phe Leu Leu Leu Gly Ser Ser Lys
            900                 905


<210> SEQ ID NO 20
<211> LENGTH: 695
<212> TYPE: PRT
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (144)..(187)
<223> OTHER INFORMATION: WDL (WD-like) repeat
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<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (188)..(237)
<223> OTHER INFORMATION: WDL (WD-like) repeat
<220> FEATURE:
<221> NAME/KEY: REPEAT
<222> LOCATION: (238)..(278)
<223> OTHER INFORMATION: WDL (WD-like) repeat
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (308)..(599)
<223> OTHER INFORMATION: BEACH domain
<220> FEATURE:
<221> NAME/KEY: SITE
<222> LOCATION: (345)..(352)
<223> OTHER INFORMATION: Tyrosine kinase recognition site
<220> FEATURE:
<221> NAME/KEY: BINDING
<222> LOCATION: (353)..(356)
<223> OTHER INFORMATION: SH3 binding site
<220> FEATURE:
<221> NAME/KEY: BINDING
<222> LOCATION: (411)..(414)
<223> OTHER INFORMATION: SH2 binding site

<400> SEQUENCE: 20

Gly Arg Leu Leu Ser Gln Thr Met Lys Asp His Leu Val Arg Val Ala
1 5 10 15

Asn Glu Ala Glu Phe Ile Leu Ser Arg Gln Arg Ala Glu Asp Ile His
20 25 30

Arg His Ala Glu Phe Glu Ser Leu Cys Ala Gln Tyr Ser Ala Asp Lys
35 40 45

Arg Glu Glu Glu Lys Met Cys Asp His Leu Ile Arg Ala Ala Lys Tyr
50 55 60

Arg Asp His Val Thr Ala Thr Gln Leu Ile Gln Lys Ile Ile Asn Leu
65 70 75 80

Leu Thr Asp Lys His Gly Ala Trp Gly Ser Ser Ala Val Ser Arg Pro
85 90 95

Arg Glu Phe Trp Arg Leu Asp Tyr Trp Glu Asp Asp Leu Arg Arg Arg
100 105 110

Arg Arg Phe Val Arg Asn Pro Leu Gly Ser Thr His Pro Glu Ala Thr
115 120 125

Leu Lys Thr Ala Val Glu His Ala Ala Asp Glu Asp Ile Leu Ala Lys
130 135 140

Gly Lys Gln Ser Ile Lys Ser Gln Ala Leu Gly Asn Gln Asn Ser Glu
145 150 155 160

Asn Glu Ala Leu Leu Glu Gly Asp Asp Asp Thr Leu Ser Ser Val Asp
165 170 175

Glu Lys Asp Leu Glu Asn Leu Ala Gly Pro Val Ser Leu Ser Thr Pro
180 185 190

Ala Gln Leu Val Ala Pro Ser Val Val Val Lys Gly Thr Leu Ser Val
195 200 205

Thr Ser Ser Glu Leu Tyr Phe Glu Val Asp Glu Glu Asp Pro Asn Phe
210 215 220

Lys Lys Ile Asp Pro Lys Ile Leu Ala Tyr Thr Glu Gly Leu His Gly
225 230 235 240

Lys Trp Leu Phe Thr Glu Ile Arg Ser Ile Phe Ser Arg Arg Tyr Leu
245 250 255

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Leu Gln Asn Thr Ala Leu Glu Ile Phe Met Ala Asn Arg Val Ala Val
            260                 265                 270

Met Phe Asn Phe Pro Asp Pro Ala Thr Val Lys Lys Val Val Asn Tyr
        275                 280                 285

Leu Pro Arg Val Gly Val Gly Thr Ser Phe Gly Leu Pro Gln Thr Arg
    290                 295                 300

Arg Ile Ser Leu Ala Thr Pro Arg Gln Leu Phe Lys Ala Ser Asn Met
305                 310                 315                 320

Thr Gln Arg Trp Gln His Arg Glu Ile Ser Asn Phe Glu Tyr Leu Met
                325                 330                 335

Phe Leu Asn Thr Ile Ala Gly Arg Ser Tyr Asn Asp Leu Asn Gln Tyr
            340                 345                 350

Pro Val Phe Pro Trp Val Ile Thr Asn Tyr Glu Ser Glu Glu Leu Asp
        355                 360                 365

Leu Thr Leu Pro Ser Asn Phe Arg Asp Leu Ser Lys Pro Ile Gly Ala
    370                 375                 380

Leu Asn Pro Lys Arg Ala Ala Phe Phe Ala Glu Arg Phe Glu Ser Trp
385                 390                 395                 400

Glu Asp Asp Gln Val Pro Lys Phe His Tyr Gly Thr His Tyr Ser Thr
                405                 410                 415

Ala Ser Phe Val Leu Ala Trp Leu Leu Arg Ile Glu Pro Phe Thr Thr
            420                 425                 430

Tyr Phe Leu Asn Leu Gln Gly Gly Lys Phe Asp His Ala Asp Arg Thr
        435                 440                 445

Phe Ser Ser Val Ser Arg Ala Trp Arg Asn Ser Gln Arg Asp Thr Ser
    450                 455                 460

Asp Ile Lys Glu Leu Ile Pro Glu Phe Tyr Tyr Leu Pro Glu Met Phe
465                 470                 475                 480

Val Asn Phe Asn Asn Tyr Asn Leu Gly Val Met Asp Asp Gly Thr Val
                485                 490                 495

Val Ser Asp Val Glu Leu Pro Pro Trp Ala Lys Thr Ser Glu Glu Phe
            500                 505                 510

Val Arg Ile Asn Arg Leu Ala Leu Glu Ser Glu Phe Val Ser Cys Gln
        515                 520                 525

Leu His Gln Trp Ile Asp Leu Ile Phe Gly Tyr Lys Gln Gln Gly Pro
    530                 535                 540

Glu Ala Val Arg Ala Leu Asn Val Phe Tyr Tyr Leu Thr Tyr Glu Gly
545                 550                 555                 560

Ala Val Asn Leu Asn Ser Ile Thr Asp Pro Val Leu Arg Glu Ala Val
                565                 570                 575

Glu Ala Gln Ile Arg Ser Phe Gly Gln Thr Pro Ser Gln Leu Leu Ile
            580                 585                 590

Glu Pro His Pro Pro Arg Gly Ser Ala Met Gln Ala Ser Pro Leu Met
        595                 600                 605

Phe Thr Asp Gln Ala Gln Gln Asp Val Ile Met Val Leu Lys Phe Pro
    610                 615                 620

Ser Asn Ser Pro Val Thr His Val Ala Ala Asn Thr Gln Pro Gly Leu
625                 630                 635                 640

Ala Met Pro Ala Val Ile Thr Val Thr Ala Asn Arg Leu Phe Ala Val
                645                 650                 655

Asn Lys Trp His Asn Leu Pro Ala His Gln Gly Ala Val Gln Asp Gln
            660                 665                 670
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Pro Tyr Gln Leu Pro Val Glu Ile Asp Pro Leu Ile Gly Leu Pro Leu
        675                 680                 685

Leu Ser Leu Phe Ala Ile His
    690                 695


<210> SEQ ID NO 21
<211> LENGTH: 2586
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (1)..(72)
<223> OTHER INFORMATION: G peptide
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (82)..(393)
<223> OTHER INFORMATION: HSH (helix-sheet-helix) domain
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (979)..(1302)
<223> OTHER INFORMATION: SET Domain (Rich in Serine, Glutamic acid and
      Threonine)
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (2035)..(2169)
<223> OTHER INFORMATION: WDL (WD-like) domain
<220> FEATURE:
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<222> LOCATION: (2212)..(2489)
<223> OTHER INFORMATION: BEACH domain

<400> SEQUENCE: 21

Met Ala Ser Glu Asp Asn Arg Val Pro Ser Pro Pro Pro Thr Gly Asp
1               5                   10                  15

Asp Gly Gly Gly Gly Gly Arg Glu Glu Thr Pro Thr Glu Gly Gly Ala
            20                  25                  30

Leu Ser Leu Lys Pro Gly Leu Pro Ile Arg Gly Ile Arg Met Lys Phe
        35                  40                  45

Ala Val Leu Thr Gly Leu Val Glu Val Gly Glu Val Ser Asn Arg Asp
    50                  55                  60

Ile Val Glu Thr Val Phe Asn Leu Leu Val Gly Gly Gln Phe Asp Leu
65                  70                  75                  80

Glu Met Asn Phe Ile Ile Gln Glu Gly Glu Ser Ile Asn Cys Met Val
                85                  90                  95

Asp Leu Leu Glu Lys Cys Asp Ile Thr Cys Gln Ala Glu Val Trp Ser
            100                 105                 110

Met Phe Thr Ala Ile Leu Lys Lys Ser Ile Arg Asn Leu Gln Val Cys
        115                 120                 125

Thr Glu Val Gly Leu Val Glu Lys Val Leu Gly Lys Ile Glu Lys Val
    130                 135                 140

Asp Asn Met Ile Ala Asp Leu Leu Val Asp Met Leu Gly Val Leu Ala
145                 150                 155                 160

Ser Tyr Asn Leu Thr Val Arg Glu Leu Lys Leu Phe Phe Ser Lys Leu
                165                 170                 175

Gln Gly Asp Lys Gly Arg Trp Pro Pro His Ala Gly Lys Leu Leu Ser
            180                 185                 190

Val Leu Lys His Met Pro Gln Lys Tyr Gly Pro Asp Ala Phe Phe Asn
        195                 200                 205

Phe Pro Gly Lys Ser Ala Ala Ala Ile Ala Leu Pro Pro Ile Ala Lys
    210                 215                 220

Trp Pro Tyr Gln Asn Gly Phe Thr Phe His Thr Trp Leu Arg Met Asp
225                 230                 235                 240
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```
Pro Val Asn Asn Ile Asn Val Asp Lys Asp Lys Pro Tyr Leu Tyr Cys
                245                 250                 255

Phe Arg Thr Ser Lys Gly Leu Gly Tyr Ser Ala His Phe Val Gly Gly
            260                 265                 270

Cys Leu Ile Val Thr Ser Ile Lys Ser Lys Gly Lys Gly Phe Gln His
        275                 280                 285

Cys Val Lys Phe Asp Phe Lys Pro Gln Lys Trp Tyr Met Val Thr Ile
    290                 295                 300

Val His Ile Tyr Asn Arg Trp Lys Asn Ser Glu Leu Arg Cys Tyr Val
305                 310                 315                 320

Asn Gly Glu Leu Ala Ser Tyr Gly Glu Ile Thr Trp Phe Val Asn Thr
                325                 330                 335

Ser Asp Thr Phe Asp Lys Cys Phe Leu Gly Ser Ser Glu Thr Ala Asp
            340                 345                 350

Ala Asn Arg Val Phe Cys Gly Gln Met Thr Ala Val Tyr Leu Phe Ser
        355                 360                 365

Glu Ala Leu Asn Ala Ala Gln Ile Phe Ala Ile Tyr Gln Leu Gly Leu
    370                 375                 380

Gly Tyr Lys Gly Thr Phe Lys Phe Lys Ala Glu Ser Asp Leu Phe Leu
385                 390                 395                 400

Ala Glu His His Lys Leu Leu Leu Tyr Asp Gly Lys Leu Ser Ser Ala
                405                 410                 415

Ile Ala Phe Thr Tyr Asn Pro Arg Ala Thr Asp Ala Gln Leu Cys Leu
            420                 425                 430

Glu Ser Ser Pro Lys Asp Asn Pro Ser Ile Phe Val His Ser Pro His
        435                 440                 445

Ala Leu Met Leu Gln Asp Val Lys Ala Val Leu Thr His Ser Ile Gln
    450                 455                 460

Ser Ala Met His Ser Ile Gly Gly Val Gln Val Leu Phe Pro Leu Phe
465                 470                 475                 480

Ala Gln Leu Asp Tyr Arg Gln Tyr Leu Ser Asp Glu Ile Asp Leu Thr
                485                 490                 495

Ile Cys Ser Thr Leu Leu Ala Phe Ile Met Glu Leu Leu Lys Asn Ser
            500                 505                 510

Ile Ala Met Gln Glu Gln Met Leu Ala Cys Lys Gly Phe Leu Val Ile
        515                 520                 525

Gly Tyr Ser Leu Glu Lys Ser Ser Lys Ser His Val Ser Arg Ala Val
    530                 535                 540

Leu Glu Leu Cys Leu Ala Phe Ser Lys Tyr Leu Ser Asn Leu Gln Asn
545                 550                 555                 560

Gly Met Pro Leu Leu Lys Gln Leu Cys Asp His Val Leu Leu Asn Pro
                565                 570                 575

Ala Ile Trp Ile His Thr Pro Ala Lys Val Gln Leu Met Leu Tyr Thr
            580                 585                 590

Tyr Leu Ser Thr Glu Phe Ile Gly Thr Val Asn Ile Tyr Asn Thr Ile
        595                 600                 605

Arg Arg Val Gly Thr Val Leu Leu Ile Met His Thr Leu Lys Tyr Tyr
    610                 615                 620

Tyr Trp Ala Val Asn Pro Gln Asp Arg Ser Gly Ile Thr Pro Lys Gly
625                 630                 635                 640

Leu Asp Gly Pro Arg Pro Asn Gln Lys Glu Met Leu Ser Leu Arg Ala
                645                 650                 655
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Phe Leu Leu Met Phe Ile Lys Gln Leu Val Met Lys Asp Ser Gly Val
            660                 665                 670

Lys Glu Asp Glu Leu Gln Ala Ile Leu Asn Tyr Leu Leu Thr Met His
        675                 680                 685

Glu Asp Asp Asn Leu Met Asp Val Leu Gln Leu Leu Val Ala Leu Met
    690                 695                 700

Ser Glu His Pro Asn Ser Met Ile Pro Ala Phe Asp Gln Arg Asn Gly
705                 710                 715                 720

Leu Arg Val Ile Tyr Lys Leu Leu Ala Ser Lys Ser Glu Gly Ile Arg
                725                 730                 735

Val Gln Ala Leu Lys Ala Met Gly Tyr Phe Leu Lys His Arg Pro Pro
            740                 745                 750

Lys Arg Lys Ala Glu Val Met Leu Gly His Gly Leu Phe Ser Leu Leu
        755                 760                 765

Ala Glu Arg Leu Met Leu Gln Thr Asn Leu Ile Thr Met Thr Thr Tyr
    770                 775                 780

Asn Val Leu Phe Glu Ile Leu Ile Glu Gln Ile Gly Thr Gln Val Ile
785                 790                 795                 800

His Lys Gln His Pro Asp Pro Asp Ser Ser Val Lys Ile Gln Asn Pro
                805                 810                 815

Gln Ile Leu Lys Val Ile Ala Thr Leu Leu Arg Asn Ser Pro Gln Cys
            820                 825                 830

Pro Glu Ser Met Glu Val Arg Arg Ala Phe Leu Ser Asp Met Ile Lys
        835                 840                 845

Leu Phe Asn Asn Ser Arg Glu Asn Arg Arg Ser Leu Leu Gln Cys Ser
    850                 855                 860

Val Trp Gln Glu Trp Met Leu Ser Leu Cys Tyr Phe Asn Pro Lys Asn
865                 870                 875                 880

Ser Asp Glu Gln Lys Ile Thr Glu Met Val Tyr Ala Ile Phe Arg Ile
                885                 890                 895

Leu Leu Tyr His Ala Val Lys Tyr Glu Trp Gly Gly Trp Arg Val Trp
            900                 905                 910

Val Asp Thr Leu Ser Ile Thr His Ser Lys Val Thr Phe Glu Ile His
        915                 920                 925

Lys Glu Asn Leu Ala Asn Ile Phe Arg Glu Gln Gln Gly Lys Val Asp
    930                 935                 940

Glu Glu Ile Gly Leu Cys Ser Ser Thr Ser Val Gln Ala Ala Ser Gly
945                 950                 955                 960

Ile Arg Arg Asp Ile Asn Val Ser Val Gly Ser Gln Gln Pro Asp Thr
                965                 970                 975

Lys Asp Ser Pro Val Cys Pro His Phe Thr Thr Asn Gly Asn Glu Asn
            980                 985                 990

Ser Ser Ile Glu Lys Thr Ser Ser  Leu Glu Ser Ala Ser  Asn Ile Glu
        995                 1000                1005

Leu Gln  Thr Thr Asn Thr Ser  Tyr Glu Glu Met Lys  Ala Glu Gln
    1010                1015                1020

Glu Asn  Gln Glu Leu Pro Asp  Glu Gly Thr Leu Glu  Glu Thr Leu
    1025                1030                1035

Thr Asn  Glu Thr Arg Asn Ala  Asp Asp Leu Glu Val  Ser Ser Asp
    1040                1045                1050

Ile Ile  Glu Ala Val Ala Ile  Ser Ser Asn Ser Phe  Ile Thr Thr
    1055                1060                1065
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Gly Lys  Asp Ser Met Thr Val  Ser Glu Val Thr Ala  Ser Ile Ser
    1070                1075                1080

Ser Pro  Ser Glu Glu Asp Ala  Ser Glu Met Pro Glu  Phe Leu Asp
    1085                1090                1095

Lys Ser  Ile Val Glu Glu Glu  Glu Asp Asp Asp Tyr  Val Glu Leu
    1100                1105                1110

Lys Val  Glu Gly Ser Pro Thr  Glu Glu Ala Asn Leu  Pro Thr Glu
    1115                1120                1125

Leu Gln  Asp Asn Ser Leu Ser  Pro Ala Ala Ser Glu  Ala Gly Glu
    1130                1135                1140

Lys Leu  Asp Met Phe Gly Asn  Asp Asp Lys Leu Ile  Phe Gln Glu
    1145                1150                1155

Gly Lys  Pro Val Thr Glu Lys  Gln Thr Asp Thr Glu  Thr Gln Asp
    1160                1165                1170

Ser Lys  Asp Ser Gly Ile Gln  Thr Met Thr Ala Ser  Gly Ser Ser
    1175                1180                1185

Ala Met  Ser Pro Glu Thr Thr  Val Ser Gln Ile Ala  Val Glu Ser
    1190                1195                1200

Asp Leu  Gly Gln Met Leu Glu  Glu Gly Lys Lys Ala  Thr Asn Leu
    1205                1210                1215

Thr Arg  Glu Thr Lys Leu Ile  Asn Asp Cys His Gly  Ser Val Ser
    1220                1225                1230

Glu Ala  Ser Ser Glu Gln Lys  Ile Ala Lys Leu Asp  Val Ser Asn
    1235                1240                1245

Val Ala  Thr Asp Thr Glu Arg  Leu Glu Leu Lys Ala  Ser Pro Asn
    1250                1255                1260

Val Glu  Ala Pro Gln Pro His  Arg His Val Leu Glu  Ile Ser Arg
    1265                1270                1275

Gln His  Glu Gln Pro Gly Gln  Gly Ile Ala Pro Asp  Ala Val Asn
    1280                1285                1290

Gly Gln  Arg Arg Asp Ser Arg  Ser Thr Val Phe Arg  Ile Pro Glu
    1295                1300                1305

Phe Asn  Trp Ser Gln Met His  Gln Arg Leu Leu Thr  Asp Leu Leu
    1310                1315                1320

Phe Ser  Ile Glu Thr Asp Ile  Gln Met Trp Arg Ser  His Ser Thr
    1325                1330                1335

Lys Thr  Val Met Asp Phe Val  Asn Ser Ser Asp Asn  Val Ile Phe
    1340                1345                1350

Val His  Asn Thr Ile His Leu  Ile Ser Gln Val Met  Asp Asn Met
    1355                1360                1365

Val Met  Ala Cys Gly Gly Ile  Leu Pro Leu Leu Ser  Ala Ala Thr
    1370                1375                1380

Ser Ala  Thr His Glu Leu Glu  Asn Ile Glu Pro Thr  Gln Gly Leu
    1385                1390                1395

Ser Ile  Glu Ala Ser Val Thr  Phe Leu Gln Arg Leu  Ile Ser Leu
    1400                1405                1410

Val Asp  Val Leu Ile Phe Ala  Ser Ser Leu Gly Phe  Thr Glu Ile
    1415                1420                1425

Glu Ala  Glu Lys Ser Met Ser  Ser Gly Gly Ile Leu  Arg Gln Cys
    1430                1435                1440

Leu Arg  Leu Val Cys Ala Val  Ala Val Arg Asn Cys  Leu Glu Cys
    1445                1450                1455
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Gln Gln  His Ser Gln Leu Lys  Thr Arg Gly Asp Lys  Ala Leu Lys
    1460                 1465                 1470

Pro Met  His Ser Leu Ile Pro  Leu Gly Lys Ser Ala  Ala Lys Ser
    1475                 1480                 1485

Pro Val  Asp Ile Val Thr Gly  Gly Ile Ser Pro Val  Arg Asp Leu
    1490                 1495                 1500

Asp Arg  Leu Leu Gln Asp Met  Asp Ile Asn Arg Leu  Arg Ala Val
    1505                 1510                 1515

Val Phe  Arg Asp Ile Glu Asp  Ser Lys Gln Ala Gln  Phe Leu Ala
    1520                 1525                 1530

Leu Ala  Val Val Tyr Phe Ile  Ser Val Leu Met Val  Ser Lys Tyr
    1535                 1540                 1545

Arg Asp  Ile Leu Glu Pro Gln  Asn Glu Arg His Ser  Gln Ser Cys
    1550                 1555                 1560

Thr Glu  Thr Gly Ser Glu Asn  Glu Asn Val Ser Leu  Ser Glu Ile
    1565                 1570                 1575

Thr Pro  Ala Ala Phe Ser Thr  Leu Thr Thr Ala Ser  Val Glu Glu
    1580                 1585                 1590

Ser Glu  Ser Thr Ser Ser Ala  Arg Arg Arg Asp Ser  Gly Ile Gly
    1595                 1600                 1605

Glu Glu  Thr Ala Thr Gly Leu  Gly Ser His Val Glu  Val Thr Pro
    1610                 1615                 1620

His Thr  Ala Pro Pro Gly Val  Ser Ala Gly Pro Asp  Ala Ile Ser
    1625                 1630                 1635

Glu Val  Leu Ser Thr Leu Ser  Leu Glu Val Asn Lys  Ser Pro Glu
    1640                 1645                 1650

Thr Lys  Asn Asp Arg Gly Asn  Asp Leu Asp Thr Lys  Ala Thr Pro
    1655                 1660                 1665

Ser Val  Ser Val Ser Lys Asn  Val Asn Val Lys Asp  Ile Leu Arg
    1670                 1675                 1680

Ser Leu  Val Asn Ile Pro Ala  Asp Gly Val Thr Val  Asp Pro Ala
    1685                 1690                 1695

Leu Leu  Pro Pro Ala Cys Leu  Gly Ala Leu Gly Asp  Leu Ser Val
    1700                 1705                 1710

Glu Gln  Pro Val Gln Phe Arg  Ser Phe Asp Arg Ser  Val Ile Val
    1715                 1720                 1725

Ala Ala  Lys Lys Ser Ala Val  Ser Pro Ser Thr Phe  Asn Thr Ser
    1730                 1735                 1740

Ile Pro  Thr Asn Ala Val Ser  Val Val Ser Ser Val  Asp Ser Ala
    1745                 1750                 1755

Gln Ala  Ser Asp Met Gly Gly  Glu Ser Pro Gly Ser  Arg Ser Ser
    1760                 1765                 1770

Asn Ala  Lys Leu Pro Ser Val  Pro Thr Val Asp Ser  Val Ser Gln
    1775                 1780                 1785

Asp Pro  Val Ser Asn Met Ser  Ile Thr Glu Arg Leu  Glu His Ala
    1790                 1795                 1800

Leu Glu  Lys Ala Ala Pro Leu  Leu Arg Glu Ile Phe  Val Asp Phe
    1805                 1810                 1815

Ala Pro  Phe Leu Ser Arg Thr  Leu Leu Gly Ser His  Gly Gln Glu
    1820                 1825                 1830

Leu Leu  Ile Glu Gly Thr Ser  Leu Val Cys Met Lys  Ser Ser Ser
    1835                 1840                 1845
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Ser Val  Val Glu Leu Val Met  Leu Leu Cys Ser Gln  Glu Trp Gln
    1850                 1855                 1860

Asn Ser  Ile Gln Lys Asn Ala  Gly Leu Ala Phe Ile  Glu Leu Val
    1865                 1870                 1875

Asn Glu  Gly Arg Leu Leu Ser  Gln Thr Met Lys Asp  His Leu Val
    1880                 1885                 1890

Arg Val  Ala Asn Glu Ala Glu  Phe Ile Leu Ser Arg  Gln Arg Ala
    1895                 1900                 1905

Glu Asp  Ile His Arg His Ala  Glu Phe Glu Ser Leu  Cys Ala Gln
    1910                 1915                 1920

Tyr Ser  Ala Asp Lys Arg Glu  Asp Glu Lys Met Cys  Asp His Leu
    1925                 1930                 1935

Ile Arg  Ala Ala Lys Tyr Arg  Asp His Val Thr Ala  Thr Gln Leu
    1940                 1945                 1950

Ile Gln  Lys Ile Ile Asn Ile  Leu Thr Asp Lys His  Gly Ala Trp
    1955                 1960                 1965

Gly Asn  Ser Ala Val Ser Arg  Pro Leu Glu Phe Trp  Arg Leu Asp
    1970                 1975                 1980

Tyr Trp  Glu Asp Asp Leu Arg  Arg Arg Arg Arg Phe  Val Arg Asn
    1985                 1990                 1995

Pro Leu  Gly Ser Thr His Pro  Glu Ala Thr Leu Lys  Thr Ala Val
    2000                 2005                 2010

Glu His  Val Cys Ile Phe Lys  Leu Arg Glu Asn Ser  Lys Ala Thr
    2015                 2020                 2025

Asp Glu  Asp Ile Leu Ala Lys  Gly Lys Gln Ser Ile  Arg Ser Gln
    2030                 2035                 2040

Ala Leu  Gly Asn Gln Asn Ser  Glu Asn Glu Ile Leu  Leu Glu Gly
    2045                 2050                 2055

Asp Asp  Asp Thr Leu Ser Ser  Val Asp Glu Lys Asp  Leu Glu Asn
    2060                 2065                 2070

Leu Ala  Gly Pro Val Ser Leu  Ser Thr Pro Ala Gln  Leu Val Ala
    2075                 2080                 2085

Pro Ser  Val Val Val Lys Gly  Thr Leu Ser Val Thr  Ser Ser Glu
    2090                 2095                 2100

Leu Tyr  Phe Glu Val Asp Glu  Glu Asp Pro Asn Phe  Lys Lys Ile
    2105                 2110                 2115

Asp Pro  Lys Ile Leu Ala Tyr  Thr Glu Gly Leu His  Gly Lys Trp
    2120                 2125                 2130

Leu Phe  Thr Glu Ile Arg Ser  Ile Phe Ser Arg Arg  Tyr Leu Leu
    2135                 2140                 2145

Gln Asn  Thr Ala Leu Glu Ile  Phe Met Ala Asn Arg  Val Ala Val
    2150                 2155                 2160

Met Phe  Asn Phe Pro Asp Pro  Ala Thr Val Lys Lys  Val Val Asn
    2165                 2170                 2175

Phe Leu  Pro Arg Val Gly Val  Gly Thr Ser Phe Gly  Leu Pro Gln
    2180                 2185                 2190

Thr Arg  Arg Ile Ser Leu Ala  Ser Pro Arg Gln Leu  Phe Lys Ala
    2195                 2200                 2205

Ser Asn  Met Thr Gln Arg Trp  Gln His Arg Glu Ile  Ser Asn Phe
    2210                 2215                 2220

Glu Tyr  Leu Met Phe Leu Asn  Thr Ile Ala Gly Arg  Ser Tyr Asn
    2225                 2230                 2235
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Asp Leu  Asn Gln Tyr Pro Val  Phe Pro Trp Val Ile  Thr Asn Tyr
    2240                2245                2250

Glu Ser  Glu Glu Leu Asp Leu  Thr Leu Pro Thr Asn  Phe Arg Asp
    2255                2260                2265

Leu Ser  Lys Pro Ile Gly Ala  Leu Asn Pro Lys Arg  Ala Ala Phe
    2270                2275                2280

Phe Ala  Glu Arg Tyr Glu Ser  Trp Glu Asp Asp Gln  Val Pro Lys
    2285                2290                2295

Phe His  Tyr Gly Thr His Tyr  Ser Thr Ala Ser Phe  Val Leu Ala
    2300                2305                2310

Trp Leu  Leu Arg Ile Glu Pro  Phe Thr Thr Tyr Phe  Leu Asn Leu
    2315                2320                2325

Gln Gly  Gly Lys Phe Asp His  Ala Asp Arg Thr Phe  Ser Ser Ile
    2330                2335                2340

Ser Arg  Ala Trp Arg Asn Ser  Gln Arg Asp Thr Ser  Asp Ile Lys
    2345                2350                2355

Glu Leu  Ile Pro Glu Phe Tyr  Tyr Leu Pro Glu Met  Phe Val Asn
    2360                2365                2370

Phe Asn  Asn Tyr Asn Leu Gly  Val Met Asp Asp Gly  Thr Val Val
    2375                2380                2385

Ser Asp  Val Glu Leu Pro Pro  Trp Ala Lys Thr Ser  Glu Glu Phe
    2390                2395                2400

Val His  Ile Asn Arg Leu Ala  Leu Glu Ser Glu Phe  Val Ser Cys
    2405                2410                2415

Gln Leu  His Gln Trp Ile Asp  Leu Ile Phe Gly Tyr  Lys Gln Gln
    2420                2425                2430

Gly Pro  Glu Ala Val Arg Ala  Leu Asn Val Phe Tyr  Tyr Leu Thr
    2435                2440                2445

Tyr Glu  Gly Ala Val Asn Leu  Asn Ser Ile Thr Asp  Pro Val Leu
    2450                2455                2460

Arg Glu  Ala Val Glu Ala Gln  Ile Arg Ser Phe Gly  Gln Thr Pro
    2465                2470                2475

Ser Gln  Leu Leu Ile Glu Pro  His Pro Pro Arg Gly  Ser Ala Met
    2480                2485                2490

Gln Val  Ser Pro Leu Met Phe  Thr Asp Lys Ala Gln  Gln Asp Val
    2495                2500                2505

Ile Met  Val Leu Lys Phe Pro  Ser Asn Ser Pro Val  Thr His Val
    2510                2515                2520

Ala Ala  Asn Thr Gln Pro Gly  Leu Ala Thr Pro Ala  Val Ile Thr
    2525                2530                2535

Val Thr  Ala Asn Arg Leu Phe  Ala Val Asn Lys Trp  His Asn Leu
    2540                2545                2550

Pro Ala  His Gln Gly Ala Val  Gln Asp Gln Pro Tyr  Gln Leu Pro
    2555                2560                2565

Val Glu  Ile Asp Pro Leu Ile  Gly Leu Ser Leu Pro  Ser Leu Phe
    2570                2575                2580

Ala Ile  His
    2585


<210> SEQ ID NO 22
<211> LENGTH: 2868
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
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<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (1)..(72)
<223> OTHER INFORMATION: G peptide
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (82)..(393)
<223> OTHER INFORMATION: HSH (helix-sheet-helix) domain
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (979)..(1302)
<223> OTHER INFORMATION: SET Domain (Rich in Serine, Glutamic acid and Threonine)
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (2035)..(2169)
<223> OTHER INFORMATION: WDL (WD-like) domain
<220> FEATURE:
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<222> LOCATION: (2212)..(2489)
<223> OTHER INFORMATION: BEACH domain
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<223> OTHER INFORMATION: WD repeat
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<400> SEQUENCE: 22

Met Ala Ser Glu Asp Asn Arg Val Pro Ser Pro Pro Pro Thr Gly Asp
1 5 10 15

Asp Gly Gly Gly Gly Gly Arg Glu Glu Thr Pro Thr Glu Gly Gly Ala
20 25 30

Leu Ser Leu Lys Pro Gly Leu Pro Ile Arg Gly Ile Arg Met Lys Phe
35 40 45

Ala Val Leu Thr Gly Leu Val Glu Val Gly Glu Val Ser Asn Arg Asp
50 55 60

Ile Val Glu Thr Val Phe Asn Leu Leu Val Gly Gly Gln Phe Asp Leu
65 70 75 80

Glu Met Asn Phe Ile Ile Gln Glu Gly Glu Ser Ile Asn Cys Met Val
85 90 95

Asp Leu Leu Glu Lys Cys Asp Ile Thr Cys Gln Ala Glu Val Trp Ser
100 105 110

Met Phe Thr Ala Ile Leu Lys Lys Ser Ile Arg Asn Leu Gln Val Cys
115 120 125

Thr Glu Val Gly Leu Val Glu Lys Val Leu Gly Lys Ile Glu Lys Val
130 135 140

Asp Asn Met Ile Ala Asp Leu Leu Val Asp Met Leu Gly Val Leu Ala
145 150 155 160

Ser Tyr Asn Leu Thr Val Arg Glu Leu Lys Leu Phe Phe Ser Lys Leu
165 170 175

Gln Gly Asp Lys Gly Arg Trp Pro Pro His Ala Gly Lys Leu Leu Ser
180 185 190

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Val Leu Lys His Met Pro Gln Lys Tyr Gly Pro Asp Ala Phe Phe Asn
        195                 200                 205

Phe Pro Gly Lys Ser Ala Ala Ala Ile Ala Leu Pro Pro Ile Ala Lys
    210                 215                 220

Trp Pro Tyr Gln Asn Gly Phe Thr Phe His Thr Trp Leu Arg Met Asp
225                 230                 235                 240

Pro Val Asn Asn Ile Asn Val Asp Lys Asp Lys Pro Tyr Leu Tyr Cys
                245                 250                 255

Phe Arg Thr Ser Lys Gly Leu Gly Tyr Ser Ala His Phe Val Gly Gly
            260                 265                 270

Cys Leu Ile Val Thr Ser Ile Lys Ser Lys Gly Lys Gly Phe Gln His
        275                 280                 285

Cys Val Lys Phe Asp Phe Lys Pro Gln Lys Trp Tyr Met Val Thr Ile
    290                 295                 300

Val His Ile Tyr Asn Arg Trp Lys Asn Ser Glu Leu Arg Cys Tyr Val
305                 310                 315                 320

Asn Gly Glu Leu Ala Ser Tyr Gly Glu Ile Thr Trp Phe Val Asn Thr
                325                 330                 335

Ser Asp Thr Phe Asp Lys Cys Phe Leu Gly Ser Ser Glu Thr Ala Asp
            340                 345                 350

Ala Asn Arg Val Phe Cys Gly Gln Met Thr Ala Val Tyr Leu Phe Ser
        355                 360                 365

Glu Ala Leu Asn Ala Ala Gln Ile Phe Ala Ile Tyr Gln Leu Gly Leu
    370                 375                 380

Gly Tyr Lys Gly Thr Phe Lys Phe Lys Ala Glu Ser Asp Leu Phe Leu
385                 390                 395                 400

Ala Glu His His Lys Leu Leu Leu Tyr Asp Gly Lys Leu Ser Ser Ala
                405                 410                 415

Ile Ala Phe Thr Tyr Asn Pro Arg Ala Thr Asp Ala Gln Leu Cys Leu
            420                 425                 430

Glu Ser Ser Pro Lys Asp Asn Pro Ser Ile Phe Val His Ser Pro His
        435                 440                 445

Ala Leu Met Leu Gln Asp Val Lys Ala Val Leu Thr His Ser Ile Gln
    450                 455                 460

Ser Ala Met His Ser Ile Gly Gly Val Gln Val Leu Phe Pro Leu Phe
465                 470                 475                 480

Ala Gln Leu Asp Tyr Arg Gln Tyr Leu Ser Asp Glu Ile Asp Leu Thr
                485                 490                 495

Ile Cys Ser Thr Leu Leu Ala Phe Ile Met Glu Leu Leu Lys Asn Ser
            500                 505                 510

Ile Ala Met Gln Glu Gln Met Leu Ala Cys Lys Gly Phe Leu Val Ile
        515                 520                 525

Gly Tyr Ser Leu Glu Lys Ser Ser Lys Ser His Val Ser Arg Ala Val
    530                 535                 540

Leu Glu Leu Cys Leu Ala Phe Ser Lys Tyr Leu Ser Asn Leu Gln Asn
545                 550                 555                 560

Gly Met Pro Leu Leu Lys Gln Leu Cys Asp His Val Leu Leu Asn Pro
                565                 570                 575

Ala Ile Trp Ile His Thr Pro Ala Lys Val Gln Leu Met Leu Tyr Thr
            580                 585                 590

Tyr Leu Ser Thr Glu Phe Ile Gly Thr Val Asn Ile Tyr Asn Thr Ile
        595                 600                 605
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Arg Arg Val Gly Thr Val Leu Leu Ile Met His Thr Leu Lys Tyr Tyr
    610                 615                 620

Tyr Trp Ala Val Asn Pro Gln Asp Arg Ser Gly Ile Thr Pro Lys Gly
625                 630                 635                 640

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

Phe Leu Leu Met Phe Ile Lys Gln Leu Val Met Lys Asp Ser Gly Val
            660                 665                 670

Lys Glu Asp Glu Leu Gln Ala Ile Leu Asn Tyr Leu Leu Thr Met His
        675                 680                 685

Glu Asp Asp Asn Leu Met Asp Val Leu Gln Leu Leu Val Ala Leu Met
    690                 695                 700

Ser Glu His Pro Asn Ser Met Ile Pro Ala Phe Asp Gln Arg Asn Gly
705                 710                 715                 720

Leu Arg Val Ile Tyr Lys Leu Leu Ala Ser Lys Ser Glu Gly Ile Arg
                725                 730                 735

Val Gln Ala Leu Lys Ala Met Gly Tyr Phe Leu Lys His Arg Pro Pro
            740                 745                 750

Lys Arg Lys Ala Glu Val Met Leu Gly His Gly Leu Phe Ser Leu Leu
        755                 760                 765

Ala Glu Arg Leu Met Leu Gln Thr Asn Leu Ile Thr Met Thr Thr Tyr
    770                 775                 780

Asn Val Leu Phe Glu Ile Leu Ile Glu Gln Ile Gly Thr Gln Val Ile
785                 790                 795                 800

His Lys Gln His Pro Asp Pro Asp Ser Ser Val Lys Ile Gln Asn Pro
                805                 810                 815

Gln Ile Leu Lys Val Ile Ala Thr Leu Leu Arg Asn Ser Pro Gln Cys
            820                 825                 830

Pro Glu Ser Met Glu Val Arg Arg Ala Phe Leu Ser Asp Met Ile Lys
        835                 840                 845

Leu Phe Asn Asn Ser Arg Glu Asn Arg Arg Ser Leu Leu Gln Cys Ser
    850                 855                 860

Val Trp Gln Glu Trp Met Leu Ser Leu Cys Tyr Phe Asn Pro Lys Asn
865                 870                 875                 880

Ser Asp Glu Gln Lys Ile Thr Glu Met Val Tyr Ala Ile Phe Arg Ile
                885                 890                 895

Leu Leu Tyr His Ala Val Lys Tyr Glu Trp Gly Gly Trp Arg Val Trp
            900                 905                 910

Val Asp Thr Leu Ser Ile Thr His Ser Lys Val Thr Phe Glu Ile His
        915                 920                 925

Lys Glu Asn Leu Ala Asn Ile Phe Arg Glu Gln Gln Gly Lys Val Asp
    930                 935                 940

Glu Glu Ile Gly Leu Cys Ser Ser Thr Ser Val Gln Ala Ala Ser Gly
945                 950                 955                 960

Ile Arg Arg Asp Ile Asn Val Ser Val Gly Ser Gln Gln Pro Asp Thr
                965                 970                 975

Lys Asp Ser Pro Val Cys Pro His Phe Thr Thr Asn Gly Asn Glu Asn
            980                 985                 990

Ser Ser Ile Glu Lys Thr Ser Ser  Leu Glu Ser Ala Ser  Asn Ile Glu
        995                 1000                1005

Leu Gln  Thr Thr Asn Thr Ser  Tyr Glu Glu Met Lys  Ala Glu Gln
    1010                1015                1020
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Glu Asn  Gln Glu Leu Pro Asp  Glu Gly Thr Leu Glu  Glu Thr Leu
    1025                 1030                 1035

Thr Asn  Glu Thr Arg Asn Ala  Asp Asp Leu Glu Val  Ser Ser Asp
    1040                 1045                 1050

Ile Ile  Glu Ala Val Ala Ile  Ser Ser Asn Ser Phe  Ile Thr Thr
    1055                 1060                 1065

Gly Lys  Asp Ser Met Thr Val  Ser Glu Val Thr Ala  Ser Ile Ser
    1070                 1075                 1080

Ser Pro  Ser Glu Glu Asp Ala  Ser Glu Met Pro Glu  Phe Leu Asp
    1085                 1090                 1095

Lys Ser  Ile Val Glu Glu Glu  Glu Asp Asp Asp Tyr  Val Glu Leu
    1100                 1105                 1110

Lys Val  Glu Gly Ser Pro Thr  Glu Glu Ala Asn Leu  Pro Thr Glu
    1115                 1120                 1125

Leu Gln  Asp Asn Ser Leu Ser  Pro Ala Ala Ser Glu  Ala Gly Glu
    1130                 1135                 1140

Lys Leu  Asp Met Phe Gly Asn  Asp Asp Lys Leu Ile  Phe Gln Glu
    1145                 1150                 1155

Gly Lys  Pro Val Thr Glu Lys  Gln Thr Asp Thr Glu  Thr Gln Asp
    1160                 1165                 1170

Ser Lys  Asp Ser Gly Ile Gln  Thr Met Thr Ala Ser  Gly Ser Ser
    1175                 1180                 1185

Ala Met  Ser Pro Glu Thr Thr  Val Ser Gln Ile Ala  Val Glu Ser
    1190                 1195                 1200

Asp Leu  Gly Gln Met Leu Glu  Glu Gly Lys Lys Ala  Thr Asn Leu
    1205                 1210                 1215

Thr Arg  Glu Thr Lys Leu Ile  Asn Asp Cys His Gly  Ser Val Ser
    1220                 1225                 1230

Glu Ala  Ser Ser Glu Gln Lys  Ile Ala Lys Leu Asp  Val Ser Asn
    1235                 1240                 1245

Val Ala  Thr Asp Thr Glu Arg  Leu Glu Leu Lys Ala  Ser Pro Asn
    1250                 1255                 1260

Val Glu  Ala Pro Gln Pro His  Arg His Val Leu Glu  Ile Ser Arg
    1265                 1270                 1275

Gln His  Glu Gln Pro Gly Gln  Gly Ile Ala Pro Asp  Ala Val Asn
    1280                 1285                 1290

Gly Gln  Arg Arg Asp Ser Arg  Ser Thr Val Phe Arg  Ile Pro Glu
    1295                 1300                 1305

Phe Asn  Trp Ser Gln Met His  Gln Arg Leu Leu Thr  Asp Leu Leu
    1310                 1315                 1320

Phe Ser  Ile Glu Thr Asp Ile  Gln Met Trp Arg Ser  His Ser Thr
    1325                 1330                 1335

Lys Thr  Val Met Asp Phe Val  Asn Ser Ser Asp Asn  Val Ile Phe
    1340                 1345                 1350

Val His  Asn Thr Ile His Leu  Ile Ser Gln Val Met  Asp Asn Met
    1355                 1360                 1365

Val Met  Ala Cys Gly Gly Ile  Leu Pro Leu Leu Ser  Ala Ala Thr
    1370                 1375                 1380

Ser Ala  Thr His Glu Leu Glu  Asn Ile Glu Pro Thr  Gln Gly Leu
    1385                 1390                 1395

Ser Ile  Glu Ala Ser Val Thr  Phe Leu Gln Arg Leu  Ile Ser Leu
    1400                 1405                 1410
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Val Asp  Val Leu Ile Phe Ala  Ser Ser Leu Gly Phe  Thr Glu Ile
    1415                 1420                 1425

Glu Ala  Glu Lys Ser Met Ser  Ser Gly Gly Ile Leu  Arg Gln Cys
    1430                 1435                 1440

Leu Arg  Leu Val Cys Ala Val  Ala Val Arg Asn Cys  Leu Glu Cys
    1445                 1450                 1455

Gln Gln  His Ser Gln Leu Lys  Thr Arg Gly Asp Lys  Ala Leu Lys
    1460                 1465                 1470

Pro Met  His Ser Leu Ile Pro  Leu Gly Lys Ser Ala  Ala Lys Ser
    1475                 1480                 1485

Pro Val  Asp Ile Val Thr Gly  Gly Ile Ser Pro Val  Arg Asp Leu
    1490                 1495                 1500

Asp Arg  Leu Leu Gln Asp Met  Asp Ile Asn Arg Leu  Arg Ala Val
    1505                 1510                 1515

Val Phe  Arg Asp Ile Glu Asp  Ser Lys Gln Ala Gln  Phe Leu Ala
    1520                 1525                 1530

Leu Ala  Val Val Tyr Phe Ile  Ser Val Leu Met Val  Ser Lys Tyr
    1535                 1540                 1545

Arg Asp  Ile Leu Glu Pro Gln  Asn Glu Arg His Ser  Gln Ser Cys
    1550                 1555                 1560

Thr Glu  Thr Gly Ser Glu Asn  Glu Asn Val Ser Leu  Ser Glu Ile
    1565                 1570                 1575

Thr Pro  Ala Ala Phe Ser Thr  Leu Thr Thr Ala Ser  Val Glu Glu
    1580                 1585                 1590

Ser Glu  Ser Thr Ser Ser Ala  Arg Arg Arg Asp Ser  Gly Ile Gly
    1595                 1600                 1605

Glu Glu  Thr Ala Thr Gly Leu  Gly Ser His Val Glu  Val Thr Pro
    1610                 1615                 1620

His Thr  Ala Pro Pro Gly Val  Ser Ala Gly Pro Asp  Ala Ile Ser
    1625                 1630                 1635

Glu Val  Leu Ser Thr Leu Ser  Leu Glu Val Asn Lys  Ser Pro Glu
    1640                 1645                 1650

Thr Lys  Asn Asp Arg Gly Asn  Asp Leu Asp Thr Lys  Ala Thr Pro
    1655                 1660                 1665

Ser Val  Ser Val Ser Lys Asn  Val Asn Val Lys Asp  Ile Leu Arg
    1670                 1675                 1680

Ser Leu  Val Asn Ile Pro Ala  Asp Gly Val Thr Val  Asp Pro Ala
    1685                 1690                 1695

Leu Leu  Pro Pro Ala Cys Leu  Gly Ala Leu Gly Asp  Leu Ser Val
    1700                 1705                 1710

Glu Gln  Pro Val Gln Phe Arg  Ser Phe Asp Arg Ser  Val Ile Val
    1715                 1720                 1725

Ala Ala  Lys Lys Ser Ala Val  Ser Pro Ser Thr Phe  Asn Thr Ser
    1730                 1735                 1740

Ile Pro  Thr Asn Ala Val Ser  Val Val Ser Ser Val  Asp Ser Ala
    1745                 1750                 1755

Gln Ala  Ser Asp Met Gly Gly  Glu Ser Pro Gly Ser  Arg Ser Ser
    1760                 1765                 1770

Asn Ala  Lys Leu Pro Ser Val  Pro Thr Val Asp Ser  Val Ser Gln
    1775                 1780                 1785

Asp Pro  Val Ser Asn Met Ser  Ile Thr Glu Arg Leu  Glu His Ala
    1790                 1795                 1800
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Leu Glu  Lys Ala Ala Pro Leu  Leu Arg Glu Ile Phe  Val Asp Phe
    1805                 1810                 1815

Ala Pro  Phe Leu Ser Arg Thr  Leu Leu Gly Ser His  Gly Gln Glu
    1820                 1825                 1830

Leu Leu  Ile Glu Gly Thr Ser  Leu Val Cys Met Lys  Ser Ser Ser
    1835                 1840                 1845

Ser Val  Val Glu Leu Val Met  Leu Leu Cys Ser Gln  Glu Trp Gln
    1850                 1855                 1860

Asn Ser  Ile Gln Lys Asn Ala  Gly Leu Ala Phe Ile  Glu Leu Val
    1865                 1870                 1875

Asn Glu  Gly Arg Leu Leu Ser  Gln Thr Met Lys Asp  His Leu Val
    1880                 1885                 1890

Arg Val  Ala Asn Glu Ala Glu  Phe Ile Leu Ser Arg  Gln Arg Ala
    1895                 1900                 1905

Glu Asp  Ile His Arg His Ala  Glu Phe Glu Ser Leu  Cys Ala Gln
    1910                 1915                 1920

Tyr Ser  Ala Asp Lys Arg Glu  Asp Glu Lys Met Cys  Asp His Leu
    1925                 1930                 1935

Ile Arg  Ala Ala Lys Tyr Arg  Asp His Val Thr Ala  Thr Gln Leu
    1940                 1945                 1950

Ile Gln  Lys Ile Ile Asn Ile  Leu Thr Asp Lys His  Gly Ala Trp
    1955                 1960                 1965

Gly Asn  Ser Ala Val Ser Arg  Pro Leu Glu Phe Trp  Arg Leu Asp
    1970                 1975                 1980

Tyr Trp  Glu Asp Asp Leu Arg  Arg Arg Arg Arg Phe  Val Arg Asn
    1985                 1990                 1995

Pro Leu  Gly Ser Thr His Pro  Glu Ala Thr Leu Lys  Thr Ala Val
    2000                 2005                 2010

Glu His  Val Cys Ile Phe Lys  Leu Arg Glu Asn Ser  Lys Ala Thr
    2015                 2020                 2025

Asp Glu  Asp Ile Leu Ala Lys  Gly Lys Gln Ser Ile  Arg Ser Gln
    2030                 2035                 2040

Ala Leu  Gly Asn Gln Asn Ser  Glu Asn Glu Ile Leu  Leu Glu Gly
    2045                 2050                 2055

Asp Asp  Asp Thr Leu Ser Ser  Val Asp Glu Lys Asp  Leu Glu Asn
    2060                 2065                 2070

Leu Ala  Gly Pro Val Ser Leu  Ser Thr Pro Ala Gln  Leu Val Ala
    2075                 2080                 2085

Pro Ser  Val Val Val Lys Gly  Thr Leu Ser Val Thr  Ser Ser Glu
    2090                 2095                 2100

Leu Tyr  Phe Glu Val Asp Glu  Glu Asp Pro Asn Phe  Lys Lys Ile
    2105                 2110                 2115

Asp Pro  Lys Ile Leu Ala Tyr  Thr Glu Gly Leu His  Gly Lys Trp
    2120                 2125                 2130

Leu Phe  Thr Glu Ile Arg Ser  Ile Phe Ser Arg Arg  Tyr Leu Leu
    2135                 2140                 2145

Gln Asn  Thr Ala Leu Glu Ile  Phe Met Ala Asn Arg  Val Ala Val
    2150                 2155                 2160

Met Phe  Asn Phe Pro Asp Pro  Ala Thr Val Lys Lys  Val Val Asn
    2165                 2170                 2175

Phe Leu  Pro Arg Val Gly Val  Gly Thr Ser Phe Gly  Leu Pro Gln
    2180                 2185                 2190
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Thr Arg  Arg Ile Ser Leu Ala  Ser Pro Arg Gln Leu  Phe Lys Ala
    2195                 2200                 2205

Ser Asn  Met Thr Gln Arg Trp  Gln His Arg Glu Ile  Ser Asn Phe
    2210                 2215                 2220

Glu Tyr  Leu Met Phe Leu Asn  Thr Ile Ala Gly Arg  Ser Tyr Asn
    2225                 2230                 2235

Asp Leu  Asn Gln Tyr Pro Val  Phe Pro Trp Val Ile  Thr Asn Tyr
    2240                 2245                 2250

Glu Ser  Glu Glu Leu Asp Leu  Thr Leu Pro Thr Asn  Phe Arg Asp
    2255                 2260                 2265

Leu Ser  Lys Pro Ile Gly Ala  Leu Asn Pro Lys Arg  Ala Ala Phe
    2270                 2275                 2280

Phe Ala  Glu Arg Tyr Glu Ser  Trp Glu Asp Asp Gln  Val Pro Lys
    2285                 2290                 2295

Phe His  Tyr Gly Thr His Tyr  Ser Thr Ala Ser Phe  Val Leu Ala
    2300                 2305                 2310

Trp Leu  Leu Arg Ile Glu Pro  Phe Thr Thr Tyr Phe  Leu Asn Leu
    2315                 2320                 2325

Gln Gly  Gly Lys Phe Asp His  Ala Asp Arg Thr Phe  Ser Ser Ile
    2330                 2335                 2340

Ser Arg  Ala Trp Arg Asn Ser  Gln Arg Asp Thr Ser  Asp Ile Lys
    2345                 2350                 2355

Glu Leu  Ile Pro Glu Phe Tyr  Tyr Leu Pro Glu Met  Phe Val Asn
    2360                 2365                 2370

Phe Asn  Asn Tyr Asn Leu Gly  Val Met Asp Asp Gly  Thr Val Val
    2375                 2380                 2385

Ser Asp  Val Glu Leu Pro Pro  Trp Ala Lys Thr Ser  Glu Glu Phe
    2390                 2395                 2400

Val His  Ile Asn Arg Leu Ala  Leu Glu Ser Glu Phe  Val Ser Cys
    2405                 2410                 2415

Gln Leu  His Gln Trp Ile Asp  Leu Ile Phe Gly Tyr  Lys Gln Gln
    2420                 2425                 2430

Gly Pro  Glu Ala Val Arg Ala  Leu Asn Val Phe Tyr  Tyr Leu Thr
    2435                 2440                 2445

Tyr Glu  Gly Ala Val Asn Leu  Asn Ser Ile Thr Asp  Pro Val Leu
    2450                 2455                 2460

Arg Glu  Ala Val Glu Ala Gln  Ile Arg Ser Phe Gly  Gln Thr Pro
    2465                 2470                 2475

Ser Gln  Leu Leu Ile Glu Pro  His Pro Pro Arg Gly  Ser Ala Met
    2480                 2485                 2490

Gln Val  Tyr Leu Leu Leu Gln  Ser Pro Leu Met Phe  Thr Asp Lys
    2495                 2500                 2505

Ala Gln  Gln Asp Val Ile Met  Val Leu Lys Phe Pro  Ser Asn Ser
    2510                 2515                 2520

Pro Val  Thr His Val Ala Ala  Asn Thr Gln Pro Gly  Leu Ala Thr
    2525                 2530                 2535

Pro Ala  Val Ile Thr Val Thr  Ala Asn Arg Leu Phe  Ala Val Asn
    2540                 2545                 2550

Lys Trp  His Asn Leu Pro Ala  His Gln Gly Ala Val  Gln Asp Gln
    2555                 2560                 2565

Pro Tyr  Gln Leu Pro Val Glu  Ile Asp Pro Leu Ile  Ala Ser Asn
    2570                 2575                 2580
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Thr Gly  Met His Arg Arg Gln  Ile Thr Asp Leu Leu  Asp Gln Ser
    2585                 2590                 2595

Ile Gln  Val His Ser Gln Cys  Phe Val Ile Thr Ser  Asp Asn Arg
    2600                 2605                 2610

Tyr Ile  Leu Val Cys Gly Phe  Trp Asp Lys Ser Phe  Arg Val Tyr
    2615                 2620                 2625

Ser Thr  Asp Thr Gly Arg Leu  Ile Gln Val Val Phe  Gly His Trp
    2630                 2635                 2640

Asp Val  Val Thr Cys Leu Ala  Arg Ser Glu Ser Tyr  Ile Gly Gly
    2645                 2650                 2655

Asn Cys  Tyr Ile Leu Ser Gly  Ser Arg Asp Ala Thr  Leu Leu Leu
    2660                 2665                 2670

Trp Tyr  Trp Asn Gly Lys Cys  Ser Gly Ile Gly Asp  Asn Pro Gly
    2675                 2680                 2685

Ser Glu  Thr Ala Ala Pro Arg  Ala Ile Leu Thr Gly  His Asp Tyr
    2690                 2695                 2700

Glu Val  Thr Cys Ala Ala Val  Cys Ala Glu Leu Gly  Leu Val Leu
    2705                 2710                 2715

Ser Gly  Ser Gln Glu Gly Pro  Cys Leu Ile His Ser  Met Asn Gly
    2720                 2725                 2730

Asp Leu  Leu Arg Thr Leu Glu  Gly Pro Glu Asn Cys  Leu Lys Pro
    2735                 2740                 2745

Lys Leu  Ile Gln Ala Ser Arg  Glu Gly His Cys Val  Ile Phe Tyr
    2750                 2755                 2760

Glu Asn  Gly Leu Phe Cys Thr  Phe Ser Val Asn Gly  Lys Leu Gln
    2765                 2770                 2775

Ala Thr  Met Glu Thr Asp Asp  Asn Ile Arg Ala Ile  Gln Leu Ser
    2780                 2785                 2790

Arg Asp  Gly Gln Tyr Leu Leu  Thr Gly Gly Asp Arg  Gly Val Val
    2795                 2800                 2805

Val Val  Arg Gln Val Ser Asp  Leu Lys Gln Leu Phe  Ala Tyr Pro
    2810                 2815                 2820

Gly Cys  Asp Ala Gly Ile Arg  Ala Met Ala Leu Ser  Tyr Asp Gln
    2825                 2830                 2835

Arg Cys  Ile Ile Ser Gly Met  Ala Ser Gly Ser Ile  Val Leu Phe
    2840                 2845                 2850

Tyr Asn  Asp Phe Asn Arg Trp  His His Glu Tyr Gln  Thr Arg Tyr
    2855                 2860                 2865


<210> SEQ ID NO 23
<211> LENGTH: 2411
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (1)..(72)
<223> OTHER INFORMATION: G peptide
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (82)..(393)
<223> OTHER INFORMATION: HSH (helix-sheet-helix) domain
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (979)..(1302)
<223> OTHER INFORMATION: SET Domain (Rich in Serine, Glutamic acid and
      Threonine)
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (2035)..(2169)
<223> OTHER INFORMATION: WDL (WD-like) domain
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-continued

<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (2212)..(2409)
<223> OTHER INFORMATION: BEACH domain

<400> SEQUENCE: 23

Met Ala Ser Glu Asp Asn Arg Val Pro Ser Pro Pro Pro Thr Gly Asp
1 5 10 15

Asp Gly Gly Gly Gly Gly Arg Glu Glu Thr Pro Thr Glu Gly Gly Ala
20 25 30

Leu Ser Leu Lys Pro Gly Leu Pro Ile Arg Gly Ile Arg Met Lys Phe
35 40 45

Ala Val Leu Thr Gly Leu Val Glu Val Gly Glu Val Ser Asn Arg Asp
50 55 60

Ile Val Glu Thr Val Phe Asn Leu Leu Val Gly Gly Gln Phe Asp Leu
65 70 75 80

Glu Met Asn Phe Ile Ile Gln Glu Gly Glu Ser Ile Asn Cys Met Val
85 90 95

Asp Leu Leu Glu Lys Cys Asp Ile Thr Cys Gln Ala Glu Val Trp Ser
100 105 110

Met Phe Thr Ala Ile Leu Lys Lys Ser Ile Arg Asn Leu Gln Val Cys
115 120 125

Thr Glu Val Gly Leu Val Glu Lys Val Leu Gly Lys Ile Glu Lys Val
130 135 140

Asp Asn Met Ile Ala Asp Leu Leu Val Asp Met Leu Gly Val Leu Ala
145 150 155 160

Ser Tyr Asn Leu Thr Val Arg Glu Leu Lys Leu Phe Phe Ser Lys Leu
165 170 175

Gln Gly Asp Lys Gly Arg Trp Pro Pro His Ala Gly Lys Leu Leu Ser
180 185 190

Val Leu Lys His Met Pro Gln Lys Tyr Gly Pro Asp Ala Phe Phe Asn
195 200 205

Phe Pro Gly Lys Ser Ala Ala Ala Ile Ala Leu Pro Pro Ile Ala Lys
210 215 220

Trp Pro Tyr Gln Asn Gly Phe Thr Phe His Thr Trp Leu Arg Met Asp
225 230 235 240

Pro Val Asn Asn Ile Asn Val Asp Lys Asp Lys Pro Tyr Leu Tyr Cys
245 250 255

Phe Arg Thr Ser Lys Gly Leu Gly Tyr Ser Ala His Phe Val Gly Gly
260 265 270

Cys Leu Ile Val Thr Ser Ile Lys Ser Lys Gly Lys Gly Phe Gln His
275 280 285

Cys Val Lys Phe Asp Phe Lys Pro Gln Lys Trp Tyr Met Val Thr Ile
290 295 300

Val His Ile Tyr Asn Arg Trp Lys Asn Ser Glu Leu Arg Cys Tyr Val
305 310 315 320

Asn Gly Glu Leu Ala Ser Tyr Gly Glu Ile Thr Trp Phe Val Asn Thr
325 330 335

Ser Asp Thr Phe Asp Lys Cys Phe Leu Gly Ser Ser Glu Thr Ala Asp
340 345 350

Ala Asn Arg Val Phe Cys Gly Gln Met Thr Ala Val Tyr Leu Phe Ser
355 360 365

Glu Ala Leu Asn Ala Ala Gln Ile Phe Ala Ile Tyr Gln Leu Gly Leu
370 375 380

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Gly Tyr Lys Gly Thr Phe Lys Phe Lys Ala Glu Ser Asp Leu Phe Leu
385                 390                 395                 400

Ala Glu His His Lys Leu Leu Leu Tyr Asp Gly Lys Leu Ser Ser Ala
                405                 410                 415

Ile Ala Phe Thr Tyr Asn Pro Arg Ala Thr Asp Ala Gln Leu Cys Leu
            420                 425                 430

Glu Ser Ser Pro Lys Asp Asn Pro Ser Ile Phe Val His Ser Pro His
        435                 440                 445

Ala Leu Met Leu Gln Asp Val Lys Ala Val Leu Thr His Ser Ile Gln
    450                 455                 460

Ser Ala Met His Ser Ile Gly Gly Val Gln Val Leu Phe Pro Leu Phe
465                 470                 475                 480

Ala Gln Leu Asp Tyr Arg Gln Tyr Leu Ser Asp Glu Ile Asp Leu Thr
                485                 490                 495

Ile Cys Ser Thr Leu Leu Ala Phe Ile Met Glu Leu Leu Lys Asn Ser
            500                 505                 510

Ile Ala Met Gln Glu Gln Met Leu Ala Cys Lys Gly Phe Leu Val Ile
        515                 520                 525

Gly Tyr Ser Leu Glu Lys Ser Ser Lys Ser His Val Ser Arg Ala Val
    530                 535                 540

Leu Glu Leu Cys Leu Ala Phe Ser Lys Tyr Leu Ser Asn Leu Gln Asn
545                 550                 555                 560

Gly Met Pro Leu Leu Lys Gln Leu Cys Asp His Val Leu Leu Asn Pro
                565                 570                 575

Ala Ile Trp Ile His Thr Pro Ala Lys Val Gln Leu Met Leu Tyr Thr
            580                 585                 590

Tyr Leu Ser Thr Glu Phe Ile Gly Thr Val Asn Ile Tyr Asn Thr Ile
        595                 600                 605

Arg Arg Val Gly Thr Val Leu Leu Ile Met His Thr Leu Lys Tyr Tyr
    610                 615                 620

Tyr Trp Ala Val Asn Pro Gln Asp Arg Ser Gly Ile Thr Pro Lys Gly
625                 630                 635                 640

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

Phe Leu Leu Met Phe Ile Lys Gln Leu Val Met Lys Asp Ser Gly Val
            660                 665                 670

Lys Glu Asp Glu Leu Gln Ala Ile Leu Asn Tyr Leu Leu Thr Met His
        675                 680                 685

Glu Asp Asp Asn Leu Met Asp Val Leu Gln Leu Leu Val Ala Leu Met
    690                 695                 700

Ser Glu His Pro Asn Ser Met Ile Pro Ala Phe Asp Gln Arg Asn Gly
705                 710                 715                 720

Leu Arg Val Ile Tyr Lys Leu Leu Ala Ser Lys Ser Glu Gly Ile Arg
                725                 730                 735

Val Gln Ala Leu Lys Ala Met Gly Tyr Phe Leu Lys His Arg Pro Pro
            740                 745                 750

Lys Arg Lys Ala Glu Val Met Leu Gly His Gly Leu Phe Ser Leu Leu
        755                 760                 765

Ala Glu Arg Leu Met Leu Gln Thr Asn Leu Ile Thr Met Thr Thr Tyr
    770                 775                 780

Asn Val Leu Phe Glu Ile Leu Ile Glu Gln Ile Gly Thr Gln Val Ile
785                 790                 795                 800
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His Lys Gln His Pro Asp Pro Asp Ser Ser Val Lys Ile Gln Asn Pro
                805                 810                 815

Gln Ile Leu Lys Val Ile Ala Thr Leu Leu Arg Asn Ser Pro Gln Cys
            820                 825                 830

Pro Glu Ser Met Glu Val Arg Arg Ala Phe Leu Ser Asp Met Ile Lys
        835                 840                 845

Leu Phe Asn Asn Ser Arg Glu Asn Arg Arg Ser Leu Leu Gln Cys Ser
    850                 855                 860

Val Trp Gln Glu Trp Met Leu Ser Leu Cys Tyr Phe Asn Pro Lys Asn
865                 870                 875                 880

Ser Asp Glu Gln Lys Ile Thr Glu Met Val Tyr Ala Ile Phe Arg Ile
                885                 890                 895

Leu Leu Tyr His Ala Val Lys Tyr Glu Trp Gly Gly Trp Arg Val Trp
            900                 905                 910

Val Asp Thr Leu Ser Ile Thr His Ser Lys Val Thr Phe Glu Ile His
        915                 920                 925

Lys Glu Asn Leu Ala Asn Ile Phe Arg Glu Gln Gln Gly Lys Val Asp
    930                 935                 940

Glu Glu Ile Gly Leu Cys Ser Ser Thr Ser Val Gln Ala Ala Ser Gly
945                 950                 955                 960

Ile Arg Arg Asp Ile Asn Val Ser Val Gly Ser Gln Gln Pro Asp Thr
                965                 970                 975

Lys Asp Ser Pro Val Cys Pro His Phe Thr Thr Asn Gly Asn Glu Asn
            980                 985                 990

Ser Ser Ile Glu Lys Thr Ser Ser  Leu Glu Ser Ala Ser  Asn Ile Glu
        995                 1000                1005

Leu Gln  Thr Thr Asn Thr Ser  Tyr Glu Glu Met Lys  Ala Glu Gln
    1010                1015                1020

Glu Asn  Gln Glu Leu Pro Asp  Glu Gly Thr Leu Glu  Glu Thr Leu
    1025                1030                1035

Thr Asn  Glu Thr Arg Asn Ala  Asp Asp Leu Glu Val  Ser Ser Asp
    1040                1045                1050

Ile Ile  Glu Ala Val Ala Ile  Ser Ser Asn Ser Phe  Ile Thr Thr
    1055                1060                1065

Gly Lys  Asp Ser Met Thr Val  Ser Glu Val Thr Ala  Ser Ile Ser
    1070                1075                1080

Ser Pro  Ser Glu Glu Asp Ala  Ser Glu Met Pro Glu  Phe Leu Asp
    1085                1090                1095

Lys Ser  Ile Val Glu Glu Glu  Glu Asp Asp Asp Tyr  Val Glu Leu
    1100                1105                1110

Lys Val  Glu Gly Ser Pro Thr  Glu Glu Ala Asn Leu  Pro Thr Glu
    1115                1120                1125

Leu Gln  Asp Asn Ser Leu Ser  Pro Ala Ala Ser Glu  Ala Gly Glu
    1130                1135                1140

Lys Leu  Asp Met Phe Gly Asn  Asp Asp Lys Leu Ile  Phe Gln Glu
    1145                1150                1155

Gly Lys  Pro Val Thr Glu Lys  Gln Thr Asp Thr Glu  Thr Gln Asp
    1160                1165                1170

Ser Lys  Asp Ser Gly Ile Gln  Thr Met Thr Ala Ser  Gly Ser Ser
    1175                1180                1185

Ala Met  Ser Pro Glu Thr Thr  Val Ser Gln Ile Ala  Val Glu Ser
    1190                1195                1200
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Asp Leu  Gly Gln Met Leu Glu  Glu Gly Lys Lys Ala  Thr Asn Leu
    1205                 1210                 1215

Thr Arg  Glu Thr Lys Leu Ile  Asn Asp Cys His Gly  Ser Val Ser
    1220                 1225                 1230

Glu Ala  Ser Ser Glu Gln Lys  Ile Ala Lys Leu Asp  Val Ser Asn
    1235                 1240                 1245

Val Ala  Thr Asp Thr Glu Arg  Leu Glu Leu Lys Ala  Ser Pro Asn
    1250                 1255                 1260

Val Glu  Ala Pro Gln Pro His  Arg His Val Leu Glu  Ile Ser Arg
    1265                 1270                 1275

Gln His  Glu Gln Pro Gly Gln  Gly Ile Ala Pro Asp  Ala Val Asn
    1280                 1285                 1290

Gly Gln  Arg Arg Asp Ser Arg  Ser Thr Val Phe Arg  Ile Pro Glu
    1295                 1300                 1305

Phe Asn  Trp Ser Gln Met His  Gln Arg Leu Leu Thr  Asp Leu Leu
    1310                 1315                 1320

Phe Ser  Ile Glu Thr Asp Ile  Gln Met Trp Arg Ser  His Ser Thr
    1325                 1330                 1335

Lys Thr  Val Met Asp Phe Val  Asn Ser Ser Asp Asn  Val Ile Phe
    1340                 1345                 1350

Val His  Asn Thr Ile His Leu  Ile Ser Gln Val Met  Asp Asn Met
    1355                 1360                 1365

Val Met  Ala Cys Gly Gly Ile  Leu Pro Leu Leu Ser  Ala Ala Thr
    1370                 1375                 1380

Ser Ala  Thr His Glu Leu Glu  Asn Ile Glu Pro Thr  Gln Gly Leu
    1385                 1390                 1395

Ser Ile  Glu Ala Ser Val Thr  Phe Leu Gln Arg Leu  Ile Ser Leu
    1400                 1405                 1410

Val Asp  Val Leu Ile Phe Ala  Ser Ser Leu Gly Phe  Thr Glu Ile
    1415                 1420                 1425

Glu Ala  Glu Lys Ser Met Ser  Ser Gly Gly Ile Leu  Arg Gln Cys
    1430                 1435                 1440

Leu Arg  Leu Val Cys Ala Val  Ala Val Arg Asn Cys  Leu Glu Cys
    1445                 1450                 1455

Gln Gln  His Ser Gln Leu Lys  Thr Arg Gly Asp Lys  Ala Leu Lys
    1460                 1465                 1470

Pro Met  His Ser Leu Ile Pro  Leu Gly Lys Ser Ala  Ala Lys Ser
    1475                 1480                 1485

Pro Val  Asp Ile Val Thr Gly  Gly Ile Ser Pro Val  Arg Asp Leu
    1490                 1495                 1500

Asp Arg  Leu Leu Gln Asp Met  Asp Ile Asn Arg Leu  Arg Ala Val
    1505                 1510                 1515

Val Phe  Arg Asp Ile Glu Asp  Ser Lys Gln Ala Gln  Phe Leu Ala
    1520                 1525                 1530

Leu Ala  Val Val Tyr Phe Ile  Ser Val Leu Met Val  Ser Lys Tyr
    1535                 1540                 1545

Arg Asp  Ile Leu Glu Pro Gln  Asn Glu Arg His Ser  Gln Ser Cys
    1550                 1555                 1560

Thr Glu  Thr Gly Ser Glu Asn  Glu Asn Val Ser Leu  Ser Glu Ile
    1565                 1570                 1575

Thr Pro  Ala Ala Phe Ser Thr  Leu Thr Thr Ala Ser  Val Glu Glu
    1580                 1585                 1590
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Ser Glu  Ser Thr Ser Ser Ala  Arg Arg Arg Asp Ser  Gly Ile Gly
    1595                 1600                 1605

Glu Glu  Thr Ala Thr Gly Leu  Gly Ser His Val Glu  Val Thr Pro
    1610                 1615                 1620

His Thr  Ala Pro Pro Gly Val  Ser Ala Gly Pro Asp  Ala Ile Ser
    1625                 1630                 1635

Glu Val  Leu Ser Thr Leu Ser  Leu Glu Val Asn Lys  Ser Pro Glu
    1640                 1645                 1650

Thr Lys  Asn Asp Arg Gly Asn  Asp Leu Asp Thr Lys  Ala Thr Pro
    1655                 1660                 1665

Ser Val  Ser Val Ser Lys Asn  Val Asn Val Lys Asp  Ile Leu Arg
    1670                 1675                 1680

Ser Leu  Val Asn Ile Pro Ala  Asp Gly Val Thr Val  Asp Pro Ala
    1685                 1690                 1695

Leu Leu  Pro Pro Ala Cys Leu  Gly Ala Leu Gly Asp  Leu Ser Val
    1700                 1705                 1710

Glu Gln  Pro Val Gln Phe Arg  Ser Phe Asp Arg Ser  Val Ile Val
    1715                 1720                 1725

Ala Ala  Lys Lys Ser Ala Val  Ser Pro Ser Thr Phe  Asn Thr Ser
    1730                 1735                 1740

Ile Pro  Thr Asn Ala Val Ser  Val Val Ser Ser Val  Asp Ser Ala
    1745                 1750                 1755

Gln Ala  Ser Asp Met Gly Gly  Glu Ser Pro Gly Ser  Arg Ser Ser
    1760                 1765                 1770

Asn Ala  Lys Leu Pro Ser Val  Pro Thr Val Asp Ser  Val Ser Gln
    1775                 1780                 1785

Asp Pro  Val Ser Asn Met Ser  Ile Thr Glu Arg Leu  Glu His Ala
    1790                 1795                 1800

Leu Glu  Lys Ala Ala Pro Leu  Leu Arg Glu Ile Phe  Val Asp Phe
    1805                 1810                 1815

Ala Pro  Phe Leu Ser Arg Thr  Leu Leu Gly Ser His  Gly Gln Glu
    1820                 1825                 1830

Leu Leu  Ile Glu Gly Thr Ser  Leu Val Cys Met Lys  Ser Ser Ser
    1835                 1840                 1845

Ser Val  Val Glu Leu Val Met  Leu Leu Cys Ser Gln  Glu Trp Gln
    1850                 1855                 1860

Asn Ser  Ile Gln Lys Asn Ala  Gly Leu Ala Phe Ile  Glu Leu Val
    1865                 1870                 1875

Asn Glu  Gly Arg Leu Leu Ser  Gln Thr Met Lys Asp  His Leu Val
    1880                 1885                 1890

Arg Val  Ala Asn Glu Ala Glu  Phe Ile Leu Ser Arg  Gln Arg Ala
    1895                 1900                 1905

Glu Asp  Ile His Arg His Ala  Glu Phe Glu Ser Leu  Cys Ala Gln
    1910                 1915                 1920

Tyr Ser  Ala Asp Lys Arg Glu  Asp Glu Lys Met Cys  Asp His Leu
    1925                 1930                 1935

Ile Arg  Ala Ala Lys Tyr Arg  Asp His Val Thr Ala  Thr Gln Leu
    1940                 1945                 1950

Ile Gln  Lys Ile Ile Asn Ile  Leu Thr Asp Lys His  Gly Ala Trp
    1955                 1960                 1965

Gly Asn  Ser Ala Val Ser Arg  Pro Leu Glu Phe Trp  Arg Leu Asp
    1970                 1975                 1980
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Tyr Trp  Glu Asp Asp Leu Arg  Arg Arg Arg Arg Phe  Val Arg Asn
    1985                 1990                 1995

Pro Leu  Gly Ser Thr His Pro  Glu Ala Thr Leu Lys  Thr Ala Val
    2000                 2005                 2010

Glu His  Val Cys Ile Phe Lys  Leu Arg Glu Asn Ser  Lys Ala Thr
    2015                 2020                 2025

Asp Glu  Asp Ile Leu Ala Lys  Gly Lys Gln Ser Ile  Arg Ser Gln
    2030                 2035                 2040

Ala Leu  Gly Asn Gln Asn Ser  Glu Asn Glu Ile Leu  Leu Glu Gly
    2045                 2050                 2055

Asp Asp  Asp Thr Leu Ser Ser  Val Asp Glu Lys Asp  Leu Glu Asn
    2060                 2065                 2070

Leu Ala  Gly Pro Val Ser Leu  Ser Thr Pro Ala Gln  Leu Val Ala
    2075                 2080                 2085

Pro Ser  Val Val Val Lys Gly  Thr Leu Ser Val Thr  Ser Ser Glu
    2090                 2095                 2100

Leu Tyr  Phe Glu Val Asp Glu  Glu Asp Pro Asn Phe  Lys Lys Ile
    2105                 2110                 2115

Asp Pro  Lys Ile Leu Ala Tyr  Thr Glu Gly Leu His  Gly Lys Trp
    2120                 2125                 2130

Leu Phe  Thr Glu Ile Arg Ser  Ile Phe Ser Arg Arg  Tyr Leu Leu
    2135                 2140                 2145

Gln Asn  Thr Ala Leu Glu Ile  Phe Met Ala Asn Arg  Val Ala Val
    2150                 2155                 2160

Met Phe  Asn Phe Pro Asp Pro  Ala Thr Val Lys Lys  Val Val Asn
    2165                 2170                 2175

Phe Leu  Pro Arg Val Gly Val  Gly Thr Ser Phe Gly  Leu Pro Gln
    2180                 2185                 2190

Thr Arg  Arg Ile Ser Leu Ala  Ser Pro Arg Gln Leu  Phe Lys Ala
    2195                 2200                 2205

Ser Asn  Met Thr Gln Arg Trp  Gln His Arg Glu Ile  Ser Asn Phe
    2210                 2215                 2220

Glu Tyr  Leu Met Phe Leu Asn  Thr Ile Ala Gly Arg  Ser Tyr Asn
    2225                 2230                 2235

Asp Leu  Asn Gln Tyr Pro Val  Phe Pro Trp Val Ile  Thr Asn Tyr
    2240                 2245                 2250

Glu Ser  Glu Glu Leu Asp Leu  Thr Leu Pro Thr Asn  Phe Arg Asp
    2255                 2260                 2265

Leu Ser  Lys Pro Ile Gly Ala  Leu Asn Pro Lys Arg  Ala Ala Phe
    2270                 2275                 2280

Phe Ala  Glu Arg Tyr Glu Ser  Trp Glu Asp Asp Gln  Val Pro Lys
    2285                 2290                 2295

Phe His  Tyr Gly Thr His Tyr  Ser Thr Ala Ser Phe  Val Leu Ala
    2300                 2305                 2310

Trp Leu  Leu Arg Ile Glu Pro  Phe Thr Thr Tyr Phe  Leu Asn Leu
    2315                 2320                 2325

Gln Gly  Gly Lys Phe Asp His  Ala Asp Arg Thr Phe  Ser Ser Ile
    2330                 2335                 2340

Ser Arg  Ala Trp Arg Asn Ser  Gln Arg Asp Thr Ser  Asp Ile Lys
    2345                 2350                 2355

Glu Leu  Ile Pro Glu Phe Tyr  Tyr Leu Pro Glu Met  Phe Val Asn
    2360                 2365                 2370
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Phe Asn  Asn Tyr Asn Leu Gly  Val Met Asp Asp Gly  Thr Val Val
    2375                 2380                 2385

Ser Asp  Val Glu Leu Pro Pro  Trp Ala Lys Thr Ser  Glu Glu Phe
    2390                 2395                 2400

Val His  Ile Asn Arg Leu Val  Arg
    2405                 2410


<210> SEQ ID NO 24
<211> LENGTH: 72
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: DOMAIN
<222> LOCATION: (1)..(72)
<223> OTHER INFORMATION: G peptide

<400> SEQUENCE: 24

Met Ala Ser Glu Asp Asn Arg Val Pro Ser Pro Pro Pro Thr Gly Asp
1               5                   10                  15

Asp Gly Gly Gly Gly Gly Arg Glu Glu Thr Pro Thr Glu Gly Gly Ala
            20                  25                  30

Leu Ser Leu Lys Pro Gly Leu Pro Ile Arg Gly Ile Arg Met Lys Phe
        35                  40                  45

Ala Val Leu Thr Gly Leu Val Glu Val Gly Glu Val Ser Asn Arg Asp
    50                  55                  60

Ile Val Glu Thr Val Phe Asn Leu
65                  70


<210> SEQ ID NO 25
<211> LENGTH: 341
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 25

Leu Thr Gly Leu Val Glu Val Gly Glu Val Ser Asn Arg Asp Ile Val
1               5                   10                  15

Glu Thr Val Phe Asn Leu Leu Val Gly Gly Gln Phe Asp Leu Glu Met
            20                  25                  30

Asn Phe Ile Ile Gln Glu Gly Glu Ser Ile Met Cys Met Val Glu Leu
        35                  40                  45

Leu Glu Lys Cys Asp Val Thr Cys Gln Ala Glu Val Trp Ser Met Phe
    50                  55                  60

Thr Ala Ile Leu Lys Lys Ser Ile Arg Asn Leu Gln Val Cys Thr Glu
65                  70                  75                  80

Val Gly Leu Val Glu Lys Val Leu Gly Lys Ile Glu Lys Val Asp Ser
                85                  90                  95

Met Ile Ala Asp Leu Leu Val Asp Met Leu Gly Val Leu Ala Ser Tyr
            100                 105                 110

Asn Leu Thr Val Arg Glu Leu Lys Leu Phe Phe Ser Lys Leu Gln Gly
        115                 120                 125

Asp Lys Gly Gln Trp Pro Pro His Ala Gly Lys Leu Leu Ser Val Leu
    130                 135                 140

Lys His Met Pro Gln Lys Tyr Gly Pro Asp Ala Phe Phe Asn Phe Pro
145                 150                 155                 160

Gly Lys Ser Ala Ala Ala Ile Ala Leu Pro Pro Ile Ala Arg Trp Pro
                165                 170                 175

Tyr Gln Asn Gly Phe Thr Phe His Thr Trp Leu Arg Met Asp Pro Val
            180                 185                 190
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Asn Asn Ile Asn Val Asp Lys Asp Lys Pro Tyr Leu Tyr Cys Phe Arg
        195                 200                 205

Thr Ser Lys Gly Leu Gly Tyr Ser Ala His Phe Val Gly Gly Cys Leu
    210                 215                 220

Ile Ile Thr Ser Ile Lys Ser Lys Gly Lys Gly Phe Gln His Cys Val
225                 230                 235                 240

Lys Phe Asp Phe Lys Pro Gln Lys Trp Tyr Met Val Thr Ile Val His
                245                 250                 255

Ile Tyr Asn Arg Trp Lys Asn Ser Glu Leu Arg Cys Tyr Val Asn Gly
            260                 265                 270

Glu Leu Ala Ser Tyr Gly Glu Ile Thr Trp Phe Val Asn Thr Ser Asp
        275                 280                 285

Thr Phe Asp Lys Cys Phe Leu Gly Ser Ser Glu Thr Ala Asp Ala Asn
    290                 295                 300

Arg Val Phe Cys Gly Gln Met Thr Ala Val Tyr Leu Phe Ser Asp Ala
305                 310                 315                 320

Leu Asn Ala Ala Gln Ile Phe Ala Ile Tyr Gln Leu Gly Leu Gly Tyr
                325                 330                 335

Lys Gly Thr Phe Lys
            340


<210> SEQ ID NO 26
<211> LENGTH: 341
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

Leu Thr Gly Leu Val Glu Val Gly Glu Val Ser Asn Arg Asp Ile Val
1               5                   10                  15

Glu Thr Val Phe Asn Leu Leu Val Gly Gly Gln Phe Asp Leu Glu Met
            20                  25                  30

Asn Phe Ile Ile Gln Glu Gly Glu Ser Ile Asn Cys Met Val Asp Leu
        35                  40                  45

Leu Glu Lys Cys Asp Ile Thr Cys Gln Ala Glu Val Trp Ser Met Phe
    50                  55                  60

Thr Ala Ile Leu Lys Lys Ser Ile Arg Asn Leu Gln Val Cys Thr Glu
65                  70                  75                  80

Val Gly Leu Val Glu Lys Val Leu Gly Lys Ile Glu Lys Val Asp Asn
                85                  90                  95

Met Ile Ala Asp Leu Leu Val Asp Met Leu Gly Val Leu Ala Ser Tyr
            100                 105                 110

Asn Leu Thr Val Arg Glu Leu Lys Leu Phe Phe Ser Lys Leu Gln Gly
        115                 120                 125

Asp Lys Gly Arg Trp Pro Pro His Ala Gly Lys Leu Leu Ser Val Leu
    130                 135                 140

Lys His Met Pro Gln Lys Tyr Gly Pro Asp Ala Phe Phe Asn Phe Pro
145                 150                 155                 160

Gly Lys Ser Ala Ala Ala Ile Ala Leu Pro Pro Ile Ala Lys Trp Pro
                165                 170                 175

Tyr Gln Asn Gly Phe Thr Phe His Thr Trp Leu Arg Met Asp Pro Val
            180                 185                 190

Asn Asn Ile Asn Val Asp Lys Asp Lys Pro Tyr Leu Tyr Cys Phe Arg
        195                 200                 205

Thr Ser Lys Gly Leu Gly Tyr Ser Ala His Phe Val Gly Gly Cys Leu
    210                 215                 220
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Ile Val Thr Ser Ile Lys Ser Lys Gly Lys Gly Phe Gln His Cys Val
225                 230                 235                 240

Lys Phe Asp Phe Lys Pro Gln Lys Trp Tyr Met Val Thr Ile Val His
                245                 250                 255

Ile Tyr Asn Arg Trp Lys Asn Ser Glu Leu Arg Cys Tyr Val Asn Gly
            260                 265                 270

Glu Leu Ala Ser Tyr Gly Glu Ile Thr Trp Phe Val Asn Thr Ser Asp
        275                 280                 285

Thr Phe Asp Lys Cys Phe Leu Gly Ser Ser Glu Thr Ala Asp Ala Asn
    290                 295                 300

Arg Val Phe Cys Gly Gln Met Thr Ala Val Tyr Leu Phe Ser Glu Ala
305                 310                 315                 320

Leu Asn Ala Ala Gln Ile Phe Ala Ile Tyr Gln Leu Gly Leu Gly Tyr
                325                 330                 335

Lys Gly Thr Phe Lys
            340


<210> SEQ ID NO 27
<211> LENGTH: 206
<212> TYPE: PRT
<213> ORGANISM: Drosophila melanogaster

<400> SEQUENCE: 27

Leu Leu Phe Asn Ile Ala Leu Val Val Lys Phe Glu Leu Leu Leu Ile
1               5                   10                  15

Ala Phe Arg Ser His Phe Arg Phe Arg Phe Thr Phe Val Gln Ala Met
            20                  25                  30

Val Leu Pro Pro Leu Ala Lys Trp Pro Tyr Glu Asn Gly Phe Thr Phe
        35                  40                  45

Thr Thr Trp Cys Arg Leu Asp Pro Ile Asn Ser Val Asn Ile Glu Arg
    50                  55                  60

Glu Lys Pro Tyr Leu Tyr Ser Phe Lys Thr Ser Lys Gly Val Gly Tyr
65                  70                  75                  80

Thr Ala His Phe Val Gly Asn Cys Leu Val Leu Thr Ser Met Lys Val
                85                  90                  95

Lys Gly Lys Gly Phe Gln His Cys Val Lys Tyr Glu Phe Gln Pro Pro
            100                 105                 110

Lys Trp Tyr Met Ile Ala Ile Val Tyr Ile Tyr Asn Arg Trp Thr Lys
        115                 120                 125

Ser Glu Ile Lys Cys Leu Val Asn Gly Gln Leu Ala Ser Ser Thr Glu
    130                 135                 140

Met Ala Trp Phe Val Ser Thr Asn Asp Pro Phe Asp Lys Cys Tyr Ile
145                 150                 155                 160

Gly Ala Thr Pro Glu Leu Asp Glu Glu Arg Val Phe Cys Gly Gln Met
                165                 170                 175

Ser Ala Ile Tyr Leu Phe Ser Glu Ala Leu Thr Thr Gln Gln Ile Cys
            180                 185                 190

Ala Met His Arg Leu Gly Pro Gly Tyr Lys Ser Gln Phe Arg
        195                 200                 205


<210> SEQ ID NO 28
<211> LENGTH: 333
<212> TYPE: PRT
<213> ORGANISM: Caenorhabditis elegans
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<400> SEQUENCE: 28

Val Val Asp Asn Leu Phe Asn Leu Leu Val Gly Gly His Phe Asp Gln
1 5 10 15

Glu Ser Lys Phe Val Ile Glu Asp Ala Ala Asn Val Asp His Met Leu
20 25 30

Thr Leu Leu Ser His Cys Asp Tyr Asp Leu Gln Asn Glu Ile Trp Ser
35 40 45

Leu Phe Leu Ala Val Met Lys Lys Ser Asn Arg Asn Leu Glu Ala Cys
50 55 60

Thr Arg Val Gly Leu Ile Ser Lys Thr Gln Leu Phe Phe Arg Val Leu
65 70 75 80

Asp Ile Leu Pro Glu Ala Pro Pro Leu Leu Ala Asp Leu Leu Val Gln
85 90 95

Ile Ile Ala Ala Leu Val Ala Tyr Ser Ile Asn Val Lys Gln Thr Lys
100 105 110

His Leu Leu Arg Ala Leu Lys Ser Thr Lys Glu Gln Trp Pro Pro Asn
115 120 125

Ser Leu Lys Leu Leu His Val Leu Lys Glu Met Pro Gln His Asp Ser
130 135 140

Ala Asp Val Phe Phe Ser Phe Pro Gly Lys Asp Gln Ser Gly Ile Ile
145 150 155 160

Leu Pro Pro Ile Lys Thr Met Pro Tyr Gln Gln Gly Trp Thr Phe Ala
165 170 175

Thr Trp Leu Arg Met Glu Pro Leu Asn Ser Val Thr Phe Glu Lys Glu
180 185 190

Gln Pro Val Leu Tyr Ser Phe Arg Thr Ser Lys Gly Val Gly Tyr Ser
195 200 205

Cys His Phe Thr Gly Asn Cys Leu Val Val Asn Val Glu Lys Thr Lys
210 215 220

Gly Lys Glu Gln Ser Arg Cys Val Arg Ala Glu Leu Gly Ala Arg Lys
225 230 235 240

Trp His His Ile Ala Ile Ala His Cys Tyr Ser Arg Trp Gly Arg Ser
245 250 255

Asp Ile Lys Cys Phe Ile Asp Gly Gln Leu Ala Glu Thr Ile Glu Leu
260 265 270

Ser Trp Val Val Thr Ser Ala Thr Asn Trp Asp Arg Cys Ser Ile Gly
275 280 285

Val Ser Ala Asp Gly Thr Ala Asn Ser Ala Phe Cys Gly Gln Met Gly
290 295 300

Ala Met Tyr Leu Phe Ala Glu Ala Leu Thr Leu Gln Gln Ala Asn Ser
305 310 315 320

Leu Phe Cys Leu Gly Pro Val Tyr Gln Ser Thr Phe Lys
325 330

<210> SEQ ID NO 29
<211> LENGTH: 328
<212> TYPE: PRT
<213> ORGANISM: Arabidopsis thaliana

<400> SEQUENCE: 29

Ile Leu Pro Ser Cys Thr Arg Asn Arg Ala Met Cys Ser Thr Ala Gly
1 5 10 15

Leu Leu Gly Val Leu Leu Arg Ser Val Glu Ala Ile Thr Ser Lys Asp
20 25 30

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```
Val Asp Met Lys Trp Asn Ala Ala Ala Ile Leu Leu Leu Cys Ile Gln
        35                  40                  45

His Leu Ala Gly His Ser Leu Ser Val Asp Asp Leu His Arg Trp Leu
    50                  55                  60

Gln Val Ile Lys Ala Ala Ile Thr Thr Ala Trp Ser Ser Pro Leu Met
65                  70                  75                  80

Leu Ala Leu Glu Lys Ala Met Ser Gly Lys Glu Ser Arg Gly Pro Ala
                85                  90                  95

Cys Thr Phe Glu Phe Asp Gly Glu Ser Ser Gly Leu Leu Gly Pro Gly
            100                 105                 110

Glu Ser Arg Trp Pro Phe Thr Asn Gly Tyr Ala Phe Ala Thr Trp Ile
        115                 120                 125

Tyr Ile Glu Ser Phe Ala Asp Thr Leu Asn Ala Ala Thr Ala Ala Ala
    130                 135                 140

Ala Ile Ala Ala Ala Ala Ala Ala Lys Ser Gly Lys Thr Ser Ala Met
145                 150                 155                 160

Ser Ala Ala Ala Ala Ala Ser Ala Leu Ala Gly Glu Gly Thr Ala His
                165                 170                 175

Met Pro Arg Leu Phe Ser Phe Leu Ser Ala Asp Asn Gln Gly Ile Glu
            180                 185                 190

Ala Tyr Phe His Ala Gln Phe Leu Val Val Glu Ser Gly Ser Gly Lys
        195                 200                 205

Gly Arg Lys Ser Ser Leu His Phe Thr His Ala Phe Lys Pro Gln Cys
    210                 215                 220

Trp Tyr Phe Ile Gly Leu Glu His Ser Cys Lys Gln Gly Leu Leu Gly
225                 230                 235                 240

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

Ser Arg Pro Phe Asp Phe Pro Arg Ile Ser Lys Pro Leu Ser Phe Cys
            260                 265                 270

Cys Ile Gly Thr Asn Pro Pro Pro Thr Met Ala Gly Leu Gln Arg Arg
        275                 280                 285

Arg Arg Cys Cys Pro Leu Phe Ala Glu Met Gly Pro Val Tyr Ile Phe
    290                 295                 300

Lys Glu Pro Ile Gly Pro Glu Arg Met Ala Arg Leu Ala Ser Arg Gly
305                 310                 315                 320

Gly Asp Val Leu Pro Cys Phe Gly
                325


<210> SEQ ID NO 30
<211> LENGTH: 373
<212> TYPE: PRT
<213> ORGANISM: Dictyostelium discoideum

<400> SEQUENCE: 30

Ile Met Thr Gly Val Leu Gly Thr Glu Phe Ser Lys Ser Val Val Asp
1               5                   10                  15

Phe Ile Phe Asp Met Val Thr Glu Asn Leu Asn Ala Ser Asp Gln Ile
            20                  25                  30

Ser Asn Gln Met Ile Ile Asn Asn Val Glu Ser Phe Asn Val Ile Leu
        35                  40                  45

Asp Ile Ile Pro His Ile Glu Asn Lys Asp Phe Arg Leu Gln Ile Ile
    50                  55                  60

Ser Arg Ile Asn Lys Met Ala Glu Tyr Gly Arg Tyr Asn Gln Glu Ala
65                  70                  75                  80
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```
Leu Ser Lys Leu Ser Ile Pro Ile Trp Ile Leu Ser Arg Phe Pro Ser
                85                  90                  95

Asn Leu Ser Asn Ala Asn Asp Pro Leu Gln Pro Leu Leu Leu Ser Leu
            100                 105                 110

Ile Gln Thr Val Gly Ala Asn Cys Leu Ser Gly Ser Glu Leu Arg Gln
        115                 120                 125

Phe Val Lys Leu Leu Gln Pro Glu His Ser Pro Glu Val Leu Leu Lys
    130                 135                 140

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

Phe Asn Leu Ser Lys Ile Pro Phe Gly Tyr Ile Arg Val Pro Ile Thr
                165                 170                 175

Glu Arg Ala Trp Pro Pro Thr Asn Gly Tyr Thr Ile Met Phe Trp Leu
            180                 185                 190

Tyr Ile Asp Lys Phe Pro Thr Val Asn Asn Asn Asn Asn Asn Asn Asn
        195                 200                 205

Ser Ser Asn Asn Ser Asn Asn Ser Asn Asn Ser Asn Asn Asn Asn Asn
    210                 215                 220

Asn Asn Asn Asn Asn Asp Gln Ile Asp Leu Val His Ile Tyr Ser Asp
225                 230                 235                 240

Asp Lys Lys Ser Ser Leu Tyr Ile Tyr Leu Lys Asn Gly Ile Ile Thr
                245                 250                 255

Val Asn Ile Ile Asn Ser Ser Lys Tyr Val Ile Glu Ile Pro Ser Tyr
            260                 265                 270

Lys Phe Val Glu Gly Lys Trp Tyr His Ile Gly Ile Val His Ala Arg
        275                 280                 285

Arg Leu Leu Gly Gly Thr Asp Phe Lys Leu Phe Val Asp Gly Phe Leu
    290                 295                 300

Lys Tyr Thr Ala Thr Lys Ala Gln Tyr Pro Ala Gln Ile Thr Ser Gly
305                 310                 315                 320

Ser Met Leu Ile Cys Asp Ile Gly Val Ser Asn Gln Asn Arg Phe Pro
                325                 330                 335

Thr Asp Ser Ile Trp Arg Ile Gly Thr Phe Tyr Leu Leu Glu Asp Ser
            340                 345                 350

Leu Gly Ala Lys His Ile Asn Thr Ile Tyr Phe Leu Gly Pro Asn Tyr
        355                 360                 365

Ala Ser Asn Phe Lys
    370
```

<210> SEQ ID NO 31
<211> LENGTH: 374
<212> TYPE: PRT
<213> ORGANISM: Arabidopsis thaliana

<400> SEQUENCE: 31

```
Thr Ala Leu Ala Thr Ile Pro Glu Asn Glu Asn Thr Thr Phe Val Val
1               5                   10                  15

Thr Thr Pro Ser Gly Gln Phe Asn Pro Asp Lys Glu Arg Ile Tyr Asn
            20                  25                  30

Ala Gly Ala Val Arg Val Leu Ile Arg Ser Leu Leu Leu Phe Ser Pro
        35                  40                  45

Lys Met Gln Leu Glu Phe Leu Arg Leu Leu Glu Ser Leu Ala Arg Ala
    50                  55                  60

Ser Pro Phe Asn Gln Glu Asn Leu Thr Ser Ile Gly Cys Val Glu Leu
65                  70                  75                  80
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```
Leu Leu Glu Ile Ile Tyr Pro Phe Leu Ala Gly Ser Ser Pro Phe Leu
                85                  90                  95

Ser Tyr Ala Leu Lys Ile Val Glu Ile Leu Gly Ala Tyr Arg Leu Ser
            100                 105                 110

Pro Ser Glu Leu Arg Met Leu Phe Arg Tyr Val Leu Gln Met Arg Ile
        115                 120                 125

Met Asn Ser Gly His Ala Ile Val Gly Met Met Glu Lys Leu Ile Leu
    130                 135                 140

Met Glu Asp Thr Ala Leu Glu His Leu Ser Leu Ala Pro Phe Val Glu
145                 150                 155                 160

Leu Asp Met Ser Lys Thr Gly His Ala Ser Val Gln Val Ser Leu Gly
                165                 170                 175

Glu Arg Ser Trp Pro Pro Ala Ala Gly Tyr Ser Phe Val Cys Trp Phe
            180                 185                 190

Gln Phe Arg Asn Phe Leu Thr Thr Gln Gly Lys Glu Ser Glu Ala Ser
        195                 200                 205

Lys Ala Gly Gly Ser Ser Lys Thr Arg Met Thr Ser Ala Gln Gln His
    210                 215                 220

Glu Gln Asn Ile Phe Arg Met Phe Ser Val Gly Ala Val Ser Asn Glu
225                 230                 235                 240

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

Leu Ala Thr Ser Asn Ser His Ser Leu Ser Phe Ser Gly Leu Glu Ile
            260                 265                 270

Glu Glu Gly Arg Trp His His Leu Ala Val Val His Ser Lys Pro Asn
        275                 280                 285

Ala Leu Ala Gly Leu Phe Gln Ala Ser Val Ala Tyr Val Tyr Leu Asp
    290                 295                 300

Gly Lys Leu Arg His Thr Gly Lys Leu Gly Tyr Ser Pro Ser Pro Val
305                 310                 315                 320

Gly Lys Ser Leu Gln Val Thr Val Gly Thr Pro Ala Thr Cys Ala Arg
                325                 330                 335

Val Ser Asp Leu Thr Trp Lys Thr Arg Ser Cys Tyr Leu Phe Glu Glu
            340                 345                 350

Val Leu Thr Ser Gly Cys Ile Gly Phe Met Tyr Ile Leu Gly Arg Gly
        355                 360                 365

Tyr Lys Gly Leu Phe Gln
    370


<210> SEQ ID NO 32
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(5)
<223> OTHER INFORMATION: inserted amino acid sequence in human LRBA-g

<400> SEQUENCE: 32

Tyr Leu Leu Leu Gln
1               5


<210> SEQ ID NO 33
<211> LENGTH: 646
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (248)..(250)
<223> OTHER INFORMATION: translation initiation codon
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (248)..(466)
<223> OTHER INFORMATION: ORF encodes the first 73 amino acids of the lrba protein
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (464)..(466)
<223> OTHER INFORMATION: in-frame translation termination codon
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (484)..(486)
<223> OTHER INFORMATION: out-of-frame translation termination codon
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (466)..(598)
<223> OTHER INFORMATION: extra exon interrupting LRBA sequence
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (487)..(489)
<223> OTHER INFORMATION: out-of-frame translation termination codon
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (492)..(494)
<223> OTHER INFORMATION: out-of-frame translation termination codon
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (499)..(501)
<223> OTHER INFORMATION: out-of-frame translation termination codon
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (517)..(519)
<223> OTHER INFORMATION: out-of-frame translation termination codon
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (551)..(553)
<223> OTHER INFORMATION: in-frame translation termination codon
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (566)..(568)
<223> OTHER INFORMATION: in-frame translation termination codon
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (570)..(572)
<223> OTHER INFORMATION: out-of-frame translation termination codon
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (590)..(592)
<223> OTHER INFORMATION: in-frame translation termination codon

<400> SEQUENCE: 33

ggggtgagga cgagtccgga gtatctgggg tttggcgttg ttgtcagcct cggggagaga 60

gattggacaa atattctcca agaggaggag ggcgacgcca aggactttcc acatcaactg 120

ctttggggta tctccacaag ttggaagagg gacccttttcg ttttgcattg cgtgtgttgt 180

gctcattacc agtgcagcga ctgccgtccc agggtgactc tgagttgtcc tttatcgtga 240

gctagcaatg gctagcgaag acaatcgtgt cccttccccg ccaccaacag gtgatgacgg 300

gggaggtgga gggagagaag aaacccctac tgaaggggggt gcattgtctc tgaaaccagg 360

gctccccatc aggggcatca gaatgaaatt tgccgtgttg accggtttgg ttgaagttgg 420

agaagtatcc aatagggata ttgtagaaac tgtctttaac ctgtgagaaa cagaaatttg 480

tggtagtaat ataatccata attacttatt tgtgtgtgaa gacacaacat cttttggcag 540

aaggaggatt tgaactcctg ttctttagaa tgtgctgtgt tggagtggat gaccaaactt 600

ggtaggagga cagtttgatc tggaaatgaa tttcattatc caagaa 646

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<210> SEQ ID NO 34
<211> LENGTH: 72
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

Met Ala Ser Glu Asp Asn Arg Val Pro Ser Pro Pro Pro Thr Gly Asp
1 5 10 15

Asp Gly Gly Gly Gly Gly Arg Glu Glu Thr Pro Thr Glu Gly Gly Ala
20 25 30

Leu Ser Leu Lys Pro Gly Leu Pro Ile Arg Gly Ile Arg Met Lys Phe
35 40 45

Ala Val Leu Thr Gly Leu Val Glu Val Gly Glu Val Ser Asn Arg Asp
50 55 60

Ile Val Glu Thr Val Phe Asn Leu
65 70

<210> SEQ ID NO 35
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

Met Asn Phe Ile Ile Gln Glu
1 5

<210> SEQ ID NO 36
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

Leu Val Gly Gly Gln Phe Asp Leu Glu
1 5

<210> SEQ ID NO 37
<211> LENGTH: 1920
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: protein_bind
<222> LOCATION: (786)..(793)
<223> OTHER INFORMATION: E2F transcription binding site
<220> FEATURE:
<221> NAME/KEY: protein_bind
<222> LOCATION: (824)..(831)
<223> OTHER INFORMATION: E2F transcription binding site
<220> FEATURE:
<221> NAME/KEY: protein_bind
<222> LOCATION: (1066)..(1073)
<223> OTHER INFORMATION: E2F transcription binding site
<220> FEATURE:
<221> NAME/KEY: protein_bind
<222> LOCATION: (1187)..(1196)
<223> OTHER INFORMATION: Sp1 transcription binding site
<220> FEATURE:
<221> NAME/KEY: protein_bind
<222> LOCATION: (1290)..(1299)
<223> OTHER INFORMATION: Sp1 transcription binding site
<220> FEATURE:
<221> NAME/KEY: protein_bind
<222> LOCATION: (1295)..(1304)
<223> OTHER INFORMATION: Sp1 transcription binding site
<220> FEATURE:
<221> NAME/KEY: protein_bind
<222> LOCATION: (1303)..(1312)
<223> OTHER INFORMATION: c-ETs transcription binding site

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<220> FEATURE:
<221> NAME/KEY: protein_bind
<222> LOCATION: (1411)..(1416)
<223> OTHER INFORMATION: AML-1a transcription binding site
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1353)..(1353)
<223> OTHER INFORMATION: transcription start site
<220> FEATURE:
<221> NAME/KEY: protein_bind
<222> LOCATION: (1533)..(1546)
<223> OTHER INFORMATION: Tst-1 transcription binding site
<220> FEATURE:
<221> NAME/KEY: protein_bind
<222> LOCATION: (1537)..(1543)
<223> OTHER INFORMATION: CdxA transcription binding site
<220> FEATURE:
<221> NAME/KEY: protein_bind
<222> LOCATION: (1541)..(1550)
<223> OTHER INFORMATION: HSF2 transcription binding site
<220> FEATURE:
<221> NAME/KEY: protein_bind
<222> LOCATION: (1543)..(1549)
<223> OTHER INFORMATION: CdxA transcription binding site
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1566)..(1566)
<223> OTHER INFORMATION: transcription start site
<220> FEATURE:
<221> NAME/KEY: protein_bind
<222> LOCATION: (1614)..(1622)
<223> OTHER INFORMATION: Sp1 transcription binding site
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1621)..(1621)
<223> OTHER INFORMATION: transcription start site
<220> FEATURE:
<221> NAME/KEY: protein_bind
<222> LOCATION: (1646)..(1651)
<223> OTHER INFORMATION: AML-1a transcription binding site
<220> FEATURE:
<221> NAME/KEY: protein_bind
<222> LOCATION: (1651)..(1658)
<223> OTHER INFORMATION: E2F transcription binding site
<220> FEATURE:
<221> NAME/KEY: protein_bind
<222> LOCATION: (1676)..(1691)
<223> OTHER INFORMATION: C/EBPa transcription binding site
<220> FEATURE:
<221> NAME/KEY: protein_bind
<222> LOCATION: (1679)..(1687)
<223> OTHER INFORMATION: GATA-3 transcription binding site
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1680)..(1680)
<223> OTHER INFORMATION: transcription start site
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1868)..(1870)
<223> OTHER INFORMATION: translation initiation codon

<400> SEQUENCE: 37

cccggcttct gtccacttct caaggccatc tcaaataact ttttcttcag gaaactattt 60

ctcaaaccac tataattttt tcctaagttc tctagaattc ttcctttgtt taatcccact 120

ttttgcttca ctttcatttt aggagctagg cgtatttttа aaaaggccct ttgacctcaa 180

aggatacacg tgggtgaaaa accaccttcc tctaaattta tttttcactc actaggaaga 240

atggtttact gttaatagcg ggtggaaaga agggacactg agtatgagga cctatctgta 300

ctacctaata taatttatct tttgatctac tctgagaatg acgcgagcct aatcttcaca 360

ttggaaaatc acgagaggaa aaaacccttc ggaggtctac aggcacaagg aaccctgtct 420

ccacgctgtt tatagcagct gtctcaggaa tcctctgcct agaatgaatg tgggagaggt 480

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ttcgtggcgc ggcagctgca aagcaaggaa tctttcccat tcctcgtcga ctcggtcccc 540

tcccctcccc tcccgaatgg cggcagctgc cgaggtatcc cagtggaaat ctccaagtct 600

ccgccgagag cggcgggcgg gcaacagctg aaagcagcca ggggtgggga ctcctcgctc 660

ccattgggca gggacagcag cctcactggc tccagcgccg tcacctctct ggctcgtaga 720

ggtgcctcag gtgttcttct ccaagtccaa tgagacacct aggcaacgca gcgcgtgttc 780

cctccgcgcc aagagaccct acggtaactt aacaacagca ggagcgccaa aatccccgcc 840

tcaggacttg gcagaagcac ctcccgaggt ccgagagtgg gagaggggaa agtgtaggcc 900

ctcggacgga agggtctctc ctcgccgggc cgggtacaca cctggtgcta ccagagcagc 960

gcgcctagtg cagccggaag ccccagccca gcactccggc tggctcgggg cccccttggc 1020

tgtccgcgcg tgtaaccgcg cccccggccg cgcgggtggc tccgctttgg cgccctcccc 1080

gcccgcgcac tcgcgctcgc gcacgcgcac gccgcgcccg gcagcactcg gcgctgtcat 1140

ggcggccggg agcagcttca gtgggcacac gacagccgcg cgacccgtgg cggggcgagc 1200

tgtggcagta gcatcctcac cactcgcagc agcctcagcc gcggcgcccg tagcgccagc 1260

agcggctgct tttgcaaagg ctgagcgcag gggcggggcg ggccaggaag ccatggagtt 1320

ctgtgcagcc gcggactccc ggggagcgga ctagggaaac ttggaggctg cgaccaggtg 1380

cactgacctc tctgtcctcc cttctctccc tgcggtggcc gctgggtttc tctggccgct 1440

cccctccctt cctgccacca cacacacctc cccacccctt cccgtcgaat ctcaggtgcc 1500

tgagagaggt gcttcactcc tcccactggg ccgagcattt agaataatca ccgccccctt 1560

cccccgcctt ttcctgccct ggatctccgc cgccacctcg gtctcgctgc tcctgggcgg 1620

ggggtgagga cgagtccgga gtatctgggg tttggcgttg ttgtcagcct cggggagaga 1680

gattggacaa atattctcca agaggaggag ggcgacgcca aggactttcc acatcaactg 1740

ctttggggta tctccacaag ttggaagagg gacccttttcg ttttgcattg cgtgtgttgt 1800

gctcattacc agtgcagcga ctgccgtccc agggtgactc tgagttgtcc tttatcgtga 1860

gctagcaatg gctagcgaag acaatcgtgt cccttccccg ccaccaacag gtgatgacgg 1920

<210> SEQ ID NO 38
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: lrba siRNA antisense strand
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(21)
<223> OTHER INFORMATION: combined DNA/RNA sequence
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: deoxythymidine

<400> SEQUENCE: 38

uagccaagac cuuugcuggt t 21

<210> SEQ ID NO 39
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: lrba siRNA (siRNA2)
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(21)
<223> OTHER INFORMATION: combined DNA/RNA sequence

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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: deoxythymidine

<400> SEQUENCE: 39

gggcacucuu ucugucacct t 21

<210> SEQ ID NO 40
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 40

agagaagagg agaagatgtg tgatc 25

<210> SEQ ID NO 41
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 41

ccaggctcca tgcttgtctg tgag 24

<210> SEQ ID NO 42
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 42

agcaagttca gcctggttaa gt 22

<210> SEQ ID NO 43
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 43

ttatgagtat ttcttccagg g 21

<210> SEQ ID NO 44
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 44

actgcagcaa gctcctcctg ttttctc 27

<210> SEQ ID NO 45
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

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<400> SEQUENCE: 45

tgggcgaaga gcggaaacag aac 23

<210> SEQ ID NO 46
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 46

gagtgatgga tgatgggaca gtggtg 26

<210> SEQ ID NO 47
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 47

gccacctccg tctcgctgc 19

<210> SEQ ID NO 48
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 48

gggcactggg gagaatttcg aagtagg 27

<210> SEQ ID NO 49
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 49

ttcaggcagt tttcaggacc ctccaag 27

<210> SEQ ID NO 50
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 50

tagtgtctga tgttgaactt cctcctg 27

<210> SEQ ID NO 51
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 51

ggcacaacct tcctgctcac 20

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<210> SEQ ID NO 52
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 52

cctgtccccc atttgaaccc 20

<210> SEQ ID NO 53
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 53

acggctgctt ctgcaccttc 20

<210> SEQ ID NO 54
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 54

ttttgggaca gggcttctct g 21

<210> SEQ ID NO 55
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 55

ggcacaacct tcctgctcac 20

<210> SEQ ID NO 56
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 56

gcagatgctc tcctcgctcc 20

<210> SEQ ID NO 57
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 57

cacacagagc attgtagcaa gctcctc 27

<210> SEQ ID NO 58
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

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<400> SEQUENCE: 58

tgcagacttg aagattccg 19

<210> SEQ ID NO 59
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (56)..(56)
<223> OTHER INFORMATION: v = a, g, or c
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (57)..(57)
<223> OTHER INFORMATION: n = a, c, g, or t

<400> SEQUENCE: 59

aagcagtggt atcaacgcag agtacttttt ttttttttttt ttttttttttt tttttvn 57

<210> SEQ ID NO 60
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 60

gagtgatgga tgatgggaca gtagtg 26

<210> SEQ ID NO 61
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic oligonucleotide

<400> SEQUENCE: 61

cgagaagatg agaagatgtg tgatc 25

<210> SEQ ID NO 62
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 1 5' spice donor

<400> SEQUENCE: 62

agtatctggg tgaggaag 18

<210> SEQ ID NO 63
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 2 5' spice donor

<400> SEQUENCE: 63

tttaacctgg taagtcca 18

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<210> SEQ ID NO 64
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 3 5' spice donor

<400> SEQUENCE: 64

tgatagcagg tatgattt 18

<210> SEQ ID NO 65
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 4 5' spice donor

<400> SEQUENCE: 65

ggacgatggg taaaaaaa 18

<210> SEQ ID NO 66
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(17)
<223> OTHER INFORMATION: Exon 5 5' spice donor

<400> SEQUENCE: 66

agtgctgcag taagtaa 17

<210> SEQ ID NO 67
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 6 5' spice donor

<400> SEQUENCE: 67

tttgtattgg tatgtatt 18

<210> SEQ ID NO 68
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 7 5' spice donor

<400> SEQUENCE: 68

ccacaaaagg tacatgat 18

<210> SEQ ID NO 69
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 8 5' spice donor

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<400> SEQUENCE: 69

actagcgatg taagtagt 18

<210> SEQ ID NO 70
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 9 5' spice donor

<400> SEQUENCE: 70

ggatacaagg tagtttgc 18

<210> SEQ ID NO 71
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 10 5' spice donor

<400> SEQUENCE: 71

atgctccagg tactaact 18

<210> SEQ ID NO 72
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 11 5' spice donor

<400> SEQUENCE: 72

gactatatgg tgagtgcc 18

<210> SEQ ID NO 73
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 12 5' spice donor

<400> SEQUENCE: 73

cttgaaaagg taaagtat 18

<210> SEQ ID NO 74
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 13 5' spice donor

<400> SEQUENCE: 74

ccagccaagg taatatat 18

<210> SEQ ID NO 75
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 14 5' spice donor

<400> SEQUENCE: 75

aaggattagg tatataat 18

<210> SEQ ID NO 76
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 15 5' spice donor

<400> SEQUENCE: 76

gtgatgaagg taggttca 18

<210> SEQ ID NO 77
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 16 5' spice donor

<400> SEQUENCE: 77

atgcatgagg taatatat 18

<210> SEQ ID NO 78
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 17 5' spice donor

<400> SEQUENCE: 78

tgggttacgg taagagtt 18

<210> SEQ ID NO 79
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 18 5' spice donor

<400> SEQUENCE: 79

ggccccaaag taagtatg 18

<210> SEQ ID NO 80
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 19 5' spice donor

<400> SEQUENCE: 80

ctgtttgagg taggaatg 18

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<210> SEQ ID NO 81
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 20 5' spice donor

<400> SEQUENCE: 81

aaacccctcg tatgtatg 18

<210> SEQ ID NO 82
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 21 5' spice donor

<400> SEQUENCE: 82

aaacaggagg taagctga 18

<210> SEQ ID NO 83
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 22 5' spice donor

<400> SEQUENCE: 83

cattcaaagg taagtttc 18

<210> SEQ ID NO 84
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 23 5' spice donor

<400> SEQUENCE: 84

gtgcttgagg tgatttta 18

<210> SEQ ID NO 85
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 24 5' spice donor

<400> SEQUENCE: 85

gtggagaagg tttgtcta 18

<210> SEQ ID NO 86
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 25 5' spice donor

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<400> SEQUENCE: 86

tcggctacag taaggact 18

<210> SEQ ID NO 87
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 26 5' spice donor

<400> SEQUENCE: 87

tccgactagg tgagctgc 18

<210> SEQ ID NO 88
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 27 5' spice donor

<400> SEQUENCE: 88

gcagcgaagg taagtata 18

<210> SEQ ID NO 89
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 28 5' spice donor

<400> SEQUENCE: 89

agagacatag taagttac 18

<210> SEQ ID NO 90
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 29 5' spice donor

<400> SEQUENCE: 90

cactctctgg taagtttg 18

<210> SEQ ID NO 91
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 30 5' spice donor

<400> SEQUENCE: 91

ttttgacagg tactgata 18

<210> SEQ ID NO 92
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 31 5' spice donor

<400> SEQUENCE: 92

aatcaccagg tgagttag 18

<210> SEQ ID NO 93
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 32 5' spice donor

<400> SEQUENCE: 93

aaatatgagg tatttaag 18

<210> SEQ ID NO 94
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 33 5' spice donor

<400> SEQUENCE: 94

aaggaacaag taagtggt 18

<210> SEQ ID NO 95
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 34 5' spice donor

<400> SEQUENCE: 95

tgttctcagg tgagtggc 18

<210> SEQ ID NO 96
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 35 5' spice donor

<400> SEQUENCE: 96

atgaggaagg taatttat 18

<210> SEQ ID NO 97
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 36 5' spice donor

<400> SEQUENCE: 97

gaatttgagg taggttac 18

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<210> SEQ ID NO 98
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 37 5' spice donor

<400> SEQUENCE: 98

tgcagtgagg taaaggga 18

<210> SEQ ID NO 99
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(17)
<223> OTHER INFORMATION: Exon 38 5' spice donor

<400> SEQUENCE: 99

tggaacatgg tcagtgg 17

<210> SEQ ID NO 100
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 39 5' spice donor

<400> SEQUENCE: 100

acagcaaagg taagcatt 18

<210> SEQ ID NO 101
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 40 5' spice donor

<400> SEQUENCE: 101

atcttgccgg taaatttg 18

<210> SEQ ID NO 102
<211> LENGTH: 11
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(11)
<223> OTHER INFORMATION: Exon 41 5' spice donor

<400> SEQUENCE: 102

gaccccaagg t 11

<210> SEQ ID NO 103
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 42 5' spice donor

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<400> SEQUENCE: 103

caaacagagg taatgtgt 18

<210> SEQ ID NO 104
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 43 5' spice donor

<400> SEQUENCE: 104

tcaaaccagg tactgttt 18

<210> SEQ ID NO 105
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 44 5' spice donor

<400> SEQUENCE: 105

cgatagcagg taacctaa 18

<210> SEQ ID NO 106
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 45 5' spice donor

<400> SEQUENCE: 106

ttgtccaagg taatttct 18

<210> SEQ ID NO 107
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 46 5' spice donor

<400> SEQUENCE: 107

ctaagaatag taagttca 18

<210> SEQ ID NO 108
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 47 5' spice donor

<400> SEQUENCE: 108

gatattaagg tacagaaa 18

<210> SEQ ID NO 109
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 48 5' spice donor

<400> SEQUENCE: 109

aacagattgg taagataa 18

<210> SEQ ID NO 110
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 49 5' spice donor

<400> SEQUENCE: 110

ttgagagagg taagttat 18

<210> SEQ ID NO 111
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 50 5' spice donor

<400> SEQUENCE: 111

atgcaagtgg taagtgct 18

<210> SEQ ID NO 112
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 51 5' spice donor

<400> SEQUENCE: 112

accttcctgg taagtaaa 18

<210> SEQ ID NO 113
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 52 5' spice donor

<400> SEQUENCE: 113

ctctcatagg tctgtcac 18

<210> SEQ ID NO 114
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 53 5' spice donor

<400> SEQUENCE: 114

cagacacagg taattttc 18

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<210> SEQ ID NO 115
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 54 5' spice donor

<400> SEQUENCE: 115

acccaggcag taagtatg 18

<210> SEQ ID NO 116
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 55 5' spice donor

<400> SEQUENCE: 116

gttcacaagg taaacctg 18

<210> SEQ ID NO 117
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 56 5' spice donor

<400> SEQUENCE: 117

aacataagag tgagtgcc 18

<210> SEQ ID NO 118
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Exon 57 5' spice donor

<400> SEQUENCE: 118

cgaccagagg taacactg 18

<210> SEQ ID NO 119
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 1 3' splice acceptor

<400> SEQUENCE: 119

tccaataagg gtttggcg 18

<210> SEQ ID NO 120
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 2 3' splice acceptor

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<400> SEQUENCE: 120

ccttgtaagt tggtagga 18

<210> SEQ ID NO 121
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 3 3' splice acceptor

<400> SEQUENCE: 121

tgtttccaga tcttttgg 18

<210> SEQ ID NO 122
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 4 3' splice acceptor

<400> SEQUENCE: 122

tcttcatagc ctccacat 18

<210> SEQ ID NO 123
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 5 3' splice acceptor

<400> SEQUENCE: 123

ttcctttagg ctattgca 18

<210> SEQ ID NO 124
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 6 3' splice acceptor

<400> SEQUENCE: 124

tctttatagt ttcagaac 18

<210> SEQ ID NO 125
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 7 3' splice acceptor

<400> SEQUENCE: 125

cttctgcagt ggtatatg 18

<210> SEQ ID NO 126
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 8 3' splice acceptor

<400> SEQUENCE: 126

cttttacaga cctttgac 18

<210> SEQ ID NO 127
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 9 3' splice acceptor

<400> SEQUENCE: 127

ttcttagagg gtacattt 18

<210> SEQ ID NO 128
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 10 3' splice acceptor

<400> SEQUENCE: 128

tcttacaagg atgtaaag 18

<210> SEQ ID NO 129
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 11 3' splice acceptor

<400> SEQUENCE: 129

aaattctagt tcaacctt 18

<210> SEQ ID NO 130
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 12 3' splice acceptor

<400> SEQUENCE: 130

tttttgcagt cttccaaa 18

<210> SEQ ID NO 131
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 13 3' splice acceptor

<400> SEQUENCE: 131

attctgtagg ttcaactg 18

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<210> SEQ ID NO 132
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 14 3' splice acceptor

<400> SEQUENCE: 132

ttttaaaaga tggaccgc 18

<210> SEQ ID NO 133
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 15 3' splice acceptor

<400> SEQUENCE: 133

tttttgaagg attctgga 18

<210> SEQ ID NO 134
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 16 3' splice acceptor

<400> SEQUENCE: 134

tgattatagg atgacaat 18

<210> SEQ ID NO 135
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 17 3' splice acceptor

<400> SEQUENCE: 135

ttcattcagt gttatcta 18

<210> SEQ ID NO 136
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 18 3' splice acceptor

<400> SEQUENCE: 136

taattgcagg aggaaagc 18

<210> SEQ ID NO 137
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 19 3' splice acceptor

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<400> SEQUENCE: 137

cttctgtaga ttcttata 18

<210> SEQ ID NO 138
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 20 3' splice acceptor

<400> SEQUENCE: 138

agattacaga gatactaa 18

<210> SEQ ID NO 139
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 21 3' splice acceptor

<400> SEQUENCE: 139

aattttcagg agcttgct 18

<210> SEQ ID NO 140
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 22 3' splice acceptor

<400> SEQUENCE: 140

ttcacctagg tcactttt 18

<210> SEQ ID NO 141
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 23 3' splice acceptor

<400> SEQUENCE: 141

tgtattaaga tatcaagg 18

<210> SEQ ID NO 142
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 24 3' splice acceptor

<400> SEQUENCE: 142

tttggacagc cattcaac 18

<210> SEQ ID NO 143
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 25 3' splice acceptor

<400> SEQUENCE: 143

tctttacagc atgaactg 18

<210> SEQ ID NO 144
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 26 3' splice acceptor

<400> SEQUENCE: 144

aaattacagt ttgtgcag 18

<210> SEQ ID NO 145
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 27 3' splice acceptor

<400> SEQUENCE: 145

cttaaataga gcccagtg 18

<210> SEQ ID NO 146
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 28 3' splice acceptor

<400> SEQUENCE: 146

ttttcccagg aggatagc 18

<210> SEQ ID NO 147
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 29 3' splice acceptor

<400> SEQUENCE: 147

atgatataga aatcacac 18

<210> SEQ ID NO 148
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 30 3' splice acceptor

<400> SEQUENCE: 148

ttattacaga agtgtcat 18

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<210> SEQ ID NO 149
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 31 3' splice acceptor

<400> SEQUENCE: 149

cttttatagg cagtagat 18

<210> SEQ ID NO 150
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 32 3' splice acceptor

<400> SEQUENCE: 150

tttccttagt attacaga 18

<210> SEQ ID NO 151
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 33 3' splice acceptor

<400> SEQUENCE: 151

ttaaaatagg tctggttt 18

<210> SEQ ID NO 152
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 34 3' splice acceptor

<400> SEQUENCE: 152

tttttatagg agtggcaa 18

<210> SEQ ID NO 153
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 35 3' splice acceptor

<400> SEQUENCE: 153

ttcttacagg ttgcttag 18

<210> SEQ ID NO 154
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 36 3' splice acceptor

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<400> SEQUENCE: 154

ctctccaagt cactgtgt 18

<210> SEQ ID NO 155
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(17)
<223> OTHER INFORMATION: Intron 37 3' splice acceptor

<400> SEQUENCE: 155

cattgtagtc gtcctct 17

<210> SEQ ID NO 156
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 38 3' splice acceptor

<400> SEQUENCE: 156

atgttttagt gtgcattt 18

<210> SEQ ID NO 157
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 39 3' splice acceptor

<400> SEQUENCE: 157

tcatttcagc cacagatg 18

<210> SEQ ID NO 158
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 40 3' splice acceptor

<400> SEQUENCE: 158

ttttggcagg tcctgtta 18

<210> SEQ ID NO 159
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 41 3' splice acceptor

<400> SEQUENCE: 159

cctcattaga tcttggca 18

<210> SEQ ID NO 160
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 42 3' splice acceptor

<400> SEQUENCE: 160

ctgttgtagt tgctgtga 18

<210> SEQ ID NO 161
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 43 3' splice acceptor

<400> SEQUENCE: 161

ttcttgcaga cgtatttc 18

<210> SEQ ID NO 162
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 44 3' splice acceptor

<400> SEQUENCE: 162

ccctatcagg acggagtt 18

<210> SEQ ID NO 163
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 45 3' splice acceptor

<400> SEQUENCE: 163

tattggcagc caatagga 18

<210> SEQ ID NO 164
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 46 3' splice acceptor

<400> SEQUENCE: 164

attttttagg aacccttt 18

<210> SEQ ID NO 165
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 47 3' splice acceptor

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<400> SEQUENCE: 165

tttatatagg agttgatc 18

<210> SEQ ID NO 166
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 48 3' splice acceptor

<400> SEQUENCE: 166

ttttttcagg ccctggag 18

<210> SEQ ID NO 167
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 49 3' splice acceptor

<400> SEQUENCE: 167

cctttttcagg ctgttgaa 18

<210> SEQ ID NO 168
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 50 3' splice acceptor

<400> SEQUENCE: 168

ctcctgcaga gtccattg 18

<210> SEQ ID NO 169
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 51 3' splice acceptor

<400> SEQUENCE: 169

gaattccagc tcatcaag 18

<210> SEQ ID NO 170
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 52 3' splice acceptor

<400> SEQUENCE: 170

ttcttacagc cagcaata 18

<210> SEQ ID NO 171
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

-continued

<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 53 3' splice acceptor

<400> SEQUENCE: 171

gcattacagg aagattga 18

<210> SEQ ID NO 172
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 54 3' splice acceptor

<400> SEQUENCE: 172

ttcctaaagg tgagactg 18

<210> SEQ ID NO 173
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 55 3' splice acceptor

<400> SEQUENCE: 173

tcttctcaga aggaccat 18

<210> SEQ ID NO 174
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 56 3' splice acceptor

<400> SEQUENCE: 174

gtctcacagg ccatccag 18

<210> SEQ ID NO 175
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(18)
<223> OTHER INFORMATION: Intron 57 3' splice acceptor

<400> SEQUENCE: 175

ttctcctagg tgcatcat 18

<210> SEQ ID NO 176
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: p21 RAS motif

<400> SEQUENCE: 176

Leu Leu Gly Val Gly Gly Phe Asp
1 5

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<210> SEQ ID NO 177
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: lrba siRNA (siRNA1)

<400> SEQUENCE: 177

ccagcaaagg ucuuggcua 19

<210> SEQ ID NO 178
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: lrba siRNA

<400> SEQUENCE: 178

cagucggguu ugcgacugg 19

<210> SEQ ID NO 179
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: lrba siRNA antisense strand

<400> SEQUENCE: 179

uagccaagac cuuugcugg 19

<210> SEQ ID NO 180
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: lrba siRNA (siRNA2)

<400> SEQUENCE: 180

gggcacucuu ucugucacc 19

<210> SEQ ID NO 181
<211> LENGTH: 165
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 181

ugagaaacag aaauuugugg uaguaauaua auccauaauu acuuauuugu gugugaagac 60

acaacaucuu uuggcagaag gaggauuuga acuccuguuc uuuagaaugu gcuguguugg 120

aguggaugac caaacuuggu aggaggacag uuugaucugg aaaug 165

<210> SEQ ID NO 182
<211> LENGTH: 2818
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 182

Met Ala Ser Glu Asp Asn Arg Val Pro Ser Pro Pro Pro Thr Gly Asp
1 5 10 15

Asp Gly Gly Gly Gly Gly Arg Glu Glu Thr Pro Thr Glu Gly Gly Ala
20 25 30

Leu Ser Leu Lys Pro Gly Leu Pro Ile Arg Gly Ile Arg Met Lys Phe
35 40 45

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```
Ala Val Leu Thr Gly Leu Val Glu Val Gly Glu Val Ser Asn Arg Asp
    50                  55                  60

Ile Val Glu Thr Val Phe Asn Leu Leu Val Gly Gly Gln Phe Asp Leu
65                  70                  75                  80

Glu Met Asn Phe Ile Ile Gln Glu Gly Glu Ser Ile Asn Cys Met Val
                85                  90                  95

Asp Leu Leu Glu Lys Cys Asp Ile Thr Cys Gln Ala Glu Val Trp Ser
            100                 105                 110

Met Phe Thr Ala Ile Leu Lys Lys Ser Ile Arg Asn Leu Gln Val Cys
        115                 120                 125

Thr Glu Val Gly Leu Val Glu Lys Val Leu Gly Lys Ile Glu Lys Val
    130                 135                 140

Asp Asn Met Ile Ala Asp Leu Leu Val Asp Met Leu Gly Val Leu Ala
145                 150                 155                 160

Ser Tyr Asn Leu Thr Val Arg Glu Leu Lys Leu Phe Phe Ser Lys Leu
                165                 170                 175

Gln Gly Asp Lys Gly Arg Trp Pro Pro His Ala Gly Lys Leu Leu Ser
            180                 185                 190

Val Leu Lys His Met Pro Gln Lys Tyr Gly Pro Asp Ala Phe Phe Asn
        195                 200                 205

Phe Pro Gly Lys Ser Ala Ala Ala Ile Ala Leu Pro Pro Ile Ala Lys
    210                 215                 220

Trp Pro Tyr Gln Asn Gly Phe Thr Phe His Thr Trp Leu Arg Met Asp
225                 230                 235                 240

Pro Val Asn Asn Ile Asn Val Asp Lys Asp Lys Pro Tyr Leu Tyr Cys
                245                 250                 255

Phe Arg Thr Ser Lys Gly Leu Gly Tyr Ser Ala His Phe Val Gly Gly
            260                 265                 270

Cys Leu Ile Val Thr Ser Ile Lys Ser Lys Gly Lys Gly Phe Gln His
        275                 280                 285

Cys Val Lys Phe Asp Phe Lys Pro Gln Lys Trp Tyr Met Val Thr Ile
    290                 295                 300

Val His Ile Tyr Asn Arg Trp Lys Asn Ser Glu Leu Arg Cys Tyr Val
305                 310                 315                 320

Asn Gly Glu Leu Ala Ser Tyr Gly Glu Ile Thr Trp Phe Val Asn Thr
                325                 330                 335

Ser Asp Thr Phe Asp Lys Cys Phe Leu Gly Ser Ser Glu Thr Ala Asp
            340                 345                 350

Ala Asn Arg Val Phe Cys Gly Gln Met Thr Ala Val Tyr Leu Phe Ser
        355                 360                 365

Glu Ala Leu Asn Ala Ala Gln Ile Phe Ala Ile Tyr Gln Leu Gly Leu
    370                 375                 380

Gly Tyr Lys Gly Thr Phe Lys Phe Lys Ala Glu Ser Asp Leu Phe Leu
385                 390                 395                 400

Ala Glu His His Lys Leu Leu Leu Tyr Asp Gly Lys Leu Ser Ser Ala
                405                 410                 415

Ile Ala Phe Thr Tyr Asn Pro Arg Ala Thr Asp Ala Gln Leu Cys Leu
            420                 425                 430

Glu Ser Ser Pro Lys Asp Asn Pro Ser Ile Phe Val His Ser Pro His
        435                 440                 445

Ala Leu Met Leu Gln Asp Val Lys Ala Val Leu Thr His Ser Ile Gln
    450                 455                 460
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Ser Ala Met His Ser Ile Gly Gly Val Gln Val Leu Phe Pro Leu Phe
465                 470                 475                 480

Ala Gln Leu Asp Tyr Arg Gln Tyr Leu Ser Asp Glu Ile Asp Leu Thr
                485                 490                 495

Ile Cys Ser Thr Leu Leu Ala Phe Ile Met Glu Leu Leu Lys Asn Ser
            500                 505                 510

Ile Ala Met Gln Glu Gln Met Leu Ala Cys Lys Gly Phe Leu Val Ile
        515                 520                 525

Gly Tyr Ser Leu Glu Lys Ser Ser Lys Ser His Val Ser Arg Ala Val
    530                 535                 540

Leu Glu Leu Cys Leu Ala Phe Ser Lys Tyr Leu Ser Asn Leu Gln Asn
545                 550                 555                 560

Gly Met Pro Leu Leu Lys Gln Leu Cys Asp His Val Leu Leu Asn Pro
                565                 570                 575

Ala Ile Trp Ile His Thr Pro Ala Lys Val Gln Leu Met Leu Tyr Thr
            580                 585                 590

Tyr Leu Ser Thr Glu Phe Ile Gly Thr Val Asn Ile Tyr Asn Thr Ile
        595                 600                 605

Arg Arg Val Gly Thr Val Leu Leu Ile Met His Thr Leu Lys Tyr Tyr
    610                 615                 620

Tyr Trp Ala Val Asn Pro Gln Asp Arg Ser Gly Ile Thr Pro Lys Gly
625                 630                 635                 640

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

Phe Leu Leu Met Phe Ile Lys Gln Leu Val Met Lys Asp Ser Gly Val
            660                 665                 670

Lys Glu Asp Glu Leu Gln Ala Ile Leu Asn Tyr Leu Leu Thr Met His
        675                 680                 685

Glu Asp Asp Asn Leu Met Asp Val Leu Gln Leu Leu Val Ala Leu Met
    690                 695                 700

Ser Glu His Pro Asn Ser Met Ile Pro Ala Phe Asp Gln Arg Asn Gly
705                 710                 715                 720

Leu Arg Val Ile Tyr Lys Leu Leu Ala Ser Lys Ser Glu Gly Ile Arg
                725                 730                 735

Val Gln Ala Leu Lys Ala Met Gly Tyr Phe Leu Lys His Arg Pro Pro
            740                 745                 750

Lys Arg Lys Ala Glu Val Met Leu Gly His Gly Leu Phe Ser Leu Leu
        755                 760                 765

Ala Glu Arg Leu Met Leu Gln Thr Asn Leu Ile Thr Met Thr Thr Tyr
    770                 775                 780

Asn Val Leu Phe Glu Ile Leu Ile Glu Gln Ile Gly Thr Gln Val Ile
785                 790                 795                 800

His Lys Gln His Pro Asp Pro Asp Ser Ser Val Lys Ile Gln Asn Pro
                805                 810                 815

Gln Ile Leu Lys Val Ile Ala Thr Leu Leu Arg Asn Ser Pro Gln Cys
            820                 825                 830

Pro Glu Ser Met Glu Val Arg Arg Ala Phe Leu Ser Asp Met Ile Lys
        835                 840                 845

Leu Phe Asn Asn Ser Arg Glu Asn Arg Arg Ser Leu Leu Gln Cys Ser
    850                 855                 860

Val Trp Gln Glu Trp Met Leu Ser Leu Cys Tyr Phe Asn Pro Lys Asn
865                 870                 875                 880
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```
Ser Asp Glu Gln Lys Ile Thr Glu Met Val Tyr Ala Ile Phe Arg Ile
               885                 890                 895

Leu Leu Tyr His Ala Val Lys Tyr Glu Trp Gly Gly Trp Arg Val Trp
           900                 905                 910

Val Asp Thr Leu Ser Ile Thr His Ser Lys Val Thr Phe Glu Ile His
        915                 920                 925

Lys Glu Asn Leu Ala Asn Ile Phe Arg Glu Gln Gln Gly Lys Val Asp
    930                 935                 940

Glu Glu Ile Gly Leu Cys Ser Ser Thr Ser Val Gln Ala Ala Ser Gly
945                 950                 955                 960

Ile Arg Arg Asp Ile Asn Val Ser Val Gly Ser Gln Gln Pro Asp Thr
               965                 970                 975

Lys Asp Ser Pro Val Cys Pro His Phe Thr Thr Asn Gly Asn Glu Asn
           980                 985                 990

Ser Ser Ile Glu Lys Thr Ser Ser  Leu Glu Ser Ala Ser  Asn Ile Glu
        995                 1000                1005

Leu Gln  Thr Thr Asn Thr Ser  Tyr Glu Glu Met Lys  Ala Glu Gln
    1010                1015                1020

Glu Asn  Gln Glu Leu Pro Asp  Glu Gly Thr Leu Glu  Glu Thr Leu
    1025                1030                1035

Thr Asn  Glu Thr Arg Asn Ala  Asp Asp Leu Glu Val  Ser Ser Asp
    1040                1045                1050

Ile Ile  Glu Ala Val Ala Ile  Ser Ser Asn Ser Phe  Ile Thr Thr
    1055                1060                1065

Gly Lys  Asp Ser Met Thr Val  Ser Glu Val Thr Ala  Ser Ile Ser
    1070                1075                1080

Ser Pro  Ser Glu Glu Asp Ala  Ser Glu Met Pro Glu  Phe Leu Asp
    1085                1090                1095

Lys Ser  Ile Val Glu Glu Glu  Glu Asp Asp Asp Tyr  Val Glu Leu
    1100                1105                1110

Lys Val  Glu Gly Ser Pro Thr  Glu Glu Ala Asn Leu  Pro Thr Glu
    1115                1120                1125

Leu Gln  Asp Asn Ser Leu Ser  Pro Ala Ala Ser Glu  Ala Gly Glu
    1130                1135                1140

Lys Leu  Asp Met Phe Gly Asn  Asp Asp Lys Leu Ile  Phe Gln Glu
    1145                1150                1155

Gly Lys  Pro Val Thr Glu Lys  Gln Thr Asp Thr Glu  Thr Gln Asp
    1160                1165                1170

Ser Lys  Asp Ser Gly Ile Gln  Thr Met Thr Ala Ser  Gly Ser Ser
    1175                1180                1185

Ala Met  Ser Pro Glu Thr Thr  Val Ser Gln Ile Ala  Val Glu Ser
    1190                1195                1200

Asp Leu  Gly Gln Met Leu Glu  Glu Gly Lys Lys Ala  Thr Asn Leu
    1205                1210                1215

Thr Arg  Glu Thr Lys Leu Ile  Asn Asp Cys His Gly  Ser Val Ser
    1220                1225                1230

Glu Ala  Ser Ser Glu Gln Lys  Ile Ala Lys Leu Asp  Val Ser Asn
    1235                1240                1245

Val Ala  Thr Asp Thr Glu Arg  Leu Glu Leu Lys Ala  Ser Pro Asn
    1250                1255                1260

Val Glu  Ala Pro Gln Pro His  Arg His Val Leu Glu  Ile Ser Arg
    1265                1270                1275
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Gln His  Glu Gln Pro Gly Gln  Gly Ile Ala Pro Asp  Ala Val Asn
    1280                 1285                 1290

Gly Gln  Arg Arg Asp Ser Arg  Ser Thr Val Phe Arg  Ile Pro Glu
    1295                 1300                 1305

Phe Asn  Trp Ser Gln Met His  Gln Arg Leu Leu Thr  Asp Leu Leu
    1310                 1315                 1320

Phe Ser  Ile Glu Thr Asp Ile  Gln Met Trp Arg Ser  His Ser Thr
    1325                 1330                 1335

Lys Thr  Val Met Asp Phe Val  Asn Ser Ser Asp Asn  Val Ile Phe
    1340                 1345                 1350

Val His  Asn Thr Ile His Leu  Ile Ser Gln Val Met  Asp Asn Met
    1355                 1360                 1365

Val Met  Ala Cys Gly Gly Ile  Leu Pro Leu Leu Ser  Ala Ala Thr
    1370                 1375                 1380

Ser Ala  Thr His Glu Leu Glu  Asn Ile Glu Pro Thr  Gln Gly Leu
    1385                 1390                 1395

Ser Ile  Glu Ala Ser Val Thr  Phe Leu Gln Arg Leu  Ile Ser Leu
    1400                 1405                 1410

Val Asp  Val Leu Ile Phe Ala  Ser Ser Leu Gly Phe  Thr Glu Ile
    1415                 1420                 1425

Glu Ala  Glu Lys Ser Met Ser  Ser Gly Gly Ile Leu  Arg Gln Cys
    1430                 1435                 1440

Leu Arg  Leu Val Cys Ala Val  Ala Val Arg Asn Cys  Leu Glu Cys
    1445                 1450                 1455

Gln Gln  His Ser Gln Leu Lys  Thr Arg Gly Asp Lys  Ala Leu Lys
    1460                 1465                 1470

Pro Met  His Ser Leu Ile Pro  Leu Gly Lys Ser Ala  Ala Lys Ser
    1475                 1480                 1485

Pro Val  Asp Ile Val Thr Gly  Gly Ile Ser Pro Val  Arg Asp Leu
    1490                 1495                 1500

Asp Arg  Leu Leu Gln Asp Met  Asp Ile Asn Arg Leu  Arg Ala Val
    1505                 1510                 1515

Val Phe  Arg Asp Ile Glu Asp  Ser Lys Gln Ala Gln  Phe Leu Ala
    1520                 1525                 1530

Leu Ala  Val Val Tyr Phe Ile  Ser Val Leu Met Val  Ser Lys Tyr
    1535                 1540                 1545

Arg Asp  Ile Leu Glu Pro Gln  Asn Glu Arg His Ser  Gln Ser Cys
    1550                 1555                 1560

Thr Glu  Thr Gly Ser Glu Asn  Glu Asn Val Ser Leu  Ser Glu Ile
    1565                 1570                 1575

Thr Pro  Ala Ala Phe Ser Thr  Leu Thr Thr Ala Ser  Val Glu Glu
    1580                 1585                 1590

Ser Glu  Ser Thr Ser Ser Ala  Arg Arg Arg Asp Ser  Gly Ile Gly
    1595                 1600                 1605

Glu Glu  Thr Ala Thr Gly Leu  Gly Ser His Val Glu  Val Thr Pro
    1610                 1615                 1620

His Thr  Ala Pro Pro Gly Val  Ser Ala Gly Pro Asp  Ala Ile Ser
    1625                 1630                 1635

Glu Val  Leu Ser Thr Leu Ser  Leu Glu Val Asn Lys  Ser Pro Glu
    1640                 1645                 1650

Thr Lys  Asn Asp Arg Gly Asn  Asp Leu Asp Thr Lys  Ala Thr Pro
    1655                 1660                 1665
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```
Ser Val  Ser Val Ser Lys Asn  Val Asn Val Lys Asp  Ile Leu Arg
    1670                 1675                 1680

Ser Leu  Val Asn Ile Pro Ala  Asp Gly Val Thr Val  Asp Pro Ala
    1685                 1690                 1695

Leu Leu  Pro Pro Ala Cys Leu  Gly Ala Leu Gly Asp  Leu Ser Val
    1700                 1705                 1710

Glu Gln  Pro Val Gln Phe Arg  Ser Phe Asp Arg Ser  Val Ile Val
    1715                 1720                 1725

Ala Ala  Lys Lys Ser Ala Val  Ser Pro Ser Thr Phe  Asn Thr Ser
    1730                 1735                 1740

Ile Pro  Thr Asn Ala Val Ser  Val Val Ser Ser Val  Asp Ser Ala
    1745                 1750                 1755

Gln Ala  Ser Asp Met Gly Gly  Glu Ser Pro Gly Ser  Arg Ser Ser
    1760                 1765                 1770

Asn Ala  Lys Leu Pro Ser Val  Pro Thr Val Asp Ser  Val Ser Gln
    1775                 1780                 1785

Asp Pro  Val Ser Asn Met Ser  Ile Thr Glu Arg Leu  Glu His Ala
    1790                 1795                 1800

Leu Glu  Lys Ala Ala Pro Leu  Leu Arg Glu Ile Phe  Val Asp Phe
    1805                 1810                 1815

Ala Pro  Phe Leu Ser Arg Thr  Leu Leu Gly Ser His  Gly Gln Glu
    1820                 1825                 1830

Leu Leu  Ile Glu Gly Thr Ser  Leu Val Cys Met Lys  Ser Ser Ser
    1835                 1840                 1845

Ser Val  Val Glu Leu Val Met  Leu Leu Cys Ser Gln  Glu Trp Gln
    1850                 1855                 1860

Asn Ser  Ile Gln Lys Asn Ala  Gly Leu Ala Phe Ile  Glu Leu Val
    1865                 1870                 1875

Asn Glu  Gly Arg Leu Leu Ser  Gln Thr Met Lys Asp  His Leu Val
    1880                 1885                 1890

Arg Val  Ala Asn Glu Ala Glu  Phe Ile Leu Ser Arg  Gln Arg Ala
    1895                 1900                 1905

Glu Asp  Ile His Arg His Ala  Glu Phe Glu Ser Leu  Cys Ala Gln
    1910                 1915                 1920

Tyr Ser  Ala Asp Lys Arg Glu  Asp Glu Lys Met Cys  Asp His Leu
    1925                 1930                 1935

Ile Arg  Ala Ala Lys Tyr Arg  Asp His Val Thr Ala  Thr Gln Leu
    1940                 1945                 1950

Ile Gln  Lys Ile Ile Asn Ile  Leu Thr Asp Lys His  Gly Ala Trp
    1955                 1960                 1965

Gly Asn  Ser Ala Val Ser Arg  Pro Leu Glu Phe Trp  Arg Leu Asp
    1970                 1975                 1980

Tyr Trp  Glu Asp Asp Leu Arg  Arg Arg Arg Arg Phe  Val Arg Asn
    1985                 1990                 1995

Pro Leu  Gly Ser Thr His Pro  Glu Ala Thr Leu Lys  Thr Ala Val
    2000                 2005                 2010

Glu His  Val Cys Ile Phe Lys  Leu Arg Glu Asn Ser  Lys Ala Thr
    2015                 2020                 2025

Asp Glu  Asp Ile Leu Ala Lys  Gly Lys Gln Ser Ile  Arg Ser Gln
    2030                 2035                 2040

Ala Leu  Gly Asn Gln Asn Ser  Glu Asn Glu Ile Leu  Leu Glu Gly
    2045                 2050                 2055
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Asp Asp  Asp Thr Leu Ser Ser  Val Asp Glu Lys Asp  Leu Glu Asn
    2060                2065                2070

Leu Ala  Gly Pro Val Ser Leu  Ser Thr Pro Ala Gln  Leu Val Ala
    2075                2080                2085

Pro Ser  Val Val Val Lys Gly  Thr Leu Ser Val Thr  Ser Ser Glu
    2090                2095                2100

Leu Tyr  Phe Glu Val Asp Glu  Glu Asp Pro Asn Phe  Lys Lys Ile
    2105                2110                2115

Asp Pro  Lys Ile Leu Ala Tyr  Thr Glu Gly Leu His  Gly Lys Trp
    2120                2125                2130

Leu Phe  Thr Glu Ile Arg Ser  Ile Phe Ser Arg Arg  Tyr Leu Leu
    2135                2140                2145

Gln Asn  Thr Ala Leu Glu Ile  Phe Met Ala Asn Arg  Val Ala Val
    2150                2155                2160

Met Phe  Asn Phe Pro Asp Pro  Ala Thr Val Lys Lys  Val Val Asn
    2165                2170                2175

Phe Leu  Pro Arg Val Gly Val  Gly Thr Ser Phe Gly  Leu Pro Gln
    2180                2185                2190

Thr Arg  Arg Ile Ser Leu Ala  Ser Pro Arg Gln Leu  Phe Lys Ala
    2195                2200                2205

Ser Asn  Met Thr Gln Arg Trp  Gln His Arg Glu Ile  Ser Asn Phe
    2210                2215                2220

Glu Tyr  Leu Met Phe Leu Asn  Thr Ile Ala Gly Arg  Ser Tyr Asn
    2225                2230                2235

Asp Leu  Asn Gln Tyr Pro Val  Phe Pro Trp Val Ile  Thr Asn Tyr
    2240                2245                2250

Glu Ser  Glu Glu Leu Asp Leu  Thr Leu Pro Thr Asn  Phe Arg Asp
    2255                2260                2265

Leu Ser  Lys Pro Ile Gly Ala  Leu Asn Pro Lys Arg  Ala Ala Phe
    2270                2275                2280

Phe Ala  Glu Arg Tyr Glu Ser  Trp Glu Asp Asp Gln  Val Pro Lys
    2285                2290                2295

Phe His  Tyr Gly Thr His Tyr  Ser Thr Ala Ser Phe  Val Leu Ala
    2300                2305                2310

Trp Leu  Leu Arg Ile Glu Pro  Phe Thr Thr Tyr Phe  Leu Asn Leu
    2315                2320                2325

Gln Gly  Gly Lys Phe Asp His  Ala Asp Arg Thr Phe  Ser Ser Ile
    2330                2335                2340

Ser Arg  Ala Trp Arg Asn Ser  Gln Arg Asp Thr Ser  Asp Ile Lys
    2345                2350                2355

Glu Leu  Ile Pro Glu Phe Tyr  Tyr Leu Pro Glu Met  Phe Val Asn
    2360                2365                2370

Phe Asn  Asn Tyr Asn Leu Gly  Val Met Asp Asp Gly  Thr Val Val
    2375                2380                2385

Ser Asp  Val Glu Leu Pro Pro  Trp Ala Lys Thr Ser  Glu Glu Phe
    2390                2395                2400

Val His  Ile Asn Arg Leu Val  Arg Ala Leu Glu Ser  Glu Phe Val
    2405                2410                2415

Ser Cys  Gln Leu His Gln Trp  Ile Asp Leu Ile Phe  Gly Tyr Lys
    2420                2425                2430

Gln Gln  Gly Pro Glu Ala Val  Arg Ala Leu Asn Val  Phe Tyr Tyr
    2435                2440                2445
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-continued

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Leu Thr  Tyr Glu Gly Ala Val  Asn Leu Asn Ser Ile  Thr Asp Pro
    2450                 2455                 2460

Val Leu  Arg Glu Ala Val Glu  Ala Gln Ile Arg Ser  Phe Gly Gln
    2465                 2470                 2475

Thr Pro  Ser Gln Leu Leu Ile  Glu Pro His Pro Pro  Arg Gly Ser
    2480                 2485                 2490

Ala Met  Gln Val Tyr Leu Leu  Leu Gln Ser Pro Leu  Met Phe Thr
    2495                 2500                 2505

Asp Lys  Ala Gln Gln Asp Val  Ile Met Val Leu Lys  Phe Pro Ser
    2510                 2515                 2520

Asn Ser  Pro Val Thr His Val  Ala Ala Asn Thr Gln  Pro Gly Leu
    2525                 2530                 2535

Ala Thr  Pro Ala Val Ile Thr  Val Thr Ala Asn Arg  Leu Phe Ala
    2540                 2545                 2550

Val Asn  Lys Trp His Asn Leu  Pro Ala His Gln Gly  Ala Val Gln
    2555                 2560                 2565

Asp Gln  Pro Tyr Gln Leu Pro  Val Glu Ile Asp Pro  Leu Ile Gly
    2570                 2575                 2580

Leu Ser  Leu Pro Ser Leu Phe  Ala Ile His Ala Ser  Asn Thr Gly
    2585                 2590                 2595

Met His  Arg Arg Gln Ile Thr  Asp Leu Leu Asp Gln  Ser Ile Gln
    2600                 2605                 2610

Val His  Ser Gln Cys Phe Val  Ile Thr Ser Asp Asn  Arg Tyr Ile
    2615                 2620                 2625

Leu Val  Cys Gly Phe Trp Asp  Lys Ser Phe Arg Val  Tyr Ser Thr
    2630                 2635                 2640

Asp Thr  Gly Arg Leu Ile Gln  Val Val Phe Gly His  Trp Asp Val
    2645                 2650                 2655

Val Thr  Cys Leu Ala Arg Ser  Glu Ser Tyr Ile Gly  Gly Asn Cys
    2660                 2665                 2670

Tyr Ile  Leu Ser Gly Ser Arg  Asp Ala Thr Leu Leu  Leu Trp Tyr
    2675                 2680                 2685

Trp Asn  Gly Lys Cys Ser Gly  Ile Gly Asp Asn Pro  Gly Ser Glu
    2690                 2695                 2700

Thr Ala  Ala Pro Arg Ala Ile  Leu Thr Gly His Asp  Tyr Glu Val
    2705                 2710                 2715

Thr Cys  Ala Ala Val Cys Ala  Glu Leu Gly Leu Val  Leu Ser Gly
    2720                 2725                 2730

Ser Gln  Glu Gly Pro Cys Leu  Ile His Ser Met Asn  Gly Asp Leu
    2735                 2740                 2745

Leu Arg  Thr Leu Glu Gly Pro  Glu Asn Cys Leu Lys  Pro Lys Leu
    2750                 2755                 2760

Ile Gln  Ala Ser Arg Glu Gly  His Cys Val Ile Phe  Tyr Glu Asn
    2765                 2770                 2775

Gly Leu  Phe Cys Thr Phe Ser  Val Asn Gly Lys Leu  Gln Ala Thr
    2780                 2785                 2790

Met Glu  Thr Asp Asp Asn Ile  Arg Ala Ile Gln Leu  Ser Arg Asp
    2795                 2800                 2805

Gly Gln  Tyr Leu Leu Thr Gly  Gly Asp Arg
    2810                 2815
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The invention claimed is:

1. A method for inhibiting the growth of a tumor characterized by overexpression of the LPS-responsive CHS1/beige-like anchor gene (lrba) in a mammal, comprising directly administering an effective amount of an interfering RNA molecule to the tumor, wherein the interfering RNA is specific for lrba mRNA within the mammal and reduces lrba expression within the tumor, and wherein the interfering RNA inhibits growth of the tumor in the mammal.

2. The method according to claim 1, wherein the interfering RNA is single-stranded RNA selected from the group consisting of SEQ ID NO. 177, SEQ ID NO. 178, SEQ ID NO. 179, and SEQ ID NO. 180.

3. The method according to claim 1, wherein the interfering RNA is double-stranded RNA comprising SEQ ID NO. 177, SEQ ID NO. 178, SEQ ID NO. 179, or SEQ ID NO. 180.

4. The method of claim 1, wherein the mammal is a human.

5. The method according to claim 1, wherein the tumor is of a cancer type selected from the group consisting of breast, prostate, melanoma, cervical cancer, adenocarcinoma, colorectal cancer, and lung carcinoma.

6. The method according to claim 1, wherein the tumor is of a cancer type selected from breast cancer or prostate cancer.

7. A method for inhibiting the growth of mammalian cancer cells characterized by overexpression of the LPS-responsive CHS1/beige-like anchor gene (lrba), comprising directly administering an effective amount of an interfering RNA molecule to the cancer cells in vitro or in vivo, wherein the interfering RNA is specific for lrba mRNA within the cancer cells and reduces lrba expression within the cancer cells, and wherein the interfering RNA inhibits growth of the cancer cells.

8. The method according to claim 7, wherein the cancer cells are of a cancer type selected from the group consisting of breast, prostate, melanoma, cervical cancer, adenocarcinoma, colorectal cancer, and lung carcinoma.

9. The method according to claim 7, wherein the cancer cells are of a cancer type selected from breast cancer or prostate cancer.

10. The method according to claim 7, wherein the cancer cells are human cells.

11. The method according to claim 7, wherein said administering is carried out in vivo.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,704,963 B2
APPLICATION NO. : 10/473741
DATED : April 27, 2010
INVENTOR(S) : William G. Kerr and Jia-Wang Wang

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

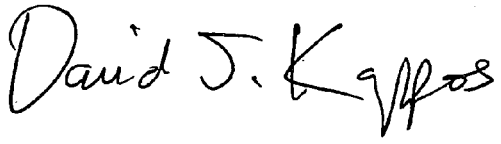
Column 32,
Line 63, "HFAN," should read --hFAN,--.

Column 35, Table 2, row 4,
Column 5'Splice donor, "GGA CGA TCG gtaaaaaaa" should read
--GGA CGA TGG gtaaaaaaa--.

Column 37, Table 2, row 49,
Column 5'Splice donor, "TTG AGA GAG gtaa9ttat" should read
--TTG AGA GAG gtaagttat--.

Signed and Sealed this

Twenty-seventh Day of July, 2010



David J. Kappos
Director of the United States Patent and Trademark Office