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(71) Applicant *(for all designated States except US)*: **THE ROTHBERG INSTITUTE FOR CHILDHOOD DISEASES** [US/US]; 530 Whitfield Street, Guilford, CT 06437 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SQUILLACE, Rachel** [US/US]; Guilford, CT 06437 (US). **WEINER, Michael, P.** [US/US]; 52 Leighton Trail, Guilford, CT 06437 (US).

(74) Agent: **ELRIFI, ivor, R.**; Mintz, Levin, Cohn, Ferris, Glosky and Popeo,P.C., One Financial Center, Boston, MA 02111 (US).

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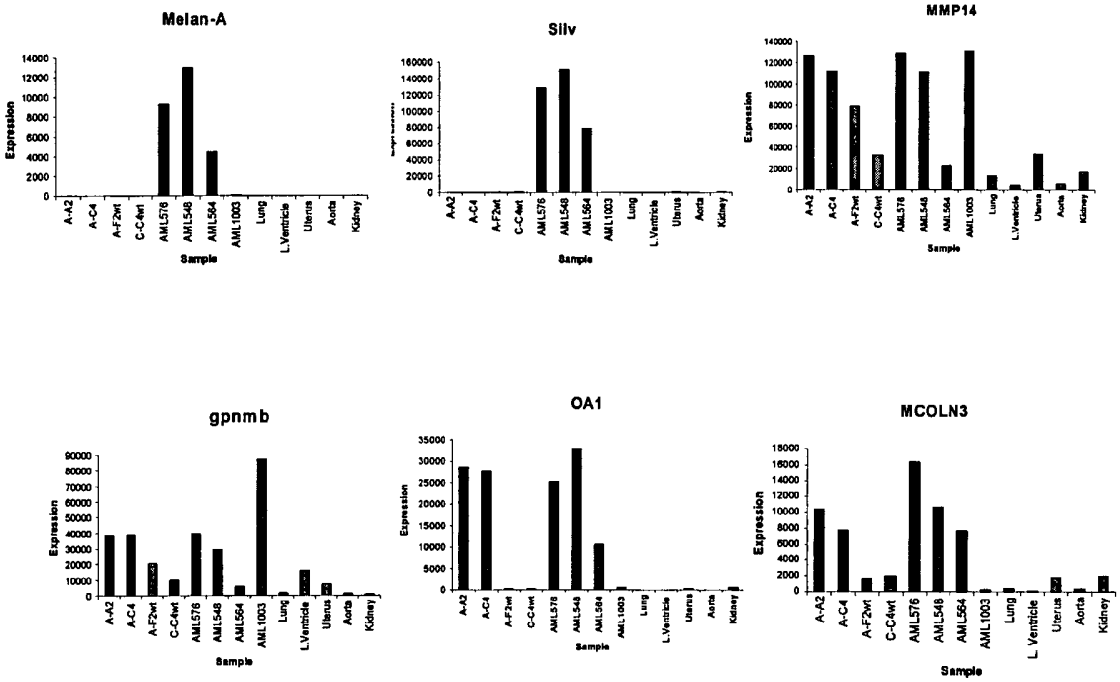
(54) Title: IMMORTALIZED HUMAN TUBEROUS SCLEROSIS NULL ANGIOMYOLIPOMA CELL AND METHOD OF USE THEREOF



(57) Abstract: Disclosed are immortalized cells and cell lines that do not express the Tuberous Sclerosis Complex(TSC)-2 gene. Also sisclosed are methods of detecting TSC-related disorders using differentially expressed genes.

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IMMORTALIZED HUMAN TUBEROUS SCLEROSIS NULL ANGIOMYOLIPOMA CELL AND METHOD OF USE THEREOF

FIELD OF THE INVENTION

The invention relates compositions and methods of treating and preventing Tuberous Sclerosis Complex (TSC) related disorders. More specifically, the invention provides a novel $TSC^{-/-}$ cell line.

BACKGROUND OF THE INVENTION

TSC is an autosomal dominant disorder characterized by widespread benign hamartomas, epilepsy, mental retardation, and autism. Occurring once in 6,000 live births, TSC is linked to mutations in the tumor suppressor genes, TSC1 and TSC2. Mutation in either of these two genes leads to the clinical manifestations of TSC. Interestingly, loss of TSC gene function does not result in neoplastic transformation, but rather in increased cellular growth and benign tumor formation. While many of the features of TSC are neurological in nature, renal dysfunction is a common characteristic of the disease. Approximately 70-80% of TSC patients develop renal angiomyolipomas (AMLs). AMLs are heterogeneous, benign tumors composed of three distinct cell types including smooth muscle, blood vessel, and adipose cells.

TSC patients also present with evidence of a devastating form of lung disease called Lymphangioleiomyomatosis (LAM). LAM is a unique and rare cystic pulmonary disease that afflicts predominately premenopausal women. While its prevalence is not precisely known, up to one thousand women may be affected by LAM annually in the United States. The clinical symptoms are dysapnea, chronic cough, wheezing, pneumothorax, and chest pain. These symptoms occur and worsen as LAM cells migrate into the lung, causing cystic parenchymal destruction and progressive respiratory failure. LAM can occur as an independent condition (sporadic LAM) or as a

secondary condition of TSC (TSC-LAM). The genetic connection between LAM and TSC is evident in work done by Henske et al., revealing inactivating mutations in the TSC2 gene in both TSC-LAM patients and sporadic LAM patients. TSC patients with clinically diagnosed LAM were thought to be quite rare (<4%), but recent studies using High Resolution Computed Tomography (HRCT) scans indicate evidence of LAM in 26-42% of women with TSC. Currently, the only treatment for LAM is lung transplantation.

AMLs are symptomatic of both LAM (50% of patients presenting) and TSC (70% of patients presenting), and there are no radiological, morphological, or genetic differences between AMLs from the two disorder. Designing therapies against AMLs has been slowed by the lack of reliable protein markers against which to design therapeutics. AMLs exhibit a characteristic expression of melanocyte differentiation markers such as silv/pMel17/gp100 (silv) and melanA/MART1 (melan-A). However these markers have been shown to be upregulated in no more then 50% of AMLs from either TSC or LAM patients renewing the importance of identifying better candidate therapeutic targets. Because silv and melan-A are not expressed in many AMLs, the only reliable method for AML cell determination is $TSC1^{-/-}$ or $TSC2^{-/-}$ status determined by genomic sequencing. Thus, there is a need to identify other molecular markers to distinguish an AML cell, from a non-AML cell .

SUMMARY OF THE INVENTION

The invention provides an immortalized cell that does not express a Tuberous Sclerosis-2 (TSC2) gene. The cell is refered to herein as $TSC2^{-/-}$ cell or a TSC2 null cell. The cell is capable of phosporylating, e.g. constitutively, ribosomal S6 or S6 kinase. Additionally, the invention features a $TSC2^{-/-}$ cell culture, e.g., an *in-vitro* culture. The culture is an adhesion culture. Alternatively, the cells in the culture are in suspension. The cell is from a mammal such as human, a primate, mouse, rat, dog, cat, cow, horse, pig. The cell contains a mutation in a TSC2 gene. The mutation is in exon 16 of the TSC2 gene. The mutation results in a single nucleotide transition. The transition is a guanine to adenine transition. The mutation is for example at nucleotide position 1832 of a TSC2 gene when numbered in accordance with a wild-type (i.e., non-mutated TSC2 gene). The cell contains a TSC2 gene that has a *Pvu* II restriction site. The Pvyu II restriction site is upstream of nucleotide position 1832 in exon 16, when numbered in accordance with a wild type TSC2 gene. Alternatively, the *Pvu* II restriction site is downstream of nucleotide position 1832 in exon 16, when numbered in accordance with a wild type TSC2 gene. For example, the *Pvu* II restriction site is at least 2, 4, 6, 8 10, 20 , 40, 50, 75 or more nucleotides upstream or down stream of nucleotide

position 1832 in exon 16 of a TSC2 gene.

Also included in the invention is the $TSC^{-/-}$ cell line which was deposited at the American Type Tissue Collection and assigned ATCC designation ____, _____, and ____.

The invention is further based the discovery of a pattern of gene expression correlated with angiomyolipomas. The genes that are differentially expressed in angiomyolipomas are collectively referred to herein as "TSC nucleic acids" or "TSC polynucleotides" and the corresponding encoded polypeptides are referred to as "TSCpolypeptides" or "TSC proteins."

Accordingly, the invention features a method of diagnosing or determining a predisposition to a TSC-related disorder by providing a biological sample conataining genomic DNA, amplifying a region of the genomic DNA which contains position 1832 of Exon 16 of the *TSC2* gene and digesting amplification product from with a *Pvu* II restriction endonucleases. Identifying a *Pvu* II restriction site upstream or downstream from position 1832 in the TSC2 gene indicates a TSC-related disorder or a predisposition to developing TSC related disorder in the subject.

TSC-related disorders or a predisposition to a TSC-related disorder is determined in a subject by determining a level of expression of TSC-associated gene in a patient derived tissue sample. By TSC- associated gene is meant a gene that is characterized by a level of expression which differs in a cell obtained from a cell from a patient with a TSC-related disorder compared to a normal cell. A normal cell is one obtained from a patiet without a TSC-related disorder. An TSC-associated gene includes for example TSC 1-26. An alteration, *e.g.*, increase or decrease of the level of expression of the gene compared to a normal control level of the gene indicates that the subject suffers from or is at risk of developing a TSC-related disorder.

By normal control level is meant a level of gene expression detected in a normal, healthy individual or in a population of individuals known not to be suffering from a TSC-related disorder. A control level is a single expression pattern derived from a single reference population or from a plurality of expression patterns. For example, the control level can be a database of expression patterns from previously tested cells.

An increase in the level of TSC1-25 detected in a test sample compared to a normal control level indicates the subject (from which the sample was obtained) suffers from or is at risk of developing. In contrast, a decrease in the level of TSC 26 detected in a test sample compared to a normal control level indicates said subject suffers from or is at risk of developing A TSC-related disorder.

A TSC-related disorder includes for example seizures, mental retardation, autism, benign tumors, hamartomas, renal disease, angiomyolipomas, renal cell carcinoma, kidney disorders, polycystic kidney disease, Lymphangioleiomyomatosis, brain tumors such as cortical tubers, subependymal nodules, and giant-cell astrocytomas, fibromas of the finger and toenails, pitted teeth, dermatological lesions, hypomelanotic macules, confetti skin lesions, facial angiofibromas, ungual fibromas, Shagreen's patches, and forehead plaque .

Alternatively, expression of a panel of TSC-associated genes in the sample is compared to a TSC control level of the same panel of genes. By TSC control level is meant the expression profile of the TSC-associated genes found in a population suffering from a TSC related-disorder.

Gene expression is increased or decreased 10%, 25%, 50% compared to the control level. Alternately, gene expression is increased or decreased 1, 2, 5, 10, 20, 25 or more fold compared to the control level. Expression is determined by detecting hybridization, *e.g.*, on a chip, of TSC gene probe to a gene transcript of the patient-derived tissue sample.

The alteration is statistically significant. By statistically significant is meant that the alteration is greater than what might be expected to happen by change alone. Statistical significance is determined by method known in the art. An alteration is statistically significant if the p-value is at least 0.05. Preferably, the p-value is 0.04, 0.03, 0.02, 0.01, 0.005, 0.001 or less.

The patient derived tissue sample is any tissue from a test subject, e.g., a patient known to or suspected of having a TSC related-disorder. For example, the tissue contains a primary angiomyolipmoma cancer cell.

The invention also provides TSC reference expression profile of a gene expression level of one or more of TSC 2, 4-26. Alternatively, the invention provides a TSC reference expression profile of the levels of expression two or more of TSC 1-26

The invention further provides methods of identifying an agent that inhibits or enhances the expression or activity of TSC-associated gene, *e.g.*, TSC 1-26 by contacting a test cell expressing TSC associated gene with a test agent and determining the expression level of the TSC-associated gene. The test cell is a brain cell, a skin cell ,an eye cell, a heart cell, a kidney cell, a bone cell, a lung cell or an intestinal cell. A decrease of the level compared to a normal control level of the gene indicates that the test agent is an inhibitor of the TSC-associated gene and reduces a TSC-related disorder. Alternatively, an increase of the level or activity compared to a normal control level or activity of the gene indicates that said test agent is an enhancer of expression or function of the TSC-

associated gene.

The invention also provides a kit with a detection reagent which binds to two or more TSC nucleic acid sequences or which binds to a gene product encoded by the nucleic acid sequences. Also provided is an array of nucleic acids that binds to two or more TSC nucleic acids.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

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

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A (left panel) is a photograph of a Southern Blot showing genomic analysis of TSC2 in AML primary sample and clones.

Figure 1A (right panel) is an illustration showing that missense mutation in exon 16 of the TSC2 gene that results in a new *Pvu*II restriction enzyme site and the elimination of an *Hpa*II site.

Figure 1B is a series of photomicrographs of AML TSC2-/- (AML-1, AML-2) and TSC2+/+ (wt1, wt2) clones. Images of each clone were taken at 100X magnification using a Zeiss Axiovert 25 microscope.

Figure 2 is a series of photographs of Western Blots showing protein expression analysis of AML clones.

Figure 3 is a series of line graphs showing that AML TSC2-/- cell lines are rapamycin sensitive.

Figure 4 is a schematic showing hierarchical clustering of AMLs and normal tissue.

Figure 5 is a series of bar graphs showing RTQ-PCR expression analysis of genes up-regulated in AMLs.

Figure 6A is a photograph of a Western Blot showing GPNMB expression in melanoma

and AML tissues. Expression of housekeeping genes varies between different tissues, but coomassie staining indicated equal protein loads.

Figure 6B is a photograph of a Western Blot showingOA1expression in melanoma and AML tissues. Expression of housekeeping genes varies between different tissues, but coomassie staining indicated equal protein loads.

Figure 7 is a schematic representation of the TSC signaling pathway.

DETAILED DESCRIPTION

The present invention is based in part upon the establishment and characterization of several continuous cell lines of immortalized human angiomyolypoma (AML) cell lines. Specifically, a human $TSC^{-/-}$AML cell line and a set of matching TSC gene knock-in control cell lines have been developed. These cells lines provide an *in vitro* cellular model for Lymphangioleiomyomatosis (LAM) and Tuberous Sclerosis Complex (TSC) and are useful for differential gene expression profiling, the identification of therapeutically beneficial compounds for LAM and TSC, the elucidation the molecular mechanisms of aberrant LAM and TSC cell behavior and small molecule chemical screening and compound validation for compounds affecting the mTOR pathway, which is known to be involved in cancer and inflammation. The invention is further based on the discovery of changes in expression patterns of multiple nucleic acid sequences in cancer tissue from patients with sporadic LAM. The differences in gene expression were identified by using RTQ-PCR and a comprehensive cDNA microarray system. Microarray analysis of 4 primary AML tissues and a novel human AML $TSC2^{-/-}$ cell lines compared with normal tissues has identified 289 transcripts over-expressed ($t < 0.05$) in AMLs by > 3-fold, 115 > 5-fold, and 25 > 10-fold. Of the up-regulated genes 26 have been identified as transmembrane or secreted proteins, including 7 Melanoma Associated Antigens (MAAs). These 26 genes and their encoded polypeptides (i.e., TSC1-26) are candidate targets for vaccine and antibody therapy development for TSC-related disorders. (See Table A)

The differntially expressed genes identified herein are used for diagnositic and prognostic purposes and to develop gene or protein targeted therapeutic approaches to TSC related disorders. The genes whose expression levels increased in patients with AML are summarized in Tables A-D and are collectively referred to herein as " TSC-associated genes", "TSC nucleic acids" or "TSC polynucleotides" and the corresponding encoded polypeptides are referred to as "TSC polypeptides" or "TSC proteins." Unless indicated otherwise, "TSC" is meant to refer to any of the sequences

disclosed herein. The genes have been previously described and are presented along with a database accession number.

Table A Transmembrane or Secreted Proteins Associated with TSC-Related Disorders

TSC No.t	ProbeSet ID Affymetrix	Gene Symbol	Gene Name	Descriptions	Gene Family Name	Cellular localization
	1206427_s_at	MLANA	melan-A	gb:U06654.1 /DB_XREF=gi:517022 /FEA=FLmRNA /CNT=66 /TID=Hs.154069.0 /TIER=FL /STK=5 /UG=Hs.154069 /LL=2315 /UG_GENE=MLANA /DEF=Human differentiation antigen melan-A protein mRNA, complete cds. /PROD=melan-A protein /FL=gb:U06654.1 gb:NM_005511.1	---	integral to plasma membrane
	2206696_at	OA1/GPR143	Ocular albinism 1/G-rotein-coupled receptor 143	gb:NM_000273.1 /DB_XREF=gi:4557806 /GEN=OA1 /FEA=FLmRNA /CNT=14 /TID=Hs.74124.0 /TIER=FL+Stack /STK=9 /UG=Hs.74124 /LL=4935 /DEF=Homo sapiens ocular albinism 1 (Nettleship-Falls) (OA1), mRNA. /PROD=ocular albinism 1 (Nettleship-Falls) protein /FL=gb:NM_00	GPCRs	membrane fraction /// cytoplasm /// integral to membrane
	3209848_s_at	SILV	silver/gp100/pMel17	gb:U01874.1 /DB_XREF=gi:494939 /FEA=FLmRNA /CNT=177 /TID=Hs.95972.0 /TIER=FL /STK=0 /UG=Hs.95972 /LL=6490 /UG_GENE=SILV /DEF=Human me20m mRNA, complete cds. /PROD=me20m /FL=gb:NM_006928.1 gb:BC001414.1 gb:U01874.1	Pmel-17/NMB family	plasma membrane /// integral to membrane
	4218468_s_at	GREM1/DRM	gremlin 1 homolog, cysteine knot superfamily (Xenopus laevis)	gb:AF154054.1 /DB_XREF=gi:10863087 /GEN=DRM /FEA=FLmRNA /CNT=228 /TID=Hs.40098.0 /TIER=FL+Stack /STK=20 /UG=Hs.40098 /LL=26585 /DEF=Homo sapiens DRM (DRM) mRNA, complete cds. /PROD=DRM /FL=gb:NM_013372.1 gb:AF110137.2 gb:AF045800.1 gb:AF154054.1	---	extracellular space
	5243167_at	ABCB5	ATP-binding cassette, sub-family B (MDR/TAP), member 5	gb:AL040763 /DB_XREF=gi:5409709 /DB_XREF=DKFZp434C1815_s1 /CLONE=DKFZp434C1815 /FEA=EST /CNT=6 /TID=Hs.310735.0 /TIER=ConsEnd /STK=2 /UG=Hs.310735 /UG_TITLE=ESTs, Moderately similar to ALU7_HUMAN ALU SUBFAMILY SQ SEQUENCE CONTAMINATION WARNING ENTRY (H.sa	---	---

6206638_at	HTR2B	5-hydroxytryptamine (serotonin) receptor 2B	gb:NM_000867.1 /DB_XREF=gi:4504538 /GEN=HTR2B /FEA=FLmRNA /CNT=13 /TID=Hs.2507.0 /TIER=FL+Stack /STK=10 /UG=Hs.2507 /LL=3357 /DEF=Homo sapiens 5-hydroxytryptamine (serotonin) receptor 2B (HTR2B), mRNA. /PROD=5-hydroxytryptamine (serotonin) receptor 2B /FL	GPCRs	integral to plasma membrane
7220484_at	MCOLN3	mucolipin 3	gb:NM_018298.1 /DB_XREF=gi:8922819 /GEN=FLJ11006 /FEA=FLmRNA /CNT=6 /TID=Hs.49344.0 /TIER=FL /STK=0 /UG=Hs.49344 /LL=55283 /DEF=Homo sapiens hypothetical protein FLJ11006 (FLJ11006), mRNA. /PROD=hypothetical protein FLJ11006 /FL=gb:NM_018298.1	---	integral to membrane
8213790_at	ADAM12	a disintegrin and metalloproteinase domain 12 (meltrin alpha)	gb:W46291 /DB_XREF=gi:1330989 /DB_XREF=zc31b08.s1 /CLONE=IMAGE:323895 /FEA=EST /CNT=27 /TID=Hs.8850.2 /TIER=Stack /STK=12 /UG=Hs.8850 /LL=8038 /UG_GENE=ADAM12 /UG_TITLE=a disintegrin and metalloproteinase domain 12 (meltrin alpha)	peptidase family M12B	plasma membrane /// integral to membrane
9214156_at	MYRIP	myosin VIIA and Rab interacting protein	gb:AL050090.1 /DB_XREF=gi:4884109 /GEN=DKFZp586F1018 /FEA=mRNA /CNT=28 /TID=Hs.26970.0 /TIER=Stack /STK=19 /UG=Hs.26970 /LL=25924 /DEF=Homo sapiens mRNA; cDNA DKFZp586F1018 (from clone DKFZp586F1018). /PROD=hypothetical protein	---	---
10229150_at	MLPH	melanophilin	gb:AI810764 /DB_XREF=gi:5397330 /DB_XREF=tu04c11.x1 /CLONE=IMAGE:2250068 /FEA=EST /CNT=25 /TID=Hs.102406.0 /TIER=Stack /STK=19 /UG=Hs.102406 /UG_TITLE=ESTs	---	mitochondrion
11210246_s_at	ABCC8	ATP-binding cassette, sub-family C (CFTR/MRP), member 8	gb:AF087138.1 /DB_XREF=gi:3643189 /GEN=SUR1 /FEA=FLmRNA /CNT=31 /TID=Hs.54470.0 /TIER=FL /STK=0 /UG=Hs.54470 /LL=6833 /DEF=Homo sapiens sulfonylurea receptor 1 (SUR1) mRNA, complete cds. /PROD=sulfonylurea receptor 1 /FL=gb:NM_000352.2 gb:L78207.1 gb:AF08	ABC transporter	integral to membrane
12205946_at	VIPR2	vasoactive intestinal peptide receptor 2	gb:X95097.2 /DB_XREF=gi:4837717 /GEN=VIP2r /FEA=FLmRNA /CNT=29 /TID=Hs.2126.0 /TIER=ConsEnd /STK=0 /UG=Hs.2126 /LL=7434 /DEF=Homo sapiens mRNA for VIP receptor 2. /PROD=VIP2 receptor /FL=gb:NM_003382.1 gb:L36566.1	GPCRs	integral to plasma membrane

[illegible]	[illegible]	[illegible]	[illegible]	gb:AL833418.1 /DB_XREF=gi:21734059 /TID=Hs2.376864.1 /CNT=7 /FEA=mRNA /TIER=ConsEnd /STK=0 /UG=Hs.376864 /UG_TITLE=Homo sapiens mRNA; cDNA DKFZp313P1022 (from clone DKFZp313P1022) /DEF=Homo sapiens mRNA; cDNA DKFZp313P1022 (from clone DKFZp313P1022).	---	lysosome (lumen)
13	1558846_at	PNLIPRP3	pancreatic lipase-related protein 3			
14	244444_at	PKD1L2	polycystic kidney disease 1-like 2	gb:AW082870 /DB_XREF=gi:6038022 /DB_XREF=xb71f11.x1 /CLONE=IMAGE:2581773 /FEA=EST /CNT=3 /TID=Hs.210954.0 /TIER=ConsEnd /STK=3 /UG=Hs.210954 /UG_TITLE=ESTs	---	integral to membrane
15	213745_at	ATRNL1	attractin-like 1	gb:AW151108 /DB_XREF=gi:6199006 /DB_XREF=xg33d03.x1 /CLONE=IMAGE:2629349 /FEA=mRNA /CNT=40 /TID=Hs.196012.0 /TIER=Stack /STK=12 /UG=Hs.196012 /LL=26033 /UG_GENE=KIAA0534 /UG_TITLE=KIAA0534 protein	---	membrane
16	244353_s_at	SLC2A12	solute carrier family 2 (facilitated glucose transporter), member 12	gb:AI675682 /DB_XREF=gi:4876162 /DB_XREF=wc45f07.x1 /CLONE=IMAGE:2321605 /FEA=EST /CNT=8 /TID=Hs.26691.1 /TIER=ConsEnd /STK=0 /UG=Hs.26691 /UG_TITLE=ESTs	---	integral to membrane
17	207938_at	PI15	protease inhibitor 15	gb:NM_015886.1 /DB_XREF=gi:7705675 /GEN=R3HDM /FEA=FLmRNA /CNT=2 /TID=Hs.129732.0 /TIER=FL /STK=0 /UG=Hs.129732 /LL=51050 /DEF=Homo sapiens R3H domain (binds single-stranded nucleic acids) containing (R3HDM), mRNA. /PROD=R3H domain-containing preproprotei	Allergen V5/Tpx-1 related	extracellular
18	210609_s_at	TP53I3	tumor protein p53 inducible protein 3	gb:BC000474.1 /DB_XREF=gi:12653408 /FEA=FLmRNA /CNT=7 /TID=Hs.50649.1 /TIER=FL /STK=0 /UG=Hs.50649 /LL=9540 /UG_GENE=PIG3 /DEF=Homo sapiens, quinone oxidoreductase homolog, clone MGC:8642, mRNA, complete cds. /PROD=quinone oxidoreductase homolog /FL=gb:BC	---	---
19	213197_at	ASTN	astrotactin	gb:AB006627.1 /DB_XREF=gi:2564325 /GEN=KIAA0289 /FEA=mRNA /CNT=84 /TID=Hs.6788.0 /TIER=Stack /STK=40 /UG=Hs.6788 /LL=460 /UG_TITLE=astrotactin /DEF=Homo sapiens mRNA for KIAA0289 gene, partial cds.	---	integral to membrane
20	1554018_at	GPNMB	glycoprotein (transmembrane) nmb	gb:BC011595.1 /DB_XREF=gi:15079529 /TID=Hs2.82226.2 /CNT=21 /FEA=FLmRNA /TIER=FL /STK=6 /LL=10457 /UG_GENE=GPNMB /UG=Hs.82226 /DEF=Homo sapiens, Similar to glycoprotein (transmembrane) nmb, clone MGC:1696 IMAGE:3345861, mRNA, complete cds. /PROD=Similar t	Polycystic kidney disease proteins	plasma membrane /// integral to membrane

21	227202_at	CNTN1	contactin 1	gb:AW072790 /DB_XREF=gi:6027788 /DB_XREF=xa42a10.x1 /CLONE=IMAGE:2569434 /FEA=EST /CNT=43 /TID=Hs.143434.2 /TIER=Stack /STK=9 /UG=Hs.143434 /LL=1272 /UG_GENE=CNTN1 /UG_TITLE=contactin 1	---	membrane fraction
22	203413_at	NELL2	neural epidermal growth factor like like-2	gb:NM_006159.1 /DB_XREF=gi:5453765 /GEN=NELL2 /FEA=FLmRNA /CNT=141 /TID=Hs.79389.0 /TIER=FL+Stack /STK=32 /UG=Hs.79389 /LL=4753 /DEF=Homo sapiens nel (chicken)-like 2 (NELL2), mRNA. /PROD=nel (chicken)-like 2 /FL=gb:D83018.1 gb:NM_006159.1		Secreted glycoprotein
23	205122_at	TMEFF1	transmembrane protein with EGF-like and two follistatin-like domains 1	gb:BF439316 /DB_XREF=gi:11451833 /DB_XREF=nab62g12.x1 /CLONE=IMAGE:3272638 /FEA=FLmRNA /CNT=65 /TID=Hs.78531.0 /TIER=Stack /STK=27 /UG=Hs.78531 /LL=8577 /UG_GENE=TMEFF1 /UG_TITLE=transmembrane protein with EGF-like and two follistatin-like domains 1 /FL=gb:U19878.1 gb:NM_003692.1		Integral to membrane
24	1569141_a_at	PPARGC1A	peroxisome proliferative activated receptor, gamma, coactivator 1, alpha	gb:BC029800.1 /DB_XREF=gi:20987590 /TID=Hs2.284627.1 /CNT=7 /FEA=mRNA /TIER=ConsEnd /STK=0 /UG=Hs.284627 /UG_TITLE=Homo sapiens, Similar to peroxisome proliferative activated receptor, gamma, coactivator 1, clone IMAGE:5187727, mRNA /DEF=Homo sapiens, Sim	---	nucleus /// DNA-directed RNA polymerase II, core complex
25	202828_s_at	MMP14	matrix metalloproteinase 14 (membrane-inserted)	gb:NM_004995.2 /DB_XREF=gi:13027797 /GEN=MMP14 /FEA=FLmRNA /CNT=120 /TID=Hs.2399.0 /TIER=FL+Stack /STK=10 /UG=Hs.2399 /LL=4323 /DEF=Homo sapiens matrix metalloproteinase 14 (membrane-inserted) (MMP14), mRNA. /PROD=matrix metalloproteinase 14 preproprotein	---	extracellular matrix (sensu Metazoa) /// integral to plasma membrane
26	206742_at	FIGF	vascular endothelial growth factor D	gb:NM_004469.1 /DB_XREF=gi:4758377 /GEN=FIGF /FEA=FLmRNA /CNT=16 /TID=Hs.11392.0 /TIER=FL+Stack /STK=11 /UG=Hs.11392 /LL=2277 /DEF=Homo sapiens c-fos induced growth factor (vascular endothelial growth factor D) (FIGF), mRNA. /PROD=c-fos induced growth factor (vascularendothelial growth factor D) /FL=gb:NM_004469.1 gb:D89630.1		secreted glycoprotein

TSC$^{-/-}$ Cell Lines

The invention provides an immortalized cell that does not express the Tuberous Sclerosis

" Complex-2 gene(TSC2). By not expressing the TSC2 gene is meant that the gene is not functionally active in the cell. A TSC function includes for example, serum dependent S6 an S6K phosphorylation. The cell and cells lines are refered to herein as a $TSC2^{-/-}$ cell or a TSC2 null cell. A $TSC2^{-/-}$ cell is capable of self-maintenance, such that with each cell division, at least one daughter cell will also be a $TSC^{-/-}$ cell. A $TSC^{-/-}$ cell line is capable of being expanded (passaged) 10, 20, 50, 100, 250, 500, 1000, 2000, 3000, 4000, 5000 or more fold. The cells are adherent in culture.

By "normal cells", "primary cells" or "non-immortalized cells" is meant to designate cells of which are collected from the a healthy adult not having crippling physiological or genetic deficiencies, and which can be cultured for a limited time without losing their original differentiation characteristics.

By "immortalized cells" is meant to designate cells which have undergone a genetic manipulation, by means of a DNA construct, which makes them capable of multiplying indefinitely.

By "passage" is meant the the process consisting in taking an aliquot of a confluent culture of a cell line, in inoculating into fresh medium, and in culturing the line until confluence or saturation is obtained. The cell lines are thus traditionally cultured by successive passages in fresh media.

Genomic sequencing determined that the cells possessed a missense mutation in one copy of the TSC2 gene and the other copy of the TSC2 was lossed due to a loss of heterozygosity (LOH) of the TSC2 gene locus. The missense mutation is a specific point mutation resulting is a guanine to adenine transition at position 1832 in exon 16 of the TSC2 gene. This mutation results in the loss of a *HpaII* restriction endonuclease site and the creation of a diagnostic *PvuII* restriction endonuclease site A $TSC2^{-/-}$ cell line maintains in culture the elongated morphology of the primary AML cells.

The loss of TSC function is measured by phosphorylation of S6Kinase (S6K) and its substrate, ribosomal protein S6 (S6), in the absence of serum. In both $TSC1^{-/-}$ or $TSC2^{-/-}$ cells, the absence of the inhibitory TSC complex mimics mitogenic stimulation and results in constitutively active S6K signaling.

General Methods for Measuring Gene Expression

By measuring expression of the various genes in a sample of cells, a TSC related disorder can be determined in a cell or population of cells. Similarly, by measuring the expression of these genes in response to various agents, and agents for treating TSC related disorders can be identified.

The invention involves determining (*e.g.*, measuring) the expression of at least one, and up to all the TSC sequences listed in Table B. Using sequence information provided by the GeneBank database entries for the known sequences or the sequences provides herein the TSC-associated genes

are detected and measured using techniques well known to one of ordinary skill in the art. For example, sequences within the sequence database entries corresponding to TSC sequences, can be used to construct probes for detecting TSC RNA sequences in, *e.g.*, northern blot hybridization analyses. As another example, the sequences can be used to construct primers for specifically amplifying the TSC sequences in, *e.g*, amplification-based detection methods such as reverse-transcription based polymerase chain reaction. "Probes" refer to nucleic acid sequences of variable length, preferably between at least about 10 nucleotides (nt), 10 nt, 30 nt, 40 nt, 50nt, 75 nt, 100 nt, 250 nt, 500 nt or as many as about, *e.g.*, 6,000 nt, depending on use. Probes are used in the detection of identical, similar, or complementary nucleic acid sequences. Longer length probes are usually obtained from a natural or recombinant source, are highly specific and much slower to hybridize than oligomers. Probes may be single- or double-stranded and designed to have specificity in PCR, membrane-based hybridization technologies, or ELISA-like technologies.

Hybridization is under stringent, moderate or low conditions. As used herein, the phrase "stringent hybridization conditions" refers to conditions under which a probe, primer or oligonucleotide will hybridize to its target sequence, but to no other sequences. Stringent conditions are sequence-dependent and will be different in different circumstances. Longer sequences hybridize specifically at higher temperatures than shorter sequences. Generally, stringent conditions are selected to be about 5°C lower than the thermal melting point (Tm) for the specific sequence at a defined ionic strength and pH. The Tm is the temperature (under defined ionic strength, pH and nucleic acid concentration) at which 50% of the probes complementary to the target sequence hybridize to the target sequence at equilibrium. Since the target sequences are generally present at excess, at Tm, 50% of the probes are occupied at equilibrium. Typically, stringent conditions will be those in which the salt concentration is less than about 1.0 M sodium ion, typically about 0.01 to 1.0 M sodium ion (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30°C for short probes, primers or oligonucleotides (*e.g.*, 10 nt to 50 nt) and at least about 60°C for longer probes, primers and oligonucleotides. Stringent conditions may also be achieved with the addition of destabilizing agents, such as formamide.

Stringent conditions are known to those skilled in the art and can be found in Ausubel *et al.*, (eds.), CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. Preferably, the conditions are such that sequences at least about 65%, 70%, 75%, 85%, 90%, 95%, 98%, or 99% homologous to each other typically remain hybridized to each other.

A non-limiting example of stringent hybridization conditions are hybridization in a high salt buffer comprising 6X SSC, 50 mM Tris-HCl (pH 7.5), 1 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.02% BSA, and 500 mg/ml denatured salmon sperm DNA at 65°C, followed by one or more washes in 0.2X SSC, 0.01% BSA at 50°C.

Moderate stringency hybridization conditions are for example, hybridization in 6X SSC, 5X Denhardt's solution, 0.5% SDS and 100 mg/ml denatured salmon sperm DNA at 55°C, followed by one or more washes in 1X SSC, 0.1% SDS at 37°C. Other conditions of moderate stringency that may be used are well-known in the art. See, *e.g.*, Ausubel *et al.* (eds.), 1993, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, NY, and Kriegler, 1990, GENE TRANSFER AND EXPRESSION, A LABORATORY MANUAL, Stockton Press, NY.

Low stringency hybridization conditions arefor example hybridization in 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 mg/ml denatured salmon sperm DNA, 10% (wt/vol) dextran sulfate at 40°C, followed by one or more washes in 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS at 50°C. Other conditions of low stringency that may be used are well known in the art (*e.g.*, as employed for cross-species hybridizations). See, *e.g.*, Ausubel *et al.* (eds.), 1993, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, NY, and Kriegler, 1990, GENE TRANSFER AND EXPRESSION, A LABORATORY MANUAL, Stockton Press, NY; Shilo and Weinberg, 1981, *Proc Natl Acad Sci USA 78*: 6789-6792.

Expression level of one or more of the TSC sequences in the test cell population, *e.g.*, a patient derived tissues sample is then compared to expression levels of the some sequences in a reference population. The reference cell population includes one or more cells for which the compared parameter is known, *i.e.*, cancerous, non-cancerous, TSC or non-TSC.

Whether or not the gene expression levels in the test cell population compared to the reference cell population reveals the presence of the measured parameter depends upon on the composition of the reference cell population. For example, if the reference cell population is composed of non- cancer cells, a similar gene expression level in the test cell population and reference cell population indicates the test cell population is non- cancer. Conversely, if the reference cell population is made up of cancer cells, a similar gene expression profile between the test cell population and the reference cell population that the test cell population includes cancer cells.

An TSC sequence in a test cell population can be considered altered in levels of expression if its expression level varies from the reference cell population by more than 1.0, 1.5, 2.0, 5.0, 10.0 or more fold from the expression level of the corresponding TSC sequence in the reference cell population.

The alteration is statistically significant. By statistically significant is meant that the alteration is greater than what might be expected to happen by change alone. Statistical significance is determined by method known in the art. For example statistical significance is determined by p-value. The p-values is a measure of probability that a difference between groups during an experiment happened by chance. ($P(z \geq z_{observed})$). For example, a p-value of 0.01 means that there is a 1 in 100 chance the result occurred by chance. The lower the p-value, the more likely it is that the difference between groups was caused by treatment. An alteration is statistically significant if the p-value is at least 0.05. Preferably, the p-value is 0.04, 0.03, 0.02, 0.01, 0.005, 0.001 or less.

If desired, comparison of differentially expressed sequences between a test cell population and a reference cell population can be done with respect to a control nucleic acid whose expression is independent of the parameter or condition being measured. For example, a control nucleic acid is one which is known not to differ depending on the cancerous or non-cancerous state of the cell. Expression levels of the control nucleic acid in the test and reference nucleic acid can be used to normalize signal levels in the compared populations. Control genes can be, *e.g.*. β-actin, glyceraldehyde 3- phosphate dehydrogenase or ribosomal protein P1 (36B4).

The test cell population is compared to multiple reference cell populations. Each of the multiple reference populations may differ in the known parameter. Thus, a test cell population may be compared to a second reference cell population known to contain, *e.g.*, TSC-related disorder as well as a second reference population known to contain, *e.g.*, non-TSC-related disorder (normal cells). The test cell is included in a tissue type or cell sample from a subject known to, or to be suspected of having a TSC-related disorder.

The test cell is obtained from a bodily tissue or a bodily fluid, *e.g.*, biological fluid (such as blood, serum, or sputum). For example, the test cell is purified from a tissue. Preferably, the test cell population comprises a tumor cell. Alternatively, the test cell population is a lung cell, a kidney cell, an adipose cell , a smooth muscle cell, a blood vessel cell or a neuronal cell.

Cells in the reference cell population are derived from a tissue type as similar to test cell. Alternatively, the control cell population is derived from a database of molecular information derived from cells for which the assayed parameter or condition is known.

The subject is preferably a mammal. The mammal can be, *e.g.*, a human, non-human primate, mouse, rat, dog, cat, horse, or cow.

The expression of 1, 2, 3, 4, 5, 25, 35, 50, or 100 or more of the sequences represented by TSC 1-26 is determined and if desired, expression of these sequences can be determined along with other sequences whose level of expression is known to be altered according to one of the herein described parameters or conditions, *e.g.*, a TSC-related disorder.

Expression of the genes disclosed herein is determined at the RNA level using any method known in the art. For example, Northern hybridization analysis using probes which specifically recognize one or more of these sequences can be used to determine gene expression. Alternatively, expression is measured using reverse-transcription-based PCR assays, *e.g.*, using primers specific for the differentially expressed sequences.

Expression is also determined at the protein level, *i.e.*, by measuring the levels of polypeptides encoded by the gene products described herein. Such methods are well known in the art and include, *e.g.*, immunoassays based on antibodies to proteins encoded by the genes.

When alterations in gene expression are associated with gene amplification or deletion, sequence comparisons in test and reference populations can be made by comparing relative amounts of the examined DNA sequences in the test and reference cell populations.

Diagnosing TSC Related Disorders

A TSC related disorder is diagnosed by examining the expression of one or more TSC nucleic acid sequences from a test population of cells, (*i.e.*, a patient derived tissue sample). Preferably, the test cell population comprises a primary cancer cell. Alternatively, the test cell is a lung cell, a kidney cell, an adipose cell , a smooth muscle cell, a blood vessel cell or a neuronal cell. Gene expression is also measured from blood or other bodily fluids such as sputum.

Expression of one or more of TSC-associated gene, *e.g.*, TSC 1-26 is determined in the test cell and compared to the expression of the normal control level. By normal control level is meant the expression profile of the TSC-associated genes typically found in a population not suffering

from a TSC related disorder. An increase or a decrease of the level of expression in the patient derived tissue sample of the TSC-associated genes indicates that the subject is suffering from or is at risk of developing a TSC-related disorder.

When one or more of the TSC-associated genes are altered in the test population compared to the normal control level indicates that the subject suffers from or is at risk of developing a TSC-related disorder. 50%, 60%, 80%, 90% or more of the TSC -associated genes are altered.

Identifying Agents that inhibit TSC-associated gene expression

An agent that inhibits the expression or activity of TSC-associated gene is identified by contacting a test cell population expressing a TSC-associated upregulated gene with a test agent and determining the expression level of the TSC-associated gene. A decrease in expression compared to the normal control level indicates the agent is an inhibitor of a TSC-associated upregulated gene and useful to inhibit a TSC-related disorder.

The test cell population is any cell expressing the TSC-associated genes. For example, the test cell population contains a primary cancer cell or is derived from a primary cancer cell. For example, the test cell is immortalized cell line derived from a primary cancer cell such as a $TSC2^{-/-}$ of the invention.

Assessing efficacy of treatment of a TSC-related disorder in a subject

The differentially expressed TSC sequences identified herein also allow for the course of treatment of of a TSC-related disorder to be monitored. In this method, a test cell population is provided from a subject undergoing treatment for a TSC-related disorder. If desired, test cell populations are obtained from the subject at various time points before, during, or after treatment. Expression of one or more of the TSC sequences, in the cell population is then determined and compared to a reference cell population which includes cells whose TSC-related disorder state is known. The reference cells have not been exposed to the treatment.

If the reference cell population contains non-TSC related disorder cells, a similarity in expression between TSC sequences in the test cell population and the reference cell population indicates that the treatment is efficacious. However, a difference in expression between TSC sequences in the test population and this reference cell population indicates the a less favorable clinical outcome or prognosis.

By "efficacious" is meant that the treatment leads to a reduction in expression of a pathologically upregulated gene, increase in expression of a pathologically down-regulated gene or a decrease in size, prevalence, or metastatic potential of a TSC-related disorder in a subject. When treatment is applied prophylactically, "efficacious" means that the treatment retards or prevents a TSC-related disorder. Assesment of a TSC-related disorder is made using standard clinical protocols.

Efficaciousness is determined in association with any known method for diagnosing or treating a TSC-related disorder. TSC-realated disorders are diagnosed for example, by determing whether the subject has either two "Major Features" of TSC or one "Major Feature" and two "Minor Features".. The clinician should consider TSC *probable* when the patienthas one "Major Feature" and one "Minor Feature," while a *possible* diagnosis results from the presence ofeither one "Major Feature" or two or more "Minor Features." Major Features of TSC include: Facial angiofibromas or forehead plaque; Nontraumatic ungual or periungual fibroma; Hypomelanotic macules (three or more); Shagreen patch (connective tissue nevus); Multiple retinal nodular hamartomas; Cortical tuber; Subependymal nodule; Subependymal giant cell astrocytoma; Cardiac rhabdomyoma, single or multiple; Lymphangiomyomatosis; or Renal angiomyolipoma. Minor Features of TSC include: Multiple, randomly distributed pits in dental enamel; Hamartomatous rectal polypsc; Bone cystsd; Cerebral white matter radial migration linesa,d; Gingival fibromas; Nonrenal hamartomac; Retinal achromic patch; 'Confetti' skin lesions; or Multiple renal cysts.

Selecting a therapeutic agent for treating a TSC-related disorder that is appropriate for a particular individual

Differences in the genetic makeup of individuals can result in differences in their relative abilities to metabolize various drugs. An agent that is metabolized in a subject to act as an anti-colorectal cancer agent can manifest itself by inducing a change in gene expression pattern in the subject's cells from that characteristic of a TSC-rleated disorder state to a gene expression pattern characteristic of a non-TSC-related disorder state. Accordingly, the differentially expressed TSC sequences disclosed herein allow for a putative therapeutic or prophylactic anti-TSC-related disorder agent to be tested in a test cell population from a selected subject in order to determine if the agent is a suitable anti- TSC-related disorder agent in the subject.

To identify an anti-TSC-related disorder agent, that is appropriate for a specific subject, a test cell population from the subject is exposed to a therapeutic agent, and the expression of one or more of TSC 1-26 sequences is determined.

The test cell population contains a cell expressing TSC-associated gene. For example a test cell population is incubated in the presence of a candidate agent and the pattern of gene expression of the test sample is measured and compared to one or more reference profiles, *e.g.,* TSC-related disorder reference expression profile or an non-TSC-related disorder reference expression profile.

A decrease in expression of one or more of the sequences TSC 1-26 in a test cell population relative to a reference cell population that has not been contacted with the candidate agent is indicative that the agent is therapeutic.

The test agent can be any compound or composition.

Screening assays for identifying therapeutic agents

The differentially expressed sequences disclosed herein can also be used to identify candidate therapeutic agents for treating a TSC-related disorder. The method is based on screening a candidate therapeutic agent to determine if it converts an expression profile of TSC 1-26 sequences characteristic of a TSC-related disorder state to a pattern indicative of a non-TSC-related disorder state.

In the method, a cell is exposed to a test agent or a combination of test agents (sequentially or consequentially) and the expression of one or more TSC 1-26 sequences in the cell is measured. The expression profile of the TSC sequences in the test population is compared to expression level of the TSC sequences in a reference cell population that is not exposed to the test agent.

An agent effective in stimulating expression of underexpressed genes, or in suppressing expression of overexpressed genes is deemed to lead to a clinical benefit such compounds are further tested for the ability to inhibit the progression of a TSC-related disorder.

Such screening of the present invention comprises, for example, the steps described below. Cells expressing a target gene include, for example, cell lines established from a subject having a TSC-related disorder ; such cells can be used for this purpose.

(1) the step of contacting a candidate agent with cells expressing a target gene; and

(2) the step of selecting a candidate agent that alters the expression level of the target gene as compared with that in a control.

Alternatively, the screening of the present invention may comprise the steps described below. A protein required for the screening can be obtained as a recombinant protein by using the nucleotide sequence of the target gene. Based on the information on the target gene, one skilled in the art can select the biological activity of a protein as an index of screening and a measurement method for the activity.

(1) the step of contacting a candidate agent with the protein encoded by a target gene; and

(2) the step of selecting a candidate agent that alters the activity of the protein as compared with that in a control.

Alternatively, the screening of the present invention may comprise the steps described below. A reporter construct required for the screening can be prepared by using the transcriptional regulatory region of a target gene. When the transcriptional regulatory region of a target gene has been known to those skilled in the art, a reporter construct can be prepared by using the previous sequence information. When the transcriptional regulatory region of a target gene remains unidentified, a nucleotide segment containing the transcriptional regulatory region can be isolated from a genome library based on the nucleotide sequence information of the target gene.

(1) the step of preparing a reporter construct that ensures the expression of the reporter gene under control of the transcriptional regulatory region of the target gene;

(2) the step of contacting a candidate agent with host cells containing and capable of expressing the above-mentioned reporter construct; and

(3) the step of measuring the expression level of the reporter gene, and selecting a candidate agent that has an activity of altering the expression level when compared with that in a control.

In the screening method of the present invention, candidate agents to be selected have the activity of decreasing the expression levels as compared with those in a control. There is no limitation on the type of candidate agent in the screening of the present invention. The candidates of the present invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the "one-bead one-compound" library method; and synthetic library methods using affinity chromatography selection.

The biological library approach is limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam (1997)Anticancer Drug Des. 12:145).

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt et al. (1993) Proc. Natl. Acad. Sci. USA 90:6909; Erb et al. (1994) Proc. Natl. Acad. Sci. USA 91:11422; Zuckermann et al. (1994). J. Med. Chem. 37:2678; Cho et al. (1993) Science 261:1303; Carrell et al. (1994) Angew. Chem. Int. Ed. Engl. 33:2059; Carell et al. (1994) Angew. Chem. Int. Ed. Engl. 33:2061; and Gallop et al. (1994) J. Med. Chem. 37:1233. Libraries of compounds may be presented in solution (e.g., Houghten (1992) Bio Techniques 13:412), or on beads (Lam (1991) Nature 354:82), chips (Fodor (1993) Nature 364:555), bacteria (U.S. Pat. No. 5,223,409), spores (U.S. Pat. Nos. 5,571,698; 5,403,484; and 5,223,409), plasmids (Cull et al. (1992) Proc. Natl. Acad. Sci. USA 89:1865) or phage (Scott and Smith (1990) Science 249:386; Devlin (1990) Science 249:404; Cwirla et al. (1990) Proc. Natl. Acad. Sci. USA 87:6378; and Felici (1991) J. Mol. Biol. 222:301).(United States Patent Application 20020103360)

Assessing the prognosis of a subject with a TSC-related disorder

Also provided is a method of assessing the prognosis of a subject with a TSC-related disorder by comparing the expression of one or more TSC sequences in a test cell population to the expression of the sequences in a reference cell population derived from patients over a spectrum of disease stages. By comparing gene expression of one or more TSC sequences in the test cell population and the reference cell population(s), or by comparing the pattern of gene expression over time in test cell populations derived from the subject, the prognosis of the subject can be assessed.

An increase of expression of one or more of the sequences TSC 1-26 compared to a normal control indicates less favorable prognosis.

Methods of treating a TSC-related disorder

The invention provides a method for alleviating a symptom of a TSC-related disorder, inhibiting tumor growth or treating lesions of a TSC-related disorder in a subject. Therapeutic compounds are administered prophylactically or therapeutically to subject suffering from at risk of (or susceptible to) developing a TSC-related disorder. Such subjects are identified using standard clinical methods or by detecting an aberrant level of expression or activity of (*e.g.*, TSC 1-26).

The method includes decreasing the expression, or function, or both, of one or more gene products of genes whose expression is aberrantly increased ("overexpressed gene"). Expression is inhibited in any of several ways known in the art. For example, expression is inhibited by

administering to the subject a nucleic acid that inhibits, or antagonizes, the expression of the overexpressed gene or genes, e.g., an antisense oligonucleotide which disrupts expression of the overexpressed gene or genes.

Alternatively, function of one or more gene products of the overexpressed genes is inhibited by administering a compound that binds to or otherwise inhibits the function of the gene products. For example, the compound is an antibody which binds to the overexpressed gene product or gene products.

These modulatory methods are performed *ex vivo* or *in vitro* (*e.g.*, by culturing the cell with the agent) or, alternatively, *in vivo* (*e.g.*, by administering the agent to a subject). The method involves administering a protein or combination of proteins or a nucleic acid molecule or combination of nucleic acid, molecules as therapy to counteract aberrant expression or activity of the differentially expressed genes.

Diseases and disorders that are characterized by increased (relative to a subject not suffering from the disease or disorder) levels or biological activity of the genes may be treated with therapeutics that antagonize (*i.e.*, reduce or inhibit) activity of the overexpressed gene or genes. Therapeutics that antagonize activity are administered therapeutically or prophylactically.

Therapeutics that may be utilized include, *e.g.*, (*i*) a polypeptide, or analogs, derivatives, fragments or homologs thereof of the overexpressed or underexpressed sequence or sequences; (*ii*) antibodies to the overexpressed or underexpressed sequence or sequences; (*iii*) nucleic acids encoding the over or underexpressed sequence or sequences; (*iv*) antisense nucleic acids or nucleic acids that are "dysfunctional" (*i.e.*, due to a heterologous insertion within the coding sequences of coding sequences of one or more overexpressed or underexpressed sequences); or (*v*) modulators (*i.e.*, inhibitors, agonists and antagonists that alter the interaction between an over/underexpressed polypeptide and its binding partner. The dysfunctional antisense molecule are utilized to "knockout" endogenous function of a polypeptide by homologous recombination (see, *e.g.*, Capecchi, *Science* 244: 1288-1292 1989)

Diseases and disorders that are characterized by decreased (relative to a subject not suffering from the disease or disorder) levels or biological activity may be treated with therapeutics that increase (*i.e.*, are agonists to) activity. Therapeutics that upregulate activity may be administered in a therapeutic or prophylactic manner. Therapeutics that may be utilized include, but are not limited

to, a polypeptide (or analogs, derivatives, fragments or homologs thereof) or an agonist that increases bioavailability.

Increased or decreased levels can be readily detected by quantifying peptide and/or RNA, by obtaining a patient tissue sample (*e.g.,* from biopsy tissue) and assaying it *in vitro* for RNA or peptide levels, structure and/or activity of the expressed peptides (or mRNAs of a gene whose expression is altered). Methods that are well-known within the art include, but are not limited to, immunoassays (*e.g.,* by Western blot analysis, immunoprecipitation followed by sodium dodecyl sulfate (SDS) polyacrylamide gel electrophoresis, immunocytochemistry, etc.) and/or hybridization assays to detect expression of mRNAs (*e.g.,* Northern assays, dot blots, *in situ* hybridization, etc.).

Prophylactic administration occurs prior to the manifestation of overt clinical symptoms of disease, such that a disease or disorder is prevented or, alternatively, delayed in its progression.

Therapeutic methods includes contacting a cell with an agent that modulates one or more of the activities of the gene products of the differentially expressed genes. An agent that modulates protein activity includes a nucleic acid or a protein, a naturally-occurring cognate ligand of these proteins, a peptide, a peptidomimetic, or other small molecule. For example, the agent stimulates one or more protein activities of one or more of a differentially under-expressed gene.

Pharmaceutical compositions for treating a TSC-related disorder

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration, or for administration by inhalation or insufflation. The formulations are optionally packaged in discrete dosage units

Pharmaceutical formulations suitable for oral administration include capsules, cachets or tablets, each containing a predetermined amount of the active ingredient. Formulations also include powders, granules or solutions, suspensions or emulsions. The active ingredient os optionally administered as a bolus electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrant or wetting agents. A tablet may be made by compression or molding, optionally with one or more formulational ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as a powder or granules, optionally mixed with a binder,

lubricant, inert diluent, lubricating, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may be coated according to methods well known in the art. Oral fluid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservatives. The tablets may optionally be formulated so as to provide slow or controlled release of the active ingredient therein. A package of tablets may contain one tablet to be taken on ech of the month. The formulation or does of medicament varies with respect to the phase (probe or sucretary) of the menstrual cycle.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline, water-for-injection, immediately prior to use. Alternatively, the formulations may be presented for continuous infusion. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for rectal administration include suppositories with standard carriers such as cocoa butter or polyethylene glycol. Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges, which contain the active ingredient in a flavored base such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a base such as gelatin and glycerin or sucrose and acacia. For intra-nasal administration the compounds of the invention may be used as a liquid spray or dispersible powder or in the form of drops. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilizing agents or suspending agents.

For administration by inhalation the compounds are conveniently delivered from an insufflator, nebulizer, pressurized packs or other convenient means of delivering an aerosol spray.

Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichiorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation or insufflation, the compounds may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form, in for example, capsules, cartridges, gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflators.

Other formulations include implantable devices and adhesive patches; which release a therapeutic agent.

When desired, the above described formulations, adapted to give sustained release of the active ingredient, may be employed. The pharmaceutical compositions may also contain other active ingredients such as antimicrobial agents, immunosuppressants or preservatives.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example, those suitable for oral administration may include flavoring agents.

Preferred unit dosage formulations are those containing an effective dose, as recited below, or an appropriate fraction thereof, of the active ingredient.

For each of the aforementioned conditions, the compositions, e.g., polypeptides and organic compounds are administered orally or via injection at a dose of from about 0.1 to about 250 mg/kg per day. The dose range for adult humans is generally from about 5 mg to about 17.5 g/day, preferably about 5 mg to about 10 g/day, and most preferably about 100 mg to about 3 g/day. Tablets or other unit dosage forms of presentation provided in discrete units may conveniently contain an amount which is effective at such dosage or as a multiple of the same, for instance, units containing about 5 mg to about 500 mg, usually from about 100 mg to about 500 mg.

The dose employed will depend upon a number of factors, including the age and sex of the subject, the precise disorder being treated, and its severity. Also the route of administration may

vary depending upon the condition and its severity.

Kits

The invention also includes an TSC-detection reagent, e.g., a nucleic acid that specifically binds to or identifies one or more TSC nucleic acids such as oligonucleotide sequences, which are complementary to a portion of an TSC nucleic acid or antibodies which bind to proteins encoded by an TSC nucleic acid. An oligonucleotide is at least 5, 10, 15, 20, 25, 30, 40, 50, 75 or more nucleic acids in length. The reagents are packaged together in the form of a kit. The reagents are packaged in separate containers, e.g., a nucleic acid or antibody (either bound to a solid matrix or packaged separately with reagents for binding them to the matrix) , a control reagent (positive and/or negative), and/or a detectable label. Instructions (e.g., written, tape, VCR, CD-ROM, etc.) for carrying out the assay are included in the kit. The assay format of the kit is a Northern hybridization or a sandwich ELISA known in the art.

For example, TSC detection reagent, is immobilized on a solid matrix such as a porous strip to form at least one TSC detection site. The measurement or detection region of the porous strip may include a plurality of sites containing a nucleic acid. A test strip may also contain sites for negative and/or positive controls. Alternatively, control sites are located on a separate strip from the test strip. Optionally, the different detection sites may contain different amounts of immobilized nucleic acids, *i.e.*, a higher amount in the first detection site and lesser amounts in subsequent sites. Upon the addition of test sample, the number of sites displaying a detectable signal provides a quantitative indication of the amount of TSC present in the sample. The detection sites may be configured in any suitably detectable shape and are typically in the shape of a bar or dot spanning the width of a teststrip.

Alternatively, the kit contains a nucleic acid substrate array comprising one or more nucleic acid sequences. The nucleic acids on the array specifically identify one or more nucleic acid sequences represented by TSC 1-26. The expression of 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 40 or 50 or more of the sequences represented by TSC 1-26 are identified by virtue if the level of binding to an array test strip or chip. The substrate array can be on, *e.g.*, a solid substrate, *e.g.*, a "chip" as described in U.S. Patent No.5,744,305.

Arrays and pluralities

The invention also includes a nucleic acid substrate array comprising one or more nucleic acid sequences. The nucleic acids on the array specifically corresponds to one or more nucleic acid sequences represented by TSC 1-26. The level expression of 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 40 or 50 or more of the sequences represented by TSC 1-26 are identified by detecting nucleic acid binding to the array.

The invention also includes an isolated plurality (*i.e.*, a mixture if two or more nucleic acids) of nucleic acid sequences. The nucleic acid sequence are in a liquid phase or a solid phase, *e.g.*, immobilized on a solid support such as a nitrocellulose membrane. The plurality includes one or more of the nucleic acid sequences represented by TSC 1-26. In various embodiments, the plurality includes 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 40 or 50 or more of the sequences represented by TSC 1-26.

Chips

The DNA chip is a device that is convenient to compare expression levels of a number of genes at the same time. DNA chip-based expression profiling can be carried out, for example, by the method as disclosed in "Microarray Biochip Technology " (Mark Schena, Eaton Publishing, 2000), etc.

A DNA chip comprises immobilized high-density probes to detect a number of genes. Thus, expression levels of many genes can be estimated at the same time by a single-round analysis. Namely, the expression profile of a specimen can be determined with a DNA chip. The DNA chip-based method of the present invention comprises the following steps of:

(1) synthesizing cRNAs or cDNAs corresponding to the marker genes;

(2) hybridizing the cRNAs or cDNAs with probes for marker genes; and

(3) detecting the cRNA or cDNA hybridizing with the probes and quantifying the amount of mRNA thereof.

The cRNA refers to RNA transcribed from a template cDNA with RNA polymerase. A cRNA transcription kit for DNA chip-based expression profiling is commercially available. With such a kit, cRNA can be synthesized from T7 promoter-attached cDNA as a template by using T7 RNA polymerase. On the other hand, by PCR using random primer, cDNA can be amplified using as a template a cDNA synthesized from mRNA.

On the other hand, the DNA chip comprises probes, which have been spotted thereon, to detect the marker genes of the present invention. There is no limitation on the number of marker

genes spotted on the DNA chip. For example, it is allowed to select 5% or more, preferably 20% or more, more preferably 50% or more, still more preferably 70 % or more of the marker genes of the present invention. Any other genes as well as the marker genes can be spotted on the DNA chip. For example, a probe for a gene whose expression level is hardly altered may be spotted on the DNA chip. Such a gene can be used to normalize assay results when assay results are intended to be compared between multiple chips or between different assays.

A probe is designed for each marker gene selected, and spotted on a DNA chip. Such a probe may be, for example, an oligonucleotide comprising 5-50 nucleotide residues. A method for synthesizing such oligonucleotides on a DNA chip is known to those skilled in the art. Longer DNAs can be synthesized by PCR or chemically. A method for spotting long DNA, which is synthesized by PCR or the like, onto a glass slide is also known to those skilled in the art. A DNA chip that is obtained by the method as described above can be used for diagnosing a disease X according to the present invention.

The prepared DNA chip is contacted with cRNA, followed by the detection of hybridization between the probe and cRNA. The cRNA can be previously labeled with a fluorescent dye. A fluorescent dye such as Cy3(red) and Cy5 (blue) can be used to label a cRNA. cRNAs from a subject and a control are labeled with different fluorescent dyes, respectively. The difference in the expression level between the two can be estimated based on a difference in the signal intensity. The signal of fluorescent dye on the DNA chip can be detected by a scanner and analyzed by using a special program. For example, the Suite from Affymetrix is a software package for DNA chip analysis.

Also the expression level of the marker gene(s) can be analyzed based on activity or quantity of protein(s) encoded by the marker gene(s). A method for determining the quantity of the protein(s) is known to those skilled in the art. For example, immunoasssay method is useful for determination of the protein in biological material. Any biological materials can be used for the determination of the protein or it's activity. For example, blood sample is analyzed for estimation of the protein encoded by serum markers. Another hand, a suitable method can be selected for the determination of the activity protein(s) encoded by the marker gene(s) according to the activity of each protein to be analyzed.

The invention will be further described in the following examples, which do not limit the scope of the invention described in the claims. The following examples illustrate the identification and characterization of genes differentially expressed in AML cells.

EXAMPLE 1: GENERAL METHODS

Cell and tissue Acquistion

A heterogeneous population of primary AML cells obtained from a sporadic LAM patient, designated #621 was acquired from Dr. E.P. Henske (Fox Chase Cancer Research Center, Philadelphia, PA). AML cells within the population were determined to be $TSC2^{-/-}$ by genomic sequencing (Yu, J., et al. 2003). Frozen AML tissue (AML548, AML564, AML576, AML823, AML1003) and normal donor tissue (kidney, liver, lung, heart, aorta, adipose donor 1 and 2) was obtained from the Maryland Brain and Tissue Bank (Baltimore, MA) via IRB approved protocols. Human melanoma cell lines; Malme3M, Sk-Mel2, Sk-Mel5, Sk-Mel28, UACC62, UACC257, and M14, were obtained from the Tumor Repository of the Division of Cancer Treatment and Diagnosis, National Cancer Institute, Frederick, MA. Melanoma cell line A375 was obtained from American Type Culture Collection (ATCC, Manassus, VA). Amphotropic retroviral producing cell line expressing the E6E7 genes of the human papilloma virus 16 (PA317 pLXSN 16E6E7) and the vector expressing control helper line (PA317 pLXSN) were obtained from ATCC.

Cell culture

Primary AML cells and AML cell lines were grown in DMEM/F12 basal media including 15% FBS, 0.2uM hydrocortisone, 10uU/mL vasopressin, 1X FeSO4, 10ng/mL EGF, 1X ITS, 0.01nM triiolythryonine, 0.12% sodium bicarbonate, 1X cholesterol, 500ug/ml G418 (for clones only) and 1X penicillin/streptomycin/amphotericinB (PSA). Amphotropic retroviral helper cell lines from ATCC were grown in DMEM plus, 10% FBS, PSA in a BSL-2 level facility. Melanoma cell lines were grown according to ATCC and NCI instructions.

Cellular immortalization

AML#621 heterogeneous cell suspension was infected with a replication deficient Moloney Murine Leukemia Virus (MoMLV) that carries the pLXSN vector encoding the E6, E7, and gentamicin (G418) resistance genes (ATCC). Retrovirus containing only the pLXSN vector with G418-resistance was used as a control. AML cells were plated the day before infection into 2, T-25 flasks at a density of 500,000 cells/flask, and incubated overnight at 37°C. Retroviral producing cell lines were grown to confluency in T-75 flasks. Medium was replaced with 10mL of fresh growth media and incubated overnight at 32°C. Virus containing media was sterile filtered using a 0.45 micro syringe filter and polybrene added at a final concentration of 8ug/mL. Medium from the AML cells was replaced with 5 mL viral sup and flasks were centrifuged at 2,500 rpm at 32°C for 90 minutes. AMLs plus viral sup were then incubated overnight at 32°C to continue the infection. 24

hours later cells were returned to 37°C and virus containing medium replaced with fresh growth medium. 48 hours ost infection, successfully transduced clones were isolated via growth in G418-containing (800ug/mL) medium. Once antibiotic-resistant cells were generated, individual clonal colonies were isolated by collaring, then expanded and frozen down.

PCR restriction digest analysis of AML clones

AML clones were assessed for the presence of a G1831A mutation in exon 16 of the TSC2 gene by pcr-based restriction digest identification. This mutation results in a new *Pvu*II restriction enzyme site and the elimination of a *Hpa*II site. Genomic DNA was harvested and primary pcr was performed using primer pair 5' – gaagcacgcactctagagcag – 3'; 5' – ccttcacagattgtgcagca – 3'. One microliter of primary reaction was amplified in a nested reaction using primers 5' - gacca agctgtacac cctgcct – 3'; 5' - cagaccgtcc ctcctctgca cccactgtgg ccgcagcctc cccagtcctg – 3'. PCR products were digested with either *hpaII* or *pvuII* to assess the presence of the mutation. A wildtype clone obtained from a different AML sample that does not exhibit a mutation in exon 16 was used as a control.

Rapamycin growth assay.

1,000 cells/well were plated in triplicate of mouse embryonic fibroblasts (MEF's) $TSC2^{+/+}$; $p53^{-/-}$ and $TSC2^{-/-}$; $p53^{-/-}$, and 3,000 cells/well in triplicate of 2 AML $TSC2^{-/-}$ cell lines and 2 $TSC2^{+/+}$ control lines generated from the same AML tumor. Rapamycin was added to cells at final concentrations of 0.01nM, 0.1nM, 1nM, 10nM, 100nM, 1000nM. Cells were grown for 72 hours and cell growth determined by MTS assay (Promega, Madison, WI).

Microarrays analysis

Total RNA was harvested using the commercially available Trizol Reagent ® [Life Technologies, GibcoBRL, (Gaithers-burg, MD)]. Icoria (Research Triangle Park, NC) was provided with 100ug total RNA from 2 TSC2-/- AML cell lines, and 4 primary AML tumors from different patients. Total RNA from 7 donor pooled normal tissues was purchased from Invitrogen (Carlsbad, CA) and provided to Icoria for gene expression profiling analysis. Hybridizations were performed with 1ug of RNA converted to ssDNA of target on the GeneChip human genome U133 plus 2.0 oligonucleotide array containing over 54,000 probe sets representing more than 38,500 human genes (Affymetrix, Santa Clara, CA). Heirarchical clustering microarray data analysis was performed using the *Spotfire DecisionSite for Functional Genomics*™ software platform (Spotfire, Somerville, MA) and principal component anlysis was performed using Microsoft Excel. Genes that were up-regulated in AML tissues by > 5-fold *and* determined to be likely cell surface expressed, were assessed by rtq-pcr.

RTQ-PCR

PCT Five nanograms of total RNA for housekeeping genes and 500 ng for experimental genes, from AML cell lines, AML primary tissue, and normal tissue was added to a first-strand cDNA synthesis reaction using the commercially available Taqman Multiscribe ® Reverse Transcriptase Kit from ABI. Using the ABI Prism 7700 Thermocycler, complementary DNA (cDNA) synthesis on these samples was performed under the following conditions: 10 min at 25°C, 30 min at 48°C, followed by inactivation of the enzyme at 95°C for 5 min. Fifty µl of the first-strand cDNA synthesis was placed into a TaqMan PCR reaction in triplicate. PCR conditions will be performed as follows: stage 1, 2 min at 50°C; stage 2, 10 min at 95°C; stage 3, 40 cycles of 15 s of melting at 95°C followed by DNA synthesis for 1 min at 60°C. This PCR protocol will be optimized based on primer melting points (Tm) and experimental observations. PCR primers were designed using the computer program Primer Express® by ABI and based upon published or Genbank sequences. To assess the quantity and quality of the RNA/DNA, 2 housekeeping genes, GAPDH and β-actin, and were amplified for all samples and expression evaluated.

Immunoblotting

New AML and control cell lines were assessed for TSC2 expression by immunoblotting (C-20; Santa Cruz Biotechnology, Inc., Santa Cruz, CA), and constituitive phosphorylation of S6 (Ser 235/236) and S6kinase (Thr389) (Cell Signaling Technologies, Inc., Beverly, MA). AML and melanoma cell lines, AML and normal primary tissues were immunoblotted with antibodies against gpnmb (CR011; CuraGen Corp., Branford, CT), MelanA (C-20; Santa Cruz, CA), Silv (ZMD.254; Zymed, South San Francisco, CA), OA1 (W7; a gift from Dr. Schiaffino, Italy), mmp14 (Santa Cruz Biotechnology, Inc., Santa Cruz, CA).

EXAMPLE 2: GENERATION OF $TSC2^{-/-}$ AML CELL LINES

A heterogeneous AML tumor was obtained surgically from a sporadic LAM patient, designated patient #621. Genomic sequencing determined that the majority of cells present within the tumor possessed a missense mutation in one copy of the TSC2 gene. $TSC2^{-/-}$ cells within the tumor resulted from a LOH of the TSC2 gene locus. Because patient #621 has sporadic LAM and not TSC-LAM, non-AML cells within the tumor mass are $TSC2^{+/+}$. The specific point mutation is a nucleotide G to A transition at position 1832 in exon 16 of the TSC2 gene. This mutation results in the loss of a *HpaII* restriction endonuclease site and the creation of a fortuitous diagnostic *PvuII* restriction endonuclease site (figure 1, right panel). The AML621 mixed cell population was infected with a retrovirus carrying the E6E7 genes of the human papilloma virus. Successfully infected cells were plated at a low enough density so as to be clonally isolated by collaring. Eighty

individual clones were isolated, 70 $TSC2^{-/-}$ and 10 $TSC2^{+/+}$ as determined by genomic restriction digest analysis. Restriction digest confirmation of wildtype clones (wt-1, wt-2) and TSC-null clones (AML-1, AML-2, AML-3, AML-4) are shown (figure 1, lower panel).

Primary AML621 cells almost exclusively exhibit an elongated fiber-like morphology characteristic of the smooth muscle component of AMLs (figure 1, B). This is distinctly different from the epithelial shape of adjacent normal kidney cells. While most $TSC2^{-/-}$ AML clones generated maintain the elongated morphology of the primary AML cells, wildtype clones generated from the same tumor mass possess either a fibroblast-like or epithelial morphology (figure 1, bottom panel).

The loss of TSC function can be measured by phosphorylation of S6Kinase (S6K) and its substrate, ribosomal protein S6 (S6), in the absence of serum. In both $TSC1^{-/-}$ or $TSC2^{-/-}$ cells, the absence of the inhibitory TSC complex mimics mitogenic stimulation and results in constitutively active S6K signaling. To establish that AML621 clones are functionally TSC2-null, we isolated protein from wt-1, wt-2, AML-1, AML-2, AML-3, AML-4, and negative and positive TSC2 MEF control cells (TSC2-, TSC2+), and performed immunoblotting analysis for TSC2 expression and serum-independent S6 and S6K phosphorylation (figure 2). The wildtype clones express TSC2 while the AML clones do not. Wildtype-1 and 2 display serum-dependent S6 and S6K phosphorylation while AMLs1-4 express constitutively phosphorylated S6 and S6K, indicative of TSC2 loss.

The mTOR inhibitor, rapamycin, has been shown to inhibit growth of liver hemangiomas in TSC2 knockout mice, as well as of embryonic fibroblasts derived from knockout animals. We assessed rapamycin sensitivity of the AML clones (Figure 3). Dose response growth assay demonstrates that while the growth of the AML clones is differentially inhibited as compared with wildtype lines generated from the 621 tumor mass, the human cell lines are less sensitive to rapamycin than the rodent cells (MEFs). Furthermore, p53-/- MEF cell lines and the Eker rat leiomyoma cell lines grow anchorage-independent colonies in soft agar, while the AML clones we developed do not (data not shown). This indicates that expression of E6E7 in AML cells does not result in transformation. Differences between the responses of human and rodent cells to rapamycin may reflect an inherent difference between the two species in how they will respond to therapeutics.

EXAMPLE 3: MICROARRAY ANALYSIS OF GENE EXPRESSION IN AMLS

In order to identify novel protein targets for the development of immunotherapeutics to treat TSC, microarray expression profiling was performed on 4 primary AML tumor tissues (AML548, AML564, AML576, AML1003) from different patients and $TSC2^{-/-}$ AML cell lines (A-

A2, A-C4) to identify genes up-regulated in AMLs. AML expression data was compared to 7 pooled normal tissues, including kidney, lung, trachea, aorta, left ventricle, uterus, and whole brain. Total RNA was converted to labeled cDNA and then hybridized to the Affymetrix GeneChip Human Genome U133 2.0 plus array containing more then 38,500 genes. The heirachical clustering analysis was performed using the *Spotfire DecisionSite for Functional Genomics*™ software platform (Spotfire, Somerville, MA).

Heirarchical clustering algorithms are designed to assess how closely related multiple samples are to one another. In this case, how closely does the gene expression profile of one sample match the profile of every other sample, thereby generating a relative similarity percentage. As expected, the two AML clonal cell lines generated from the same AML are highly related (>99%) suggesting the immortalization process did not produce global changes in gene expression between clones (Figure 4). Although there is diversity between primary AML samples ranging from 83.8% to 94.9% similarity, the AMLs are more like each other then almost all the normal samples, including the smooth muscle tissues of aorta, uterus, and trachea. The one exception is their high similarity to kidney (>83.8%). While AMLs are found almost exclusively on the kidney, the tumors themselves are composed of smooth muscle, adipose, and blood vessel. This apparent close relationship between AML and kidney might be explained by the accidental collection of adjacent kidney tissue during resection of the tumor and the heterogeneous nature of the AML. However, the AML cell lines are also much more similar to kidney then any other tissue, and these are clonally derived pure AML cell populations.

Principal component analysis of gene expression was performed as follows. Only genes that were expressed or 'present' in at least one of the 11 samples were selected for analysis. We performed a two-tailed T-Test for each gene to determine if the expression in group 1 (4 primary AMLs plus 1 AML cell line) and group 2 (all normal tissues except brain) are significantly different. For those genes significantly (T-value > 0.05) expressed in AMLs compared with the normal tissues group, the fold change of median gene expression of group 1 compared with group 2 was determined. 115 genes were found to be up-regulated in AMLs by at least 5-fold with a T-value of <0.05 are shown (Table B). Silv, the antigen for the HNB45 antibody, known to be over-expressed in TSC-null cells, was expressed 50-fold greater in AMLs in this experiment. The membrane-type 1 matrix metalloproteinase (mmp14/MT1-MMP) shown to be highly expressed in LAM, is overexpressed 5-fold in AMLs as well (Matsui K., et al. 2000). In addition to silv, several genes associated with melanomas are also up-regulated in AMLs (Table D). MelanA, melanophillin, mmp14, OA1, ABCB5, gpnmb are all expressed significantly higher in TSC tissue.

However not all genes associated with melanoma are overexpressed in AMLs as evident by nearly equal levels of expression between CD63, Dct, Tyrp1, and MAGE-1 and normal tissue. Transmembrane or secreted proteins that were identified as up-regulated in AMLs are listed in Table C.

Cytototoxic T lymphocytes (CTL) frequently recognize nonmutated endogenous proteins that are expressed both in normal tissues and in growing tumors. These Ags may be useful as vaccine targets, and CTLs targeted against them can cause tumor regression upon adoptive transfer. Tumor-associated antigens recognized by tumor-reactive T lymphocytes has led to the development of antigen-specific immunotherapy of cancer. Melanoma is particularly resistant to traditional chemotherapy and radiation treatments and has become an important target for the development of antibody therapies and peptide-based vaccines. Several proteins required for proper melanosomal function in melanocytes, are commonly over-expressed in various forms of melanoma. melan-A, silv, Tyrosinase, Trp2/DCT, Trp1/Tyrp1, OA1, and gpnmb/osteoactivin (gpnmb), are all transmembrane proteins normally expressed in melanosomes, but are upregulated in melanoma and have been dubbed, melanoma-associated antigens (MAAs). Several MAAs has shown promise as a target for vaccine development and CTL therapy for melanoma. Vaccine-induced circulating CD8+ T cells specific for melan-A, silv, and tyrosinase-derived peptides have already been tested successfully in clinical trials in patients with advanced melanoma. Thus, MAAs are potential targets for vaccine development in TSC-related disorders.

Table B

Probe set ID	Accession No.	Gene	Clone	Protein	Fold Δ
206696_at	NM_000273.1	*OA1/GPR143*		Ocular albinism 1	36.7
209348_s_at	U01874.1	*SILV/PMEL17*		Silver/pMEL17/gp100	30.6
229947_at	AI088609	*PI15*		protease inhibitor 15 preproprotein	35.6
229290_at	AI692575	*OCT6*		transcription factor Oct-6	32.4
218468_s_at	AF154054.1	*DRM/GREM1*		DRM/Gremlin-1	28.3
215767_at	AF052145.1	*EST*	24400 mRNA		25.5
218469_at	NM_013372.1	*DRM/GREM1*		DRM/Gremlin-1	25.3
213482_at	BF593175	*DOCK3*		dedicator of cyto-kinesis 3	24.8
214156_at	AL050090.1	*MYRIP*		myosin VIIA and Rab interacting protein	23.0
232195_at	R41459	*EST*	IMAGE:29255	KIAA1136	17.6
219279_at	NM_017718.1	*EST*	FLJ20220	hypothetical protein FLJ20220	13.7
214046_at	AA017721	*EST*	DKFZp564N1662		12.1
1558846_at	AL833418.1	*PNLIPRP3*		Pancreatic lipase-related protein 3	12.0
203381_s_at	N33009	*APOE*		apolipoprotein E	12.0
214586_at	T16257	*GPR37*		protein-coupled receptor 37 (endothelin receptor type B-like)	11.8
244444_at	AW082870	*PKD1L2*		Polycystic kidney disease 1-like 2	11.7
244353_s_at	AI675682	*TBPL1*		TBP-like 1	11.3
213790_at	W46291	*ADAM12*		disintegrin and metalloproteinase domain 12	11.0
203382_s_at	NM_000041.1	*APOE*		apolipoprotein E	10.8
230401_at	BF197705	*NUPL2*		Nucleoporin like 2	10.6
212806_at	AL138349	*EST*	DKFZp762I1914	KIAA0367	10.6
238969_at	BF512162	*EST*	IMAGE:3070060		10.3
240423_at	R54953	*ABCB6*		ATP-binding cassette, sub-family B, member 6	10.3
207938_at	NM_015886.1	*PI15*		protease inhibitor 15 preproprotein	10.2
226777_at	AA147933	*ADAM12*		disintegrin and metalloproteinase domain 12 (meltrin alpha	10.1
219578_s_at	NM_030594.1	*CPEB1*		cytoplasmic polyadenylation element binding protein 1	9.9
211207_s_at	AF129166.1	*LACS5*		long-chain acyl-CoA synthetase 5	9.7
1558473_at	AK096402.1	*EST*	FLJ39083		9.6
218959_at	NM_017409.1	*HOXC10*		homeo box C10	9.5
212805_at	AB002365.1	*EST*		KIAA0367	9.4
211162_x_at	AF116616.1	*SCD*		PRO0998	9.1
206030_at	NM_000049.1	*ASPA*		Aspartoacylase (aminoacylase 2, Canavan disease)	9.0

240101_at	BF508153	*EST*	IMAGE:3089055		8.9
226390_at	AA628398	*EST*	IMAGE:1032745		8.8
212884_x_at	AI358867	*APOE*		apolipoprotein E	8.7
1556346_at	AJ227860.1	*EST*			8.5
229725_at	AV705292	*ACSL6*		Acyl-CoA synthetase long-chain family member 6	8.2
243885_x_at	AA526937	*EST*	IMAGE:969076		8.2
202952_s_at	NM_003474.2	*ADAM12*		disintegrin and metalloproteinase domain 12 (meltrin alpha), var. 1	8.1
211708_s_at	BC005807.1	*EST*	MGC:10264		7.8
237265_at	BF062257	*EST*	IMAGE:3481213		7.8
1562247_at	AL833160.1	*EST*	DKFZp686J2011		7.8
202450_s_at	NM_000396.1	*CTSK*		cathepsin K	7.7
207400_at	NM_006174.1	*NPY5R*		neuropeptide Y receptor Y5	7.6
1554018_at	BC011595.1	*GPNMB*		glycoprotein nmb	7.5
244684_at	AI432340	*EST*	IMAGE:2112610		7.4
1560683_at	AL832227.1	*EST*	DKFZp686P1536		7.4
235737_at	AW118681	*EST*	IMAGE:2605355		7.3
204044_at	NM_014298.2	*QPRT*		quinolinate phosphoribosyltransferase	7.3
1557890_at	BC035182.1	*EST*	IMAGE:5266307		7.2
1563787_a_at	AK097760.1	*CAGE1*		cancertestis antigen gene 1	7.2
229715_at	AW006182	*EST*	IMAGE:2566376		7.1
1564383_s_at	AK093253.1	*EST*	IMAGE:4869921		7.1
203069_at	NM_014849.1	*EST*	KIAA0736		7.0
218211_s_at	NM_024101.1	*MLPH*		melanophilin/Slac2-c	6.9
214147_at	AL046350	*EST*	DKFZp434J097		6.7
208510_s_at	NM_015869.1	*PPARG*		peroxisome proliferative activated receptor, gamma	6.6
220484_at	NM_018298.1	*MCOLN3*		Mucolipin3	6.6
201907_x_at	U49262.1	*DVL*		dishevelled	6.6
239326_at	AA988134	*EST*	IMAGE:1604651		6.6
214680_at	BF674712	*NTRK2*		neurotrophic tyrosine kinase, receptor, type 2	6.5
237070_at	AI277662	*EST*	IMAGE:1878472		6.5
227498_at	AI480314	*EST*	IMAGE:2157753		6.5
205122_at	BF439316	*TMEFF1*		transmembrane protein with EGF-like and two follistatin-like domains 1	6.5
228116_at	AW167298	*EST*	IMAGE:2634005		6.4
224494_x_at	BC006283.1	*DHRS10*		dehydrogenase/reductase (SDR family) member 10	6.4
200832_s_at	AB032261.1	*SCD*		stearoyl-CoA desaturase	6.4

240236_at	N50117	*EST*	IMAGE:282792		6.3
200831_s_at	AA678241	*SCD*		stearoyl-CoA desaturase (delta-9-desaturase)	6.3
1565544_at	AI758773	*EST*	IMAGE:2279989		6.3
228274_at	BE963955	*EST*	IMAGE:3875860		6.2
1561513_at	BC043294.1	*EST*	IMAGE:5298087		6.2
1562102_at	BC014579.1	*EST*	IMAGE:3681106		6.2
219113_x_at	NM_016246.1	*DHRS10*		retinal short-chain dehydrogenasereductase	6.2
206617_s_at	NM_002910.4	*RENBP*		renin-binding protein	6.1
224497_x_at	BC006294.1	*DHRS10*		dehydrogenase/reductase (SDR family) member 10	6.1
242546_at	BE738279	*EST*	IMAGE:3839194		6.1
229797_at	AI636080	*EST*	IMAGE:2296074		6.0
229550_at	AB037830.1	*EST*	KIAA1409		6.0
1553768_a_at	NM_173674.1	*DCBLD1*		discoidin, CUB and LCCL domain containing 1	6.0
210609_s_at	BC000474.1	*TP53I3*		tumor protein p53 inducible protein 3, transcript, var.2	5.9
1563840_at	BC040569.1	*EFTUD1*		elongation factor Tu GTP binding domain containing 1	5.9
231936_at	AK000445.1	*HOXC9*		homeo box C9	5.8
235050_at	AI742672	*SLC2A12*		Solute carrier family 2 (facilitated glucose transporter), member 12	5.8
207091_at	NM_002562.1	*P2RX7*		purinergic receptor P2X, ligand-gated ionchannel 7	5.8
228415_at	AA205444	*AP1S2*		adaptor-related protein complex 1, sigma 2 subunit	5.8
215003_at	AA921844	*DGS-A*		DiGeorge Syndrome gene A	5.8
204694_at	NM_001134.1	*AFP*		alpha-fetoprotein	5.7
1562656_at	BC043591.1	*EST*	IMAGE:5248626		5.7
205249_at	NM_000399.2	*EGR2*		early growth response 2	5.7
205240_at	NM_013296.1	*LGN*		LGN protein	5.7
213107_at	R59093	*EST*	IMAGE:41943	KIAA0551	5.6
216222_s_at	AI561354	*MYO10*		myosin X	5.6
1570125_at	BC037977.1	*EST*	IMAGE:5229457		5.6
238232_at	AI634355	*EST*	IMAGE:2232868		5.5
211267_at	U82811.1	*HANF/HESX1*		homeodomain-containing protein	5.5
1557348_at	AI915861	*EST*	IMAGE:2378957		5.5
204527_at	NM_000259.1	*MYO5A*		myosin VA (heavy polypeptide 12, myoxin)	5.5
212664_at	AL567012	*TUBB5*		tubulin, beta, 5	5.5
220324_at	NM_024882.1	*ORF*		Hypothetical protein FLJ13189	5.4
229526_at	AI886656	*AQP11*		Aquaporin 11	5.4
1559789_a_at	AK097019.1	*ORF*		Hypothetical protein FLJ37549	5.3

1557292_a_at	AW665790	*MCOLN3*		Mucolipin 3	5.3
232606_at	AK021894.1	*ANK2*		Ankyrin 2, neuronal	5.3
237034_at	AW002876	*EST*	IMAGE:2480346		5.2
221530_s_at	BE857425	*DEC2*		bHLH protein DEC2	5.2
228262_at	AW237462	*EST*	IMAGE:2689732	Hypothetical protein FLJ14503	5.2
227084_at	AW339310	*DTNA*		Dystrobrevin, alpha	5.2
1554121_at	BC012536.1	*HSD17B12*		Hydroxysteroid (17-beta) dehydrogenase 12	5.1
228807_at	AI078764	*EST*	IMAGE:1677212		5.1
1553260_s_at	NM_152525.1	*EST*		hypothetical protein FLJ25351	5.1
237608_at	AW665177	*EST*	IMAGE:2979327		5.1
217279_x_at	X83535.1	*MMP14*		membrane-type matrix metalloproteinase 14	5.0
1557745_at	BE551038	*EST*	IMAGE:3233325		5.0
1554636_at	BC032569.1	*EST*	IMAGE:5242641		5.0

Table C

TSC No.	Gene Name	Gene Family Name	Biological Process	Molecular Function	AML 1003	AML 564	AML 548	AML 576	A-C4 line	Brain	Lung	Left Ventricle	Uterus	Aorta	Trachea	Kidney	T-Test (no brain)	Fold Change (no Brain)
1	melan-A	---	---	---	10.5	2155.7	9168.7	7604.2	15.6	29.4	1.9	3.2	3.3	19.2	3.3	19.8	0.0583	653.2
2	Ocular albinism 1/G-rotein-coupled receptor 143	GPCRs	eye pigment biosynthesis /// signal transduction /// G-protein coupled receptor protein signaling pathway /// visual perception	G-protein coupled receptor activity	7.3	283.8	1034.9	662.2	872	24.5	31.7	4.8	3	8.5	5.2	76.3	0.0105	127.3
3	silver/gp100/pMel17	Pmel-17/NMB family	melanin biosynthesis from tyrosine	---	30.6	1821.2	5586.2	4340.8	7.2	13.8	72.4	13.6	87.5	53.9	18.1	11.3	0.0496	100.6
4	gremlin 1 homolog, cysteine knot superfamily	---	development /// neurogenesis	protein binding	16.6	752.8	9928.2	6565.7	13048.5	417.2	127.3	11.9	332.4	341	37	355.4	0.0308	51.6

	(Xenopus laevis)																									
5	ATP-binding cassette, sub-family B (MDR/TAP), member 5	—	—		19.4	171.2	959	998.8	76.6	2.1	5.1	5.4	2.1	14.3	2.2	3.6	0.0536	47.6								
6	5-hydroxytryptamine (serotonin) receptor 2B	GPCRs	G-protein signaling, coupled to IP3 second messenger (phospholipase C activating) /// circulation /// positive regulation of I-kappaB kinase/NF-kappaB cascade	rhodopsin-like receptor activity /// signal transducer activity /// serotonin receptor activity	121.3	1412.9	10599	8012.4	201.8	8.7	2.5	143.5	442.6	458.1	23.4	40.2	0.0811	35.1								
7	mucolipin 3	—	cation transport	cation channel activity	2.2	320.9	575.1	595.4	487.8	13.6	11.2	2.8	114.6	15.3	118.9	121	0.0102	31.9								
8	a disintegrin and metalloproteinase domain 12 (meltrin alpha)	peptidase family M12B	proteolysis and peptidolysis /// cell adhesion /// myoblast fusion	metalloendopeptidase activity /// protein binding /// zinc ion binding /// hydrolase activity	134.5	230.3	690.9	196	834.8	28.1	72.2	8.6	33.3	5.6	59.7	2.7	0.0158	26.8								
9	myosin VIIA and Rab interacting protein	—	—		3092.4	418.3	2741.3	1819.5	1.8	867.7	107	59.3	473.7	88	53.1	70.2	0.0271	25.9								
10	melanophilin	—	melanin synthesis		1009.5	166.9	1929.9	1229.3	150.8	25.1	1037.9	57.7	41.2	11.1	256.8	5.1	0.0951	24.5								
11	ATP-binding cassette, sub-family C (CFTR/MRP), member 8	ABC transporter	carbohydrate metabolism /// transport /// potassium ion transport	nucleotide binding /// receptor activity /// ATP binding /// sulfonylurea receptor activity /// potassium ion transporter activity /// ATPase activity, coupled to transmembrane movement of substances	3.5	298.8	1856.9	1211.7	3.8	524.3	19.2	19.4	12.6	14.1	12	8.5	0.0788	23.7								

12	vasoactive intestinal peptide receptor 2	GPCRs	signal transduction /// G-protein coupled receptor protein signaling /// cell-pathway /// cell signaling	G-protein coupled receptor activity /// vasoactive intestinal polypeptide receptor activity	750.5	12.7	274.8	255.4	11.7	17.5	26.8	27.1	13.3	16.8	7	8.7	0.0757	19.2
13	pancreatic lipase-related protein 3	---	---	---	10.5	117.3	115.6	138.2	351.3	2.1	22.6	1.1	13.3	6.2	1.7	29.5	0.0265	18.9
14	polycystic kidney disease 1-like 2	---	cation transport /// neuropeptide signaling pathway	cation channel activity /// sugar binding	200.5	216.3	316.6	686.8	20	50.4	30	19.2	17.8	88.4	3.6	1.9	0.0292	12.2
15	attractin-like 1	---	development	receptor activity /// structural molecule activity /// sugar binding	1010.8	175.6	345.9	247	20.2	878.3	20.4	25	69.2	88.1	2.2	12.9	0.0668	12.1
16	solute carrier family 2 (facilitated glucose transporter), member 12	---	carbohydrate transport	transporter activity /// sugar porter activity	1023.2	499.7	1597.9	1481.4	26.1	194.5	45	370.5	54.7	118	93.2	87.7	0.0171	11.7
17	protease inhibitor 15	Allergen V5/Tpx-1 related	---	peptidase activity /// trypsin inhibitor activity	335.2	40.4	530.6	405.6	50.5	11.1	7.9	33.6	32	65.3	42.1	16	0.0244	10.5
18	tumor protein p53 inducible protein 3	---	induction of apoptosis by oxidative stress	alcohol dehydrogenase activity, zinc-dependent /// zinc ion binding	1283	751.1	2534	1900	510	82.4	515.7	88.3	127.5	106.3	308.8	584.9	0.0114	10.1
19	astrotactin	---	cell adhesion /// neuronal cell adhesion /// cell migration	protein binding	870.8	98.1	719.5	210.1	7.9	1806.4	84.5	53	31.3	24.7	13.6	9.1	0.0557	8.5
20	glycoprotein (transmembrane) nmb	Polycystic kidney disease proteins	negative regulation of cell proliferation	---	3079.7	228.5	2072.3	1922	2027.1	80.8	58.1	894.8	373.4	252.6	299.3	71.5	0.0065	8.0
21	contactin 1	---	cell adhesion	protein binding	17.4	245.1	1110.5	1551.8	1.2	1424.8	31	14	65.8	94.7	28.1	63.1	0.0928	7.9
22	neural epidermal growth factor like like-2				82.8	798.7	6293.4	9085.7	43.9	8064.2	436.9	119	124.3	125	420.5	181.9	0.1062	6.4
23	transmembrane protein with EGF-like and two		signalling		256	183	2119.7	1123.2	507.2	2308.3	21.1	120.2	64.3	201.2	102.7	79.5	0.0498	6.4

	follistatin-like domains 1																						
24	peroxisome proliferative activated receptor, gamma, coactivator 1, alpha		thermoregulation /// cell glucose homeostasis /// gluconeogenesis /// regulation of transcription, DNA-dependent /// mRNA processing /// mitochondrion organization and biogenesis /// RNA splicing /// response to cold /// fatty acid oxidation /// response	RNA binding /// transcription factor binding /// ligand-dependent nuclear receptor transcription coactivator activity	7.3	61	563.9	393.9	6.6	22.3	8.6	20.5	19.9	9.8	4	34.8	0.0999	6.2
25	matrix metalloproteinase 14 (membrane-inserted)		proteolysis and peptidolysis	metalloendopeptidase activity /// zinc ion binding /// hydrolase activity	575	111.7	572.4	351.8	494.9	16.6	98.7	27.9	240.4	164.8	164.7	39.3	0.0076	5.0
26	vascular endothelial growth factor D		PDGF signalling		29.8	409.8	6947.4	1953.3	27.3	51	55.6	472.7	477.9	438.3	2541	26.6	0.3648	-1.1

Table D.

ProbeSet ID	Gene	AML 1003	AML 564	AML 548	AML 578	A-C4 line	Lung	L. Ventricle	Uterus	Aorta	Trachea	Kidney	T-test	Fold
209427_s_at	Melan-A/MART1[1]	10.5	2155.7	9188.7	7604.2	15.6	1.9	3.2	3.3	19.2	3.3	19.8	0.0583	653.2
243187_at	ABCB5/p-glycoprotein[1]	19.4	171.2	959	998.8	76.6	5.1	5.4	2.1	14.3	2.2	3.6	0.0536	39.4
209848_s_at	Silv/pMel17/gp100[1]	30.6	1821.2	5586.2	4340.8	7.2	72.4	13.6	87.5	53.9	18.1	11.3	0.0496	50.6
209426_at	Melan-A/MART1[1]	15.1	678.1	4319.2	3405.1	1.3	34.3	8.1	18.3	34.5	21.2	29.1	0.0739	27.0
206696_at	Ocular Albinism 1 (OA1)[1]	7.3	283.8	1034.9	662.2	872	31.7	4.8	3	8.5	5.2	76.3	0.0105	96.7
1569072_s_at	ABCB5/p-glycoprotein[1]	32.4	213.1	1600	1192	35.2	1.2	12.9	50.7	11.8	11.9	31.7	0.0752	17.2
214156_at	MYRIP	3092.4	418.3	2741.3	1819.5	1.8	107	59.3	473.7	88	53.1	70.2	0.0271	23.0
213790_at	ADAM12 variant 1[2]	134.5	230.3	690.9	196	834.8	72.2	8.8	33.3	5.8	59.7	2.7	0.0158	11.0
218211_s_at	Melanophilin (MLPH)	4732.1	1217	6663.4	6886.4	2834.5	2777	1092.4	204.9	274.5	1470.2	110.3	0.0152	6.9
223795_at	Oculospanin (OCSP)	131	72.1	785.2	1557.1	517	116.1	42.7	22.5	81.5	42.4	70.9	0.0508	9.1
202952_s_at	ADAM12 variant 1[2]	189.7	327.3	694.2	282.2	1837.2	55.5	39.5	44.9	9.6	41.4	36	0.0400	8.1
1554018_at	gpnmb/osteoactivin	3079.7	228.5	2072.3	1922	2027.1	58.1	894.8	373.4	252.6	299.3	71.5	0.0065	7.3
201141_at	gpnmb/osteoactivin	19783.6	7228.6	19413.1	21795.3	15081.2	2735.4	7953.5	5021.4	8042.4	4753.2	1308.3	0.0017	4.0
202828_s_at	MMP14/MT1-MMP[1]	575	111.7	572.4	351.8	494.9	98.7	27.9	240.4	164.8	164.7	39.3	0.0078	3.8
202827_s_at	MMP14/MT1-MMP[1]	764.9	43.9	998.5	404.4	666.2	252.5	68.1	233.5	151.7	219.1	153.3	0.0278	3.6
221261_x_at	MAGE1[1]	124.4	67.9	281.2	196	133.9	220.2	8.3	190.4	120.7	40.7	59.3	0.31277	1.5
211602_s_at	TRYP1/TRP-1[1]	76.8	110.9	407.8	467.6	146.5	27.8	111.1	437.1	116.7	130.2	67.8	0.3682	1.3
205338_s_at	DCT/TRP-2[1]	38.9	39.8	41.9	50.2	10.5	64.9	37.2	15.1	42.2	24	20.4	0.8281	1.3
200663_at	melanoma 1 antigen (CD63)[1]	12593	8328.4	14208.5	14690.7	14782.9	17485.9	9808.9	11460.8	13589.8	10212.8	8787.5	0.5739	1.3
206630_at	Tyrosinase[1]	A	A	A	A	A	A	A	A	A	A	A	N/A	N/A

[1] = Associated with melanoma
[2] = Associated with carcinoma
A = Expression absent

EXAMPLE 4: RTQ-PCR VALIDATION OF GENE EXPRESSION IN AMLS

RTQ-PCR validation was performed on 32 genes identified by microarray analysis as expressed higher in AML tissue samples than normal control tissues by > 5-fold, and are likely to be expressed on the cell surface. Of these genes, 22 were verified as up-regulated in at least 3 of 4 AML tissue samples. High expression of the melanoma associated genes, melanA, silv, OA1, gpnmb, and mmp14 as determined by microarray, was supported by the RTQ-PCR results (Figure 5). Interestingly, some genes appear to have nearly identical tissue expression patterns. Expression of silv and melanA are quite similar with a notably lack of expression in the AML cell lines, little to no expression in AML1003, and the highest expression in AML548. While this phenomena could be artifactual, it is possible that both genes may be regulated by the same signaling mechanism in the absence of TSC2.

Variation of gene expression between different AML tissue samples is evident by Most genes identified as up-regulated in AMLs, are not expressed in all 4 primary AMLs or cell lines. OA1 and mcoln3 are almost absent in AML1003, while mmp14 and gpnmb are only found at very low levels in AML564. This reflects the normal variation in gene expression found in AMLs between patients. The absence of expression some genes in the AML cell lines could be due to the inherent difference between gene expression in a 2-dimensional (cell line) and a 3-dimensional (primary tissue) environment, or the normal variation of gene expression between patients.

EXAMPLE 5: GPNMB AND OA1 EXPRESSION IN MELANOMA AND AMLS

To assess the correlation between RNA levels and protein expression of gpnmb and OA1, we performed immunoblotting on 4 primary AMLs, 8 melanoma cell lines, 1 AML cell line and 1 control line, and 6 normal tissues from 2 donors (figure 6). Expression of gpnmb is very robust in

primary AMLs and the TSC2 AML cell line, with expression varying in the melanoma lines, and the lowest level observed the $TSC2^{+/+}$ AML control line. Interestingly, expression of this MAA is actually higher in AML samples then melanoma, and appears to be TSC2 status dependent as indicated by the near absence of expression in the wildtype control line. There was no appreciable expression in any normal tissue tested. Housekeeping genes are traditionally used as load controls between samples, however expression varies between different tissues. GAPDH was used to compare loading of normal tissues. Despite the disparity of signal, similarity of GAPDH expression within a tissue type from different donors indicates tissue-dependent expression, not inequity of protein load. Coomassie staining verified that equal protein was loaded in all lanes.

OA1 expression also was strongest in AML primary tissue, although only in 2 of the 4 samples, and was not prevalent in the AML cell line. Expression was present in most melanoma lines as expected. OA1 was found to be significantly expressed in liver and to a lower extent, in heart.

Example 6: TSC Nucleotide and Protein Sequences

Exemplary TSC nucleic acid and TSC polypeptide sequences are described below:

TSC1 Melan-A.

Both U06654.1 and NM_005511 encode the protein sequence shown in Table 1C.

Table 1A. melan-A (U06654.1) nucleotide sequence (SEQ ID NO:1).

CCGTCAGAAATCTAAACCCGTGACTATCATGGGACTCAAAACCAGCCCAAAAAATAAGTCAAAACGATTAAG
AGCCAGAGAAGCAGTCTTCATACACGCGGCCAGCCAGCAGACAGAGGACTCTCATTAAGGAAGGTGTCCTGT
GCCCTGACCCTACAAG**ATG**CCAAGAGAAGATGCTCACTTCATCTATGGTTACCCCAAGAAGGGGCACGGCCA
CTCTTACACCACGGCTGAAGAGGCCGCTGGGATCGGCATCCTGACAGTGATCCTGGGAGTCTTACTGCTCAT
CGGCTGTTGGTATTGTAGAAGACGAAATGGATACAGAGCCTTGATGGATAAAAGTCTTCATGTTGGCACTCA
ATGTGCCTTAACAAGAAGATGCCCACAAGAAGGGTTTGATCATCGGGACAGCAAAGTGTCTCTTCAAGAGAA
AAACTGTGAACCTGTGGTTCCCAATGCTCCACCTGCTTATGAGAAACTCTCTGCAGAACAGTCACCACCACC
TTATTCACCT**TAA**GAGCCAGCGAGACACCTGAGACATGCTGAAATTATTTCTCTCACACTTTTGCTTGAATT
TAATACAGACATCTAATGTTCTCCTTTGGAATGGTGTAGGAAAAATGCAAGCCATCTCTAATAATAAGTCAG
TGTTAAAATTTTAGTAGGTCCGCTAGCAGTACTAATCATGTGAGGAAATGATGAGAAATATTAAATTGGGAA
AACTCCATCAATAAATGTTGCAATGCATGATA

Table 1B. melan-A (NM_005511) nucleotide sequence (SEQ ID NO:2).

AGCAGACAGAGGACTCTCATTAAGGAAGGTGTCCTGTGCCCTGACCCTACAAG**ATG**CCAAGAGAAGATGCTC
ACTTCATCTATGGTTACCCCAAGAAGGGGCACGGCCACTCTTACACCACGGCTGAAGAGGCCGCTGGGATCG
GCATCCTGACAGTGATCCTGGGAGTCTTACTGCTCATCGGCTGTTGGTATTGTAGAAGACGAAATGGATACA
GAGCCTTGATGGATAAAAGTCTTCATGTTGGCACTCAATGTGCCTTAACAAGAAGATGCCCACAAGAAGGGT
TTGATCATCGGGACAGCAAAGTGTCTCTTCAAGAGAAAAACTGTGAACCTGTGGTTCCCAATGCTCCACCTG
CTTATGAGAAACTCTCTGCAGAACAGTCACCACCACCTTATTCACCT**TAA**GAGCCAGCGAGACACCTGAGAC
ATGCTGAAATTATTTCTCTCACACTTTTGCTTGAATTTAATACAGACATCTAATGTTCTCCTTTGGAATGGT
GTAGGAAAAATGCAAGCCATCTCTAATAATAAGTCAGTGTTAAAATTTTAGTAGGTCCGCTAGCAGTACTAA
TCATGTGAGGAAATGATGAGAAATATTAAATTGGGAAAACTCCATCAATAAATGTTGCAATGCATGATACTA
TCTGTGCCAGAGGTAATGTTAGTAAATCCATGGTGTTATTTTCTGAGAGACAGAATTCAAGTGGGTATTCTG
GGGCCATCCAATTTCTCTTTACTTGAAATTTGGCTAATAACAAACTAGTCAGGTTTTCGAACCTTGACCGAC

ATGAACTGTACACAGAATTGTTCCAGTACTATGGAGTGCTCACAAAGGATACTTTTACAGGTTAAGACAAAG
GGTTGACTGGCCTATTTATCTGATCAAGAACATGTCAGCAATGTCTCTTTGTGCTCTAAAATTCTATTATAC
TACAATAATATATTGTAAAGATCCTATAGCTCTTTTTTTTTGAGATGGAGTTTCGCTTTTGTTGCCCAGGCT
GGAGTGCAATGGCGCGATCTTGGCTCACCATAACCTCCGCCTCCCAGGTTCAAGCAATTCTCCTGCCTTAGC
CTCCTGAGTAGCTGGGATTACAGGCGTGCGCCACTATGCCTGACTAATTTTGTAGTTTTAGTAGAGACGGGG
TTTCTCCATGTTGGTCAGGCTGGTCTCAAACTCCTGACCTCAGGTGATCTGCCCGCCTCAGCCTCCCAAAGT
GCTGGAATTACAGGCGTGAGCCACCACGCCTGGCTGGATCCTATATCTTAGGTAAGACATATAACGCAGTCT
AATTACATTTCACTTCAAGGCTCAATGCTATTCTAACTAATGACAAGTATTTTCTACTAAACCAGAAATTGG
TAGAAGGATTTAAATAAGTAAAAGCTACTATGTACTGCCTTAGTGCTGATGCCTGTGTACTGCCTTAAATGT
ACCTATGGCAATTTAGCTCTCTTGGGTTCCCAAATCCCTCTCACAAGAATGTGCAGAAGAAATCATAAAGGA
TCAGAGATTCTG

Table 1C. Encoded melan-A protein sequence (SEQ ID NO:3).

MPREDAHFIYGYPKKGHGHSYTTAEEAAGIGILTVILGVLLLIGCWYCRRRNGYRALMDKSLHVGTQCALT
RRCPQEGFDHRDSKVSLQEKNCEPVVPNAPPAYEKLSAEQSPPPYSP

TSC2: Ocular albinism 1/G-protein-coupled receptor 143.

Table 2A. ocular albinism 1/G-protein-coupled receptor 143 (NM_000273.1) nucleotide sequence (SEQ ID NO:4).

ATGACCCAGGCAGGCCGGCGGGGTCCTGGCACACCCGAGCCGCGTCCGCGAACACAGCCCATGGCCTCCCCG
CGCCTAGGGACCTTCTGCTGCCCCACGCGGGACGCAGCCACGCAGCTCGTGCTGAGCTTCCAGCCGCGGGCC
TTCCACGCGCTCTGCCTGGGCAGCGGCGGGCTCCGCTTGGCGCTGGGCCTTCTGCAGCTGCTGCCCGGCCGC
CGGCCCGCGGGCCCCGGGTCCCCCGCGACGTCCCCGCCGGCCTCGGTCCGCATCCTGCGCGCTGCCGCTGCC
TGCGACCTTCTCGGCTGCCTGGGTATGGTGATCCGGTCCACCGTGTGGTTAGGATTCCCAAATTTTGTTGAC
AGCGTCTCGGATATGAACCACACGGAAATTTGGCCTGCTGCTTTCTGCGTGGGGAGTGCGATGTGGATCCAG
CTGTTGTACAGTGCCTGCTTCTGGTGGCTGTTTTGCTATGCAGTGGATGCTTATCTGGTGATCCGGAGATCG
GCAGGACTGAGCACCATCCTGCTGTATCACATCATGGCGTGGGGCCTGGCCACCCTGCTCTGTGTGGAGGGA
GCCGCCATGCTCTACTACCCTTCCGTGTCCAGGTGTGAGCGGGGCCTGGACCACGCCATCCCCCACTATGTC
ACCATGTACCTGCCCCTGCTGCTGGTTCTCGTGGCGAACCCCATCCTGTTCCAAAAGACAGTGACTGCAGTG
GCCTCTTTACTTAAAGGAAGACAAGGCATTTACACGGAGAACGAGAGGAGGATGGGAGCCGTGATCAAGATC
CGATTTTTCAAAATCATGCTGGTTTTAATTATTTGTTGGTTGTCGAATATCATCAATGAAAGCCTTTTATTC
TATCTTGAGATGCAAACAGATATCAATGGAGGTTCTTTGAAACCTGTCAGAACTGCAGCCAAGACCACATGG
TTTATTATGGGAATCCTGAATCCAGCCCAGGGATTTCTCTTGTCTTTGGCCTTCTACGGCTGGACAGGATGC
AGCCTGGGTTTTCAGTCTCCCAGGAAGGAGATCCAGTGGGAATCACTGACCACCTCGGCTGCTGAGGGGGCT
CACCCATCCCCACTGATGCCCCATGAAAACCCTGCTTCCGGGAAGGTGTCTCAAGTGGGTGGGCAGACTTCT
GACGAAGCCCTGAGCATGCTGTCTGAAGGTTCTGATGCCAGCACAATTGAAATTCACACTGCAAGTGAATCC
TGCAACAAAAATGAGGGTGACCCTGCTCTCCCAACCCATGGAGACCTA**TGA**AGGGGATGTGCTGGGGGTCCA
GACCCCATATTCCTCAGACTCAACAATTCTTGTTCTTTAGAACTGTGTTCTCACCTTCCCAACACTGCACTG
CCGAAGTGTAGCGGCCCCCAAACCTTGCTCTCATCACCAGCTAGAGCTTCTTCCCGAAGGGCCTTTAGGATA
GGAGAAAGGGTTCATGCACACACGTGTGAGAATGGAAGAGCCCCCTCCAGACCACTCTACAGCTGCTCTAGC
CTTAGTTGCCACTAGGAAGTTTTCTGAGGCTGGCTGTAAAGTAAGTGTAAGGTCCACATCCTTGGGGAAGTA
GTTAAATAAAATAGTTATGACTG

Table 2B. Encoded ocular albinism 1/G-protein-coupled receptor 143 protein sequence (SEQ ID NO:5).

MTQAGRRGPGTPEPRPRTQPMASPRLGTFCCPTRDAATQLVLSFQPRAFHALCLGSGGLRLALGLLQLLPG
RRPAGPGSPATSPPASVRILRAAAACDLLGCLGMVIRSTVWLGFPNFVDSVSDMNHTEIWPAAFCVGSAMW
IQLLYSACFWWLFCYAVDAYLVIRRSAGLSTILLYHIMAWGLATLLCVEGAAMLYYPSVSRCERGLDHAIP
HYVTMYLPLLLVLVANPILFQKTVTAVASLLKGRQGIYTENERRMGAVIKIRFFKIMLVLIICWLSNIINE
SLLFYLEMQTDINGGSLKPVRTAAKTTWFIMGILNPAQGFLLSLAFYGWTGCSLGFQSPRKEIQWESLTTS
AAEGAHPSPLMPHENPASGKVSQVGGQTSDEALSMLSEGSDASTIEIHTASESCNKNEGDPALPTHGDL

TSC3: Silver/gp100/pMel17.

U01874.1 and NM_006928.1/2 (1/2 are identical nucleic acid sequences) and 3 encode the protein sequence shown in Table 3D.

Table 3A. silver/gp100/pMel17 (U01874.1) nucleotide sequence (SEQ ID NO:6).

CTCGAG**ATG**GATCTGGTGCTAAAAAGATGCCTTCTTCATTTGGCTGTGATAGGTGCTTTGCTGGCTGTGGGG
GCTACAAAAGTACCCAGAAACCAGGACTGGCTTGGTGTCTCAAGGCAACTCAGAACCAAAGCCTGGAACAGG
CAGCTGTATCCAGAGTGGACAGAAGCCCAGAGACTTGACTGCTGGAGAGGTGGTCAAGTGTCCCTCAAGGTC
AGTAATGATGGGCCTACACTGATTGGTGCAAATGCCTCCTTCTCTATTGCCTTGAACTTCCCTGGAAGCCAA
AAGGTATTGCCAGATGGGCAGGTTATCTGGGTCAACAATACCATCATCAATGGGAGCCAGGTGTGGGGAGGA
CAGCCAGTGTATCCCCAGGAAACTGACGATGCCTGCATCTTCCCTGATGGTGGACCTTGCCCATCTGGCTCT
TGGTCTCAGAAGAGAAGCTTTGTTTATGTCTGGAAGACCTGGGGCCAATACTGGCAAGTTCTAGGGGGCCCA
GTGTCTGGGCTGAGCATTGGGACAGGCAGGGCAATGCTGGGCACACACACCATGGAAGTGACTGTCTACCAT
CGCCGGGGATCCCGGAGCTATGTGCCTCTTGCTCATTCCAGCTCAGCCTTCACCATTACTGACCAGGTGCCT
TTCTCCGTGAGCGTGTCCCAGTTGCGGGCCTTGGATGGAGGGAACAAGCACTTCCTGAGAAATCAGCCTCTG
ACCTTTGCCCTCCAGCTCCATGACCCCAGTGGCTATCTGGCTGAAGCTGACCTCTCCTACACCTGGGACTTT
GGAGACAGTAGTGGAACCCTGATCTCTCGGGCACTTGTGGTCACTCATACTTACCTGGAGCCTGGCCCAGTC
ACTGCCCAGGTGGTCCTGCAGGCTGCCATTCCTCTCACCTCCTGTGGCTCCTCCCCAGTTCCAGGCACCACA
GATGGGCACAGGCCAACTGCAGAGGCCCCTAACACCACAGCTGGCCAAGTGCCTACTACAGAAGTTGTGGGT
ACTACACCTGGTCAGGCGCCAACTGCAGAGCCCTCTGGAACCACATCTGTGCAGGTGCCAACCACTGAAGTC
ATAAGCACTGCACCTGTGCAGATGCCAACTGCAGAGAGCACAGGTATGACACCTGAGAAGGTGCCAGTTTCA
GAGGTCATGGGTACCACACTGGCAGAGATGTCAACTCCAGAGGCTACAGGTATGACACCTGCAGAGGTATCA
ATTGTGGTGCTTTCTGGAACCACAGCTGCACAGGTAACAACTACAGAGTGGGTGGAGACCACAGCTAGAGAG
CTACCTATCCCTGAGCCTGAAGGTCCAGATGCCAGCTCAATCATGTCTACGGAAAGTATTACAGGTTCCCTG
GGCCCCCTGCTGGATGGTACAGCCACCTTAAGGCTGGTGAAGAGACAAGTCCCCCTGGATTGTGTTCTGTAT
CGATATGGTTCCTTTTCCGTCACCCTGGACATTGTCCAGGGTATTGAAAGTGCCGAGATCCTGCAGGCTGTG
CCGTCCGGTGAGGGGGATGCATTTGAGCTGACTGTGTCCTGCCAAGGCGGGCTGCCCAAGGAAGCCTGCATG
GAGATCTCATCGCCAGGGTGCCAGCCCCCTGCCCAGCGGCTGTGCCAGCCTGTGCTACCCAGCCCAGCCTGC
CAGCTGGTTCTGCACCAGATACTGAAGGGTGGCTCGGGGACATACTGCCTCAATGTGTCTCTGGCTGATACC
AACAGCCTGGCAGTGGTCAGCACCCAGCTTATCATGCCTGGTCAAGAAGCAGGGGGCCTTGGGCAGGTTCCG
CTGATCGTGGGCATCTTGCTGGTGTTGATGGCTGTGGTCCTTGCATCTCTGATATATAGGCGCAGACTTATG
AAGCAAGACTTCTCCGTACCCCAGTTGCCACATAGCAGCAGTCACTGGCTGCGTCTACCCCGCATCTTCTGC
TCTTGTCCCATTGGTGAGAATAGCCCCCTCCTCAGTGGGCAGCAGGTC**TGA**GTACTCTCATATGATGCTGTG
ATTGCGGCCG

Table 3B. silver/gp100/pMel17 (NM_006928.1 and .2) nucleotide sequence (SEQ ID NO:7).

ATGGATCTGGTGCTAAAAAGATGCCTTCTTCATTTGGCTGTGATAGGTGCTTTGCTGGCTGTGGGGGCTACA
AAAGTACCCAGAAACCAGGACTGGCTTGGTGTCTCAAGGCAACTCAGAACCAAAGCCTGGAACAGGCAGCTG
TATCCAGAGTGGACAGAAGCCCAGAGACTTGACTGCTGGAGAGGTGGTCAAGTGTCCCTCAAGGTCAGTAAT
GATGGGCCTACACTGATTGGTGCAAATGCCTCCTTCTCTATTGCCTTGAACTTCCCTGGAAGCCAAAAGGTA
TTGCCAGATGGGCAGGTTATCTGGGTCAACAATACCATCATCAATGGTAGCCAGGTGTGGGGAGGACAGCCA
GTGTATCCCCAGGAAACTGACGATGCCTGCATCTTCCCTGATGGTGGACCTTGCCCATCTGGCTCTTGGTCT
CAGAAGAGAAGCTTTGTTTATGTCTGGAAGACCTGGGGTCAATACTGGCAAGTTCTAGGGGGCCCAGTGTCT
GGGCTGAGCATTGGGACAGGCAGGGCAATGCTGGGCACACACACCATGGAAGTGACTGTCTACCATCGCCGG
GGATCCCGGAGCTATGTGCCTCTTGCTCATTCCAGCTCAGCCTTCACCATTACTGACCAGGTGCCTTTCTCC
GTGAGCGTGTCCCAGTTGCGGGCCTTGGATGGAGGGAACAAGCACTTCCTGAGAAATCAGCCTCTGACCTTT
GCCCTCCAGCTCCATGACCCCAGTGGCTATCTGGCTGAAGCTGACCTCTCCTACACCTGGGACTTTGGAGAC
AGTAGTGGAACCCTGATCTCTCGGGCACTTGTGGTCACTCATACTTACCTGGAGCCTGGCCCAGTCACTGCC
CAGGTGGTCCTGCAGGCTGCCATTCCTCTCACCTCCTGTGGCTCCTCCCCAGTTCCAGGCACCACAGATGGG
CACAGGCCAACTGCAGAGGCCCCTAACACCACAGCTGGCCAAGTGCCTACTACAGAAGTTGTGGGTACTACA
CCTGGTCAGGCGCCAACTGCAGAGCCCTCTGGAACCACATCTGTGCAGGTGCCAACCACTGAAGTCATAAGC
ACTGCACCTGTGCAGATGCCAACTGCAGAGAGCACAGGTATGACACCTGAGAAGGTGCCAGTTTCAGAGGTC

ATGGGTAGCACACTGGCAGAGATGTCAACTCCAGAGGCTACAGGTATGACACCTGCAGAGGTATCAATTGTG
GTGCTTTCTGGAACCACAGCTGCACAGGTAACAACTACAGAGTGGGTGGAGACCACAGCTAGAGAGCTACCT
ATCCCTGAGCCTGAAGGTCCAGATGCCAGCTCAATCATGTCTACGGAAAGTATTACAGGTTCCCTGGGCCCC
CTGCTGGATGGTACAGCCACCTTAAGGCTGGTGAAGAGACAAGTCCCCCTGGATTGTGTTCTGTATCGATAT
GGTTCCTTTTCCGTCACCCTGGACATTGTCCAGGGTATTGAAAGTGCCGAGATCCTGCAGGCTGTGCCGTCC
GGTGAGGGGGATGCATTTGAGCTGACTGTGTCCTGCCAAGGCGGGCTGCCCAAGGAAGCCTGCATGGAGATC
TCATCGCCAGGGTGCCAGCCCCCTGCCCAGCGGCTGTGCCAGCCTGTGCTACCCAGCCCAGCCTGCCAGCTG
GTTCTGCACCAGATACTGAAGGGTGGCTCGGGGACATACTGCCTCAATGTGTCTCTGGCTGATACCAACAGC
CTGGCAGTGGTCAGCACCCAGCTTATCATGCCTGGTCAAGAAGCAGGCCTTGGGCAGGTTCCGCTGATCGTG
GGCATCTTGCTGGTGTTGATGGCTGTGGTCCTTGCATCTCTGATATATAGGCGCAGACTTATGAAGCAAGAC
TTCTCCGTACCCCAGTTGCCACATAGCAGCAGTCACTGGCTGCGTCTACCCCGCATCTTCTGCTCTTGTCCC
ATTGGTGAGAATAGCCCCCTCCTCAGTGGGCAGCAGGTC**TGA**

Table 3C. silver/gp100/pMel17 (NM_006928.3) nucleotide sequence (SEQ ID NO:8).

AGTGCCTTTGGTTGCTGGAGGGAAGAACACA**ATG**GATCTGGTGCTAAAAAGATGCCTTCTTCATTTGGCTGT
GATAGGTGCTTTGCTGGCTGTGGGGGCTACAAAAGTACCCAGAAACCAGGACTGGCTTGGTGTCTCAAGGCA
ACTCAGAACCAAAGCCTGGAACAGGCAGCTGTATCCAGAGTGGACAGAAGCCCAGAGACTTGACTGCTGGAG
AGGTGGTCAAGTGTCCCTCAAGGTCAGTAATGATGGGCCTACACTGATTGGTGCAAATGCCTCCTTCTCTAT
TGCCTTGAACTTCCCTGGAAGCCAAAAGGTATTGCCAGATGGGCAGGTTATCTGGGTCAACAATACCATCAT
CAATGGGAGCCAGGTGTGGGGAGGACAGCCAGTGTATCCCCAGGAAACTGACGATGCCTGCATCTTCCCTGA
TGGTGGACCTTGCCCATCTGGCTCTTGGTCTCAGAAGAGAAGCTTTGTTTATGTCTGGAAGACCTGGGGCCA
ATACTGGCAAGTTCTAGGGGGCCCAGTGTCTGGGCTGAGCATTGGGACAGGCAGGGCAATGCTGGGCACACA
CACCATGGAAGTGACTGTCTACCATCGCCGGGGATCCCGGAGCTATGTGCCTCTTGCTCATTCCAGCTCAGC
CTTCACCATTACTGACCAGGTGCCTTTCTCCGTGAGCGTGTCCCAGTTGCGGGCCTTGGATGGAGGGAACAA
GCACTTCCTGAGAAATCAGCCTCTGACCTTTGCCCTCCAGCTCCATGACCCCAGTGGCTATCTGGCTGAAGC
TGACCTCTCCTACACCTGGGACTTTGGAGACAGTAGTGGAACCCTGATCTCTCGGGCACTTGTGGTCACTCA
TACTTACCTGGAGCCTGGCCCAGTCACTGCCCAGGTGGTCCTGCAGGCTGCCATTCCTCTCACCTCCTGTGG
CTCCTCCCCAGTTCCAGGCACCACAGATGGGCACAGGCCAACTGCAGAGGCCCCTAACACCACAGCTGGCCA
AGTGCCTACTACAGAAGTTGTGGGTACTACACCTGGTCAGGCGCCAACTGCAGAGCCCTCTGGAACCACATC
TGTGCAGGTGCCAACCACTGAAGTCATAAGCACTGCACCTGTGCAGATGCCAACTGCAGAGAGCACAGGTAT
GACACCTGAGAAGGTGCCAGTTTCAGAGGTCATGGGTACCACACTGGCAGAGATGTCAACTCCAGAGGCTAC
AGGTATGACACCTGCAGAGGTATCAATTGTGGTGCTTTCTGGAACCACAGCTGCACAGGTAACAACTACAGA
GTGGGTGGAGACCACAGCTAGAGAGCTACCTATCCCTGAGCCTGAAGGTCCAGATGCCAGCTCAATCATGTC
TACGGAAAGTATTACAGGTTCCCTGGGCCCCCTGCTGGATGGTACAGCCACCTTAAGGCTGGTGAAGAGACA
AGTCCCCCTGGATTGTGTTCTGTATCGATATGGTTCCTTTTCCGTCACCCTGGACATTGTCCAGGGTATTGA
AAGTGCCGAGATCCTGCAGGCTGTGCCGTCCGGTGAGGGGGATGCATTTGAGCTGACTGTGTCCTGCCAAGG
CGGGCTGCCCAAGGAAGCCTGCATGGAGATCTCATCGCCAGGGTGCCAGCCCCCTGCCCAGCGGCTGTGCCA
GCCTGTGCTACCCAGCCCAGCCTGCCAGCTGGTTCTGCACCAGATACTGAAGGGTGGCTCGGGGACATACTG
CCTCAATGTGTCTCTGGCTGATACCAACAGCCTGGCAGTGGTCAGCACCCAGCTTATCATGCCTGGTCAAGA
AGCAGGCCTTGGGCAGGTTCCGCTGATCGTGGGCATCTTGCTGGTGTTGATGGCTGTGGTCCTTGCATCTCT
GATATATAGGCGCAGACTTATGAAGCAAGACTTCTCCGTACCCCAGTTGCCACATAGCAGCAGTCACTGGCT
GCGTCTACCCCGCATCTTCTGCTCTTGTCCCATTGGTGAGAATAGCCCCCTCCTCAGTGGGCAGCAGGTC**TG**
AGTACTCTCATATGATGCTGTGATTTTCCTGGAGTTGACAGAAACACCTATATTTCCCCCAGTCTTCCCTGG
GAGACTACTATTAACTGAAATAAATACTCAGAGCCTGAAAAAAAAAAAAAAAAAA

Table 3D. Encoded silver/gp100/pMel17 protein sequence (SEQ ID NO:9).

MDLVLKRCLLHLAVIGALLAVGATKVPRNQDWLGVSRQLRTKAWNRQLYPEWTEAQRLDCWRGGQVSLKVS
NDGPTLIGANASFSIALNFPGSQKVLPDGQVIWVNNTIINGSQVWGGQPVYPQETDDACIFPDGGPCPSGS
WSQKRSFVYVWKTWGQYWQVLGGPVSGLSIGTGRAMLGTHTMEVTVYHRRGSRSYVPLAHSSSAFTITDQV
PFSVSVSQLRALDGGNKHFLRNQPLTFALQLHDPSGYLAEADLSYTWDFGDSSGTLISRALVVTHTYLEPG
PVTAQVVLQAAIPLTSCGSSPVPGTTDGHRPTAEAPNTTAGQVPTTEVVGTTPGQAPTAEPSGTTSVQVPT
TEVISTAPVQMPTAESTGMTPEKVPVSEVMGTTLAEMSTPEATGMTPAEVSIVVLSGTTAAQVTTTEWVET
TARELPIPEPEGPDASSIMSTESITGSLGPLLDGTATLRLVKRQVPLDCVLYRYGSFSVTLDIVQGIESAE
ILQAVPSGEGDAFELTVSCQGGLPKEACMEISSPGCQPPAQRLCQPVLPSPACQLVLHQILKGGSGTYCLN
VSLADTNSLAVVSTQLIMPGQEAGGLGQVPLIVGILLVLMAVVLASLIYRRRLMKQDFSVPQLPHSSSHWL
RLPRIFCSCPIGENSPLLSGQQV

TSC4: Gremlin 1 homolog, cysteine knot superfamily (Xenopus laevis).

AF154054.1, AF110137.2 and AF045800.1 encode the protein sequence shown in Table 4D.

Table 4A. gremlin 1 homolog, cysteine knot superfamily (Xenopus laevis) (AF154054.1) nucleotide sequence (SEQ ID NO:10).

ATAATAATTAGGCCAAGCGTTGAATAGTACGGGGGGGGGGGGGGGCGAGCCCCGGCGGCTCTGGCCGCGGC
CGCACTCAGCGCCACGCGTCGAAAGCGCAGGCCCCGAGGACCCGCCGCACTGACAGT**ATG**AGCCGCACAGCC
TACACGGTGGGAGCCCTGCTTCTCCTCTTGGGGACCCTGCTGCCGGCTGCTGAAGGGAAAAAGAAAGGGTCC
CAAGGTGCCATCCCCCCGCCAGACAAGGCCCAGCACAATGACTCAGAGCAGACTCAGTCGCCCCAGCAGCCT
GGCTCCAGGAACCGGGGGCGGGGCCAAGGGCGGGGCACTGCCATGCCCGGGGAGGAGGTGCTGGAGTCCAGC
CAAGAGGCCCTGCATGTGACGGAGCGCAAATACCTGAAGCGAGACTGGTGCAAAACCCAGCCGCTTAAGCAG
ACCATCCACGAGGAAGGCTGCAACAGTCGCACCATCATCAACCGCTTCTGTTACGGCCAGTGCAACTCTTTC
TACATCCCCAGGCACATCCGGAAGGAGGAAGGTTCCTTTCAGTCCTGCTCCTTCTGCAAGCCCAAGAAATTC
ACTACCATGATGGTCACACTCAACTGCCCTGAACTACAGCCACCTACCAAGAAGAAGAGAGTCACACGTGTG
AAGCAGTGTCGTTGCATATCCATCGATTTGGAT**TAA**GCCAAATCCAGGTGCACCCAGCATGTCCTAGGAATG
CAGACCCAGGAAGTCCCAGACCTAAAACAACCAGATTCTTACTTGGCTTAAACCTAGAGGCCAGAAGAACCC
CCAGCTGCCTCCTGGCAGGAGCCTGCTTGTGCGTAGTTCGTGTGCATGAGTGTGGATGGGTGCCTGTGGGTG
TTTTTAGACACCAGAGAAAACACAGTCTCTGCTAGAGAGCACTTCCTATTTTGTAAACCTATCTGCTTTAAT
GGGGATGTACCAGAAACCCACCTCACCCCGGCTCACATCTAAAGGGGCGGGGCCGTGGTCTGGTTCTGACTT
TGTGTTTTTGTGCCCTCCTGGGGACCAGAATCTCCTTTCGGAATGAATGTTCATGGAAGAGGCTCCTCTGAG
GGCAAGAGACCTGTTTTAGTGCTGCATTCGACATGGAAAAGTCCTTTTAACCTGTGCTTGCATCCTCCTTTC
CTCCTCCTCCTCACAATCCATCTCTTCTTAAGTTGACAGTGACTATGTCAGTCTAATCTCTTGTTTGCCAGG
GTTCCTAAATTAATTCACTTAACCATGATGCAAATGTTTTTCATTTGGTGAAGACCTCCAGACTCTGGGAGA
GGCTGGTGTGGGCAAGGACAAGCAGGATAGTGGAGTGAGAAAGGGAGGGTGGAGGGTGAGGCCAAATCAGGT
CCAGCAAAAGTCAGTAGGGACATTGCAGAAGCTTGAAAGGCCAATACCAGAACACAGGCTGATGCTTCTGAG
AAAGTCTTTTCCTAGTATTTAACAAAACCCAAGTGAACAGAGGAGAAATGAGATTGCCAGAAAGTGATTAAC
TTTGGCCGTTGCAATCTGCTCAAACCTAACACCAAACTGAAAACATAAATACTGACCACTCCTATGTTCGGA
CCCAAGCAAGTTAGCTAAACCAAACCAACTCCTCTGCTTTGTCCCTCAGGTGGAAAAGAGAGGTAGTTTAGA
ACTCTCTGCATAGGGGTGGGAATTAATCAAAAACCTCAGAGGCTGAAATTCCTAATACCTTTCCTTTATCGT
GGTTATAGTCAGCTCATTTCCATTCCACTATTTCCCATAATGCTTCTGAGAGCCACTAACTTGATTGATAAA
GATCCTGCCTCTGCTGAGTGTACCTGACAGTAGTCTAAGATGAGAGAGTTTAGGGACTACTCTGTTTTAACA
AGAAATATTTTGGGGGTCTTTTTGTTTTAACTATTGTCAGGAGATTGGGCTAAAGAGAAGACGACGAGAGTA
AGGAAATAAAGGGAATTGCCTCTGGCTAGAGAGTAGTTAGGTGTTAATACCTGGTAGAGATGTAAGGGATAT
GACCTCCCTTTCTTTATGTGCTCACTTGAGGATCTGAGGGGACCCTGTTAGGAGAGCATAGCATCATGATGT
ATTAGCTGTTCATCTGCTACTGGTTGGATGGACATAACTATTGTAACTATTCAGTATTTACTGGTAGGCACT
GTCCTCTGATTAAACTTGGCCTACTGGCAATGGCTACTTAGGATTGATCTAAGGGCCAAAGTGCAGGGTGGG
TGAACTTTATTGTACTTTGGATTTGGTTAACCTGTTTTCCTCAAGCCTGAGGTTTTATATACAAACTCCCTG
AATACTCTTTTTGCCTTGTTACTTCTCAGCCTCCTAGCCAAGTCCTATGTAATATGGAAAACAAACACTGCA
GACTTGAGATTCAGTTGCCGATCAAGGCTCTGGCATTCAGAGAACCCTTGCAACTCGAGAAGCTGTTTTTGA
TTTCGTTTTTGTTTTGAACCGGTGCTCTCCCATCTAACAACTAACAAGGACCATTTCCAGGCGGGAGATATT
TTAAACACCCAAAATGTTGGGTCTGATTTCCAAACTTTTAAACTCACTACTGATGATTCTCACGCTAGGCGA
ATTTGTCCAAACACATAGTGTGTGTGTTTTGTATACACTGTATGACCCCACCCCAAATCTTTGTATTGTCCA
CATTCTCCAACAATAAAGCACAGAGTGGATTTAATTAAGCACACAAATGCTAAGGCAGAATTTTGAGGGTGG
GAGAGAAGAAAAGGGAAAGAAGCTGAAAATGTAAAACCACACCAGGGAGGAAAAATGACATTCAGAACCACC
AAACACTGAATTTCTCTTGTTGTTTTAACTCTCCCACAAGAATGCAATTTCGTTAATGGAGATGACTTAAGT
TGGCAGCAGTAATCTTCTTTTAGGAGCTTGTACCACAGTCTTGCACATAAGTGCAGATTTGCCCCAAGTAAA
GAGAATTTCCTCAACACTAACTTCACGGGGATAATCACCACGTAACTACCCTTAAAGCATATCACTAGCCAA
AGAGGGGAATATCTGTTCTTCTTACTGTGCCTATATTAAGACTAGTACAAATGTGGTGTGTCTTCCAACTTT
CATTGAAAATGCCATATCTATACCATATTTTATTCGAGTCACTGATGATGTAATGATATATTTTTTCATTAT
TATAGTAGAATATTTTTATGGCAAGAGATTTGTGGTCTTGATCATACCTATTAAAATAATGCCAAACACCAA
ATATGAATTTTATGATGTACACTTTGTGCTTGGCATTAAAAGAAAAAAACACACACGCC

Table 4B. gremlin 1 homolog, cysteine knot superfamily (Xenopus laevis) (AF110137.2) nucleotide sequence (SEQ ID NO:11).

GCGGCCGCACTCAGCGCCACGCGTCGAAAGCGCAGGCCCCGAGGACCCGCCGCACTGACAGT**ATG**AGCCGCA
CAGCCTACACGGTGGGAGCCCTGCTTCTCCTCTTGGGGACCCTGCTGCCGGCTGCTGAAGGGAAAAAGAAAG
GGTCCCAAGGTGCCATCCCCCCGCCAGACAAGGCCCAGCACAATGACTCAGAGCAGACTCAGTCGCCCCAGC
AGCCTGGCTCCAGGAACCGGGGGCGGGGCCAAGGGCGGGGCACTGCCATGCCCGGGGAGGAGGTGCTGGAGT
CCAGCCAAGAGGCCCTGCATGTGACGGAGCGCAAATACCTGAAGCGAGACTGGTGCAAAACCCAGCCGCTTA
AGCAGACCATCCACGAGGAAGGCTGCAACAGTCGCACCATCATCAACCGCTTCTGTTACGGCCAGTGCAACT
CTTTCTACATCCCCAGGCACATCCGGAAGGAGGAAGGTTCCTTTCAGTCCTGCTCCTTCTGCAAGCCCAAGA
AATTCACTACCATGATGGTCACACTCAACTGCCCTGAACTACAGCCACCTACCAAGAAGAAGAGAGTCACAC
GTGTGAAGCAGTGTCGTTGCATATCCATCGATTTGGAT**TAA**GCCAAATCCAGGTGCACCCAGCATGTCCTAG
GAATGCAGCCCCAGGAAGTCCCAGACCTAAAACAACCAGATTCTTACTTGGCTTAAACCTAGAGGCCAGAAG
AACCCCCAGCTGCCTCCTGGCAGGAGCCTGCTTGTGCGTAGTTCGTGTGCATGAGTGTGGATGGGTGCCTGT
GGGTGTTTTTAGACACCAGAGAAAACACAGTCTCTGCTAGAGAGCACTCCCTATTTTGTAAACATATCTGCT
TTAATGGGGATGTACCAGAAACCCACCTCACCCCGGCTCACATCTAAAGGGGCGGGGCCGTGGTCTGGTTCT
GACTTTGTGTTTTTGTGCCCTCCTGGGGACCAGAATCTCCTTTCGGAATGAATGTTCATGGAAGAGGCTCCT
CTGAGGGCAAGAGACCTGTTTTAGTGCTGCATTCGACATGGAAAAGTCCTTTTAACCTGTGCTTGCATCCTC
CTTTCCTCCTCCTCCTCACAATCCATCTCTTCTTAAGTTGATAGTGACTATGTCAGTCTAATCTCTTGTTTG
CCAAGGTTCCTAAATTAATTCACTTAACCATGATGCAAATGTTTTTCATTTTGTGAAGACCCTCCAGACTCT
GGGAGAGGCTGGTGTGGGCAAGGACAAGCAGGATAGTGGAGTGAGAAAGGGAGGGTGGAGGGTGAGGCCAAA
TCAGGTCCAGCAAAAGTCAGTAGGGACATTGCAGAAGCTTGAAAGGCCAATACCAGAACACAGGCTGATGCT
TCTGAGAAAGTCTTTTCCTAGTATTTAACAGAACCCAAGTGAACAGAGGAGAAATGAGATTGCCAGAAAGTG
ATTAACTTTGGCCGTTGCAATCTGCTCAAACCTAACACCAAACTGAAAACATAAATACTGACCACTCCTATG
TTCGGACCCAAGCAAGTTAGCTAAACCAAACCAACTCCTCTGCTTTGTCCCTCAGGTGGAAAAGAGAGGTAG
TTTAGAACTCTCTGCATAGGGGTGGGAATTAATCAAAAACCKCAGAGGCTGAAATTCCTAATACCTTTCCTT
TATCGTGGTTATAGTCAGCTCATTTCCATTCCACTATTTCCCATAATGCTTCTGAGAGCCACTAACTTGATT
GATAAAGATCCTGCCTCTGCTGAGTGTACCTGACAGTAAGTCTAAAGATGARAGAGTTTAGGGACTACTCTG
TTTTAGCAAGARATATTKTGGGGGTCTTTTTGTTTTAACTATTGTCAGGAGATTGGGCTARAGAGAAGACGA
CGAGAGTAAGGAAATAAAGGGRATTGCCTCTGGCTAGAGAGTAAGTTAGGTGTTAATACCTGGTAGAAATGT
AAGGGATATGACCTCCCTTTCTTTATGTGCTCACTGAGGATCTGAGGGGACCCTGTTAGGAGAGCATAGCAT
CATGATGTATTAGCTGTTCATCTGCTACTGGTTGGATGGACATAACTATTGTAACTATTCAGTATTTACTGG
TAGGCACTGTCCTCTGATTAAACTTGGCCTACTGGCAATGGCTACTTAGGATTGATCTAAGGGCCAAAGTGC
AGGGTGGGTGAACTTTATTGTACTTTGGATTTGGTTAACCTGTTTTCTTCAAGCCTGAGGTTTTATATACAA
ACTCCCTGAATACTCTTTTTGCCTTGTATCTTCTCAGCCTCCTAGCCAAGTCCTATGTAATATGGAAAACAA
ACACTGCAGACTTGAGATTCAGTTGCCGATCAAGGCTCTGGCATTCAGAGAACCCTTGCAACTCGAGAAGCT
GTTTTTATTTCGTTTTTGTTTTGATCCAGTGCTCTCCCATCTAACAACTAAACAGGAGCCATTTCAAGGCGG
GAGATATTTTAAACACCCAAAATGTTGGGTCTGATTTTCAAACTTTTAAACTCACTACTGATGATTCTCACG
CTAGGCGAATTTGTCCAAACACATAGTGTGTGTGTTTTGTATACACTGTATGACCCCACCCCAAATCTTTGT
ATTGTCCACATTCTCCAACAATAAAGCACAGAGTGGATTTAATTAAGCACACAAATGCTAAGGCAGAATTTT
GAGGGTGGGAGAGAAGAAAAGGGAAAGAAGCTGAAAATGTAAAACCACACCAGGGAGGAAAAATGACATTCA
GAACCAGCAAACACTGAATTTCTCTTGTTGTTTTAACTCTGCCACAAGAATGCAATTTCGTTAATGGAGATG
ACTTAAGTTGGCAGCAGTAATCTTCTTTTAGGAGCTTGTACCACAGTCTTGCACATAAGTGCAGATTTGGCT
CAAGTAAAGAGAATTTCCTCAACACTAACTTCACTGGGATAATCAGCAGCGTAACTACCCTAAAAGCATATC
ACTAGCCAAAGAGGGAAATATCTGTTCTTCTTACTGTGCCTATATTAAGACTAGTACAAATGTGGTGTGTCT
TCCAACTTTCATTGAAAATGCCATATCTATACCATATTTTATTCGAGTCACTGATGATGTAATGATATATTT
TTTCATTATTATAGTAGAATATTTTTATGGCAAGATATTTGTGGTCTTGATCATACCTATTAAAATAATGCC
AAACACCAAATATGAATTTTATGATGTACACTTTGTGCTTGGCATTAAAAGAAAAAAACACACATCCTGGAA
GTCTGTAAGTTGTTTTTTGTTACTGTAGGTCTTCAAAGTTAAGAGTGTAAGTGAAAAATCTGGAGGAGAGGA
TAATTTCCACTGTGTGGAATGTGAATAGTTAAATGAAAAGTTATGGTTATTTAATGTAATTATTACTTCAAA
TCCTTTGGTCACTGTGATTTCAAGCATGTTTTCTTTTTCTCCTTTATATGACTTTCTCTGAGTTGGGCAAAG
AAGAAGCTGACACACCGTATGTTGTTAGAGTCTTTTATCTGGTCAGGGGAAACAAAATCTTGACCCAGCTGA
ACATGTCTTCCTGAGTCAGTGCCTGAATCTTTATTTTTTAAATTGAATGTTCCTTAAAGGTTAACATTTCTA
AAGCAATATTAAGAAAGACTTTAAATGTTATTTTGGAAGACTTACGATGCATGTATACAAACGAATAGCAGA
TAATGATGACTAGTTCACACATAAAGTCCTTTTAAGGAGAAAATCTAAAATGAAAAGTGGATAAACAGAACA
TTTATAAGTGATCAGTTAATGCCTAAGAGTGAAAGTAGTTCTATTGACATTCCTCAAGATATTTAATATCAA
CTGCATTATGTATTATGTCTGCTTAAATCATTTAAAAACGGCAAAGAATTATATAGACTATGAGGTACCTTG
CTGTGTAGGAGGATGAAAGGGGAGTTGATAGTCTCATAAAACTAATTTGGCTTCAAGTTTCATGAATCTGTA

ACTAGAATTTAATTTCACCCAATAATGTTCTATATAGCCTTTGCTAAAGAGCAACTAATAAATTAAACCT
ATTCTTTCAAAAAAAAA

Table 4C. gremlin 1 homolog, cysteine knot superfamily (Xenopus laevis) (AF045800.1) nucleotide sequence (SEQ ID NO:12).

ATGAGCCGCACAGCCTACACGGTGGGAGCCCTGCTTCTCCTCTTGGGGACCCTGCTGCCGGCTGCTGAAGGG
AAAAAGAAAGGGTCCCAAGGTGCCATCCCCCCGCCAGACAAGGCCCAGCACAATGACTCAGAGCAGACTCAG
TCGCCCCAGCAGCCTGGCTCCAGGAACCGGGGGCGGGGCCAAGGGCGGGGCACTGCCATGCCCGGGGAGGAG
GTGCTGGAGTCCAGCCAAGAGGCCCTGCATGTGACGGAGCGCAAATACCTGAAGCGAGACTGGTGCAAAACC
CAGCCGCTTAAGCAGACCATCCACGAGGAAGGCTGCAACAGTCGCACCATCATCAACCGCTTCTGTTACGGC
CAGTGCAACTCTTTCTACATCCCCAGGCACATCCGGAAGGAGGAAGGTTCCTTTCAGTCCTGCTCCTTCTGC
AAGCCCAAGAAATTCACTACCATGATGGTCACACTCAACTGCCCTGAACTACAGCCACCTACCAAGAAGAAG
AGAGTCACACGTGTGAAGCAGTGTCGTTGCATATCCATCGATTTGGAT**TAA**

Table 4D. Encoded gremlin 1 homolog, cysteine knot superfamily (Xenopus laevis) protein sequence (SEQ ID NO:13).

MSRTAYTVGALLLLLGTLLPAAEGKKKGSQGAIPPPDKAQHNDSEQTQSPQQPGSRNRGRGQGRGTAMPGE
EVLESSQEALHVTERKYLKRDWCKTQPLKQTIHEEGCNSRTIINRFCYGQCNSFYIPRHIRKEEGSFQSCS
FCKPKKFTTMMVTLNCPELQPPTKKKRVTRVKQCRCISIDLD

TSC5: ATP-binding cassette, sub-family B (MDR/TAP), member 5.

AL040763 does not possess a reading frame beyond 50 amino acids.

Table 5A. ATP-binding cassette, sub-family B (MDR/TAP), member 5 (AL040763) nucleotide sequence (SEQ ID NO:14).

TCCCCCATAATTATGCCACATAGCTGTTATTATTTTCATATATTGCCTTCATTTTTTTCACAGTTGCTATTT
TGTGTAATTTTGGAATCAGTTTACAAACATTCTGCATTCTTCTTTTTTCACTTTTGATAGATGTTTCATATT
AACCAATAAGAATAACATTTATTAGTTTATCATGTCACCAAGCAACTATTTATTTTAAAAGTCTGAACTAGT
TTTGATTACCTAAAGTGATTACCAGTGGATGAAAATACTGCGGGCACAACATGAAACCTTCTAAACAATCAG
AGAGCCTATTACAATACATTTTTTAAAATCTTATGTAACTGGCCGGGCGCGGAGACGCACACCTGTAATCCC
AGCACTTTGGGAGGCCGAGGTGGGCGGATCACCTGAGGTCAGGAGTTTGAGACCAGCCTGGTCAACATGGCA
AAACCCCGTCTCTACTAAAAATACAAAAATTAGCCGGGTGTGGTGATGCACGCCTGTACTCCCAGCTACTCA
GGAGGCTGAGGCAGGAGAATCGCCTGAACACAGTGGGCAGAGGTTGCACTCAAGCATGGGTGACAGAGCGAG
GCTTGAATATAGTCTAAATACAGATCCCTGTCCTAGTTACTAAGTATAAAAAATGAATAAAATATTAGTCCT
GTCTTTGTATTTTCTGTACCAAGATGAACCAAATTGCCGAAGTGTCCACAGTAAACAAAGATTATTTATCAC
ACAAGC

TSC6: 5-hydroxytryptamine (serotonin) receptor 2B.

Table 6A. 5-hydroxytryptamine (serotonin) receptor 2B (NM_000867.2) nucleotide sequence (SEQ ID NO:15).

GGGGGTATTTGTTTCACTGCTTTCAACCGCCTGTGCTGGAGGCTCAGAATAAGTCAATGGGAGGAGGATTTC
AGTCACAGCAGCAAGCAAGTCTAGTGAACAGATAAGATGACATGCTCAGCAAAATAACAACGAAACCAGAGG
GGGAACTCTCTGGCATGCAAGTTCAAACACGACTCTACAACTACGGCAGAAAAAGAGAGAGAGAGAAACTAA
AAATATATATATATCCTATTTTTTTCACAGCTATCAGTTTCTTTCACTGAGCTTTCCTAAATTTAAGCCTCT
AGAAAATAATAAATACTTGGATATCTTACCTACAAACATGGACAGATGTGTGTATGCGCTCATTTTAGAGAA
CTTGAATTTTTTTTTTTAAAGGAAGGTGTCAACTTTGGCTTTTGAGTGTTTGGCATGGTTACAATGCCTTAA
AAAAACAGATGAGCAGCTTAGCTACTAACCATGCTGACCACTGTTCGGAACGGGATTGAATCACAGAAAAAC
AGCAA**ATG**GCTCTCTCTTACAGAGTGTCTGAACTTCAAAGCACAATTCCTGAGCACATTTTGCAGAGCACCT
TTGTTCACGTTATCTCTTCTAACTGGTCTGGATTACAGACAGAATCAATACCAGAGGAAATGAAACAGATTG
TTGAGGAACAGGGAAATAAACTGCACTGGGCAGCTCTTCTGATACTCATGGTGATAATACCCACAATTGGTG
GAAATACCCTTGTTATTCTGGCTGTTTCACTGGAGAAGAAGCTGCAGTATGCTACTAATTACTTTCTAATGT
CCTTGGCGGTGGCTGATTTGCTGGTTGGATTGTTTGTGATGCCAATTGCCCTCTTGACAATAATGTTTGAGG
CTATGTGGCCCCTCCCACTTGTTCTATGTCCTGCCTGGTTATTTCTTGACGTTCTCTTTTCAACCGCATCCA
TCATGCATCTCTGTGCCATTTCAGTGGATCGTTACATAGCCATCAAAAAGCCAATCCAGGCCAATCAATATA
ACTCACGGGCTACAGCATTCATCAAGATTACAGTGGTGTGGTTAATTTCAATAGGCATTGCCATTCCAGTCC
CTATTAAAGGGATAGAGACTGATGTGGACAACCCAAACAATATCACTTGTGTGCTGACAAAGGAACGTTTTG
GCGATTTCATGCTCTTTGGCTCACTGGCTGCCTTCTTCACACCTCTTGCAATTATGATTGTCACCTACTTTC
TCACTATCCATGCTTTACAGAAGAAGGCTTACTTAGTCAAAAACAAGCCACCTCAACGCCTAACATGGTTGA
CTGTGTCTACAGTTTTCCAAAGGGATGAAACACCTTGCTCGTCACCGGAAAAGGTGGCAATGCTGGATGGTT
CTCGAAAGGACAAGGCTCTGCCCAACTCAGGTGATGAAACACTTATGCGAAGAACATCCACAATTGGGAAAA
AGTCAGTGCAGACCATTTCCAACGAACAGAGAGCCTCAAAGGTCCTAGGGATTGTGTTTTTCCTCTTTTTGC
TTATGTGGTGTCCCTTCTTTATTACAAATATAACTTTAGTTTTATGTGATTCCTGTAACCAAACTACTCTCC
AAATGCTCCTGGAGATATTTGTGTGGATAGGCTATGTTTCCTCAGGAGTGAATCCTTTGGTCTACACCCTCT
TCAATAAGACATTTCGGGATGCATTTGGCCGATATATCACCTGCAATTACCGGGCCACAAAGTCAGTAAAAA
CTCTCAGAAAACGCTCCAGTAAGATCTACTTCCGGAATCCAATGGCAGAGAACTCTAAGTTTTTCAAGAAAC
ATGGAATTCGAAATGGGATTAACCCTGCCATGTACCAGAGTCCAATGAGGCTCCGAAGTTCAACCATTCAGT
CTTCATCAATCATTCTACTAGATACGCTTCTCCTCACTGAAAATGAAGGTGACAAAACTGAAGAGCGAGTTA
GTTATGTA**TAG**CAGAACTGGCAGTTGTCATCAAACATAATGATGAGTAAGATGATGAATGAGATGTAAATGT
GCCAAGAATATATTATATAAAGAATTTTATGTCATATATCAAATCATCTCTTTAACCTAAGATGTAAGTATT
AAGAATATCTAATTTTCCTAATTTGGACAAGATTATTCCATGAGGAAAATAATTTTATATAGCTACAAATGA
AAACAATCCAGCACTCTGGTTAAATTTTAAGGTATTCGAATGAAATAAAGTCAAATCAATAAATTTCAGGCC
AAAAAAAAAAAAAAAAAAAAAAAAAAA

Table 6B. Encoded 5-hydroxytryptamine (serotonin) receptor 2B protein sequence (SEQ ID NO:16).

MALSYRVSELQSTIPEHILQSTFVHVISSNWSGLQTESIPEEMKQIVEEQGNKLHWAALLILMVIIPTIGG
NTLVILAVSLEKKLQYATNYFLMSLAVADLLVGLFVMPIALLTIMFEAMWPLPLVLCPAWLFLDVLFSTAS
IMHLCAISVDRYIAIKKPIQANQYNSRATAFIKITVVWLISIGIAIPVPIKGIETDVDNPNNITCVLTKER
FGDFMLFGSLAAFFTPLAIMIVTYFLTIHALQKKAYLVKNKPPQRLTWLTVSTVFQRDETPCSSPEKVAML
DGSRKDKALPNSGDETLMRRTSTIGKKSVQTISNEQRASKVLGIVFFLFLLMWCPFFITNITLVLCDSCNQ
TTLQMLLEIFVWIGYVSSGVNPLVYTLFNKTFRDAFGRYITCNYRATKSVKTLRKRSSKIYFRNPMAENSK
FFKKHGIRNGINPAMYQSPMRLRSSTIQSSSIILLDTLLLTENEGDKTEERVSYV

TSC7: Mucolipin 3.

Table 7A. Mucolipin 3 (NM_018298.9) nucleotide sequence (SEQ ID NO:17).

CGGGGCTCGAGGCTGCTGGAGTCGCTCGCTGACTCGCCCTGCGCCCTCGCCGCGGACACCGGAGCTGCGGCC
GCTCCCCGCTGTCCCCCAGAG**ATG**GCAGATCCTGAGGTAGTTGTGAGTAGCTGCAGCTCTCATGAAGAGGAA

AATCGGTGGAATTTTAACCACGAAACATCTCCATCTGAGGAGCTTCTATTAGAAGACCAGATGAGGCGAAAA
CTCAAATTTTTTTTCATGAATCCCTGTGAGAAGTTCTGGGCTCGAGGTAGAAAACCATGGAAACTTGCCATA
CAAATTCTAAAAATTGCAATGGTGACTATCCAGCTGGTCTTATTTGGGCTAAGTAACCAGATGGTGGTAGCT
TTCAAGGAAGAGAATACTATAGCATTCAAACACCTTTTCCTAAAAGGATATATGGACCGAATGGATGACACA
TATGCAGTGTACACACAAAGTGACGTGTATGATCAGTTAATCTTCGCAGTAAACCAGTACTTGCAGCTATAC
AATGTCTCCGTTGGGAATCATGCTTATGAGAACAAAGGTACCAAGCAATCTGCTATGGCAATCTGTCAGCAC
TTCTACAAGCGAGGAAACATCTACCCTGGAAATGATACCTTTGACATCGATCCAGAAATTGAAACTGAGTGT
TTCTTTGTGGAGCCAGATGAACCTTTTCACATTGGGACACCAGCAGAAAATAAACTGAACTTAACACTGGAC
TTCCACAGACTCCTAACAGTGGAGCTTCAGTTTAAACTGAAAGCCATTAATCTGCAGACAGTTCGTCATCAA
GAACTCCCTGACTGTTATGACTTTACTCTGACTATAACATTTGACAACAAGGCCCATAGTGGAAGAATTAAA
ATAAGTTTAGATAATGACATTTCCATCAGAGAATGTAAAGACTGGCATGTATCTGGATCAATTCAGAAGAAC
ACTCATTACATGATGATCTTTGATGCCTTTGTCATTCTGACTTGCTTGGTTTCATTAATCCTCTGCATTAGA
TCTGTGATTAGAGGACTTCAGCTTCAGCAGGAGTTTGTCAATTTTTTCCTCCTCCATTATAAGAAGGAAGTT
TCTGTTTCTGATCAAATGGAATTTGTCAATGGATGGTACATTATGATTATTATTAGTGACATATTGACAATC
ATTGGATCAATTCTAAAAATGGAAATCCAAGCTAAGAGTCTAACTAGTTATGATGTCTGTAGCATACTTCTT
GGGACTTCTACCATGCTCGTGTGGCTTGGAGTCATCCGATACCTCGGTTTCTTTGCAAAGTACAACCTCCTC
ATTTTGACCCTTCAGGCAGCGCTGCCCAATGTCATCAGGTTCTGCTGCTGTGCAGCTATGATTTACTTAGGT
TACTGCTTCTGTGGATGGATCGTGCTGGGGCCTTACCATGACAAGTTTCGTTCTCTGAACATGGTCTCTGAG
TGCCTTTTCTCTCTGATAAATGGAGATGATATGTTTGCCACGTTTGCAAAAATGCAGCAAAAAAGTTACTTA
GTCTGGCTGTTTAGTAGAATTTACCTCTACTCATTCATCAGCCTCTTTATATATATGATTTTAAGTCTTTTC
ATTGCACTGATCACTGATACATACGAAACAATTAAGCAATACCAACAAGATGGCTTCCCAGAGACTGAACTT
CGTACATTTATATCAGAATGCAAAGATCTACCCAACTCTGGAAAATACAGATTAGAAGATGACCCTCCAGTA
TCTTTATTCTGCTGTTGTAAAAAG**TAG**CTATCAGGTTTATCTGTACTTTAGAGGAAAATATAATGTGTAGCT
GAGTTGGAACACTGTGGATATTCTGAGATCAGATGTAGTATGTTTGAAGACTGTTATTTTGAGCTAATTGAG
ACCTATAATTCACCAATAACTGTTTATATTTTTAAAAGCAATATTTAATGTCTTTGCAACTTTATGCTGGGA
TTGTTTTTAAAAAAACTTTAATGAGGAAAGCTATTGGATTATTATTATTTCTTGTTTATTTTGCCATGGCTT
TAGAATGTATTCTGTATGCCTCTCTTTTGCTCTGATACTGTTGCTCCTGCTATTCTGATTGTGCAGACTGTG
TAATTAGTGGAAAACAATCCTTGGTCTGACTGTGACTTTGGACAACTCAGTAACCCTGGCTTGGACCACTCT
CAGGAGTCCATCCTTGAGAGAGTGGGTGTAGTTATCATTTATACAGTAATCATTGCATTTTAAAATCTTCTC
TTGAAAGGAAGAATAAGAGTGCACCAGAATAAGAGCGCACCAGAATAAGAGCGCACCAGCTAACAATGTGAT
ACGGCCATATGTCACTTAAGGATGGAGATATGTTCTGAGAAATGTGTCATTAGGCGATTTTGTCATTAAACA
TCATAGCATGTACTTCCACAAACCTAGATGGTATAGCCTACTACACACCTAGGCTATTTGGTATAGCCTGTT
GGTCCTGGGGTACAAATCTGTACAACATGTTACTGTATTGAATACAGTAGGCAATTGTAACACAATGGTAAG
TATCTAAACATAGAAAAGGGACAGTAAAAATATGGTTTTATAATCTTCTGGGACCACCATTGTATATGCGGT
ACATCATTGACCAAAACATCGTTATCCAGCATATGACTGTATTTGGTTATGAAAGCCAACTGTTACTTGATT
CTGCTTTTAGTTCTTAAGAGGATCAGGCTTTTAAATACTCATTTACAAGTTTTCTATCCTCCTTCAGTGTTA
AAGTAGAAAGTAAAAAGAGTATCTTATACATGCATGAAATTAAAGCATATACCAAATGCAAAAAAAAAAAAA
AAAAA

Table 7B. Encoded mucolipin 3 protein sequence (SEQ ID NO:18).

MADPEVVVSSCSSHEEENRCNFNQQTSPSEELLLEDQMRRKLKFFFMNPCEKFWARGRKPWKLAIQILKIA
MVTIQLVLFGLSNQMVVAFKEENTIAFKHLFLKGYMDRMDDTYAVYTQSDVYDQLIFAVNQYLQLYNVSVG
NHAYENKGTKQSAMAICQHFYKRGNIYPGNDTFDIDPEIETECFFVEPDEPFHIGTPAENKLNLTLDFHRL
LTVELQFKLKAINLQTVRHQELPDCYDFTLTITFDNKAHSGRIKISLDNDISIRECKDWHVSGSIQKNTHY
MMIFDAFVILTCLVSLILCIRSVIRGLQLQQEFVNFFLLHYKKEVSVSDQMEFVNGWYIMIIISDILTIIG
SILKMEIQAKSLTSYDVCSILLGTSTMLVWLGVIRYLGFFAKYNLLILTLQAALPNVIRFCCCAAMIYLGY
CFCGWIVLGPYHDKFRSLNMVSECLFSLINGDDMFATFAKMQQKSYLVWLFSRIYLYSFISLFIYMILSLF
IALITDTYETIKQYQQDGFPETELRTFISECKDLPNSGKYRLEDDPPVSLFCCCKK

TSC 8: A disintegrin and metalloproteinase domain 12 (meltrin alpha).

W46291 does not possess a reading frame beyond 50 amino acids.

Table 8A. A disintegrin and metalloproteinase domain 12 (meltrin alpha) (W46291) nucleotide sequence (SEQ ID NO:19).

TTTTTTGAGGATGCATTGATGTATTGATTTGCCTGGGAACAATGGCCTATAGTTCAGCCTGAGAATTCTCAT
AAAGTTAAGAAGGCATAAAAATGCCCCCCCCCGAGACTCGTCAGGAGTATTGACTCTCCTACAGTTTAATTTG
CTGCTTTTCGTCGGTTTCTGTGATGTCATCCCACATGTGTAAGCTGGAAAAATCCACGCTGTGAAGTGTAAC
CTCCTGTGTGTATTTCCACAATGGAGAATGTTAGGCTTCGTTTCCCTCGGTTGCTACACATCTGATTACATG
TGTCAGGAAAACAAACTTAAAAAATTTCAGGAGACAAACCTTTCAGCGGAATTGCCTGGAACCCATGAAGTG
AGGTCATAGAACCTACAACTATAATAAGCTGTAGGAAGAAAAGTAGCCTCTGGGCTACTTTGTGTCTAGTCA
CATTGACTTTCCAGGTGATGGCCCTACAAAACTCAAACCACCTCTATTATTCATGCCTAAAT

TSC 9: Myosin VIIA and Rab interacting protein.

Table 9A. Myosin VIIA and Rab interacting protein (AL50090.1) nucleotide sequence (SEQ ID NO:20).

GAAAATGTATACCTGGCAGCAGGCACTGTGTATGGACTGGAGACCCAGCTGACTGAGCTAGAAGATGCCGCC
CGCTGCATCCACAGCGGCACTGATGAGACCCATCTGGCGGATCTGGAGGACCAGGTGGCCACGGCTGCAGCC
CAAGTCCACCATGCTGAACTCCAGATTTCAGATATTGAGAGCCGGATTTCAGCCCTGACCATTGCAGGATTA
AACATAGCACCATGTGTGCGCTTCACAAGAAGACGGGATCAGAAGCAAAGGACCCAGGTACAAACCATAGAT
ACATCAAGGCAGCAAAGGAGGAAACTGCCTGCTCCACCGGTGAAAGCTGAAAAAATTGAGACATCTTCAGTG
ACTACCATTAAAACATTTAACCACAACTTCATTCTCCAAGGCTCCTCAACAAACAGGACTAAGGAAAGGAAA
GGCACCACCAAGGATTTGATGGAGCCTGCTCTGGAGTCAGCTGTGATGTAC**TGA**CACCATGGAATTCCACTG
CCAGTGACCCACTGCCTCCGGCCGTACACGACAGTGCCTTGACCCAACAGCCATCGAGTACTGTATGTATTT
CCACCTGAGGAGAAGGCCTGGGGAGGCCACAGTGCACCATTGCACAGGGCTGTCCTGATACCTCATCCAGAA
AGCCGTCTCAGACTTCAGCACTGCGGTCTTGCCCACTCTCTGCCTTAGGCTCCCAGGGGAATCCAAGACAGA
AAATGAAGACACTGGCTTCCAACAGCAGCGCTCCATGTTTAAGATACATATTTTCCCTGTTTGCTTTGCTAC
TGTATGTTGACTTTAAGATCTTTTTTTAAATACATTTGATTCAGCTAGTATTCCATGTCAACAATTTGTCCA
AAGGAAAACTGCTGGAGGGAGGTGGAGGGAGGAAGGTGGGAATTATTATTTAATACATCATTAATGCTTATT
AATCTCTCACAAGCATCTTTGTCTTGCAAATCCTAAGGGAAAAGCAAGTCCCTGCAGTGAGCACTAGGGACA
GTCTAATTTGGGGATTGCTCAACCATCAAGACTGCAGGTCTCCCTTCAGCCACCTCCTTCCTGCTAAAAGCT
TAGCCTACCACACTACCAGTCATTCCCATCGCTTTGCAATCACAAGCCACAGGATGAGAAGTTCTGACTCAC
TCATGCCATGCCCAGGGCTATCTGAAACAATGTCTCATTAAGAATTTAGGGTTCTTCCATGGGCTTACTGAC
AGTTGCCCAGATCTGAAGGGGAAAGGGTCTTGAGAAAGACCATCACTGGCTCAACTTTAGGGCACTGTCCAG
AGTCAACATGATGTGGTTTAGCAGTGATCACATCTAAACAAAGTTTAGGTAAATGAATTATCGCAGAGAAAA
ACCACATGAGAAAATTTTTGTACTCCAAATTTACTTCCCAATAAATATTCAGCAAAGTAGTAAAATGACCTT
AAAGATAAAAATGATTAGGGAATAGCCTTAGAAAATTTATAGGTATAAAAAATTCAAGGACAAACTGTGCAT
TTAATGGACACAAGAATTGACTCTAACTCCATGTCTGTGGTTTCTTTGAACCCATATCAAATGTATGACTAT
TTAGAGTGTTTATAAGAGATAATGGAACTGAACTTTCACTCAATTAATTGGGCATTAACAACCTTCTTTTAT
GTTTGTTCCTGATATAGTCTGAATCTTAGGAAGAAGGTAAAAGAAAGGAGGCAAGAGAATAGTTATGATGAA
TATGTGTTAAGTGCCTGCTCTGAAGGAGGCAATGTTCTTCTCATTTGAATCCTTATGGCAACCTTATTCAAT
AGGTTTTCCCATATTTCAGATTTAATAACTGAAGGCCAGAGAGATTAATTTGCCAAAGCCACACCTTTATGC
TAATTATGATTGGAATGCATCACAAAAGCCTAACTCTGTTGTTTTCAACCTCTACGTTATTTTGCTGCTATG
TGCATTTCCAGATCTGATTTTCTGCTAACTTGTGTGCTATGATCCACTCCTGATGGGGGTCTACATTAATCT
TCCAGTACTCCTTGCTGATGCTGTGTTATGTGTCATCTAACAGAAATGACTCCTTTGAAATAAGTAAATCTT
TGGCTTTTTGTTCTGTTGGTGTGATTCAAAGCAAAACAAACAAACAAAAACAAATTTTAAGAACACAACAAA
AAAGATTTGACTTCCGAATAGAATGTTTTCTTTAAGAGGCATGAAAAGCAACTATTGTTGTGTTACAGTGTT
AAAAATATTCAGTTTTCTTTGACAAAAATGTGTACTGTGTAAGCCTTGCAAACAAAAAACAACAAAAAAGAA
GCAGCAGCAGCAGCCTGCTGTGTGGCATCTGAACTTTTATAAAGGTTTCCTTGTGCCAAATAAGTGCAAAGA
TTTAATTTACTATTAAAAACCATAAGCATATGTTATAGTTCCAGAAGAATTATTTTGTCATCAAGTGATTTT
GATCTTTAGTGTCAATATTTATATTTAGATTAATTTTTATAAATGAAAATATTTTAATGGTTTAAGAAAATG
AGGACAACAGGATAATATCTTTGATGACTTCTGAAAGTTATGCTTCCCTTCATGTTATATGCACATTGCCAA
GAATTACTGTCAAGAGAAATGATAAGTAAAAGTCATTTATGAAAATAAAAAAAAAAAAAAAAA

Table 9B. Encoded Myosin VIIA and Rab interacting protein sequence (SEQ ID NO:21).

ENVYLAAGTVYGLETQLTELEDAARCIHSGTDETHLADLEDQVATAAAQVHHAELQISDIESRISALTIAG
LNIAPCVRFTRRRDQKQRTQVQTIDTSRQQRRKLPAPPVKAEKIETSSVTTIKTFNHNFILQGSSTNRTKE
RKGTTKDLMEPALESAVMY

TSC10: Melanophilin.

AI810764 does not possess a reading frame beyond 50 amino acids.

Table 10A. Melanophilin (AI810764) nucleotide sequence (SEQ ID NO:22).

AAAGGCACAGCTTTCCCAGTGTTTGTGTTCCTTGCTTGCGCCCTGTTTTAATGTTGTAGTTACAGGTGTCCA
GCAGGGAGGAATGCAGCCCCTGTGGGCGCTTGGGGGAGCTGCTGGGAATCCAAGTTCAAGGAGCAGCTGTTT
TCTGTTTTCTGTTGCCCCACAGCGCCACCTCCTGGCCCCTTGGTGGTGATGATTTTGAAGTCAGCAGGTTCT
GGTGGGCCGTGTGAACTCCAGCAGCTCTGGGCTGAGCTGTGGAAACACTGCGTCCTTTGAAATAATACAGCT
TTCCTGAGCCCACCCCAGTCCCTAAAGACTGCCTCTGGGGTTGAGATTCTGAGATGCTTGACAGCATGGCTT
TTCCCGGTGTTATGTGTCGTTTCTATCCTTAAGCCTGTTAGGGGTGGACTGGAGGCTGGACCAAGCTCCACT
GGCTGCAGGAGGACCCTTCTGTGGGCTCCAGGCTGGCCGTGTGCGTGTGGGGAGGTGGGATTTGCTGCTAGG
CTTCATGATCACTGTGAAGAAGCAGCCCCCAAGAATAGGGTGATAGGCCCTCCCCATGTCACCG

TSC11: ATP-binding cassette, sub-family C (CFTR/MRP), member 8.

Table 11A. ATP-binding cassette, sub-family C (CFTR/MRP), member 8 (AF087138.1) nucleotide sequence (SEQ ID NO:23).

AGCTGAGCCCGAGCCCAGACCGCGCCCGCGCCGCC**ATG**CCCCTGGCCTTCTGCGGCAGCGAGAACCACTCGG
CCGCCTACCGGGTGGACCAGGGGGTCCTCAACAACGGCTGCTTTGTGGACGCGCTCAACGTGGTGCCGCACG
TCTTCCTACTCTTCATCACCTTCCCCATCCTCTTCATTGGATGGGGAAGTCAGAGCTCCAAGGTGCACATCC
ACCACAGCACATGGCTTCATTTCCCTGGGCACAACCTGCGGTGGATCCTGACCTTCATGCTGCTCTTCGTCC
TGGTGTGTGAGATTGCAGAGGGCATCCTGTCTGATGGGGTGACCGAATCCCACCATCTGCACCTGTACATGC
CAGCCGGGATGGCGTTCATGGCTGCTGTCACCTCCGTGGTCTACTATCACAACATCGAGACTTCCAACTTCC
CCAAGCTGCTAATTGCCCTGCTGGTGTATTGGACCCTGGCCTTCATCACCAAGACCATCAAGTTTGTCAAGT
TCTTGGACCACGCCATCGGCTTCTCGCAGCTACGCTTCTGCCTCACAGGGCTGCTGGTGATCCTCTATGGGA
TGCTGCTCCTCGTGGAGGTCAATGTCATCAGGGTGAGGAGATACATCTTCTTCAAGACACCGAGGGAGGTGA
AGCCTCCCGAGGACCTGCAAGACCTGGGGGTACGCTTCCTGCAGCCCTTCGTGAATCTGCTGTCCAAAGGCA
CCTACTGGTGGATGAACGCCTTCATCAAGACTGCCCACAAGAAGCCCATCGACTTGCGAGCCATCGGGAAGC
TGCCCATCGCCATGAGGGCCCTCACCAACTACCAACGGCTCTGCGAGGCCTTTGACGCCCAGGTGCGGAAGG
ACATTCAGGGCACTCAAGGTGCCCGGGCCATCTGGCAGGCACTCAGCCATGCCTTCGGGAGGCGCCTGGTCC
TCAGCAGCACTTTCCGCATCTTGGCCGACCTGCTGGGCTTCGCCGGGCCACTGTGCATCTTTGGGATCGTGG
ACCACCTTGGGAAGGAGAACGACGTCTTCCAGCCCAAGACACAATTTCTCGGGGTTTACTTTGTCTCATCCC
AAGAGTTCCTTGCCAATGCCTACGTCTTAGCTGTGCTTCTGTTCCTTGCCCTCCTACTGCAAAGGACATTTC
TGCAAGCATCCTACTATGTGGCCATTGAAACTGGAATTAACTTGAGAGGAGCAATACAGACCAAGATTTACA
ATAAAATTATGCACCTGTCCACCTCCAACCTGTCCATGGGAGAAATGACTGCTGGACAGATCTGTAATCTGG
TTGCCATCGACACCAATCAGCTCATGTGGTTTTTCTTCTTGTGCCCAAACCTCTGGGCTATGCCAGTACAGA
TCATTGTGGGTGTGATTCTCCTCTACTACATACTCGGAGTCAGTGCCTTAATTGGAGCAGCTGTCATCATTC
TACTGGCTCCTGTCCAGTACTTCGTGGCCACCAAGCTGTCTCAGGCCCAGCGGAGCACACTGGAGTATTCCA
ATGAGCGGCTGAAGCAGACCAACGAGATGCTCCGCGGCATCAAGCTGCTGAAGCTGTACGCCTGGGAGAACA
TCTTCCGCACGCGGGTGGAGACGACCCGCAGGAAGGAGATGACCAGCCTCAGGGCCTTTGCCATCTATACCT
CCATCTCCATTTTCATGAACACGGCCATCCCCATTGCAGCTGTCCTCATAACTTTCGTGGGCCATGTCAGCT
TCTTCAAAGAGGCCGACTTCTCGCCCTCCGTGGCCTTTGCCTCCCTCTCCCTCTTCCATATCTTGGTCACAC
CGCTGTTCCTGCTGTCCAGTGTGGTCCGATCTACCGTCAAAGCTCTAGTGAGCGTGCAAAAGCTAAGCGAGT
TCCTGTCCAGTGCAGAGATCCGTGAGGAGCAGTGTGCCCCCCATGAGCCCACACCTCAGGGCCCAGCCAGCA
AGTACCAGGCGGTGCCCCTCAGGGTTGTGAACCGCAAGCGTCCAGCCCGGGAGGATTGTCGGGGCCTCACCG

GCCCACTGCAGAGCCTGGTCCCAGTGCAGATGGCGATGCTGACAACTGCTGTGTCCAGATCATGGGAGGCT
ACTTCACGTGGACCCCAGATGGAATCCCCACACTGTCCAACATCACCATTCGTATCCCCCGAGGCCAGCTGA
CTATGATCGTGGGGCAGGTGGGCTGCGGCAAGTCCTCGCTCCTTCTAGCCGCACTGGGGGAGATGCAGAAGG
TCTCAGGGGCTGTCTTCTGGAGCAGCCTTCCTGACAGCGAGATAGGAGAGGACCCCAGCCCAGAGCGGGAGA
CAGCGACCGACTTGGATATCAGGAAGAGAGGCCCCGTGGCCTATGCTTCGCAGAAACCATGGCTGCTAAATG
CCACTGTGGAGGAGAACATCATCTTTGAGAGTCCCTTCAACAAACAACGGTACAAGATGGTCATTGAAGCCT
GCTCTCTGCAGCCAGACATCGACATCCTGCCCCATGGAGACCAGACCCAGATTGGGGAACGGGGCATCAACC
TGTCTGGTGGTCAACGCCAGCGAATCAGTGTGGCCCGAGCCCTCTACCAGCACGCCAACGTTGTCTTCTTGG
ATGACCCCTTCTCAGCTCTGGATATCCATCTGAGTGACCACTTAATGCAGGCCGGCATCCTTGAGCTGCTCC
GGGACGACAAGAGGACAGTGGTCTTAGTGACCCACAAGCTACAGTACCTGCCCCATGCAGACTGGATCATTG
CCATGAAGGATGGCACCATCCAGAGGGAGGGTACCCTCAAGGACTTCCAGAGGTCTGAATGCCAGCTCTTTG
AGCACTGGAAGACCCTCATGAACCGACAGGACCAAGAGCTGGAGAAGGAGACTGTCACAGAGAGAAAAGCCA
CAGAGCCACCCCAGGGCCTATCTCGTGCCATGTCCTCGAGGGATGGCCTTCTGCAGGATGAGGAAGAGGAGG
AAGAGGAGGCAGCTGAGAGCGAGGAGGATGACAACCTGTCGTCCATGCTGCACCAGCGTGCTGAGATCCCAT
GGCGAGCCTGCGCCAAGTACCTGTCCTCCGCCGGCATCCTGCTCCTGTCGTTGCTGGTCTTCTCACAGCTGC
TCAAGCACATGGTCCTGGTGGCCATCGACTACTGGCTGGCCAAGTGGACCGACAGCGCCCTGACCCTGACCC
CTGCAGCCAGGAACTGCTCCCTCAGCCAGGAGTGCACCCTCGACCAGACTGTCTATGCCATGGTGTTCACGG
TGCTCTGCAGCCTGGGCATTGTGCTGTGCCTCGTCACGTCTGTCACTGTGGAGTGGACAGGGCTGAAGGTGG
CCAAGAGACTGCACCGCAGCCTGCTAAACCGGATCATCCTAGCCCCCATGAGGTTTTTTGAGACCACGCCCC
TTGGGAGCATCCTGAACAGATTTTCATCTGACTGTAACACCATCGACCAGCACATCCCATCCACGCTGGAGT
GCCTGAGCCGCTCCACCCTGCTCTGTGTCTCAGCCCTGGCCGTCATCTCCTATGTCACACCTGTGTTCCTCG
TGGCCCTCTTGCCCCTGGCCATCGTGTGCTACTTCATCCAGAAGTACTTCCGGGTGGCGTCCAGGGACCTGC
AGCAGCTGGATGACACCACCCAGCTTCCACTTCTCTCACACTTTGCCGAAACCGTAGAAGGACTCACCACCA
TCCGGGCCTTCAGGTATGAGGCCCGGTTCCAGCAGAAGCTTCTCGAATACACAGACTCCAACAACATTGCTT
CCCTCTTCCTCACAGCTGCCAACAGATGGCTGGAAGTCCGAATGGAGTACATCGGTGCATGTGTGGTGCTCA
TCGCAGCGGTGACCTCCATCTCCAACTCCCTGCACAGGGAGCTCTCTGCTGGCCTGGTGGGCCTGGGCCTTA
CCTACGCCCTAATGGTCTCCAACTACCTCAACTGGATGGTGAGGAACCTGGCAGACATGGAGCTCCAGCTGG
GGGCTGTGAAGCGCATCCATGGGCTCCTGAAAACCGAGGCAGAGAGCTACGAGGGGCTCCTGGCACCATCGC
TGATCCCAAAGAACTGGCCAGACCAAGGGAAGATCCAGATCCAGAACCTGAGCGTGCGCTACGACAGCTCCC
TGAAGCCGGTGCTGAAGCACGTCAATGCCCTCATCTCCCCTGGACAGAAGATCGGGATCTGCGGCCGCACCG
GCAGTGGGAAGTCCTCCTTCTCTCTTGCCTTCTTCCGCATGGTGGACACGTTCGAAGGGCACATCATCATTG
ATGGCATTGACATCGCCAAACTGCCGCTGCACACCCTGCGCTCACGCCTCTCCATCATCCTGCAGGACCCCG
TCCTCTTCAGCGGCACCATCCGATTTAACCTGGACCCTGAGAGGAAGTGCTCAGATAGCACACTGTGGGAGG
CCCTGGAAATCGCCCAGCTGAAGCTGGTGGTGAAGGCACTGCCAGGAGGCCTCGATGCCATCATCACAGAAG
GCGGGGAGAATTTCAGCCAGGGACAGAGGCAGCTGTTCTGCCTGGCCCGGGCCTTCGTGAGGAAGACCAGCA
TCTTCATCATGGACGAGGCCACGGCTTCCATTGACATGGCCACGGAAAACATCCTCCAAAAGGTGGTGATGA
CAGCCTTCGCAGACCGCACTGTGGTCACCATCGCGCATCGAGTGCACACCATCCTGAGTGCAGACCTGGTGA
TCGTCCTGAAGCGGGGTGCCATCCTTGAGTTCGATAAGCCAGAGAAGCTGCTCAGCCGGAAGGACAGCGTCT
TCGCCTCCTTCGTCCGTGCAGACAAG**TGA**CCTGCCAGAGCCCAAGTGCCATCCCACATTCGGACCCTGCCCA
TA

Table 11B. ATP-binding cassette, sub-family C (CFTR/MRP), member 8 (AF087138.1) protein sequence (SEQ ID NO:24).

MPLAFCGSENHSAAYRVDQGVLNNGCFVDALNVVPHVFLLFITFPILFIGWGSQSSKVHIHHSTWLHFPGH
NLRWILTFMLLFVLVCEIAEGILSDGVTESHHLHLYMPAGMAFMAAVTSVVYYHNIETSNFPKLLIALLVY
WTLAFITKTIKFVKFLDHAIGFSQLRFCLTGLLVILYGMLLLVEVNVIRVRRYIFFKTPREVKPPEDLQDL
GVRFLQPFVNLLSKGTYWWMNAFIKTAHKKPIDLRAIGKLPIAMRALTNYQRLCEAFDAQVRKDIQGTQGA
RAIWQALSHAFGRRLVLSSTFRILADLLGFAGPLCIFGIVDHLGKENDVFQPKTQFLGVYFVSSQEFLANA
YVLAVLLFLALLLQRTFLQASYYVAIETGINLRGAIQTKIYNKIMHLSTSNLSMGEMTAGQICNLVAIDTN
QLMWFFFLCPNLWAMPVQIIVGVILLYYILGVSALIGAAVIILLAPVQYFVATKLSQAQRSTLEYSNERLK
QTNEMLRGIKLLKLYAWENIFRTRVETTRRKEMTSLRAFAIYTSISIFMNTAIPIAAVLITFVGHVSFFKE
ADFSPSVAFASLSLFHILVTPLFLLSSVVRSTVKALVSVQKLSEFLSSAEIREEQCAPHEPTPQGPASKYQ
AVPLRVVNRKRPAREDCRGLTGPLQSLVPSADGDADNCCVQIMGGYFTWTPDGIPTLSNITIRIPRGQLTM
IVGQVGCGKSSLLLAALGEMQKVSGAVFWSSLPDSEIGEDPSPERETATDLDIRKRGPVAYASQKPWLLNA
TVEENIIFESPFNKQRYKMVIEACSLQPDIDILPHGDQTQIGERGINLSGGQRQRISVARALYQHANVVFL
DDPFSALDIHLSDHLMQAGILELLRDDKRTVVLVTHKLQYLPHADWIIAMKDGTIQREGTLKDFQRSECQL

FEHWRTLMNRQDQELEKETVTERKATEPPQGLSRAMSSRDGLLQDEEEEEEEAAESEEDDNLSSMLHQRAE
IPWRACAKYLSSAGILLLSLLVFSQLLKHMVLVAIDYWLAKWTDSALTLTPAARNCSLSQECTLDQTVYAM
VFTVLCSLGIVLCLVTSVTVEWTGLKVAKRLHRSLLNRIILAPMRFFETTPLGSILNRFSSDCNTIDQHIP
STLECLSRSTLLCVSALAVISYVTPVFLVALLPLAIVCYFIQKYFRVASRDLQQLDDTTQLPLLSHFAETV
EGLTTIRAFRYEARFQQKLLEYTDSNNIASLFLTAANRWLEVRMEYIGACVVLIAAVTSISNSLHRELSAG
LVGLGLTYALMVSNYLNWMVRNLADMELQLGAVKRIHGLLKTEAESYEGLLAPSLIPKNWPDQGKIQIQNL
SVRYDSSLKPVLKHVNALISPGQKIGICGRTGSGKSSFSLAFFRMVDTFEGHIIIDGIDIAKLPLHTLRSR
LSIILQDPVLFSGTIRFNLDPERKCSDSTLWEALEIAQLKLVVKALPGGLDAIITEGGENFSQGQRQLFCL
ARAFVRKTSIFIMDEATASIDMATENILQKVVMTAFADRTVVTIAHRVHTILSADLVIVLKRGAILEFDKP
EKLLSRKDSVFASFVRADK

Table 11C. ATP-binding cassette, sub-family C (CFTR/MRP), member 8 (NM_000352.2) nucleotide sequence (SEQ ID NO:25).

CGGGGCCCGGGGGGCGGGGGCCTGACGGCCGGGCCGGGCGGCGGAGCTGCAAGGGACAGAGGCGCGGCAGGC
GCGCGGAGCCAGCGGAGCCAGCTGAGCCCGAGCCCAGCCCGCGCCCGCGCCGCC**ATG**CCCCTGGCCTTCTGC
GGCAGCGAGAACCACTCGGCCGCCTACCGGGTGGACCAGGGGGTCCTCAACAACGGCTGCTTTGTGGACGCG
CTCAACGTGGTGCCGCACGTCTTCCTACTCTTCATCACCTTCCCCATCCTCTTCATTGGATGGGGAAGTCAG
AGCTCCAAGGTGCACATCCACCACAGCACATGGCTTCATTTCCCCGGGCACAACCTGCGGTGGATCCTGACC
TTCATGCTGCTCTTCGTCCTGGTGTGTGAGATTGCAGAGGGCATCCTGTCTGATGGGGTGACCGAATCCCAC
CATCTGCACCTGTACATGCCAGCCGGGATGGCGTTCATGGCTGCTGTCACCTCCGTGGTCTACTATCACAAC
ATCGAGACTTCCAACTTCCCCAAGCTGCTAATTGCCCTGCTGGTGTATTGGACCCTGGCCTTCATCACCAAG
ACCATCAAGTTTGTCAAGCTCTTGGACCACGCCATCGGCTTCTCGCAGCTACGCTTCTGCCTCACAGGGCTG
CTGGTGATCCTCTATGGGATGCTGCTCCTCGTGGAGGTCAATGTCATCAGGGTGAGGAGATACATCTTCTTC
AAGACACCGAGGGAGGTGAAGCCTCCCGAGGACCTGCAAGACCTGGGGGTACGCTTCCTGCAGCCCTTCGTG
AATCTGCCGTCCAAAGGCACCTACTGGTGGATGAACGCCTTCATCAAGACTGCCCACAAGAAGCCCATCGAC
TTGCGAGCCATCGGGAAGCTGCCCATCGTTATGAGGGCCCTCACCAACTACCAACGGCTCTGCGAGGCCTTT
GACGCCCAGGTGCGGAAGGACATTCAGGGCACTCAAGGTGCCCGGGCCATCTGGCAGGCACTCAGCCATGCC
TTCGGGAGGCGCCTGGTCCTCAGCAGCACTTTCCGCATCTTGGCCGACCTGCTGGGCTTCGCCGGGCCACTG
TGCATCTTTGGGATCGTGGACCACCTTGGGAAGGAGAACGACGTCTTCCAGCCCAAGACACAATTTCTCGGG
GTTTACTTTGTCTCATCCCAAGAGTTCCTTGCCAATGCCTACGTCTTAGCTGTGCTTCTGTTCCTTGCCCTC
CTACTGCAAAGGACATTTCTGCAAGCATCCTACTATGTGGCCATTGAAACTGGAATTAACTTGAGAGGAGCA
ATACAGACCAAGATTTACAATAAAATTATGCACCTGTCCACCTCCAACCTGTCCATGGGAGAAATGACTGCT
GGACAGATCTGTAATCTGGTTGCCATCGACACCAATCAGCTCATGTGGTTTTTCTTCTTGTGCCCAAACCTC
TGGGCTATGCCAGTACAGATCATTGTGGGTGTGATTCTCCTCTACTACATACTCGGAGTCAGTGCCTTAATT
GGAGCAGCTGTCATCATTCTACTGGCTCCTGTCCAGTACTTCGTGGCCACCAAGCTGTCTCAGGCCCAGCGG
AGCACACTGGAGTATTCCAATGAGCGGCTGAAGCAGACCAACGAGATGCTCCGCGGCATCAAGCTGCTGAAG
CTGTACGCCTGGGAGAACATCTTCCGCACGCGGGTGGAGACGACCCGCAGGAAGGAGATGACCAGCCTCAGG
GCCTTTGCCATCTATACCTCCATCTCCATTTTCATGAACACGGCCATCCCCATTGCAGCTGTCCTCATAACT
TTCGTGGGCCATGTCAGCTTCTTCAAAGAGGCCGACTTCTCGCCCTCCGTGGCCTTTGCCTCCCTCTCCCTC
TTCCATATCTTGGTCACACCGCTGTTCCTGCTGTCCAGTGTGGTCCGATCTACCGTCAAAGCTCTAGTGAGC
GTGCAAAAGCTAAGCGAGTTCCTGTCCAGTGCAGAGATCCGTGAGGAGCAGTGTGCCCCCCATGAGCCCACA
CCTCAGGGCCCAGCCAGCAAGTACCAGGCGGTGCCCCTCAGGGTTGTGAACCGCAAGCGTCCAGCCCGGGAG
GATTGTCGGGGCCTCACCGGCCCACTGCAGAGCCTGGTCCCCAGTGCAGATGGCGATGCTGACAACTGCTGT
GTCCAGATCATGGGAGGCTACTTCACGTGGACCCCAGATGGAATCCCCACACTGTCCAACATCACCATTCGT
ATCCCCCGAGGCCAGCTGACTATGATCGTGGGGCAGGTGGGCTGCGGCAAGTCCTCGCTCCTTCTAGCCGCA
CTGGGGGAGATGCAGAAGGTCTCAGGGGCTGTCTTCTGGAGCAGCCTTCCTGACAGCGAGATAGGAGAGGAC
CCCAGCCCAGAGCGGGAGACAGCGACCGACTTGGATATCAGGAAGAGAGGCCCCGTGGCCTATGCTTCGCAG
AAACCATGGCTGCTAAATGCCACTGTGGAGGAGAACATCATCTTTGAGAGTCCCTTCAACAAACAACGGTAC
AAGATGGTCATTGAAGCCTGCTCTCTGCAGCCAGACATCGACATCCTGCCCCATGGAGACCAGACCCAGATT
GGGGAACGGGGCATCAACCTGTCTGGTGGTCAACGCCAGCGAATCAGTGTGGCCCGAGCCCTCTACCAGCAC
GCCAACGTTGTCTTCTTGGATGACCCCTTCTCAGCTCTGGATATCCATCTGAGTGACCACTTAATGCAGGCC
GGCATCCTTGAGCTGCTCCGGGACGACAAGAGGACAGTGGTCTTAGTGACCCACAAGCTACAGTACCTGCCC
CATGCAGACTGGATCATTGCCATGAAGGATGGGACCATCCAGAGGGAGGGTACCCTCAAGGACTTCCAGAGG
TCTGAATGCCAGCTCTTTGAGCACTGGAAGACCCTCATGAACCGACAGGACCAAGAGCTGGAGAAGGAGACT
GTCACAGAGAGAAAAGCCACAGAGCCACCCCAGGGCCTATCTCGTGCCATGTCCTCGAGGGATGGCCTTCTG
CAGGATGAGGAAGAGGAGGAAGAGGAGGCAGCTGAGAGCGAGGAGGATGACAACCTGTCGTCCATGCTGCAC

CAGCGTGCTGAGATCCCATGGCGAGCCTGCGCCAAGTACCTGTCCTCCGCCGGCATCCTGCTCCTGTCGTTG
CTGGTCTTCTCACAGCTGCTCAAGCACATGGTCCTGGTGGCCATCGACTACTGGCTGGCCAAGTGGACCGAC
AGCGCCCTGACCCTGACCCCTGCAGCCAGGAACTGCTCCCTCAGCCAGGAGTGCACCCTCGACCAGACTGTC
TATGCCATGGTGTTCACGGTGCTCTGCAGCCTGGGCATTGTGCTGTGCCTCGTCACGTCTGTCACTGTGGAG
TGGACAGGGCTGAAGGTGGCCAAGAGACTGCACCGCAGCCTGCTAAACCGGATCATCCTAGCCCCCATGAGG
TTTTTTGAGACCACGCCCCTTGGGAGCATCCTGAACAGATTTTCATCTGACTGTAACACCATCGACCAGCAC
ATCCCATCCACGCTGGAGTGCCTGAGCCGCTCCACCCTGCTCTGTGTCTCAGCCCTGGCCGTCATCTCCTAT
GTCACACCTGTGTTCCTCGTGGCCCTCTTGCCCCTCGCAGTCGTGTGCTACTTCATCCAGAAGTACTTCCGG
GTGGCGTCCAGGGACCTGCAGCAGCTGGATGACACCACCCAGCTTCCACTTCTCTCACACTTTGCCGAAACC
GTAGAAGGACTCACCACCATCCGGGCCTTCAGGTATGAGGCCCGGTTCCAGCAGAAGCTTCTCGAATACACA
GACTCCAACAACATTGCTTCCCTCTTCCTCACAGCTGCCAACAGATGGCTGGAAGTCCGAATGGAGTACATC
GGTGCATGTGTGGTGCTCATCGCAGCGGTGACCTCCATCTCCAACTCCCTGCACAGGGAGCTCTCTGCTGGC
CTGGTGGGCCTGGGCCTTACCTACGCCCTAATGGTCTCCAACTACCTCAACTGGATGGTGAGGAACCTGGCA
GACATGGAGCTCCAGCTGGGGGCTGTGAAGCGCATCCATGGGCTCCTGAAAACCGAGGCAGAGAGCTACGAG
GGGCTCCTGGCACCATCGCTGATCCCAAAGAACTGGCCAGACCAAGGGAAGATCCAGATCCAGAACCTGAGC
GTGCGCTACGACAGCTCCCTGAAGCCGGTGCTGAAGCACGTCAATGCCCTCATCTCCCCTGGACAGAAGATC
GGGATCTGCGGCCGCACCGGCAGTGGGAAGTCCTCCTTCTCTCTTGCCTTCTTCCGCATGGTGGACACGTTC
GAAGGGCACATCATCATTGATGGCATTGACATCCGCAAACTGCCGCTGCACACCCTGCCGTCACGCCTCTCC
ATCATCCTGCAGGACCCCGTCCTCTTCAGCGGCACCATCCGATTTAACCTGGACCCTGAGAGGAAGTGCTCA
GATAGCACACTGTGGGAGGCCCTGGAAATCGCCCAGCTGAAGCTGGTGGTGAAGGCACTGCCAGGAGGCCTC
GATGCCATCATCACAGAAGGCGGGGAGAATTTCAGCCAGGGACAGAGGCAGCTGTTCTGCCTGGCCCGGGCC
TTCGTGAGGAAGACCAGCATCTTCATCATGGACGAGGCCACGGCTTCCATTGACATGGCCACGGAAAACATC
CTCCAAAAGGTGGTGATGACAGCCTTCGCAGACCGCACTGTGGTCACCATCGCGCATCGAGTGCACACCATC
CTGAGTGCAGACCTGGTGATCGTCCTGAAGCGGGGTGCCATCCTTGAGTTCGATAAGCCAGAGAAGCTGCTC
AGCCGGAAGGACAGCGTCTTCGCCTCCTTCGTCCGTGCAGACAAG**TGA**CCTGCCAGAGCCCAAGTGCCATCC
CACATTCGGACCCTGCCCATACCCCTGCCTGGGTTTTCTAACTGTAAATCACTTGTAAATAAATAGATTTGA
TTATTTCCT

Table 11D. ATP-binding cassette, sub-family C (CFTR/MRP), member 8 (NM_000352.2) protein sequence (SEQ ID NO:26).

MPLAFCGSENHSAAYRVDQGVLNNGCFVDALNVVPHVFLLFITFPILFIGWGSQSSKVHIHHSTWLHFPGH
NLRWILTFMLLFVLVCEIAEGILSDGVTESHHLHLYMPAGMAFMAAVTSVVYYHNIETSNFPKLLIALLVY
WTLAFITKTIKFVKLLDHAIGFSQLRFCLTGLLVILYGMLLLVEVNVIRVRRYIFFKTPREVKPPEDLQDL
GVRFLQPFVNLPSKGTYWWMNAFIKTAHKKPIDLRAIGKLPIVMRALTNYQRLCEAFDAQVRKDIQGTQGA
RAIWQALSHAFGRRLVLSSTFRILADLLGFAGPLCIFGIVDHLGKENDVFQPKTQFLGVYFVSSQEFLANA
YVLAVLLFLALLLQRTFLQASYYVAIETGINLRGAIQTKIYNKIMHLSTSNLSMGEMTAGQICNLVAIDTN
QLMWFFFLCPNLWAMPVQIIVGVILLYYILGVSALIGAAVIILLAPVQYFVATKLSQAQRSTLEYSNERLK
QTNEMLRGIKLLKLYAWENIFRTRVETTRRKEMTSLRAFAIYTSISIFMNTAIPIAAVLITFVGHVSFFKE
ADFSPSVAFASLSLFHILVTPLFLLSSVVRSTVKALVSVQKLSEFLSSAEIREEQCAPHEPTPQGPASKYQ
AVPLRVVNRKRPAREDCRGLTGPLQSLVPSADGDADNCCVQIMGGYFTWTPDGIPTLSNITIRIPRGQLTM
IVGQVGCGKSSLLLAALGEMQKVSGAVFWSSLPDSEIGEDPSPERETATDLDIRKRGPVAYASQKPWLLNA
TVEENIIFESPFNKQRYKMVIEACSLQPDIDILPHGDQTQIGERGINLSGGQRQRISVARALYQHANVVFL
DDPFSALDIHLSDHLMQAGILELLRDDKRTVVLVTHKLQYLPHADWIIAMKDGTIQREGTLKDFQRSECQL
FEHWKTLMNRQDQELEKETVTERKATEPPQGLSRAMSSRDGLLQDEEEEEEEAAESEEDDNLSSMLHQRAE
IPWRACAKYLSSAGILLLSLLVFSQLLKHMVLVAIDYWLAKWTDSALTLTPAARNCSLSQECTLDQTVYAM
VFTVLCSLGIVLCLVTSVTVEWTGLKVAKRLHRSLLNRIILAPMRFFETTPLGSILNRFSSDCNTIDQHIP
STLECLSRSTLLCVSALAVISYVTPVFLVALLPLAVVCYFIQKYFRVASRDLQQLDDTTQLPLLSHFAETV
EGLTTIRAFRYEARFQQKLLEYTDSNNIASLFLTAANRWLEVRMEYIGACVVLIAAVTSISNSLHRELSAG
LVGLGLTYALMVSNYLNWMVRNLADMELQLGAVKRIHGLLKTEAESYEGLLAPSLIPKNWPDQGKIQIQNL
SVRYDSSLKPVLKHVNALISPGQKIGICGRTGSGKSSFSLAFFRMVDTFEGHIIIDGIDIRKLPLHTLPSR
LSIILQDPVLFSGTIRFNLDPERKCSDSTLWEALEIAQLKLVVKALPGGLDAIITEGGENFSQGQRQLFCL
ARAFVRKTSIFIMDEATASIDMATENILQKVVMTAFADRTVVTIAHRVHTILSADLVIVLKRGAILEFDKP
EKLLSRKDSVFASFVRADK

TSC12: Vasoactive intestinal peptide receptor 2.

X95097.2 and NM_003382.2 both encode the polypeptide sequence shown in Table 12C.

Table 12A. Vasoactive intestinal peptide receptor 2 (X95097.2) nucleotide sequence (SEQ ID NO:27).

GTGCATTGAGCGCGCTCCAGCTGCCGGGACGGAGGGGGCGGCCCCCGCGCTCGGGGCGCTCGGCTACAGCTG
CGGGGCCCGAGGTCTCCGCGCACTCGCTCCCGGCCCATGCTGGAGGCGGCGGAACCGCGGGGACCTAGGACG
GAGGCGGCGGGCGCTGGGCGGCCCCCGGCACGCTGAGCTCGGG**ATG**CGGACGCTGCTGCCTCCCGCGCTGCT
GACCTGCTGGCTGCTCGCCCCCGTGAACAGCATTCACCCAGAATGCCGATTTCATCTGGAAATACAGGAGGA
AGAAACAAAATGTGCAGAGCTTCTGAGGTCTCAAACAGAAAAACACAAAGCCTGCAGTGGCGTCTGGGACAA
CATCACGTGCTGGCGGCCTGCCAATGTGGGAGAGACCGTCACGGTGCCCTGCCCAAAAGTCTTCAGCAATTT
TTACAGCAAAGCAGGAAACATAAGCAAAAACTGTACGAGTGACGGATGGTCAGAGACGTTCCCAGATTTCGT
CGATGCCTGTGGCTACAGCGACCCGGAGGATGAGAGCAAGATCACGTTTTATATTCTGGTGAAGGCCATTTA
TACCCTGGGCTACAGTGTCTCTCTGATGTCTCTTGCAACAGGAAGCATAATTCTGTGCCTCTTCAGGAAGCT
GCACTGCACCAGGAATTACATCCACCTGAACCTGTTCCTGTCCTTCATCCTGAGAGCCATCTCAGTGCTGGT
CAAGGACGACGTTCTCTACTCCAGCTCTGGCACGTTGCACTGCCCTGACCAGCCATCCTCCTGGGTGGGCTG
CAAGCTGAGCCTGGTCTTCCTGCAGTACTGCATCATGGCCAACTTCTTCTGGCTGCTGGTGGAGGGGCTCTA
CCTCCACACCCTCCTGGTGGCCATGCTCCCCCCTAGAAGGTGCTTCCTGGCCTACCTCCTGATCGGATGGGG
CCTCCCCACCGTCTGCATCGGTGCATGGACTGCGGCCAGGCTCTACTTAGAAGACACCGGTTGCTGGGATAC
AAACGACCACAGTGTGCCCTGGTGGGTCATACGAATACCGATTTTAATTTCCATCATCGTCAATTTTGTCCT
TTTCATTAGTATTATACGAATTTTGCTGCAGAAGTTAACATCCCCAGATGTCGGCGGCAACGACCAGTCTCA
GTACAAGAGGCTGGCCAAGTCCACGCTCCTGCTTATCCCGCTGTTCGGCGTCCACTACATGGTGTTTGCCGT
GTTTCCCATCAGCATCTCCTCCAAATACCAGATACTGTTTGAGCTGTGCCTCGGGTCGTTCCAGGGCCTGGT
GGTGGCCGTCCTCTACTGTTTCCTGAACAGTGAGGTGCAGTGCGAGCTGAAGCGAAAATGGCGAAGCCGGTG
CCCGACCCCGTCCGCGAGCCGGGATTACAGGGTCTGCGGTTCCTCCTTCTCCCGCAACGGCTCGGAGGGCGC
CCTGCAGTTCCACCGCGGCTCCCGCGCCCAGTCCTTCCTGCAAACGGAGACCTCGGTCATC**TAG**CCCCACCC
CTGCCTGTCGGACGCGGCGGGAGGCCCACGGTTCGGGGCTTCTGCGGGGCTGAGACGCCGGCTTCCTCCTTC
CAGATGCCCGAGCACCGTGTCGGGCAGGTCAGCGCGGTCCTGACTCCGTCAAGCTGGTTGTCCACTAAACCC
CATACCTGGAATTGGAGTCGTGTTGTCATTGACTCGATTTAAACTCCAGCATTTAGATAATCTTGTGCAAAA
TGTGTTTCAGCCGTATAGTGGATCCACTTTTTTTTTTTTTTTTTTTGAGACGGAGTCTTGCTCTGTCGCCC
AGGCTGGAGTGCAGTGGCCTGATCTCTGCTCCCTGCAAGCTCCGCCTCCCGGGTTCACGCCATTCTCCTGCC
TCAGCCTCCCATAGCTGGGACTACAGGCGCCCGCCAACACGCCTGGCTAATTTTTTGTATTTTTAGTAGAGA
CAGGGTTTCACCATGTTAGCCAGGATGGTCTCGATCTCCTGACCTCGTGATGGGCCCGCCTCGGCCTCCCAA
AGTGCTGGGATTAAGGCGTGAGCCACTGCGCCCGGCCCAAGAGAATAGGGGAGCCAAGGAGGAAATGTGGAA
ACGCAGTTGTGTGGCCCAGCACGAGCCTGGGCGACCACCGGGTGACATCCGTCCCACATCAGGGCGGCCTCC
CAGGTCCCATAAGGGTAGCCCCCTCATCTGCAGGACAGAGGGAAGCCAGTCAGGGCCCCCCCGGACGTTAGG
ACCAGGAGAAATCAACAGGAGGGCAGCCCGTCCTCTCTCTTGGGGCGCCCACCCGGCCCGGCTGAGCCCTGC
CCCACCCAACTCCACAGGGCTGTTTTGCCTCCCCACGGAAGGCGGGCTGAGGAGACAACCAGATCAGGAGAG
CAAGGTCATGAAGGAGGGGACCTCTCCACACAGGTGTTCCGTGGGACCCTCAGCAGCTCTGGCTCTGCCTCA
GGAGGTCACCTGCCGCCCTGTGGGAGCCGCAGAGCCTGACGCTCAGCCCCAGGCCAGCTGCGGCCAGGCCTG
CGGGCCCCTGGTGATGGGGTTACGTGGGGTGCGGGATACAGCTGAGTGGGAACCGGAAACCTATTCTCTTTT
TAACAAAAATAATCTTAGGATAAGAATTATTTTAACAACATATAAAACTGTTTCAAGCCCTCCTCCCCAGAG
CTGGCGCTCAGCAGCCCTAGCGGCTGCTCCTTCAGGCGAAGGGTGGTTTGCAGATGTGGGGAGGGTGTCTGG
GGACGTTGCTGAGCTGGCTGCAGAAGGGTGGGGATATCAGGGCACAGTCTCCATGTGTGTGCCAAGCCCTGG
CCCCCACAGCGCTCGATGGACCTCAGCAAGCTGCCCAGCCCTGGCCCAGGTGCCCCGACTGTGGGACTCAGT
TGTTCTGAGCACATTTGACTCCACTTTTCCTTTAAAAATGAATGTCTTGTTCCTGTGCATTGGTGGCATCAC
AGACCCCAGCTGGGGCGCGATGTCAAAGGTCGGGACAGCTGTGCCGGGAGGCAGCCACAGGGAAGCTCACAC
ATCCTGTCAGTGTCACCTTGGTTTGCAAAACCCATATCCCCGGTAAAATGAGGCCGGACAGAGGGGCTGTTA
GGACAGCAAAGCAGCAGTGTCCAGAGACCCCTCAATCCCCAAAGGTCCGCACCCTGTCCTGCACACCCTGGG
CCACGCCGGCCACACCCCTCTGCTGCAACAAGCTCATCCCTGGACTTCTGGGAGAATGAACCCGAGGTTGGT
TTGGGGAGACAGGTGAGGCGGTTGGATCTACAGAACAACCCACCATTTCTGGGGGCCGCAGAGGATCCATCA
CAGACGGATACTGGGGAGTAAACGGCCCAGGCCAGGTGCCCAGGAAAGGACGGCTGAGCATGTGGAGCGAGA
GGGAGGCAGGTGGACGCTGCAGACCCCAGGTTCAGTGCGGCCCCTCGGCTGTTCCTCCCCTGTAGGGTTTGG
ACAGACCCACCCCCAGCCTTGCCCAGCTTTCAAAGGACAAAAGGGAGCATCCCCCACCTACTCTCAGGTTTT
TGAGGAAACAAAGATTTGTGGTAACTGAAGGTGTTGGGTCAGTGGCCAGGTGCCGACACTGAGCTGTGACCC
AGAGGGGACGCTGAGGAAGTGGGCGTGAGTGGACATGTCAGGTGGTTACCAGGCACTGGTTGTTGATGGTCG
GTGGTTGGGTGTGGGCAGTCATCAGTCATCAGGTGTGCTCAGGGGACAATCTCCCCTCAACCGCACATGTGC
CACTGTTCAGCGGAGCTGACTGGTTTCTCCTGGTAGAGGGCCGGCTGTATCCTGACAGATGCCTGGTGAGCA

GGGGAAGCAGGACCCAGTGGTCAACAGGTGTCTTTAACTGTCATTGTGTGTGGAATGTCGCAGACTCCTCCA
CGTGGCGGGAATGAGCTGTGTAAATACTTCAATAAAGCCTGATCTCACATCTGCAAAAAAAAAAAAAAAAAA
AAAAAAAAAAAAA

Table 12B. Vasoactive intestinal peptide receptor 2 (NM_003382.2) nucleotide sequence (SEQ ID NO:28).

GTGCATTGAGCGCGCTCCAGCTGCCGGGACGGAGGGGGCGGCCCCCGCGCTCGGGCGCTCGGCTACAGCTGC
GGGGCCCGAGGTCTCCGCGCACTCGCTCCCGGCCCATGCTGGAGGCGGCGGAACCGCGGGGACCTAGGACGG
AGGCGGCGGGCGCTGGGCGGCCCCCGGCACGCTGAGCTCGGG**ATG**CGGACGCTGCTGCCTCCCGCGCTGCTG
ACCTGCTGGCTGCTCGCCCCCGTGAACAGCATTCACCCAGAATGCCGATTTCATCTGGAAATACAGGAGGAA
GAAACAAAATGTGCAGAGCTTCTGAGGTCTCAAACAGAAAAACACAAAGCCTGCAGTGGCGTCTGGGACAAC
ATCACGTGCTGGCGGCCTGCCAATGTGGGAGAGACCGTCACGGTGCCCTGCCCAAAAGTCTTCAGCAATTTT
TACAGCAAAGCAGGAAACATAAGCAAAAACTGTACGAGTGACGGATGGTCAGAGACGTTCCCAGATTTCGTC
GATGCCTGTGGCTACAGCGACCCGGAGGATGAGAGCAAGATCACGTTTTATATTCTGGTGAAGGCCATTTAT
ACCCTGGGCTACAGTGTCTCTCTGATGTCTCTTGCAACAGGAAGCATAATTCTGTGCCTCTTCAGGAAGCTG
CACTGCACCAGGAATTACATCCACCTGAACCTGTTCCTGTCCTTCATCCTGAGAGCCATCTCAGTGCTGGTC
AAGGACGACGTTCTCTACTCCAGCTCTGGCACGTTGCACTGCCCTGACCAGCCATCCTCCTGGGTGGGCTGC
AAGCTGAGCCTGGTCTTCCTGCAGTACTGCATCATGGCCAACTTCTTCTGGCTGCTGGTGGAGGGGCTCTAC
CTCCACACCCTCCTGGTGGCCATGCTCCCCCCTAGAAGGTGCTTCCTGGCCTACCTCCTGATCGGATGGGGC
CTCCCCACCGTCTGCATCGGTGCATGGACTGCGGCCAGGCTCTACTTAGAAGACACCGGTTGCTGGGATACA
AACGACCACAGTGTGCCCTGGTGGGTCATACGAATACCGATTTTAATTTCCATCATCGTCAATTTTGTCCTT
TTCATTAGTATTATACGAATTTTGCTGCAGAAGTTAACATCCCCAGATGTCGGCGGCAACGACCAGTCTCAG
TACAAGAGGCTGGCCAAGTCCACGCTCCTGCTTATCCCGCTGTTCGGCGTCCACTACATGGTGTTTGCCGTG
TTTCCCATCAGCATCTCCTCCAAATACCAGATACTGTTTGAGCTGTGCCTCGGGTCGTTCCAGGGCCTGGTG
GTGGCCGTCCTCTACTGTTTCCTGAACAGTGAGGTGCAGTGCGAGCTGAAGCGAAAATGGCGAAGCCGGTGC
CCGACCCCGTCCGCGAGCCGGGATTACAGGGTCTGCGGTTCCTCCTTCTCCCGCAACGGCTCGGAGGGCGCC
CTGCAGTTCCACCGCGGCTCCCGCGCCCAGTCCTTCCTGCAAACGGAGACCTCGGTCATC**TAG**CCCCACCCC
TGCCTGTCGGACGCGGCGGGAGGCCCACGGTTCGGGGCTTCTGCGGGGCTGAGACGCCGGCTTCCTCCTTCC
AGATGCCCGAGCACCGTGTCGGGCAGGTCAGCGCGGTCCTGACTCCGTCAAGCTGGTTGTCCACTAAACCCC
ATACCTGGAATTGGAGTCGTGTTGTCATTGACTCGATTTAAACTCCAGCATTTAGATAATCTTGTGCAAAAT
GTGTTTCAGCCGTATAGTGGATCCACTTTTTTTTTTTTTTTTTTGAGACGGAGTCTTGCTCTGTCGCCCA
GGCTGGAGTGCAGTGGCCTGATCTCTGCTCCCTGCAAGCTCCGCCTCCCGGGTTCACGCCATTCTCCTGCCT
CAGCCTCCCATAGCTGGGACTACAGGCGCCCGCCAACACGCCTGGCTAATTTTTTGTATTTTTAGTAGAGAC
AGGGTTTCACCATGTTAGCCAGGATGGTCTCGATCTCCTGACCTCGTGATGGGCCCGCCTCGGCCTCCCAAA
GTGCTGGGATTAAGGCGTGAGCCACTGCGCCCGGCCCAAGAGAATAGGGGAGCCAAGGAGGAAATGTGGAAA
CGCAGTTGTGTGGCCCAGCACGAGCCTGGGCGACCACCGGGTGACATCCGTCCCACATCAGGGCGGCCTCCC
AGGTCCCATAAGGGTAGCCCCCTCATCTGCAGGACAGAGGGAAGCCAGTCAGGGCCCCCCCGACGTTAGGAC
CAGGAGAAATCAACAGGAGGGCAGCCCGTCCTCTCTCTTGGGGCGCCCACCCGGCCCGGCTGAGCCCTGCCC
CACCCAACTCCACAGGGCTGTTTTGCCTCCCCACGGAAGGCGGGCTGAGGAGACAACCAGATCAGGAGAGCA
AGGTCATGAAGGAGGGGACCTCTCCACACAGGTGTTCCGTGGGACCCTCAGCAGCTCTGGCTCTGCCTCAGG
AGGTCACCTGCCGCCCTGTGGGAGCCGCAGAGCCTGACGCTCAGCCCCAGGCCAGCTGCGGCCAGGCCTGCG
GGCCCCTGGTGATGGGGTTACGTGGGGTGCGGGATACAGCTGAGTGGGAACCGGAAACCTATTCTCTTTTTA
ACAAAAATAATCTTAGGATAAGAATTATTTTAACAACATATAAAACTGTTTCAAGCCCTCCTCCCCAGAGCT
GGCGCTCAGCAGCCCTAGCGGCTGCTCCTTCAGGCGAAGGGTGGTTTGCAGATGTGGGGAGGGTGTCTGGGG
ACGTTGCTGAGCTGGCTGCAGAAGGGTGGGGATATCAGGGCACAGTCTCCATGTGTGTGCCAAGCCCTGGCC
CCCACAGCGCTCGATGGACCTCAGCAAGCTGCCCAGCCCTGGCCCAGGTGCCCCGACTGTGGGACTCAGTTG
TTCTGAGCACATTTGACTCCACTTTTCCTTTAAAAATGAATGTCTTGTTCCTGTGCATTGGTGGCATCACAG
ACCCCAGCTGGGGCGCGATGTCAAAGGTCGGGACAGCTGTGCCGGGAGGCAGCCACAGGGAAGCTCACACAT
CCTGTCAGTGTCACCTTGGTTTGCAAAACCCATATCCCCGGTAAAATGAGGCCGGACAGAGGGGCTGTTAGG
ACAGCAAAGCAGCAGTGTCCAGAGACCCCTCAATCCCCAAAGGTCCGCACCCTGTCCTGCACACCCTGGGCC
ACGCCGGCCACACCCCTCTGCTGCAACAAGCTCATCCCTGGACTTCTGGGAGAATGAACCCGAGGTTGGTTT
GGGGAGACAGGTGAGGCGGTTGGATCTACAGAACAACCCACCATTTCTGGGGGCCGCAGAGGATCCATCACA
GACGGATACTGGGGAGTAAACGGCCCAGGCCAGGTGCCCAGGAAAGGACGGCTGAGCATGTGGAGCGAGAGG
GAGGCAGGTGGACGCTGCAGACCCCAGGTTCAGTGCGGCCCCTCGGCTGTTCCTCCCCTGTAGGGTTTGGAC
AGACCCACCCCCAGCCTTGCCCAGCTTTCAAAGGACAAAAGGGAGCATCCCCCACCTACTCTCAGGTTTTTG
AGGAAACAAAGATTTGTGGTAACTGAAGGTGTTGGGTCAGTGGCCAGGTGCCGACACTGAGCTGTGACCCAG

AGGGGACGCTGAGGAAGTGGGCGTGAGTGGACATGTCAGGTGGTTACCAGGCACTGGTTGTTGATGGTCGGT
GGTTGGGTGTGGGCAGTCATCAGTCATCAGGTGTGCTCAGGGGACAATCTCCCCTCAACCGCACATGTGCCA
CTGTTCAGCGGAGCTGACTGGTTTCTCCTGGTAGAGGGCCGGCTGTATCCTGACAGATGCCTGGTGAGCAGG
GGAAGCAGGACCCAGTGGTCAACAGGTGTCTTTAACTGTCATTGTGTGTGGAATGTCGCAGACTCCTCCACG
TGGCGGGAATGAGCTGTGTAAATACTTCAATAAAGCCTGACTTCACATCTGCAAAAAAAAAAAAAAAAAA

Table 12C. Vasoactive intestinal peptide receptor 2 (X95097/NM_003382.2) protein sequence (SEQ ID NO:29).

MRTLLPPALLTCWLLAPVNSIHPECRFHLEIQEEETKCAELLRSQTEKHKACSGVWDNITCWRPA
NVGETVTVPCPKVFSNFYSKAGNISKNCTSDGWSETFPDFVDACGYSDPEDESKITFYILVKAIY
TLGYSVSLMSLATGSIILCLFRKLHCTRNYIHLNLFLSFILRAISVLVKDDVLYSSSGTLHCPDQ
PSSWVGCKLSLVFLQYCIMANFFWLLVEGLYLHTLLVAMLPPRRCFLAYLLIGWGLPTVCIGAWT
AARLYLEDTGCWDTNDHSVPWWVIRIPILISIIVNFVLFISIIRILLQKLTSPDVGGNDQSQYKR
LAKSTLLLIPLFGVHYMVFAVFPISISSKYQILFELCLGSFQGLVVAVLYCFLNSEVQCELKRKW
RSRCPTPSASRDYRVCGSSFSRNGSEGALQFHRGSRAQSFLQTETSVI

Table 12D. Vasoactive intestinal peptide receptor 2 (L36566.1) nucleotide sequence (SEQ ID NO:30).

CGGGACGAGGGGGCGGCCCCCGCGCTCGGGGCGCTCGGCTACAGCTGCGGGGCCCGAGGTCTCCGCGCACTC
GCTCCCGGCCCATGCTGGAGGCGGCGGAACCCGGGGGACCTAGGACGGAGGCGGCGGGCGCTGGGCGGCCCC
CGGCACGCTGAGCTCGGG**ATG**CGGACGCTGCTGCCTCCCGCGCTGCTGACCTGCTGGCTGCTCGCCCCCGTG
AACAGCATTCACCCAGAATGCCGATTTCATCTGGAAATACAGGAGGAAGAAACAAAATGTACAGAGCTTCTG
AGGTCTCAAACAGAAAAACACAAAGCCTGCAGTGGCGTCTGGGACAACATCACGTGCTGGCGGCCTGCCAAT
GTGGGAGAGACCGTCACGGTGCCCTGCCCAAAAGTCTTCAGCAATTTTTACAGCAAAGCAGGAAACATAAGC
AAAAACTGTACGAGTGACGGATGGTCAGAGACGTTCCCAGATTTCGTCGATGCCTGTGGCTACAGCGACCCG
GAGGATGAGAGCAAGATCACGTTTTATATTCTGGTGAAGGCCATTTATACCCTGGGCTACAGTGTCTCTCTG
ATGTCTCTTGCAACAGGAAGCATAATTCTGTGCCTCTTCAGGAAGCTGCACTGCACCAGGAATTACATCCAC
CTGAACCTGTTCCTGTCCTTCATCCTGAGAGCCATCTCAGTGCTGGTCAAGGACGACGTTCTCTACTCCAGC
TCTGGCACGTTGCACTGCCCTGACCAGCCATCCTCCTGGGTGGGCTGCAAGCTGAGCCTGGTCTTCCTGCAG
TACTGCATCATGGCCAACTTCTTCTGGCTGCTGGTGGAGGGGCTCTACCTCCACACCCTCCTGGTGGCCATG
CTCCCCCCTAGAAGGTGCTTCCTGGCCTACCTCCTGATCGGATGGGGCCTCCCCACCGTCTGCATCGGTGCA
TGGACTGCGGCCAGGCTCTACTTAGAAGACACCGGTTGCTGGGATACAAACGACCACAGTGTGCCCTGGTGG
GTCATACGAATACCGATTTTAATTTCCATCATCGTCAATTTTGTCCTTTTCATTAGTATTATACGAATTTTG
CTGCAGAAGTTAACATCCCCAGATGTCGGCGGCAACGACCAGTCTCAGTACAAGAGGCTGGCCAAGTCCACG
CTCCTGCTTATCCCGCTGTTCGGCGTCCACTACATGGTGTTTGCCGTGTTTCCCATCAGCATCTCCTCCAAA
TACCAGATACTGTTTGAGCTGTGCCTCGGGTCGTTCCAGGGCCTGGTGGTGGCCGTCCTCTACTGTTTCCTG
AACAGTGAGGTGCAGTGCGAGCTGAAGCGAAAATGGCGAAGCCGGTGCCCGACCCCGTCCGCGAGCCGGGAT
TACAGGGTCTGCGGTTCCTCCTTCTCCCACAACGGCTCGGAGGGCGCCCTGCAGTTCCACCGCGCGTCCCGA
GCCCAGTCCTTCCTGCAAACGGAGACCTCGGTCATC**TAG**CCCCACCCCTGCCTGTCGGACGCGGCGGGAGGC
CCACGGTTCGGGGCTTCTGCGGGGCTGAGACGCCGGCTTCCTCCTTCCAGATGCCCGAGCACCGTGTCGGGC
AGGTCAGCGCGGTCCTGACTCCGTCAAGCTGGTTGTCCACTAAACCCCATACCTGG

Table 12E. Vasoactive intestinal peptide receptor 2 (L36566.1) protein sequence (SEQ ID NO:31).

MRTLLPPALLTCWLLAPVNSIHPECRFHLEIQEEETKCTELLRSQTEKHKACSGVWDNITCWRPANVGETV
TVPCPKVFSNFYSKAGNISKNCTSDGWSETFPDFVDACGYSDPEDESKITFYILVKAIYTLGYSVSLMSLA
TGSIILCLFRKLHCTRNYIHLNLFLSFILRAISVLVKDDVLYSSSGTLHCPDQPSSWVGCKLSLVFLQYCI
MANFFWLLVEGLYLHTLLVAMLPPRRCFLAYLLIGWGLPTVCIGAWTAARLYLEDTGCWDTNDHSVPWWVI
RIPILISIIVNFVLFISIIRILLQKLTSPDVGGNDQSQYKRLAKSTLLLIPLFGVHYMVFAVFPISISSKY
QILFELCLGSFQGLVVAVLYCFLNSEVQCELKRKWRSRCPTPSASRDYRVCGSSFSHNGSEGALQFHRASR

AQSFLQTETSVI

TSC13: Pancreatic lipase-related protein 3.

Table 13A. Pancreatic lipase-related protein 3 (AL833418.1) nucleotide sequence (SEQ ID NO:32).

GGGTGGGGGGAATAACATGTTCTTTTAAACGCAGAGTTTAAACATTGAGTTGCATCATTGTGAGGAAAACCA
CTTAGTATTTTTAGTGAGGTGACTTTACAAGTAAAGATCTTCAAGAAGATTTTTATGTGATTTAAAAAATCA
GCTTAG**ATG**CTTGGAATTTGGATTGTTGCATTCTTGTTCTTTGGCACATCAAGAGGAAAAGAAGTTTGCTAT
GAAAGGTTAGGGTGTTTCAAAGATGGTTTACCATGGACCAGGACTTTCTCAACAGAGTTGGTAGGTTTACCC
TGGTCTCCAGAGAAGATAAACACTCGTTTCCTGCTCTACACTATACACAATCCCAATGCCTATCAGGAGATC
AGTGCGGTTAATTCTTCAACTATCCAAGCCTCATATTTTGGAACAGACAAGATCACCCGTATCAACATAGCT
GGATGGAAAACAGATGGCAAATGGCAGAGAGACATGTGCAATGTGTTGCTACAGCTGGAAGATATAAATTGC
ATTAATTTAGATTGGATCAACGGTTCACGGGAATACATCCATGCTGTAAACAATCTCCGTGTTGTTGGTGCT
GAGGTGGCTTATTTTATTGATGTTCTCATGAAAAAATTTGAATATTCCCCTTCTAAAGTGCACTTGATTGGC
CACAGCTTGGGAGCACACCTGGCTGGGGAAGCTGGGTCAAGGATACCAGGCCTTGGAAGAATAACTGGGTTG
GACCCAGCTGGGCCATTTTTCCACAACACTCCAAAGGAAGTCAGGCTAGACCCCTCGGATGCCAACTTTGTT
GACGTTATTCATACAAATGCAGCTCGCATCCTCTTTGAGCTTGGTGTTGGAACCATTGATGCTTGTGGTCAT
CTTGACTTTTACCCAAATGGAGGGAAGCACATGCCAGGATGTGAAGACTTAATTACACCTTTACTGAAATTT
AACTTCAATGCTTACAAAAAAGAAATGGCTTCCTTCTTTGACTGTAACCATGCCCGAAGTTATCAATTTTAT
GCTGAAAGCATTCTTAATCCTGATGCATTTATTGCTTATCCTTGTAGATCCTACACATCTTTTAAAGCAGGA
AATTGCTTCTTTTGTTCCAAAGAAGGTTGCCCAACAATGGGTCATTTTGCTGATAGATTTCACTTCAAAAAT
ATGAAGACTAATGGATCACATTATTTTTTAAACACAGGGTCCCTTTCCCCATTTGCCCGTTGGAGGCACAAA
TTGTCTGTTAAACTCAGTGGAAGCGAAGTCACTCAAGGAACTGTCTTTCTTCGTGTAGGCGGGGCAATTGGG
AAAACTGGGGAGTTTGCCATTGTCAGTGGAAAACTTGAGCCAGGCATGACTTACACAAAATTAATCGATGCA
GATGTTAACGTTGGAAACATTACAAGTGTTCAGTTCATCTGGAAAAAACATTTGTTTGAAGATTCTCAGAAT
AAGTTGGGAGCAGAAATGGTGATAAATACATCTGGGAAATATGGATATAAATCTACCTACTGTAGCCAAGAC
ATTATGGGACC**TAA**TATTCTCCAGAACCTGAAACCATGCTAATCTCAGATACAGTCTTGATGGATTTCTTTA
GTAGGAGCAATGAAGAAAAGTGTCTCCTTCCACCTGGCATCCAGACCAAATTTGACCCTTGTAAATGACTTA
GTCATTTACAGGGGTCTTACTCAGAGTCAAGTACGGGTTTGCTTTTTTTCTGTGTAGAATGTTCATCTAACT
GCACCTTAAAAACACACTGAACCCTGGGACAAAAGATAATTACTATGATCTGTAGGAATCTGGATATCATTG
ACAAAATAGAGCTGTTTTGGAATTTTCCTGAATAAGAGGAGGTGATGCAAATGTATGTTGAGTGTATAAACT
CACTGGACAAAAGTAAGCCTCTGGCTTGCTGAGTTTTTGAAGTATATTTTCAGGTATAATAATCATTGTTCT
AAAATTATATAAAACTATTTGTTATGTTGTTAAATCTTGCTGAGACAAATTATGACTATAGTGCATGATATA
TAGTAGATTATAACCTTGTGGGTTGATGTGTCTATCTAGTAATAATAAAAACTAATGAGATGGCACTAGTAT
TTCCAAGGTGTTCCTTGGTGTTCAGGGTGTGCACAAGAGAGATTTTGGAGCTTATCTGTTATGTGTTCATCA
GTTAGCAATGGGACCTGAAGTTCAACAACCCAGGGTATAGCCCCCTTCCTCCAAAGTCCCTGCCACAGGAGA
ATTACTCCTCTCTCTGGGTCTTGAATGCTCTATGGTGAATTTGTATTTAGCCTCAAGGCAGCATTTCATTTG
TAAAGCACTTGGGTAACCCTTTGTTCTTGCAATAACAATATTATAATATTTAAAAAAAAAAAAAAAAAAA

Table 13B. Pancreatic lipase-related protein 3 protein sequence (SEQ ID NO:33).

MLGIWIVAFLFFGTSRGKEVCYERLGCFKDGLPWTRTFSTELVGLPWSPEKINTRFLLYTIHNPNAYQEIS
AVNSSTIQASYFGTDKITRINIAGWKTDGKWQRDMCNVLLQLEDINCINLDWINGSREYIHAVNNLRVVGA
EVAYFIDVLMKKFEYSPSKVHLIGHSLGAHLAGEAGSRIPGLGRITGLDPAGPFFHNTPKEVRLDPSDANF
VDVIHTNAARILFELGVGTIDACGHLDFYPNGGKHMPGCEDLITPLLKFNFNAYKKEMASFFDCNHARSYQ
FYAESILNPDAFIAYPCRSYTSFKAGNCFFCSKEGCPTMGHFADRFHFKNMKTNGSHYFLNTGSLSPFARW
RHKLSVKLSGSEVTQGTVFLRVGGAIGKTGEFAIVSGKLEPGMTYTKLIDADVNVGNITSVQFIWKKHLFE
DSQNKLGAEMVINTSGKYGYKSTYCSQDIMGPNILQNLKPC

TSC14: Polycystic kidney disease 1-like 2.

AW082870 does not possess a reading frame beyond 50 amino acids.

Table 14A. Polycystic kidney disease 1-like 2 (AW082870) nucleotide sequence (SEQ ID NO:34).

TTTTTCCATGTAATATTTGTTTTATTTATAATAAGAGGAAATACATTTGAACAAAGAAGCTCTCATAGTATT
GGCAATTTTACATATATCTCTGTTATTGTAATTTTTTTTACTTGCTGGGCTTGGTAATTCTTCAATGGACAT
GAAAGCTATGACCTAGAGAGACTATAGAGTCGCTGGTAAGCGTACGCCCGAGGCCCTGGGCGTCCCCACTGG
TAGATGGTGGCGTGTGGACGAACAGCTTAGTCCTTGGGCAAAGCTTGTGCTGGTCGAGAGTGGCGAGTCTGG
GACAGAGACCCAGGCTGCTCCCTGCTGCTTCCAGGCTCCTCTCTCTTAGACTTAATGCCCAGGAAACTGAGT
ATTTTCATCAGCAGCAAATCTACGATCTCCCCTTCCTCCGACAGCTGCAAGAGAAAGAACCAGGCAATGCCC
ATAGAACCATCTTCT

TSC15: Attractin-like 1.

AW151108 does not possess a reading frame beyond 50 amino acids.

Table 15A. Attractin-like 1 (AW151108) nucleotide sequence (SEQ ID NO:35).

TTTTCTAAGAATTTGTCTTATTTTTAATGCATGGAAAATAGCAAAATTATCATGCCAACATGAGGAATATAT
ACTATAATTCATAAATGCCTAATTATCAAAATAATGACATAGTCATGGTTAGATGCAACCTAGAAATCTTAT
ATAAGATGCAACTACATATTGTATGATCATTCCTCTTATATATGACATTCAATCCTCATCAAATTCAGCTAT
GTATAAATGGCATTATGAAATAAACACTTAATATCACAATAGGGTCATAGTCTGCTACTGTACAACCATGGC
ATGCAAGTAACTATGCATTAGCTGTAAACAGTAAAGTGTCATAACCTTCCAGAAATCCAAAGAATGTGAAAA
GTACATATATAGTACTAAACATCAATTGTATTTAAAGGACCTTCATATTTAACAAAGCTATATCATATACAG
CAGCTTTGGAGATTTCTGTCACTGTTATACATATCTTGTCACCCTGAAGTGAGGAAACTGCAATTCCAAACT
ATATCTGTTAATGCTACTG

TSC16: Solute carrier family 2 (facilitated glucose transporter), member 12.

AI675682 does not possess a reading frame beyond 50 amino acids.

Table 16A. Solute carrier family 2 (facilitated glucose transporter), member 12 (AI675682) nucleotide sequence (SEQ ID NO:36).

TTTTTTTTTTTTTTTTTTTTCCTTTTTTTTTAAAAAAAGGGGTTTATTTCCTTTTTTTTAAGATTCAGTAGG
ATAGCCAAATTCATAGAGAATAAAATTACATGAAAGAGTTACAAGCTCACTGTTTTAAAGACTTGACATTTT
TCATTTAGTTTTAATTAACAGTAATAAGACACCTCCTGTTTTTCAATGTTCACCAAAAAAAGAAACATAGAA
TAGGGGGAAAACATGCTTATATAGCCAAGGTACAGATCCAGATGATGTAACCTTTTTAGTATTCGCATGACT
TGAAAACTGGGCAGATCAATAGATAATCGAAGTGCTTTATCTGAAGGGAGAGGGTAAAGACAGTGTGACCAG
GTTTGTTTTCAGGGCTGCCGAATGAGCCTCACCTAACAGTGTCCATGGGTAATTCGCTAACCTTAACAAAGA
TGGGAAGA

TSC17: Protease inhibitor 15.

Table 17A. Protease inhibitor 15 (NM_015886.1) nucleotide sequence (SEQ ID NO:37).

CAAAGTAAACTCGGTGGCCTCTTCTTCTCCACCCCTCAAAATGATAGCAATCTCTGCCGTCAGCAGTGCACT
CCTGTTCTCCCTTCTCTGTGAAGCAAGTACCGTCGTCCTACTCAATTCCACTGACTCATCCCCGCCAACCAA
TAATTTCACTGATATTGAAGCAGCTCTGAAAGCACAATTAGATTCAGCGGATATCCCCAAAGCCAGGCGGAA
GCGCTACATTTCGCAGAATGACATGATCGCCATTCTTGATTATCATAATCAAGTTCGGGGCAAAGTGTTCCC
ACCGGCAGCAAATATGGAATATATGGTTTGGGATGAAAATCTTGCAAAATCGGCAGAGGCTTGGGCGGCTAC
TTGCATTTGGGACCATGGACCTTCTTACTTACTGAGATTTTTGGGCCAAAATCTATCTGTACGCACTGGAAG
ATATCGCTCTATTCTCCAGTTGGTCAAGCCATGGTATGATGAAGTGAAAGATTATGCTTTTCCATATCCCCA

GGATTGCAAGCCCAGATGTCCTATGAGATGTTTTGGTCCCATGTGCACACATTATACGCAGATGGTTTGGGC
CACTTCCAATCGGATAGGATGCGCAATTCATACTTGCCAAAACATGAATGTTTGGGGATCTGTGTGGCGACG
TGCAGTTTACTTGGTATGCAACTATGCCCCAAAGGGCAATTGGATTGGAGAAGCACCATATAAAGTAGGGGT
ACCATGTTCATCTTGTCCTCCAAGTTATGGGGGATCTTGTACTGACAATCTGTGTTTTCCAGGAGTTACGTC
AAACTACCTGTACTGGTTTAAA**TAA**GTTTACCTTTTCCTCCAGGAAATATAATGATTTCTGGGAACATGGGC
ATGTATATATATATATGGAGAGAGAATTTTGCACATATTATACATATTTTGTGCTAATCTTGTTTTCCTCTT
AGTATTCCTTTGTATAAATTAGTGTTTGTCTAGCATGTTTGTTTAATCCTTTGAAATATTTGAAACATCAAT
TTCTATTTTCTGACCTCTAAGCCTAAATTAAGATATTGTATATGTAATGATGACATAGTTGATGCATCCAAT
CCTAAAACTTACATTCCAAAGGAATTATATCATTATGTTCCTAAGGAGTAAATATATATTTGACCTGTAAGT
GTGTGTATGTATACATATACATATGTATGTGTATGGATTTATATATGCACACAAACATATAATATGTGATGT
AACATGTAGATGATAATATGATTCAGTAGTCAACTTGAGGGAAATTTTTAAAAAACTATTCTCAATTATATA
CGAGGTGATGGGACTTCTTAACACACATTTCTATAATACCCATGAAATGATAATTTGTAAAATAACACTTAG
TGATATCTGGAAATAATAATTCAATTAAGCAACCACGAATTTCACCCTGGAGATATTTTTTCTTATTTGAGT
CCACCAAAGGATAATGCCAACTTATATAAGTTCTCAAATCATGCCTTCCGCTTAGTCTCATTTTATTCATTC
AGTCGTCATGAGTTGAGTGCTTACTACATGCAAGGCACTCTGCTAGTTATATTCTAATAATGCAGAGATAAT
TAGACATGGTTCCCGCCCTCAAGAAGCTCACAAAAGTATTCAGGAAATAATGCAGACTAGTGATTTTGCTAT
AAAATTATTTTTGAAGGAAGCAGACACAGCAGTATTTACCTGTAGGTGGAGCAAGTAATAAGCCATGCTGTG
CAATATATACATAAAGCTTCTGCTTCTCATGGGAATTTAGTTACAGTGCTTGGAATGAGAAGGGGAAGGAAA
GAATTAACAAATGCCAAGATTTCTGGAGCAGATTGTACAGCTGTGACTTTGGAAAACAGAAAGTAAGACCCT
CAGAAAACCAATGAAGTCTAAGAGAAATAAAATTTAGTGGACAGGTATGAAAAGTGTAATTGCGCCTAACTA
CCAGATGGAGAGCTTCAGAATGGGCTATCCTTAGAGTCTAGTACATCTTGAGGCCTCTCAGCAGGAGACAAA
GGATTCCAAAAAGAGATGTGGAGGTGCTGAGGGCACCTCTATCTCTTTGTTGTTTAGTCTGTCATTGAATCA
ATCTACTTATCATCTTGGGTCTTTGAGTATTGTATGAAAGATCCTTCGTGCACACCACACACAGTCATGATT
TTGTTAAAGTAGCCTTCTTCAGATGCTTTTCTAAGGGCTAGTTACCAACTTTATTTCTGTGTTTCTGTAGAA
GAAACATTTTCAGTTCTTCATTGAGTTTGATTATGGAAATCCATTCAAAGTCACTATGAAAATTTTACTCAT
GTAGTTTGGAAATGCAACATTTTCCTATCATGAAATCTCTTTCAGAGAGGAGAATACAACATCTTAGTCCAG
ACATTTAACATACTGCATTTCAAGTACATGTGTGTGTGTTTTATTCAGGTTGTGTAATGCTCCCGTAGAATT
ATAGAACAATTAAATATGGTTAGTTCCAGAGTGCAAATTACAGAAGGAAGCTACTTGTTTAAAATTCCATAC
ACGTTTGCAGTTTCTTGTACACATTTGGATACTTTGAAAGATGACAGATTGTTAAATCCATTCAATGGTAAA
GAAACTCACCATCTGGAGATTGAGTCTACTTGTTAATGAATGACTAGCCCAATTATCCTTATAAATTGAATA
TGGTGACCAAATGCTTTGATATCATACTACTCTGCCTTTGTGGGCACATATGTAGACACTACTAAAAATAAA
TATTTTTGGAGATTAAAATGGAGAATAGAAGTAATTACATTATTTAGGTCTTAATCCAACTTTTTTCTAATA
TATCTAAACAATTGAAAGGGAAGCTTATTCATGGAATATTGGCTTGATTTATCTAGAAAGTTTTTCCTTCTT
CAATTTTACTATATTCATTCTACAGGAACAGCAATAAGTACTATTAAACAGAAGATGGCTACACTAAGTTCC
AATTTTGTTGCTGAATTGCTTCTGTGAGTTCACTTTTCAGTTCTAAGGAAGAATAATATTTGCTACATATTT
CACAGGGGTTCTTATGAAGGTAAATTTACCAGATTAATAAAAATTTATGAATATTAAAATTATCATTAATAA
TATAAAACACTTATTTGAGATTAAATTAAATTTTTCATGAGCCCCTCTTTGGCAGGAACTCTGTTTAATTCT
TTGTATTTATCCCAGCTTCTTAAATGGTGGCTGTAACATAATAAATGTTTAATAAATGCTTATATGAATGGA
TTTTTAGAATTAACTAAGAAGCCAAAAATGGCAACAATTTACAGAAATCCCACCTTTCCATGCTTAAGACAA
AAATGTCTTAAATATAAAGCTGTGATTATATCAAAAATCCAGATAAATCATCAAATATATCAGATTAAGACC
AGGGTTTACACACTTAGGCAATAGTCCTTTCCAAACCATGACAAAAACTACAAGTTTATTTATAATTTAACA
ACTCAGCTGAAAATATAACGGGTATATTTGTTATTCTAACTCTATTTTTTAAAGTTAATAATATAAAGTGGC
CATGTAAAATATTTTATTTTCCAGGCTAAAGCAAATGAAAGTTTGCTGGTATCAACACAGCCTGCCATATTT
TTCACAGCATGCAACAATGGTGCTAGGATAGCTATTTCTTACTGTAATTGCCAGAGGCAGAAATGGTCTGGG
TATAAGCTATTTCATAAAAGCAGCTTTAAATTGTCAGTATTAAGGTTTTCATGTGGAAAGGTGTCATTCAAA
AAAAAAGTAATTGGCATACATATTCCACATCATCGATCCTCTCTGTGGTGTTAATTTTTTTATATGACCAGT
AGAAAAATTTTAATATTCTCACAATATAGGTTTTGGGGCTTCCATATCATCAAAAGACTGAAAAATTATAAT
TTTAGAATTAAACTGATGGATTTCATTATAGAATTATCTGTGAGTTGTGTAGACACAGTCTTAATGTTTCTG
GTTATGACAGATAAGTTTGCTCAAAAAATGTGGATGAAGCCATTATTGTTATTATTGTTATTGCTTCTGTTC
AGTTGTCTAAGTATCATCCCTTCTGTGGCCCATCACGCAGCAGAGTTGCCCTACAAATTTCATTTGGCAGCG
CCATAACATTCATTTAAAAAGTTTATGAAAACATTCATTTGAAAGTTCCATGCAGCTTTAGCACAGAGTTGA
CCAAACACTGGCGTAAGTTCAATTTACACAGAATATTTGAATTGAAACAATAGAAATTTTTCTCATAATATA
TACCTATGTGAAACCAACTTATCTGCATAATTAAATCTAATACATATTTAAGCCAGTTTAAGTGCTTTGTGT
TGATGCCATGCTTATCAAATACATGCACAAGCTAAACATAATTTGAATGGGTCTATGAAGGAAAAATAATGC
TTAGACTTTGGTGTAGGTTCTTCCTGTGTAGCCATATACCCAGGCTCTGCAGTATCGAAGGATGCAAATGTT
GACATAGATGGAAGCTCTTACCTACCAAAGTGTTTAGGAAGGATAAAGTTACATTTGTCTTAATTTCTAACA
TTATCTTTGCTTTTATGTTTCATAAAAATTTGTCATTATTTATGCTGGTGAAACGTATAATCACATCCAATT
ATTTGAACACATGCAAAATAATTTTTTAAATTATGTTATTGTTTAAATTTGACTTATGGGAGATCAGTCAAA
AACTTAGAAGGTTTAACACTTCACTGATTAATGGTGCTGAAAACACGTTACAATTACCACATATCCTTGCTA

TAAGTTTTGAAGTTTGTTAGCAATTAAAGTTTTTTTATTCAGTGTGAACTGTCAGTATCTATTCTGGTGCTA
AATGTATGGTGCTAAATGAATTGTTAGTGTTGATGGCTTTAGTAATGCTCCTTTTATTCATTGCTAAATTTA
GTGTTATCCATTTGATTCCTGATTCAGAAATATCAATAAAATCCTATGTTAAATTAATCTTTACCAAAAACA
GGCAAGTTAACTCTGTTGTTTTAATTCAACAGTCCAACATTATTTAGGTGTTACAGAGTGTAAATATATTTC
TTTGGGAGTTATTTTCTTTTTAAAATCTTTTTATAGCTTGGCAATGTCCAAAGTCAAATATCACCTAAACTG
GTTAGATTACTTCTACAGCTAATAATATTGCAGGCACTGGCGCCCTCTGGTGGTTATGAAGACAAATTCTTA
ATGGCTACTTGACCTACAGCAAAAGCCATTTCTGTACCATAAAAATTTGTTGTGCAATATTAGAATTATCAT
ATGTTTCCTACATCTGACAGCACCTAAAATGTTTGATAATATTAACATGTATCTAAGAGGAAAAAAGAGTTA
ATATATTCTGGCACCCACTTTCCTAGTAATGTTTTCCATGATTTTCCAGTTCTGAGGCACTTATTAAAGTGC
TTTTTTTTTTCTGAATTAATTAGGTATTGGTAAAATATATTTTTAAATTTAGTTAGCTTTATAAACACAATT
AGAATTACAATTAATTAACAGAGGTATAATTGTCTCACTTTCAGAAGTGATCATTTATTTTTATTTAGCACA
GGTCATAAGAAAAATATATAGAAAAATAATCAATTTCATATATAAAAGGATTATTTCTCCACCTTTAATTAT
TGGCCTATCATTTGTTAGTGTTATTTGGTCATATTATTGAACTAATGTATTATTCCATTCAAAGTCTTTCTA
GATTTAAAAATGTATGCAAAAGCTTAGGATTATATCATGTGTAACTATTATAGATAACATCCTAAACCTTCA
GTTTAGATATATAATTGACTGGGTGTAATCTCTTTTGTAATCTGTTTTGACAGATTTCTTAAATTATGTTAG
CATAATCAAGGAAGATTTACCTTGAAGCACTTTCCAAATTGATACTTTCAAACTTATTTTAAAGCAGTAGAA
CCTTTTCTATGAACTAAATCACATGCAAAACTCCAACCTGTAGTATACATAAAATGGACTTACTTATTCCTC
TCACCTTCTCCAGTGCCTAGGAATATTCTTCTCTGAGCCCTAGGATTGATTCTATCACACAGAGCAACATTA
ATCTAAATGGTTTAGCTCCCTCTTTTTTCTCTAAAAACAATCAGCTAATAAAAAAAAAATTTGAGGGCCTAA
ATTATTTCAATGGTTGTTTGAAATATTCAGTTCAGTTTGTACCTGTTAGCAGTCTTTCAGTTTGGGGGAGAA
TTAAATACTGTGCTAAGCTGGTGCTTGGATACATATTACAGCATCTTGTGTTTTATTTGACAAACAGAATTT
TGGTGCCATAATATTTTGAGAATTAGAGAAGATTGTGATGCATATATATAAACACTATTTTTAAAAAATATC
TAAATATGTCTCACATATTTATATAATCCTCAAATATACTGTACCATTTTAGATATTTTTTAAACAGATTAA
TTTGGAGAAGTTTTATTCATTACCTAATTCTGTGGCAAAAATGGTGCCTCTGATGTTGTGATATAGTATTGT
CAGTGTGTACATATATAAAACCTGTGTAAACCTCTGTCCTTATGAACCATAACAAATGTAGCTTTTTAAAGT
CCATTGTATTGTTTTTTCTTTCAATAAAAGAGTATAATTAA

Table 17B. Protease inhibitor 15 protein sequence (SEQ ID NO:38).

MIAISAVSSALLFSLLCEASTVVLLNSTDSSPPTNNFTDIEAALKAQLDSADIPKARRKRYISQNDMIAIL
DYHNQVRGKVFPPAANMEYMVWDENLAKSAEAWAATCIWDHGPSYLLRFLGQNLSVRTGRYRSILQLVKPW
YDEVKDYAFPYPQDCNPRCPMRCFGPMCTHYTQMVWATSNRIGCAIHTCQNMNVWGSVWRRAVYLVCNYAP
KGNWIGEAPYKVGVPCSSCPPSYGGSCTDNLCFPGVTSNYLYWFK

TSC18: Tumor protein p53 inducible protein 3.

Table 18A. Tumor protein p53 inducible protein 3 (BC000474.1) nucleotide sequence (SEQ ID NO:39).

AGGAGCCAGAACCACTCGGCGCCGCCTGGTGCATGGGAGGGGAGCCGGGCCAGGAACAATATGTTAGCCGTG
CACTTTGACAAGCCGGGAGGACCGGAAAACCTCTACGTGAAGGAGGTGGCCAAGCCGAGCCCGGGGGAGGGT
GAAGTCCTCCTGAAGGTGGCGGCCAGCGCCCTGAACCGGGCGGACTTAATGCAGAGACAAGGCCAGTATGAC
CCACCTCCAGGAGCCAGCAACATTTTGGGACTTGAGGCATCTGGACATGTGGCAGAGCTGGGGCCTGGCTGC
CAGGGACACTGGAAGATCGGGGACACAGCCATGGCTCTGCTCCCCGGTGGGGGCCAGGCTCAGTACGTCACT
GTCCCCGAAGGGCTCCTCATGCCTATCCCAGAGGGATTGACCCTGACCCAGGCTGCAGCCATCCCAGAGGCC
TGGCTCACCGCCTTCCAGCTGTTACATCTTGTGGGAAATGTTCAGGCTGGAGACTATGTGCTAATCCATGCA
GGACTGAGTGGTGTGGGCACAGCTGCTATCCAACTCACCCGGATGGCTGGAGCTATTCCTCTGGTCACAGCT
GGCTCCCAGAAGAAGCTTCAAATGGCAGAAAAGCTTGGAGCAGCTGCTGGATTCAATTACAAAAAAGAGGAT
TTCTCTGAAGCAACGCTGAAATTCACCAAAGGTGCTGGAGTTAATCTTATTCTAGACTGCATAGGCGGATCC
TACTGGGAGAAGAACGTCAACTGCCTGGCTCTTGATGGTCGATGGGTTCTCTATGGTCTGATGGGAGGAGGT
GACATCAATGGGCCCCTGTTTTCAAAGCTACTTTTTAAGCGAGGAAGTCTGATCACCAGTTTGCTGAGGTCT
AGGGACAATAAGTACAAGCAAATGCTGGTGAATGCTTTCACGGAGCAAATTCTGCCTCACTTCTCCACGGAG
GGCCCCCAACGTCTGCTGCCGGTTCTGGACAGAATCTACCCAGTGACCGAAATCCAGGAGGCCCATAAGTAC
ATGGAGGCCAACAAGAACATAGGCAAGATCGTCCTGGAACTGCCCCAGTGAAGGAGGATGGGGCAGGACAGG
ACGCGGCCACCCCAGGCCTTTCCAGAGCAAACCTGGAGAAGATTCACAATAGACAGGCCAAGAAACCCGGTG
CTTCCTCCAGAGCCGTTTAAAGCTGATATGAGGAAATAAAGAGTGAACTGAAAAAAAAAAAAAAAAAAAAAA

AAAAAAAAAA

Table 18B. Tumor protein p53 inducible protein 3 protein sequence (SEQ ID NO:40).

MLAVHFDKPGGPENLYVKEVAKPSPGEGEVLLKVAASALNRADLMQRQGQYDPPPGASNILGLEASGHVAE
LGPGCQGHWKIGDTAMALLPGGGQAQYVTVPEGLLMPIPEGLTLTQAAAIPEAWLTAFQLLHLVGNVQAGD
YVLIHAGLSGVGTAAIQLTRMAGAIPLVTAGSQKKLQMAEKLGAAAGFNYKKEDFSEATLKFTKGAGVNLI
LDCIGGSYWEKNVNCLALDGRWVLYGLMGGGDINGPLFSKLLFKRGSLITSLLRSRDNKYKQMLVNAFTEQ
ILPHFSTEGPQRLLPVLDRIYPVTEIQEAHKYMEANKNIGKIVLELPQ

TSC19: Astrotactin.

Table 19A. Astrotactin (AB006627.1) nucleotide sequence (SEQ ID NO:41).

CCCACGCGTCCGGGCCGGGGCTCAAGATGGCTTTAGCCGGGCTCTGCGCCCTGCTCGCCTGCTGCTGGGGGC
CGGCGGCGGTGCTGGCCACGGCCGCCGGCGACGTGGATCCATCCAAGGAGCTGGAGTGCAAGCTCAAAAGCA
TCACGGTGTCGGCACTGCCCTTCCTGCGCGAGAACGACCTGAGCATCATGCACAGCCCCTCGGCCTCGGAGC
CCAAGCTCCTCTTCTCGGTGCGCAACGACTTCCCGGGAGAAATGGTCGTGGTGGACGACCTGGAGAACACGG
AGCTGCCCTACTTCGTGCTGGAGATCTCAGGGAACACAGAGGATATCCCTTTGGTGCGCTGGAGGCAGCAGT
GGCTGGAGAATGGCACTTTGCTTTTTCACATTCATCACCAAGATGGTGCCCCAAGCCTTCCTGGACAAGACC
CCACTGAAGAACCCCAACATGAGTCGGCAGAAGAGGAGCTGAGGATCCTCCACATCTCAGTCATGGGTGGCA
TGATCGCTCTGCTGCTGTCCATCTTGTGCCTGGTGATGATCCTGTATACTCGCCGGCGCTGGTGCAAACGCC
GCCGGGTCCCGCAGCCCCAGAAGAGTGCCAGTGCTGAGGCAGCCAATGAGATTCACTACATTCCTTCTGTGC
TGATCGGCGGGCACGGACGGGAGAGCCTGCGCAATGCCCGCGTGCAGGGCCACAACTCCAGTGGCACCCTGA
GCATCCGGGAGACACCTATCCTGGACGGCTATGAGTATGACATCACTGATCTGCGCCACCATCTGCAGAGGG
AGTGCATGAACGGAGGGGAGGACTTTGCCAGCCAGGTCACGCGCACCCTCGACTCCCTGCAGGGCTGCAATG
AAAAGTCGGGGATGGACCTCACACCAGGAAGTGACAATGCCAAGCTGTCACTGATGAACAAGTATAAAGATA
ATATTATAGCCACTAGCCCTGTGGACTCCAACCACCAGCAAGCCACCCTTCTCTCTCACACCTCCAGCAGCC
AGAGAAAGCGGATCAACAACAAAGCAAGAGCTGGTTCCGCCTTCTTGAACCCTGAAGGGGATTCTGGCACAG
AGGCAGAAAACGACCCCCAGCTGACCTTTTACACGGATCCTTCAAGGAGCAGGAGGCGTAGTAGAGTGGGTT
CTCCCCGAAGTCCTGTGAATAAGACCACCTTGACCCTGATCAGCATCACCAGCTGTGTGATTGGCCTCGTGT
GCTCCTCTCACGTCAACTGCCCTCTCGTTGTCAAGATCACCCTGCATGTCCCTGAGCACCTGATTGCTGATG
GGAGCCGCTTCATCTTGCTGGAGGGGAGCCAGCTGGATGCCAGTGACTGGCTGAACCCTGCCCAAGTGGTTC
TCTTCTCTCAGCAGAACTCCAGCGGACCCTGGGCCATGGACCTCTGTGCCCGGCGGCTCCTGGACCCCTGTG
AACACCAATGTGACCCCGAAACTGGGGAATGCCTCTGCTATGAAGGCTACATGAAGGATCCAGTACATAAGC
ACCTTTGCATTCGGAACGAATGGGGGACAAACCAGGGGCCATGGCCTTACACAATATTTCAGCGAGGCTTTG
ACCTGGTTTTGGGAGAGCAGCCCTCTGATAAAATATTTAGATTCACCTACACTCTTGGGGAGGGCATGTGGT
TGCCCCTCAGCAAGAGCTTTGTGATTCCACCAGCCGAACTGGCCATCAATCCATCAGCAAAGTGCAAGACGG
ACATGACTGTGATGGAGGATGCTGTGGAGGTCAGAGAGGAGCTGATGACTTCATCCTCCTTCGACAGCCTGG
AGGTTCTCTTAGATTCCTTTGGGCCGGTGCGCGACTGCAGCAAAGATAACGGGGGCTGCAGTAAGAATTTCC
GCTGTATTTCAGATCGCAAGCTGGACTCCACTGGTTGCGTGTGCCCATCTGGACTCAGTCCCATGAAGGACA
GCTCTGGCTGCTATGACCGCCACATCGGGGTGGACTGTTCCGACGGCTTCAACGGCGGCTGTGAGCAGCTGT
GCCTCCAGCAGATGGCGCCCTTCCCGGACGACCCCACCTTGTATAACATCCTCATGTTCTGTGGGTGCATCG
AGGACTACAAGCTTGGTGTGGATGGACGCTCTTGCCAACTCATCACGGAGACCTGTCCAGAGGGAAGTGACT
GTGGGGAAAGCAGGGAGCTTCCCATGAACCAGACCCTCTTTGGGGAGATGTTCTTTGGTTACAACAACCATT
CCAAGGAAGTGGCTGCCGGACAGGTGCTGAAAGGAACATTCAGGCAAAACAACTTTGCTCGTGGTTTAGACC
AGCAACTGCCAGATGGTCTTGTGGTGGCCACTGTGCCCCTGGAGAATCAATGCCTAGAGGAGATCTCGGAGC
CCACCCCTGACCCTGACTTCCTGACTGGGATGGTGAACTTCAGTGAAGTGTCTGGGTACCCTGTGCTGCAGC
ACTGGAAGGTCCGGTCTGTGATGTACCACATCAAACTCAACCAAGTGGCCATCTCTCAGGCCCTCAGCAATG
CTCTCCACTCGCTGGATGGGGCTACATCTCGTGCAGATTTTGTGGCGCTGTTGGACCAGTTCGGCAACCATT
ACATCCAGGAAGCTATCTACGGCTTTGAGGAGTCCTGTTCTATCTGGTACCCAAACAAGCAGGTCCAGCGGC
GACTCTGGCTGGAGTATGAAGACATCAGTAAAGGCAACTCCCCATCAGATGAGTCTGAGGAGCGGGAAAGAG
ACCCTAAGGTGCTGACATTCCCAGAATACATCACCAGCTTGTCAGACTCCGGCACCAAGCGCATGGCGGCTG
GAGTCCGCATGGAGTGCCAGAGCAAGGGACGATGCCCCTCGTCCTGCCCCCTGTGTCATGTGACATCCAGCC
CTGACACCCCTGCTGAGCCGGTTCTGCTGGAGGTGACCAAAGCAGCCCCCATCTATGAACTAGTGACCAACA

ACCAGACCCAGAGGCTCTTGCAGGAGGCTACCATGAGCTCTCTCTGGTGCTCAGGGACTGGAGATGTCATCG
AGGACTGGTGTCGATGTGACTCCACTGCTTTTGGAGCTGATGGACTCCCCACCTGTGCGCCTCTCCCACAGC
CTGTGCTGAGACTCTCCACGGTTCACGAGCCCAGCAGCACTCTTGTGGTCCTGGAGTGGGAACACTCAGAGC
CACCAATCGGGGTGCAGATTGTAGATTACCTCCTCCGTCAAGAGAAAGTCACTGACAGGATGGACCACTCCA
AAGTGGAGACAGAAACAGTGCTGAGCTTTGTGGACGACATCATCTCTGGAGCAAAGTCTCCTTGTGCAATGC
CATCTCAGGTGCCGGACAAGCAGCTCACCACCATCTCTCTGATCATACGATGCCTGGAACCTGACACCATTT
ACATGTTCACGCTGTGGGGAGTGGACAACACAGGACGGCGCTCCAGGCCAAGCGACGTGATCGTGAAGACCC
CATGCCCCGTGGTGGATGATGTCAAGGCTCAAGAAATAGCAGACAAGATCTACAATCTCTTCAATGGCTACA
CTAGTGGGAAGGAGCAGCAGACCGCCTACAACACCCTCCTGGATCTGGGTTCCCCCACCTTACACCGGGTCC
TCTACCACTATAACCAGCACTATGAGAGTTTTGGGGAATTCACCTGGCGATGTGAGGATGAGTTAGGTCCCA
GGAAAGCTGGTCTCATCCTTTCCCAGCTTGGGGACCTCAGCAGTTGGTGCAATGGACTCCTTCAGGAACCCA
AGATAAGCTTGCGGCGCAGCTCACTCAAGTACCTGGGGTGCCGCTACAGCGAGATCAAACCCTACGGACTTG
ACTGGGCGGAGCTCAGCCGGGACCTCAGGAAGACGTGTGAGGAGCAGACCCTGAGTATCCCCTACAACGACT
ATGGGGACAGCAAAGAGATC**TAG**CACCATAAGGCCAGGGAGCTGCTGCCAGAATGAAGTAGGAAAGAGGAGG
GATCCATCTGGGTTGGTCTGTGGATTTTTAATATTTTTTAATGGAACATGAAAACCTCCACAGCAACATCGA
AACCAGGGAGAAAGTGATCCTTGCTCCCTGCAGAACTTCTTCAGTATGATGTTCTCCATCTGCATGATTGGG
AAATCTGCCAGCCAGTGGCTTCATGCAGTGCCATATTTCTTTAGAGGATTACTTTGGGGTTTGCTTTGCCAT
TAATTTGTTCCATTCATTTTTTTTTCCCTGAGAAGTTTACCAAAATGCTCAAGAGCTCTGCCGTGCTCCCCA
TGAAAAGTCTATTAAGTAGGCACCCTGTGCTCACTCAGTTCCTAAATCCATTGCAACTGGGAGCAGAGGTGA
GGCCAGAAAGTTGTTAGGCCTGCCGCAGGCCCCACCCTCAAGCATTCCTCAGGAAGCGTCTCACTCTGGGAG
CCTTGGCCCTGCTCACAGAGAGAGACAATAGAAAATTGAGGAAGGTGGCCCTTGTCTGTGTCTCCTGGTTTT
CTTCCTAGGCCTTGCTATCACTATTTCCATACCCGAAAGGTGAAACCAGCTTTCATTATAGGCCCCAGTGGG
CCACTTGGGTTTTGAGATCCTTCCTTATTTTAAGCCAGGACTGGGATTAAATCTCCCTCTGTCAGATCTCTG
TCCCTTCCTCTGAACAACATGATCTTTGAGAGGGAACAAGATGCCATCTGTCAACTGCACCTTCAGAAAAGT
CTACCTGGGAGACTAGTTAGCAGTCCACATTCAAGAGAAGACTTGGAGTTTATTGTTTTTTAAAAAAACCAT
GCTTCCTTTGGATAGACTTCTCCAGCCTACCAATATATATCCATGTGCCTGGATTATCTTTAACCCCCACAC
CTCTTACCTTGGACAGGTAAGGCTTGGCCGATGTCTGATTGGGACCAGGAGGGGTCAACACTTTCATATCAG
TGTTACAGTGAACTAAAGCTATTATTGATCACAAAAAACTTCTGTTCATCCCCACCTTGCTAAATTTGCTTG
TGTTGCTAGTTTTGCAAATCGTTTCTCTGATGACCATAAGCAGGAGGATTCCACCATGGTCACTGCCCATCC
AGTCACAGGGATTCTGTGTAGGGAAGCACCACTGATTGCAGTTAACATCTAGAGTGTTGTTTCCATCCCACT
GCCCAAGCATTGGCATGGTCATGAATGGTGGCCCAGCCAACAGGAAGCCCAGCCTTTCAGAAAGAGCCTGGC
ACGGCCCTGTTGACTAGCAATGGCCTTAGCTGTCCCACACAACTCAGTGGCCTGAACACACACCTTCAGCCA
CCATGCCTTTGACCAGGGCTCCTCATCTGGAAACATATGAGAAAGGTCAGCAAACAGATGCAAGACCTATAA
GGCTAGTCATTGAGCTATATTGGTTTTTTTTCTAAATAGTAGTAGTGACAGATAACATTTATTGAGTGCTTG
CTGTATGCCAGGCGCTGATGTAAGCACTTTAGGTATCATTGAATTCTCACAGCAACTCCTGAGGAAAGTGCT
ATTCTTGTCTCCATTTTAGTGTTGAGGAAAACGAGGCAAAGAGAGGTTATACAACTTGCCTCAAATCCCTTG
TGCACTGTAACTCACACTGAGTTTCAGTGTGATTTCAGGCTGTTGGTCTCCAGGGCACAGGATCTTAGCTAC
TCTGGGATACCCAGTTCTGTTTTCAGTATCATCTGGCACACAACTGTCCAAGCTCTCAGCCCCACAGGGAAC
CTGCCCAGAGAGCTTTACCTTTCCCAAGCATCTGTGGCATGGACATGTCCTCTGTGCAGTGGAAGGAGGAGG
GGCGAAAGTACGCCCTTAGCCTTTGGAGCTAGAGCACCCTTGGGACCCCTAGTTCCACTGCACATGGCCCTC
CTCCCCACCCTCATGACTGGGAAGGAAGCCTGTGATGAGGCTGAGATAAAGCACAGGGTGGTTTCACTCTCC
TCTCTCCTTCTTTCCAAACACTGAAGGATTTATTTCAAACTCTCTAATGCACCTGCCTCAGAGATTCCCCTA
CTTTCAAAGCAAAGATCAGCAGAAAAATTGGCTGTCCCACCTGTGGCAAATGCTGGAGCCTCAGTTAAAGTG
CCTCAAGGGGCAAATATTTCACCATTGCCAGAGAAGATGTGACAGGCCAATCAGACAGGGCCCAGAGCATCT
CTTTGCTGCTACTGTTTTGCCATCCTTCTATTCATATCTGTGCAGAACACGGTGTTTTAAGCTTGAGTGAAA
GGAGGGTGAGGCTGCCGATGCCTTCCTGCCCAGAAGTGGATGATGTGGGAGTTGACAGGCCAGGGAGAGGGT
GAAGCAGGTATCAGAGTCACTCCTCTGTACCCTCTCCTTCTGTTTTTATTTTAGGCACACTATCTTCCTCTC
TCCTATCTTTCCCTCAATCTCCCAAGTTCCTCTACCTTCTTTATCTTTGTCTTTTACTTCTTCTTTCTGTGA
CCCTCCTTTTTTGGCCTCCTCTTTCCCCAAGACTTTCTTCCTCCTGTTTCTCGTTGAGTTCTCCCCACTGAA
TGTGTGTATGTATGTACACACACACACGTGTGCACACACAATGCACACAACTCCTATGACTGGCTCCTAC
TTACATTCAAGTTAAAAAGGCTGATATGAACAGGGCAGGGGAAAATCTTAGGATGGTTGTACAATTGACTGG
AGGATTTTTTCCCCTTGGAAGACACTATTGATCTCAACCTGCTGACTTTTCCTAATGCTTACCTGAAGGAAC
CCATCCTGGCTAGAAAGGGTGATGGTACTGGACCGGTATTCAACCTTGAGTTTTCAAGCTGCCAAACAGGTC
TTAAGGGAGGTGCTTATATCCCACCAACACTCTCCCAGCTCCCATGTCCCCAAGACCTCTGGAGTTTCCTCT
TGAATGTACATGAACCACTGTAATAGCATTAGACTTTTAATTGAGTGTGCAATCGTTTTCCATGGAGTTTGG
TCCGTTCATTATTTTTTAGTTAACTACACTTCTTGATATTCAAATGTTCTATTAAAAAAACTGAGTATGAAG
AAAAACACTTTACTACTGCAGAAGGAAGAAAGAATATAATATGACCATCTTCAGGTATAACAGTGTTGTTTA
AAAGAGAATTATTGTATGATTATAAAAGATGAAATAATTAACTGAATAATAAAACAAAGCTATTAGTAAGC

Table 19B. Astrotactin protein sequence (SEQ ID NO:42).

HASGPGLKMALAGLCALLACCWGPAAVLATAAGDVDPSKELECKLKSITVSALPFLRENDLSIMHSPSASE
PKLLFSVRNDFPGEMVVVDDLENTELPYFVLEISGNTEDIPLVRWRQQWLENGTLLFHIHHQDGAPSLPGQ
DPTEEPQHESAEEELRILHISVMGGMIALLLSILCLVMILYTRRRWCKRRRVPQPQKSASAEAANEIHYIP
SVLIGGHGRESLRNARVQGHNSSGTLSIRETPILDGYEYDITDLRHHLQRECMNGGEDFASQVTRTLDSLQ
GCNEKSGMDLTPGSDNAKLSLMNKYKDNIIATSPVDSNHQQATLLSHTSSSQRKRINNKARAGSAFLNPEG
DSGTEAENDPQLTFYTDPSRSRRRSRVGSPRSPVNKTTLTLISITSCVIGLVCSSHVNCPLVVKITLHVPE
HLIADGSRFILLEGSQLDASDWLNPAQVVLFSQQNSSGPWAMDLCARRLLDPCEHQCDPETGECLCYEGYM
KDPVHKHLCIRNEWGTNQGPWPYTIFQRGFDLVLGEQPSDKIFRFTYTLGEGMWLPLSKSFVIPPAELAIN
PSAKCKTDMTVMEDAVEVREELMTSSSFDSLEVLLDSFGPVRDCSKDNGGCSKNFRCISDRKLDSTGCVCP
SGLSPMKDSSGCYDRHIGVDCSDGFNGGCEQLCLQQMAPFPDDPTLYNILMFCGCIEDYKLGVDGRSCQLI
TETCPEGSDCGESRELPMNQTLFGEMFFGYNNHSKEVAAGQVLKGTFRQNNFARGLDQQLPDGLVVATVPL
ENQCLEEISEPTPDPDFLTGMVNFSEVSGYPVLQHWKVRSVMYHIKLNQVAISQALSNALHSLDGATSRAD
FVALLDQFGNHYIQEAIYGFEESCSIWYPNKQVQRRLWLEYEDISKGNSPSDESEERERDPKVLTFPEYIT
SLSDSGTKRMAAGVRMECQSKGRCPSSCPLCHVTSSPDTPAEPVLLEVTKAAPIYELVTNNQTQRLLQEAT
MSSLWCSGTGDVIEDWCRCDSTAFGADGLPTCAPLPQPVLRLSTVHEPSSTLVVLEWEHSEPPIGVQIVDY
LLRQEKVTDRMDHSKVETETVLSFVDDIISGAKSPCAMPSQVPDKQLTTISLIIRCLEPDTIYMFTLWGVD
NTGRRSRPSDVIVKTPCPVVDDVKAQEIADKIYNLFNGYTSGKEQQTAYNTLLDLGSPTLHRVLYHYNQHY
ESFGEFTWRCEDELGPRKAGLILSQLGDLSSWCNGLLQEPKISLRRSSLKYLGCRYSEIKPYGLDWAELSR
DLRKTCEEQTLSIPYNDYGDSKEI

TSC20: Glycoprotein (transmembrane) nmb.

Table 20A. Glycoprotein (transmembrane) nmb (BC011595.1) nucleotide sequence (SEQ ID NO:43).

GAGGAATTCAGAGTTAAACCTTGAGTGCCTGCGTCCGTGAGAATTCAGC**ATG**GAATGTCTCTACTATTTCCT
GGGATTTCTGCTCCTGGCTGCAAGATTGCCACTTGATGCCGCCAAACGATTTCATGATGTGCTGGGCAATGA
AAGACCTTCTGCTTACATGAGGGAGCACAATCAATTAAATGGCTGGTCTTCTGATGAAAATGACTGGAATGA
AAAACTCTACCCAGTGTGGAAGCGGGGAGACATGAGGTGGAAAAACTCCTGGAAGGGAGGCCGTGTGCAGGC
GGTCCTGACCAGTGACTCACCAGCCCTCGTGGGCTCAAATATAACATTTGCGGTGAACCTGATATTCCCTAG
ATGCCAAAAGGAAGATGCCAATGGCAACATAGTCTATGAGAAGAACTGCAGAAATGAGGCTGGTTTATCTGC
TGATCCATATGTTTACAACTGGACAGCATGGTCAGAGGACAGTGACGGGGAAAATGGCACCGGCCAAAGCCA
TCATAACGTCTTCCCTGATGGGAAACCTTTTCCTCACCACCCCGGATGGAGAAGATGGAATTTCATCTACGT
CTTCCACACACTTGGTTGGCTTTTACAAACCCCTAAGCTTCTTCTTTACCTTTCCTTAAAATTTCAACCTTC
TCTTTTCTTACTCTATAAT**TGA**GAATGATAACACAGAGAGTTAATAACAGTCACCCTGCTAACTTTCCTTAG
CATGAGTGAACAGTGAGAGATAAAAATGAAATCTTGGTTAACCTTGCCAAATCTCCAGGACACCGAAGAGTT
AAAAAGAGAGAAAAACAAAAAGATTAAGCTCTTTTTCAAAAAAACAAAACCACTTAATTTTTTTCTACCTAA
AACCATAACAAGAAAAAATGCTAACACTTATTTATTTGAATGGCACATGGAGACCGGGCATGTGGCTCACAC
TTGTAATCCCAGCACCTTGGAAGGCGGAGGCGGGTGGATCACCTGAAGTCAGGAGTTCAAGACCAGCCTGGC
CAACATGGTGAAGTCCCGTCCCTACTAAAAATACAAAAATTAGCCAGGTGTGGTGGTGCGCACCTGTAATCC
CAGCTACTCAGGAGGCTGAGGCAGGAGAATCACTTGAATCCGGGAGGTGGAGGTTGCAGTGAGAGGAGATTG
AGCCATTGCACTCCAGCCTGGGCAACAGAGTGAGACTCCATCTCGAAAAACAAACAAACAAACAAAAAACAG
AATGGCACATTGATGAGCATTCATTGATTGATTCTTTAGTTTTTTTATGTTCTCTAAAGAATTTTTAAGATT
TAAAGAAGCATGTGCTATTTATTTGTAGGAAATCCTCAGAAAAGGTACAAATAAAAAATAAAAATTATCCAT
AATTAATACCAGAGATTATAATTGTTAATTATTATGGTGTTTTCTTTGCTAGTATTTAAGATCATTATTAAG
ATCACATACACATTTTTGCTTACTATCATTAGCATTTGATGATATGATTTTTTTAATTTTTATACATTGTTT
TAATGGCTGCACGATATTTCATTGTGTACAAATAAAATAACTACTGTTCCGCTTTGAAAAAAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

Table 20B. Glycoprotein (transmembrane) nmb protein sequence (SEQ ID NO:44).

MECLYYFLGFLLLAARLPLDAAKRFHDVLGNERPSAYMREHNQLNGWSSDENDWNEKLYPVWKRGDMRWKN
SWKGGRVQAVLTSDSPALVGSNITFAVNLIFPRCQKEDANGNIVYEKNCRNEAGLSADPYVYNWTAWSEDS

DGENGTGQSHHNVFPDGKPFPHHPGWRRWNFIYVFHTLGWLLQTPKLLLYLSLKFQPSLFLLYN

TSC21: Contactin 1.

Table 21A. Contactin 1 (AW072790) nucleotide sequence (SEQ ID NO:45).

TTTTTTTTGGGTAACATAAGACATTTATTACTTTATACTAATTTTTTCATTCATAAAAAGGACAAAGCACAG
TCCTATACTACTCCATTGAAAAAATGATAAAAAATAACTAAAAAATCAATTCAATATTTATCAGTATCAAAT
AAAACTACTATCACCTTTCCTGAAATACAAAGAAACAACAGATGTATCTATACCTATATAAAGTTTAATTCA
GAAATCTTGCGTCTTAAAGCAGATGATTATTAGTTAGCTTGACAACAGTTTAAAACTG**ATG**GTCCCAGTTAA
ATCTGTACAACTGTATGAGAAAATGAAAAGCTTGAGTTATCAGTGTACGAGAGATTTTAAACTACTTTATCT
CTGTCAGAAGTTCAAAACTAAACAACCTCCAAAGTCTGTTTTCCTCTTACCTTTCAGAACCATTTCATGCAA
AATC**TAA**CCAGTTTTGCTCGTTATTATCATATATTAGAAAATAAAAG

Table 21B. Contactin 1 protein sequence (SEQ ID NO:46).

MVPVKSVQLYEKMKSLSYQCTRDFKLLYLCQKFKTKQPPKSVFLLPFRTISCKI

TSC22: Neural epidermal growth factor like like-2.

Table 22A. Neural epidermal growth factor like like-2 (NM_006159.1) nucleotide sequence (SEQ ID NO:47).

TTGGGAGGAGCAGTCTCTCCGCTCGTCTCCCGGAGCTTTCTCCATTGTCTCTGCCTTTACAACAGAGGGAGA
CGATGGACTGAGCTGATCCGCACC**ATG**GAGTCTCGGGTCTTACTGAGAACATTCTGTTTGATCTTCGGTCTC
GGAGCAGTTTGGGGGCTTGGTGTGGACCCTTCCCTACAGATTGACGTCTTAACAGAGTTAGAACTTGGGGAG
TCCACGACCGGAGTGCGTCAGGTCCCGGGGCTGCATAATGGGACGAAAGCCTTTCTCTTTCAAGATACTCCC
AGAAGCATAAAAGCATCCACTGCTACAGCTGAACAGTTTTTTCAGAAGCTGAGAAATAAACATGAATTTACT
ATTTTGGTGACCCTAAAACAGACCCACTTAAATTCAGGAGTTATTCTCTCAATTCACCACTTGGATCACAGG
TACCTGGAACTGGAAAGTAGTGGCCATCGGAATGAAGTCAGACTGCATTACCGCTCAGGCAGTCACCGCCCT
CACACAGAAGTGTTTCCTTACATTTTGGCTGATGACAAGTGGCACAAGCTCTCCTTAGCCATCAGTGCTTCC
CATTTGATTTTACACATTGACTGCAATAAAATTTATGAAAGGGTAGTAGAAAAGCCCTCCACAGACTTGCCT
CTAGGCACAACATTTTGGCTAGGACAGAGAAATAATGCGCATGGATATTTTAAGGGTATAATGCAAGATGTC
CAATTACTTGTCATGCCCCAGGGATTTATTGCTCAGTGCCCAGATCTTAATCGCACCTGTCCAACTTGCAAT
GACTTCCATGGACTTGTGCAGAAAATCATGGAGCTACAGGATATTTTAGCCAAAACATCAGCCAAGCTGTCT
CGAGCTGAACAGCGAATGAATAGATTGGATCAGTGCTATTGTGAAAGGACTTGCACCATGAAGGGAACCACC
TACCGAGAATTTGAGTCCTGGATAGACGGCTGTAAGAACTGCACATGCCTGAATGGAACCATCCAGTGTGAA
ACTCTAATCTGCCCAAATCCTGACTGCCCACTTAAGTCGGCTCTTGCGTATGTGGATGGCAAATGCTGTAAG
GAATGCAAATCGATATGCCAATTTCAAGGACGAACCTACTTTGAAGGAGAAAGAAATACAGTCTATTCCTCT
TCTGGAGTATGTGTTCTCTATGAGTGCAAGGACCAGACCATGAAACTTGTTGAGAGTTCAGGCTGTCCAGCT
TTGGATTGTCCAGAGTCTCATCAGATAACCTTGTCTCACAGCTGTTGCAAAGTTTGTAAAGGTTATGACTTT
TGTTCTGAAAGGCATAACTGCATGGAGAATTCCATCTGCAGAAATCTGAATGACAGGGCTGTTTGTAGCTGT
CGAGATGGTTTTAGGGCTCTTCGAGAGGATAATGCCTACTGTGAAGACATCGATGAGTGTGCTGAAGGGCGC
CATTACTGTCGTGAAAATACAATGTGTGTCAACACCCCGGGTTCTTTTATGTGCATCTGCAAAACTGGATAC
ATCAGAATTGATGATTATTCATGTACAGAACATGATGAGTGTATCACAAATCAGCACAACTGTGATGAAAAT
GCTTTATGCTTCAACACTGTTGGAGGACACAACTGTGTTTGCAAGCCGGGCTATACAGGGAATGGAACGACA
TGCAAAGCATTTTGCAAAGATGGCTGTAGGAATGGAGGAGCCTGTATTGCCGCTAATGTGTGTGCCTGCCCA
CAAGGCTTCACTGGACCCAGCTGTGAAACGGACATTGATGAATGCTCTGATGGTTTTGTTCAATGTGACAGT
CGTGCTAATTGCATTAACCTGCCTGGATGGTACCACTGTGAGTGCAGAGATGGCTACCATGACAATGGGATG
TTTTCACCAAGTGGAGAATCGTGTGAAGATATTGATGAGTGTGGGACCGGGAGGCACAGCTGTGCCAATGAT
ACCATTTGCTTCAATTTGGATGGCGGATATGATTGTCGATGTCCTCATGGAAAGAATTGCACAGGGGACTGC
ATCCATGATGGAAAAGTTAAGCACAATGGTCAGATTTGGGTGTTGGAAAATGACAGGTGCTCTGTGTGCTCA
TGTCAGAATGGATTCGTTATGTGTCGACGGATGGTCTGTGACTGTGAGAATCCCACAGTTGATCTTTTTTGC
TGCCCTGAATGTGACCCAAGGCTTAGTAGTCAGTGCCTCCATCAAAATGGGGAAACTTTGTATAACAGTGGT

GACACCTGGGTCCAGAATTGTCAACAGTGCCGCTGCTTGCAAGGGGAAGTTGATTGTTGGCCCCTGCCTTGC
CCAGATGTGGAGTGTGAATTCAGCATTCTCCCAGAGAATGAGTGCTGCCCGCGCTGTGTCACAGACCCTTGC
CAGGCTGACACCATCCGCAATGACATCACCAAGACTTGCCTGGACGAAATGAATGTGGTTCGCTTCACCGGG
TCCTCTTGGATCAAACATGGCACTGAGTGTACTCTCTGCCAGTGCAAGAATGGCCACATCTGTTGCTCAGTG
GATCCACAGTGCCTTCAGGAACTGTGAAGTTAACTGTCTCATGGGAGATTTCTGTTAAAAGAATGTTCTTTC
ATTAAAAGACCAAAAAGAAGTTAAAACTTAAATTGGGTGATTTGTGGGCAGCTAAATGCAGCTTTGTTAATA
GCTGAGTGAACTTTCAATTATGAAATTTGTGGAGCTTGACAAAATCACAAAAGGAAAATTACTGGGGCAAAA
TTAGACCTCAAGTCTGCCTCTACTGTGTCTCACATCACCATGTAGAAGAATGGGCGTACAGTATATACCGTG
ACATCCTGAACCCTGGATAGAAAGCCTGAGCCCATTGGATCTGTGAAAGCCTCTAGCTTCACTGGTGCAGAA
AATTTTCCTCTAGATCAGAATCTTCAGAATCAGTTAGGTTCCTCACTGCAAGAAATAAAATGTCAGGCAGTG
AATGAATTATATTTTCAGAAGTAAAGCAAAGAAGCTATAACATGTTATGTACAGTACACTCTGAAAAGAAAT
CTGAAACAAGTTATTGTAATGATAAAAATAATGCACAGGCATGGTTACTTAATATTTTCTAACAGGAAAAGT
CATCCCTATTTCCTTGTTTTACTGCACTTAATATTATTTGGTTGAATTTGTTCAGTATAAGCTCGTTCTTGT
GCAAAATTAAATAAATATTTCTCTTACCTT

Table 22B. Neural epidermal growth factor like like-2 protein sequence (SEQ ID NO:48).

MESRVLLRTFCLIFGLGAVWGLGVDPSLQIDVLTELELGESTTGVRQVPGLHNGTKAFLFQDTPRSIKAST
ATAEQFFQKLRNKHEFTILVTLKQTHLNSGVILSIHHLDHRYLELESSGHRNEVRLHYRSGSHRPHTEVFP
YILADDKWHKLSLAISASHLILHIDCNKIYERVVEKPSTDLPLGTTFWLGQRNNAHGYFKGIMQDVQLLVM
PQGFIAQCPDLNRTCPTCNDFHGLVQKIMELQDILAKTSAKLSRAEQRMNRLDQCYCERTCTMKGTTYREF
ESWIDGCKNCTCLNGTIQCETLICPNPDCPLKSALAYVDGKCCKECKSICQFQGRTYFEGERNTVYSSSGV
CVLYECKDQTMKLVESSGCPALDCPESHQITLSHSCCKVCKGYDFCSERHNCMENSICRNLNDRAVCSCRD
GFRALREDNAYCEDIDECAEGRHYCRENTMCVNTPGSFMCICKTGYIRIDDYSCTEHDECITNQHNCDENA
LCFNTVGGHNCVCKPGYTGNGTTCKAFCKDGCRNGGACIAANVCACPQGFTGPSCETDIDECSDGFVQCDS
RANCINLPGWYHCECRDGYHDNGMFSPSGESCEDIDECGTGRHSCANDTICFNLDGGYDCRCPHGKNCTGD
CIHDGKVKHNGQIWVLENDRCSVCSCQNGFVMCRRMVCDCENPTVDLFCCPECDPRLSSQCLHQNGETLYN
SGDTWVQNCQQCRCLQGEVDCWPLPCPDVECEFSILPENECCPRCVTDPCQADTIRNDITKTCLDEMNVVR
FTGSSWIKHGTECTLCQCKNGHICCSVDPQCLQEL

TSC 23: Transmembrane protein with EGF-like and two follistatin-like domains 1.

Table 23A. Transmembrane protein with EGF-like and two follistatin-like domains 1 (BF439316) nucleotide sequence (SEQ ID NO:49).

TTTATAGTGAAAACATTATATTATAACATGCTTTTGCAAACAAAATATTAAAATTAATAATTTTTAACATAT
TCTTTAAATTCTACATGCATACTTTTGAATATCTAAACTACATGTTAAACAGCTGAATACATTCTACTCACA
CTTCAGATCTTTAAACACCAACAATCTATGAATATTAATCTATTACTACAGGACAAATTTGGATATACGTCT
TGGATAAATTTTAAGCTCACTTTAAGAGCACCAATCATTAACAATCATTTGTGTATTTTATTCACAAACACT
GATACGATTTGTTTATTTATGTTAAAACAAACATTTTCTTTAAAAATGAATGTGTATTAAAGTAGTTTAACT
GGTAGAATAGGCTTTATTCCAATCTGTTTGTTAAACAGCCTATTTTCACAATATCTATATCTACTTTTCATT
GATCTGTTCCATCATTACTAACATATTTGTTCAAATTATTAGGACTATTTTTTCAAAGGGAGGAATAATCAA
ATTCCCCAGTCCATATATCTTATAAATATTTTACACCTAATACACACAGCTTTACAGT

Table 23B. Transmembrane protein with EGF-like and two follistatin-like domains 1 (BF439316) protein sequence (SEQ ID NO:50).

MNINLLLQDKFGYTSWINFKLTLRAPIINNHLCILFTNTDTICLFMLKQTFSLKMNVY

Table 23C. Transmembrane protein with EGF-like and two follistatin-like domains 1 (U19878.1) nucleotide sequence (SEQ ID NO:51).

AAAAAAATTAAAAAAAAAAAAAAAAACAGAAAAAAAAACATAGTACATGCCAAGATATTATTATGACAATTA
CAAATACAAATAAATTATGATCTTTGACCTCAGCATATTTATTAACTAAAAGGGAAGATAAAACAGGCACAT
AACTATAACAGGGGCACCAGTC**ATG**GGCGCCGCAGCCGCTCAGGCGCCTCTCGGGCTGCCTGCGGCCTCCGC
TCGCCTTCTGCTGCTAGCGACGTCGGTGCTTCTGCTCTTCGCCTTCTCTCTGCCCGGGAGCCGCGCGTCCAA
CCAGCCCCCGGGTGGTGGCGGCGGCACGGGCGGGGACTGTCCCGGCGGCAAAGGCAAGAGCATCAACTGCTC
AGAATTAAATGTGAGGGAGTCTGACGTAAGAGTTTGTGATGAGTCATCATGTAAATATGGAGGAGTCTGTAA
AGAAGATGGAGATGGTTTGAAATGTGCATGCCAATTTCAGTGCCATACAAATTATATTCCTGTCTGTGGATC
AAATGGGGACACTTATCAAAATGAATGCTTTCTCAGAAGGGCTGCTTGTAAGCACCAGAAAGAGATAACAGT
AATAGCAAGAGGACCATGCTACTCTGATAATGGATCTGGATCTGGAGAAGGAGAAGAGGAAGGGTCAGGGGC
AGAAGTTCACAGAAAACACTCCAAGTGTGGACCCTGCAAATATAAAGCTGAGTGTGATGAAGATGCAGAAAA
TGTTGGGTGTGTATGTAATATAGATTGCAGTGGATACAGTTTTAATCCTGTGTGTGCTTCTGATGGGAGTTC
CTATAACAATCCCTGTTTTGTTCGAGAAGCATCTTGTATAAAGCAAGAACAAATTGATATAAGGCATCTTGG
TCATTGCACAGATACAGATGACACTAGTTTGTTGGGAAAGAAAGATGATGGACTACAATATCGACCAGATGT
GAAAGATGCTAGTGATCAAAGAGAAGATGTTTATATTGGAAACCACATGCCTTGCCCTGAAAACCTCAATGG
TTACTGCATCCATGGAAAATGTGAATTCATCTATCTACTCAGAAGGGCTTCTTGTAGATGTGAATCTGGCTA
CACTGGACAGCACTGTGAAAAGACAGACTTTAGTATTCTCTATGTAGTGCCAAGTAGGCAAAAGCTCACTCA
TGTTCTTATTGCAGCAATTATTGGAGCTGTACAGATTGCCATCATAGTAGCAATTGTAATGTGCATAACAAG
AAAATGCCCCAAAAACAATAGAGGACGTCGACAGAAGCAAAACCTAGGTCATTTTACTTCAGATACGTCATC
CAGAATGGTT**TAA**ACTGATGACTTTTATATGTACACTGACCATGTGTATGTACATTTATTATGTCTTTTTTT
AAAGAATGGAAATATTTATTTCAGAAGGCCTTATTTTTGGACATTTTATAGTGTAGTACTGTTGGCTCGATA
TTTGAATATTCAGCTACGACAGTTTTGGACTGTTTAGTAGTCTTTGTTTTATGTTTTTAAATACAGAAATTG
CTTCACAAATTTGTACCACATGGTAATTCTAAGACTTGTTCTTTACCCATGGAATGTAATATTTTTGCAAAG
ATGGACTACTTCACAAATGGTTATAAAGTCATATCCACTTCTTCCACAATGACCACAGCAAATGACCCAAGC
ATGAACTAAAGAAGAG

Table 23D. Transmembrane protein with EGF-like and two follistatin-like domains 1 (U19878.1) protein sequence (SEQ ID NO:52).

MGAAAAQAPLGLPAASARLLLLATSVLLLFAFSLPGSRASNQPPGGGGGTGGDCPGGKGKSINCSELNVRE
SDVRVCDESSCKYGGVCKEDGDGLKCACQFQCHTNYIPVCGSNGDTYQNECFLRRAACKHQKEITVIARGP
CYSDNGSGSGEGEEEGSGAEVHRKHSKCGPCKYKAECDEDAENVGCVCNIDCSGYSFNPVCASDGSSYNNP
CFVREASCIKQEQIDIRHLGHCTDTDDTSLLGKKDDGLQYRPDVKDASDQREDVYIGNHMPCPENLNGYCI
HGKCEFIYLLRRASCRCESGYTGQHCEKTDFSILYVVPSRQKLTHVLIAAIIGAVQIAIIVAIVMCITRKC
PKNNRGRRQKQNLGHFTSDTSSRMV

Table 23E. Transmembrane protein with EGF-like and two follistatin-like domains 1 (NM_003692.1) nucleotide sequence (SEQ ID NO:53).

AGCGGGCGGCTGCTAGGAGGCACCGAGGCAGCGGCGGGGCTCTGGGCGCGCGGCTGGATGCCCCCGGCCTGC
GGCTCCCTGCGCTTCCCGCCGTCCAGGGGCACCAGTC**ATG**GGCGCCGCAGCCGCTGAGGCGCCGCTCCGGCT
GCCTGCCGCGCCTCCGCTCGCCTTCTGCTGCTACACGTCGGTGCTTCTGCTCTTCGCCTTCTCTCTGCCAGG
GAGCCGCGCGTCCAACCAGCCCCCGGGTGGTGGCGGCGGCAGCGGCGGGGACTGTCCCGGCGGCAAAGGCAA
GAGCATCAACTGCTCAGAATTAAATGTGAGGGAGTCTGACGTAAGAGTTTGTGATGAGTCATCATGTAAATA
TGGAGGAGTCTGTAAAGAAGATGGAGATGGTTTGAAATGTGCATGCCAATTTCAGTGCCATACAAATTATAT
TCCTGTCTGTGGATCAAATGGGGACACTTATCAAAATGAATGCTTTCTCAGAAGGGCTGCTTGTAAGCACCA
GAAAGAGATAACAGTAATAGCAAGAGGACCATGCTACTCTGATAATGGATCTGGATCTGGAGAAGGAGAAGA
GGAAGGGTCAGGGGCAGAAGTTCACAGAAAACACTCCAAGTGTGGACCCTGCAAATATAAAGCTGAGTGTGA
TGAAGATGCAGAAAATGTTGGGTGTGTATGTAATATAGATTGCAGTGGATACAGTTTTAATCCTGTGTGTGC
TTCTGATGGGAGTTCCTATAACAATCCCTGTTTTGTTCGAGAAGCATCTTGTATAAAGCAAGAACAAATTGA
TATAAGGCATCTTGGTCATTGCACAGATACAGATGACACTAGTTTGTTGGGAAAGAAAGATGATGGACTACA
ATATCGACCAGATGTGAAAGATGCTAGTGATCAAAGAGAAGATGTTTATATTGGAAACCACATGCCTTGCCC

TGAAAACGTCAATGGTTACTGCATCCATGGAAAATGTGAATTCATCTATTCTACTCAGAAGGCTTCTTGTAG
ATGTGAATCTGGCTACACTGGACAGCACTGTGAAAAGACAGACTTTAGTATTCTCTATGTAGTGCCAAGTAG
GCAAAAGCTCACTCATGTTCTTATTGCAGCAATTATTGGAGCTGTACAGATTGCCATCATAGTAGCAATTGT
AATGTGCATAACAAGAAAATGCCCCAAAAACAATAGAGGACGTCGACAGAAGCAAAACCTAGGTCATTTTAC
TTCAGATACGTCATCCAGAATGGTT**TAA**ACTGATGACTTTTATATGTACACTGACCATGTGATGTACATTTA
TTATGTCTTTTTTTAAAGAATGGAAATATTTATTTCAGAGGCCTTATTTTTGGACATTTTTAGTGTAGTACT
GTTGGCTCGTATTTAGAATATTCAGCTACGACAGTTTTGGACTGTTTAGTAGTCTTTGTTTTATGTTTTTAA
ATACAGAAATTGCTTTCACAAATTTGTACCACATGGTAATTCTAAGACTTGTTCTTTACCCATGGAATGTAA
TATTTTTGCAAAGATGGACTACTTCACAAATGGTTATAAAGTCATATCCACTTCTTCCACAATGACCACAGC
AAATGACCAAGCATGAACTAAAGGTAAAGATGTTTACAGATTACTTTTCTTACAAAAAAATCTAGAAGACAC
TGTGTTTAAATAGATATTTAAATGTTTTTGAGATTTAGTAACTGATTTTTTAGACACTGCCTATCGCATGAA
CTGTAAAGCTGTGTGTATTAGGTGTAAAATATTTATAAGATATATGGACTGGGGAATTTGATTATTCCTCCC
TTTGAAAAAATAGTCCTAATAATTTGAACAAATATGTTAGTAATGATGGAACAGATCAATGAAAAGTAGATA
TAGATATTGTGAAAATAGGCTGTTTAACAAACAGATTGGAATAAAGCCTATTCTACCAGTTAAACTACTTTA
ATACACATTCATTTTTAAAGAAAATGTTTGTTTTAACATAAATAAACAAATCGTATCAGTGTTTGTGAATAA
AATACAAAAATGATTGTTAATGATTGGTGCTCTTAAAGTGAGCTTAAAATTTATCCAAGACGTATATCCAAA
TTTGTCCTGTAGTAATAGATTAATATTCATAGATTGTTGGTGTTTAAAGATCTGAAGTGTGAGTAGAATGTA
TTCAGCTGTTTAACATGTAGTTTAGATATTCAAAAGTATGCATGTAGAATTTAAAGAATATGTTAAAAATTA
TTAATCTTAATATTTTGTTTGGAAAAGCATGTTATAATATAATGTTTTCACAAAAAAAAAAAAAAAA

Table 23F. Transmembrane protein with EGF-like and two follistatin-like domains 1 (NM_003692.1) protein sequence (SEQ ID NO:54).

MGAAAAEAPLRLPAAPPLAFCCYTSVLLLFAFSLPGSRASNQPPGGGGGSGGDCPGGKGKSINCSELNVRE
SDVRVCDESSCKYGGVCKEDGDGLKCACQFQCHTNYIPVCGSNGDTYQNECFLRRAACKHQKEITVIARGP
CYSDNGSGSGEGEEEGSGAEVHRKHSKCGPCKYKAECDEDAENVGCVCNIDCSGYSFNPVCASDGSSYNNP
CFVREASCIKQEQIDIRHLGHCTDTDDTSLLGKKDDGLQYRPDVKDASDQREDVYIGNHMPCPENLNGYCI
HGKCEFIYSTQKASCRCESGYTGQHCEKTDFSILYVVPSRQKLTHVLIAAIIGAVQIAIIVAIVMCITRKC
PKNNRGRRQKQNLGHFTSDTSSRMV

TSC24: Peroxisome proliferative activated receptor, gamma, coactivator 1, alpha.

Table 24A. Peroxisome proliferative activated receptor, gamma, coactivator 1, alpha (BC029800.1) nucleotide sequence (SEQ ID NO:55).

GTTGCCTGCATGAGTGTGTGCTCTGTGTCACTGTGGATTGGAGTTGAAAAAGCTTGACTGGCGTCATTCAGG
AGCTGG**ATG**GCGTGGGACATGTGCAACCAGGACTCTGAGTCTGTATGGAGTGACATCGAGTGTGCTGCTCTG
GTTGGTGAAGACCAGCCTCTTTGCCCAGATCTTCCTGAACTTGATCTTTCTGAACTAGATGTGAACGACTTG
GATACAGACAGCTTTCTGGGTGGACTCAAGTGGTGCAGTGACCAATCAGAAATAATATCCAATCAGTACAAC
AATGAGCCTTCAAACATATTTGAGGTAAGGACATCCTTTGGAAACATTAATTTTTCATTGAGTTTGGCTTGG
GCCCGAC**TAA**CATGGTAATAGACCTGAATGCATAATGAGTTCTTACTTTGCTATCATCAAAAGACTTTTCAT
CACAGTTACATACTTTCTAATTTATGGAAAAACAGCATTTGGAAAACAAATGTTTTGTTTTTATTTTTTTAA
AGATTTAAAAAATAAATCAACTAGGGACTAGGAATCAACAACTGTGAGTGAGTTAAACTGTGTTGAAATACT
AAAGGGTTGTGAAAGATTAGTGACAAAGAAGAACAAAAGTCTAAACCTGTTTATTCCTGTCTATTTCCCACA
GAAAGAATGAGCAATAAATGGTACCTCATATAAATTAATAAATAAGAAGGCCTTTCTTTTTAACCAAGGGGG
TAGATGTCTACCTTTGTTTGCTTTACTAATTAGGTGAGCTCTTTTGATTATTATTATTAATTATATTTTTGG
TTCATATCTCTAATTTCTTTATATAATGGGAATTGCTAAACTTGACTAATCTACTGTATACTTATAAATCAG
TCAAAATTCATTTACTTTTCAGTAGCAAGAATTACCTCCGTGACTCCGGACTCTTATTATAAGCCTACCCTA
TAATAAAGAATGTTAATCTATTCCTATTAAAGTGTTACTTTGAGAAAAGGAATTCTTTCCCACAAGATCAGT
ACTCATTTACTTGAAATACATTATTTTTTATAGGAACAAACATTTAGTGAGTACTCTGGCAAGTGAATTAAA
CGAAGGATGGCATATCGGCTAGTTTTCTTTATCACAACCGCCAGTGCCATCATCATCATCATCTAATGTTTT
CTGAGCACCTACTATGTGCTGGACTTTTCTTATTCATCAGCAAAGACATTTCTTATACTTCCATGTTATTTG
GTTGAAATCTGAGTCTTAAGAAAGCCAAGTTTAAAATATTAACTGAGTTTTGCTGGAACCCAGCATATAATA
CATGCTGAATAAATGTTTGTTAAATCATGAGAGAATGATGAATATATTAATGTTGATAACAATAATAGTAAT
GACAATAATGGCCAACATTTTGGTATACTCATGCTTAATATATGTCATCTCACTTATCCTTGAAAACAACCT
ATTGTTAGGTCCTATTGTTATCATTCCTGTTTTACATATGCAGACACTGAAACTCAGAGAGGTTATTTGTTT

TCCCAAATCACACAGTTGACAATAAAGACCTGGGATTTGAACCCCAAATTTATCGGACTTCAAAGTTTATA
TCCTTGATAAAAATAGAGAACCCATGAATTTGGGTGACAGCCATCCTTTACAAAGACATATCAAGCTGCTTC
TTTGCTCAATATATTTAAAAATAGAACAGAATCTTTCCTTTCAGTGTTGGTTGGCACGGAGGTAGAGTTAGC
TGGTGAGCCGAGACGGCTGTAGGTTCTGCCTATGGCTGAGATTTTGTAATACCTCTGGAGATTAAGTGGGTT
TTAGAAGAATGCTTAAGGTAGTAGAGTTTGGACTGGGGAGACAGAACAAGGTGGAGGGAACACTGAAGGTTG
TGGTTAGTTCTACTTTCCCAGGCTTCTCAGCCGGGTCTTAGAAAGTTCATGTGAGGACTTGGCCAGTTAGAA
CTAAATTGAACATTCCTCACTCAGTACACTTGTCAAGTTACAGGCCCATTCTAAGTCATGCTGCATTAAATA
AACAATGCTTTAAAAAATGTCCATCTCCATAGACCTCTTATCTAAAAATCACCTATTTCATATCAGGTGAAT
GCCATGCATTTTGTAGAGGCTAGAGAATAACTTAGCGGTAGGGGAGATGGCATAGGAGTCAATGCCTCTCTG
GTGGGCTACTTTAAAAAAAATACAACTTTCTCCATAACTTTTATGTCCCTATATTTTGTGTTGTGGTATTTG
TGAGAGGTACTTTGCATTTATACCTTCAGGAGACTTGGTTCAGCATCTAGTTAATTATCTACATGTAGGTGC
TTAATATATGCCATGCCACCCTTTTTGTCTCCCTGTATCATATTCTATGCTAATAAAATTATTTTCAGCACT
CTAAAAAAAAAAAAAAAAAAAAAAAAAAAA

Table 24B. Peroxisome proliferative activated receptor, gamma, coactivator 1, alpha protein sequence (SEQ ID NO:56).

MAWDMCNQDSESVWSDIECAALVGEDQPLCPDLPELDLSELDVNDLDTDSFLGGLKWCSDQSEIISNQYNN
EPSNIFEVRTSFGNINFSLSLAWARLTW

TSC25: Matrix metalloproteinase 14 (membrane-inserted).

Table 25A. Matrix metalloproteinase 14 (membrane-inserted) (NM_004995.2) nucleotide sequence (SEQ ID NO:57).

CAGACCCCAGTTCGCCGACTAAGCAGAAGAAAGATCAAAAACCGGAAAAGAGGAGAAGAGCAAACAGGCACT
TTGAGGAACAATCCCCTTTAACTCCAAGCCGACAGCGGTCTAGGAATTCAAGTTCAGTGCCTACCGAAGACA
AAGGCGCCCCGAGGGAGTGGCGGTGCGACCCCAGGGCGTGGGCCCGGCCGCGGAGCCCACACTGCCCGGCTG
ACCCGGTGGTCTCGGACC**ATG**TCTCCCGCCCCAAGACCCCCCCGTTGTCTCCTGCTCCCCCTGCTCACGCTC
GGCACCGCGCTCGCCTCCCTCGGCTCGGCCCAAAGCAGCAGCTTCAGCCCCGAAGCCTGGCTACAGCAATAT
GGCTACCTGCCTCCCGGGGACCTACGTACCCACACACAGCGCTCACCCCAGTCACTCTCAGCGGCCATCGCT
GCCATGCAGAAGTTTTACGGCTTGCAAGTAACAGGCAAAGCTGATGCAGACACCATGAAGGCCATGAGGCGC
CCCCGATGTGGTGTTCCAGACAAGTTTGGGGCTGAGATCAAGGCCAATGTTCGAAGGAAGCGCTACGCCATC
CAGGGTCTCAAATGGCAACATAATGAAATCACTTTCTGCATCCAGAATTACACCCCCAAGGTGGGCGAGTAT
GCCACATACGAGGCCATTCGCAAGGCGTTCCGCGTGTGGGAGAGTGCCACACCACTGCGCTTCCGCGAGGTG
CCCTATGCCTACATCCGTGAGGGCCATGAGAAGCAGGCCGACATCATGATCTTCTTTGCCGAGGGCTTCCAT
GGCGACAGCACGCCCTTCGATGGTGAGGGCGGCTTCCTGGCCCATGCCTACTTCCCAGGCCCCAACATTGGA
GGAGACACCCACTTTGACTCTGCCGAGCCTTGGACTGTCAGGAATGAGGATCTGAATGGAAATGACATCTTC
CTGGTGGCTGTGCACGAGCTGGGCCATGCCCTGGGGCTCGAGCATTCCAGTGACCCCTCGGCCATCATGGCA
CCCTTTTACCAGTGGATGGACACGGAGAATTTTGTGCTGCCCGATGATGACCGCCGGGGCATCCAGCAACTT
TATGGGGGTGAGTCAGGGTTCCCCACCAAGATGCCCCCTCAACCCAGGACTACCTCCCGGCCTTCTGTTCCT
GATAAACCCAAAAACCCCACCTATGGGCCCAACATCTGTGACGGGAACTTTGACACCGTGGCCATGCTCCGA
GGGGAGATGTTTGTCTTCAAGGAGCGCTGGTTCTGGCGGGTGAGGAATAACCAAGTGATGGATGGATACCCA
ATGCCCATTGGCCAGTTCTGGCGGGGCCTGCCTGCGTCCATCAACACTGCCTACGAGAGGAAGGATGGCAAA
TTCGTCTTCTTCAAAGGAGACAAGCATTGGGTGTTTGATGAGGCGTCCCTGGAACCTGGCTACCCCAAGCAC
ATTAAGGAGCTGGGCCGAGGGCTGCCTACCGACAAGATTGATGCTGCTCTCTTCTGGATGCCCAATGGAAAG
ACCTACTTCTTCCGTGGAAACAAGTACTACCGTTTCAACGAAGAGCTCAGGGCAGTGGATAGCGAGTACCCC
AAGAACATCAAAGTCTGGGAAGGGATCCCTGAGTCTCCCAGAGGGTCATTCATGGGCAGCGATGAAGTCTTC
ACTTACTTCTACAAGGGGAACAAATACTGGAAATTCAACAACCAGAAGCTGAAGGTAGAACCGGGCTACCCC
AAGTCAGCCCTGAGGGACTGGATGGGCTGCCCATCGGGAGGCCGGCCGGATGAGGGGACTGAGGAGGAGACG
GAGGTGATCATCATTGAGGTGGACGAGGAGGGCGGCGGGGCGGTGAGCGCGGCTGCCGTGGTGCTGCCCGTG
CTGCTGCTGCTCCTGGTGCTGGCGGTGGGCCTTGCAGTCTTCTTCTTCAGACGCCATGGGACCCCCAGGCGA
CTGCTCTACTGCCAGCGTTCCCTGCTGGACAAGGTC**TGA**CGCCCACCGCCGGCCCGCCCACTCCTACCACAA
GGACTTTGCCTCTGAAGGCCAGTGGCAGCAGGTGGTGGTGGGTGGGCTGCTCCCATCGTCCCGAGCCCCCTC
CCCGCAGCCTCCTTGCTTCTCTCTGTCCCCTGGCTGGCCTCCTTCACCCTGACCGCCTCCCTCCCTCCTGCC

TCGGCATTGCATCTTCCTAGATAGGTCCCCTGAGGGCTGAGTGGGAGGGCGGCCCTTTCCAGCCTCTGCCC
CTCAGGGGAACCCTGTAGCTTTGTGTCTGTCCAGCCCCATCTGAATGTGTTGGGGGCTCTGCACTTGAAGGC
AGGACCCTCAGACCTCGCTGGTAAAGGTCAAATGGGGTCATCTGCTCCTTTTCCATCCCCTGACATACCTTA
ACCTCTGAACTCTGACCTCAGGAGGCTCTGGGCACTCCAGCCCTGAAAGCCCCAGGTGTACCCAATTGGCAG
CCTCTCACTACTCTTTCTGGCTAAAAGGAATCTAATCTTGTTGAGGGTAGAGACCCTGAGACAGTGTGAGGG
GGTGGGGACTGCCAAGCCACCCTAAGACCTTGGGAGGAAAACTCAGAGAGGGTCTTCGTTGCTCAGTCAGTC
AAGTTCCTCGGAGATCTGCCTCTGCCTCACCTACCCCAGGGAACTTCCAAGGAAGGAGCCTGAGCCACTGGG
GACTAAGTGGGCAGAAGAAACCCTTGGCAGCCCTGTGCCTCTCGAATGTTAGCCTTGGATGGGGCTTTCACA
GTTAGAAGAGCTGAAACCAGGGGTGCAGCTGTCAGGTAGGGTGGGGCCGGTGGGAGAGGCCCGGGTCAGAGC
CCTGGGGGTGAGCCTGAAGGCCACAGAGAAAGAACCTTGCCCAAACTCAGGCAGCTGGGGCTGAGGCCCAAA
GGCAGAACAGCCAGAGGGGGCAGGAGGGGACCAAAAAGGAAAATGAGGACGTGCAGCAGCATTGGAAGGCTG
GGGCCGGGCAGGCCAGGCCAAGCCAAGCAGGGGGCCACAGGGTGGGCTGTGGAGCTCTCAGGAAGGGCCCTG
AGGAAGGCACACTTGCTCCTGTTGGTCCCTGTCCTTGCTGCCCAGGCAGCGTGGAGGGGAAGGGTAGGGCAG
CCAGAGAAAGGAGCAGAGAAGGCACACAAACGAGGAATGAGGGGCTTCACGAGAGGCCACAGGGCCTGGCTG
GCCACGCTGTCCCGGCCTGCTCACCATCTCAGTGAGGGGCAGGAGCTGGGGCTCGCTTAGGCTGGGTCCACG
CTTCCCTGGTGCCAGCACCCCTCAAGCCTGTCTCACCAGTGGCCTGCCCTCTCGCTCCCCCACCCAGCCCAC
CCATTGAAGTCTCCTTGGGCCACCAAAGGTGGTGGCCATGGTACCGGGGACTTGGGAGAGTGAGACCCAGTG
GAGGGAGCAAGAGGAGAGGGATGTCGGGGGGGTGGGGCACGGGGTAGGGGAAATGGGGTGAACGGTGCTGGC
AGTTCGGCTAGATTTCTGTCTTGTTTGTTTTTTTGTTTTGTTTAATGTATATTTTTATTATAATTATTATAT
ATGAATTCCAAAAAAAAAAAAAAAAAAAA

Table 25B. Matrix metalloproteinase 14 (membrane-inserted) protein sequence (SEQ ID NO:58).

MSPAPRPPRCLLLPLLTLGTALASLGSAQSSSFSPEAWLQQYGYLPPGDLRTHTQRSPQSLSAAIAAMQKF
YGLQVTGKADADTMKAMRRPRCGVPDKFGAEIKANVRRKRYAIQGLKWQHNEITFCIQNYTPKVGEYATYE
AIRKAFRVWESATPLRFREVPYAYIREGHEKQADIMIFFAEGFHGDSTPFDGEGGFLAHAYFPGPNIGGDT
HFDSAEPWTVRNEDLNGNDIFLVAVHELGHALGLEHSSDPSAIMAPFYQWMDTENFVLPDDDRRGIQQLYG
GESGFPTKMPPQPRTTSRPSVPDKPKNPTYGPNICDGNFDTVAMLRGEMFVFKERWFWRVRNNQVMDGYPM
PIGQFWRGLPASINTAYERKDGKFVFFKGDKHWVFDEASLEPGYPKHIKELGRGLPTDKIDAALFWMPNGK
TYFFRGNKYYRFNEELRAVDSEYPKNIKVWEGIPESPRGSFMGSDEVFTYFYKGNKYWKFNNQKLKVEPGY
PKSALRDWMGCPSGGRPDEGTEEETEVIIIEVDEEGGGAVSAAAVVLPVLLLLLVLAVGLAVFFFRRHGTP
RRLLYCQRSLLDKV

TSC26: Vascular endothelial growth factor D.

Table 26A. Vascular endothelial growth factor D (NM_004469.2) nucleotide sequence (SEQ ID NO:59).

CAAGACTTCTCTGCATTTTCTGCCAAAATCTGTGTCAGATTTAAGACACATGCTTCTGCAAGCTTCCATGAA
GGTTGTGCAAAAAAGTTTCAATCCAGAGTTGGGTTCCAGCTTTCTGTAGCTGTAAGCATTGGTGGCCACACC
ACCTCCTTACAAAGCAACTAGAACCTGCGGCATACATTGGAGAGATTTTTTTAATTTTCTGGACATGAAGTA
AATTTAGAGTGCTTTCTAATTTCAGGTAGAAGACATGTCCACCTTCTGATTATTTTTGGAGAACATTTTGAT
TTTTTTCATCTCTCTCTCCCCACCCCTAAGATTGTGCAAAAAAAAGCGTACCTTGCCTAATTGAAATAATTTC
ATTGGATTTTGATCAGAACTGATTATTTGGTTTTCTGTGTGAAGTTTTGAGGTTTCAAACTTTCCTTCTGGA
GAATGCCTTTTGAAACAATTTTCTCTAGCTGCCTGATGTCAACTGCTTAGTAATCAGTGGATATTGAAATAT
TCAAA**ATG**TACAGAGAGTGGGTAGTGGTGAATGTTTTCATGATGTTGTACGTCCAGCTGGTGCAGGGCTCCA
GTAATGAACATGGACCAGTGAAGCGATCATCTCAGTCCACATTGGAACGATCTGAACAGCAGATCAGGGCTG
CTTCTAGTTTGGAGGAACTACTTCGAATTACTCACTCTGAGGACTGGAAGCTGTGGAGATGCAGGCTGAGGC
TCAAAAGTTTTACCAGTATGGACTCTCGCTCAGCATCCCATCGGTCCACTAGGTTTGCGGCAACTTTCTATG
ACATTGAAACACTAAAAGTTATAGATGAAGAATGGCAAAGAACTCAGTGCAGCCCTAGAGAAACGTGCGTGG
AGGTGGCCAGTGAGCTGGGGAAGAGTACCAACACATTCTTCAAGCCCCCTTGTGTGAACGTGTTCCGATGTG
GTGGCTGTTGCAATGAAGAGAGCCTTATCTGTATGAACACCAGCACCTCGTACATTTCCAAACAGCTCTTTG
AGATATCAGTGCCTTTGACATCAGTACCTGAATTAGTGCCTGTTAAAGTTGCCAATCATACAGGTTGTAAGT
GCTTGCCAACAGCCCCCCGCCATCCATACTCAATTATCAGAAGATCCATCCAGATCCCTGAAGAAGATCGCT

GTTCCCATTCCAAGAAAGTCTGTCCTATTGACATGCTATGGGATAGCAACAAATGTAAATGTGTTTTGCAGG
AGGAAAATCCACTTGCTGGAACAGAAGACCACTCTCATCTCCAGGAACCAGCTCTCTGTGGGCCACACATGA
TGTTTGACGAAGATCGTTGCGAGTGTGTCTGTAAAACACCATGTCCCAAAGATCTAATCCAGCACCCCAAAA
ACTGCAGTTGCTTTGAGTGCAAAGAAAGTCTGGAGACCTGCTGCCAGAAGCACAAGCTATTTCACCCAGACA
CCTGCAGCTGTGAGGACAGATGCCCCTTTCATACCAGACCATGTGCAAGTGGCAAAACAGCATGTGCAAAGC
ATTGCCGCTTTCCAAAGGAGAAAAGGGCTGCCCAGGGGCCCCACAGCCGAAAGAATCCT**TGA**TTCAGCGTTC
CAAGTTCCCCATCCCTGTCATTTTTAACAGCATGCTGCTTTGCCAAGTTGCTGTCACTGTTTTTTTCCCAGG
TGTTAAAAAAAAAATCCATTTTACACAGCACCACAGTGAATCCAGACCAACCTTCCATTCACACCAGCTAAG
GAGTCCCTGGTTCATTGATGGATGTCTTCTAGCTGCAGATGCCTCTGCGCACCAAGGAATGGAGAGGAGGGG
ACCCATGTAATCCTTTTGTTTAGTTTTGTTTTTGTTTTTTGGTGAATGAGAAAGGTGTGCTGGTCATGGAAT
GGCAGGTGTCATATGACTGATTACTCAGAGCAGATGAGGAAAACTGTAGTCTCTGAGTCCTTTGCTAATCGC
AACTCTTGTGAATTATTCTGATTCTTTTTTATGCAGAATTTGATTCGTATGATCAGTACTGACTTTCTGATT
ACTGTCCAGCTTATAGTCTTCCAGTTTAATGAACTACCATCTGATGTTTCATATTTAAGTGTATTTAAAGAA
AATAAACACCATTATTCAAGCCAAAAAAAAAAAAAAAAA

Table 26B. Vascular endothelial growth factor D (NM_004469.2) protein sequence (SEQ ID NO:60).

MYREWVVVNVFMMLYVQLVQGSSNEHGPVKRSSQSTLERSEQQIRAASSLEELLRITHSEDWKLWRCRLRL
KSFTSMDSRSASHRSTRFAATFYDIETLKVIDEEWQRTQCSPRETCVEVASELGKSTNTFFKPPCVNVFRC
GGCCNEESLICMNTSTSYISKQLFEISVPLTSVPELVPVKVANHTGCKCLPTAPRHPYSIIRRSIQIPEED
RCSHSKKLCPIDMLWDSNKCKCVLQEENPLAGTEDHSHLQEPALCGPHMMFDEDRCECVCKTPCPKDLIQH
PKNCSCFECKESLETCCQKHKLFHPDTCSCEDRCPFHTRPCASGKTACAKHCRFPKEKRAAQGPHSRKNP

Table 26C. Vascular endothelial growth factor D (D89630.1) nucleotide sequence (SEQ ID NO:61).

CCAGCTTTCTGTAGCTGTAAGCATTGGTGGCCACACCACCTCCTTACAAAGCAACTAGAACCTGCGGCATAC
ATTGGAGAGATTTTTTTAATTTTCTGGACATGAAGTAAATTTAGAGTGCTTTCTAATTTCAGGTAGAAGACA
TGTCCACCTTCTGATTATTTTTGGAGAACATTTTGATTTTTTTCATCTCTCTCTCCCCACCCCTAAGATTGT
GCAAAAAAAGCGTACCTTGCCTAATTGAAATAATTTCATTGGATTTTGATCAGAACTGATCATTTGGTTTTC
TGTGTGAAGTTTTGAGGTTTCAAACTTTCCTTCTGGAGAATGCCTTTTGAAACAATTTTCTCTAGCTGCCTG
ATGTCAACTGCTTAGTAATCAGTGGATATTGAAATATTCAAA**ATG**TACAGAGAGTGGGTAGTGGTGAATGTT
TTCATGATGTTGTACGTCCAGCTGGTGCAGGGCTCCAGTAATGAACATGGACCAGTGAAGCGATCATCTCAG
TCCACATTGGAACGATCTGAACAGCAGATCAGGGCTGCTTCTAGTTTGGAGGAACTACTTCGAATTACTCAC
TCTGAGGACTGGAAGCTGTGGAGATGCAGGCTGAGGCTCAAAAGTTTTACCAGTATGGACTCTCGCTCAGCA
TCCCATCGGTCCACTAGGTTTGCGGCAACTTTCTATGACATTGAAACACTAAAAGTTATAGATGAAGAATGG
CAAAGAACTCAGTGCAGCCCTAGAGAAACGTGCGTGGAGGTGGCCAGTGAGCTGGGGAAGAGTACCAACACA
TTCTTCAAGCCCCCTTGTGTGAACGTGTTCCGATGTGGTGGCTGTTGCAATGAAGAGAGCCTTATCTGTATG
AACACCAGCACCTCGTACATTTCCAAACAGCTCTTTGAGATATCAGTGCCTTTGACATCAGTACCTGAATTA
GTGCCTGTTAAAGTTGCCAATCATACAGGTTGTAAGTGCTTGCCAACAGCCCCCCGCCATCCATACTCAATT
ATCAGAAGATCCATCCAGATCCCTGAAGAAGATCGCTGTTCCCATTCCAAGAAACTCTGTCCTATTGACATG
CTATGGGATAGCAACAAATGTAAATGTGTTTTGCAGGAGGAAAATCCACTTGCTGGAACAGAAGACCACTCT
CATCTCCAGGAACCAGCTCTCTGTGGGCCACACATGATGTTTGACGAAGATCGTTGCGAGTGTGTCTGTAAA
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AGACCATGTGCAAGTGGCAAAACAGCATGTGCAAAGCATTGCCGCTTTCCAAAGGAGAAAAGGGCTGCCCAG
GGGCCCCACAGCCGAAAGAATCCT**TGA**TTCAGCGTTCCAAGTTCCCCATCCCTGTCATTTTTAACAGCATGC
TGCTTTGCCAAGTTGCTGTCACTGTTTTTTTCCCAGGTGTTAAAAAAAAAATCCATTTTACACAGCACCACA
GTGAATCCAGACCAACCTTCCATTCACACCAGCTAAGGAGTCCCTGGTTCATTGATGGATGTCTTCTAGCTG
CAGATGCCTCTGCGCACCAAGGAATGGAGAGGAGGGGACCCATGTAATCCTTTTGTTTAGTTTTGTTTTTGT
TTTTTGGTGAATGAGAAAGGTGTGCTGGTCATGGAATGGCAGGTGTCATATGACTGATTACTCAGAGCAGAT
GAGGAAAACTGTAGTCTCTGAGTCCTTTGCTAATCGCAACTCTTGTGAATTATTCTGATTCTTTTTTATGCA
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ACCATCTGATGTTTCATATTTAAGTGTATTTAAAGAAAATAAACACCATTATTCAAGTCTAAAAAAAAAAAA
AAAAAAAAAAAA

Table 26D. Vascular endothelial growth factor D (D89630.1) protein sequence (SEQ ID NO:62).

MYREWVVVNVFMMLYVQLVQGSSNEHGPVKRSSQSTLERSEQQIRAASSLEELLRITHSEDWKLWRCRLRL
KSFTSMDSRSASHRSTRFAATFYDIETLKVIDEEWQRTQCSPRETCVEVASELGKSTNTFFKPPCVNVFRC
GGCCNEESLICMNTSTSYISKQLFEISVPLTSVPELVPVKVANHTGCKCLPTAPRHPYSIIRRSIQIPEED
RCSHSKKLCPIDMLWDSNKCKCVLQEENPLAGTEDHSHLQEPALCGPHMMFDEDRCECVCKTPCPKDLIQH
PKNCSCFECKESLETCCQKHKLFHPDTCSCEDRCPFHTRPCASGKTACAKHCRFPKEKRAAQGPHSRKNP

OTHER EMBODIMENTS

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

What is claimed is:

1. An isolated immortalized cell, wherein said cell does not express a Tuberous Sclerosis Complex-2 (TSC2) gene.
2. The cell of claim 1, wherein said cell is human.
3. The cell of claim 1, wherein said cell comprises a mutation in said TSC2 gene.
4. The cell of claim 3, wherein said mutation is in exon 16 of said TSC2 gene.
5. The cell of claim 4, wherein said mutation is a guanine to adenine transition at nucleotide position 1832 of exon 16 of said TSC2 gene.
6. The cell of claim 1, wherein said TSC2 gene comprises a *Pvu* II restriction site 6 or more nucleotides upstream or downstream from nucleotide position 1832 in Exon 16 of said *TSC2* gene.
7. The cell of claim1, wherein said cell constitutively phosphorylates ribosomal protein S6 or S6 kinase.
8. A culture comprising the cell of claim 1.
9. A cell deposited under ATCC Accession No: [].
10. A method of diagnosing tuberous sclerosis complex (TSC) or a predisposition to developing TSC in a subject comprising:
    a. providing a biological sample comprising genomic DNA;
    b. amplifying a region of the genomic DNA which comprises position 1832 of Exon 16 of the *TSC2* gene;
    c. digesting amplification product from (b) with a *Pvu* II restriction endonucleases; and
    d. identifying a *Pvu* II restriction site at least 6 bases upstream or downstream from position 1832, wherein the presence of said *Pvu* II restriction indicates TSC or a predisposition to developing TSC in said subject.

11. The method of claim 10, wherein the biological sample is a human biological sample.

12. The method of claim 10, where the biological sample is a human angiomyolipmoma tumor.

13. A method of diagnosing a TSC related disorder or a predisposition to developing TSC related disorder in a subject, comprising determining a level of expression of a TSC-associated gene in a patient derived tissue sample, wherein an increase of said level compared to a normal control level of said gene indicates that said subject suffers from or is at risk of developing a TSC related disorder.

14. The method of claim 13, wherein said TSC-associated gene is selected from the group consisting of TSC 2, and 4-26, wherein an increase in said level compared to a normal control level indicates said subject suffers from or is at risk of developing a TSC related disorder.

15. The method of claim 14, further comprising determining said level of expression of TSC1 or TSC3.

16. The method of claim 13, wherein said increase is at least 5-fold greater than said normal control level.

17. The method of claim 13, wherein said method further comprises determining said level of expression of a plurality of TSC-associated genes.

18. The method of claim 13, wherein said level of expression is determined by detecting a gene transcript of said TSC-associated gene.

19. The method of claim 13, wherein said TSC related disorder is angiomyolipmoma, lympangioleimyomatosis, cortical tubers, subependymal nodules, *or* giant-cell astrocytomas.

20. A TSC related disorder reference expression profile, comprising a pattern of gene expression of one or more genes selected from the group consisting of TSC 2 and 4-26.

21. The expression profile of claim 20, further comprising TS1 or TSC3.

22. A method of assessing the prognosis of a subject with a TSC related disorder comprising:

a. measuring over time the expression one or more nucleic acid sequences selected from the group consisting of TSC 2 and 4-26 in a subject derived cell population to yield a subject profile; and

b. comparing said subject profile to a TSC reference profile, wherein an increase in similarity between said subject profile and said referenece profile over time indicates an adverse prognosis of said subject.

23. A method of assessing the prognosis of a subject with a TSC related disorder comprising:

a. measuring over time the expression one or more nucleic acid sequences selected from the group consisting of TSC 2 and 4-26 in a subject derived cell population to yield a subject profile; and

b. comparing said subject profile to a TSC reference profile, wherein an decrease in similarity between said subject profile and said reference profile over time indicates an favorable prognosis of said subject.

24. A method of assessing the efficacy of a treatment of a TSC related disorder in a subject, comprising:

a. measuring the expression one or more nucleic acid sequences selected from the group consisting of TSC 2 and 4-26 in a subject derived cell population to yield a subject profile; and

b. comparing said subject profile to a TSC reference profile, wherein an increase in similarity between said subject profile and said reference profile over time indicates the treatment is not efficacious.

25. A method of assessing the efficacy of a treatment of a TSC related disorder, comprising:

a. measuring the expression one or more nucleic acid sequences selected from the group consisting of TSC 2 and 4-26 in a subject derived cell population to yield a subject profile; and

b. comparing said subject profile to a TSC reference profile, wherein an decrease in similarity between said subject profile and said reference profile over time indicates the treatment is efficacious.

26. A method for identifying a therapeutic agent suitable for treating a TSC related disorder in a selected subject, comprising:

a. contacting a subject derived cell population with a test agent

b. measuring the expression one or more nucleic acid sequences selected from the group consisting of TSC 2 and 4-26 in said subject derived cell population; and

c. comparing the expression of said nucleic acid sequences to the expression of said nucleic acid sequences a reference profile,

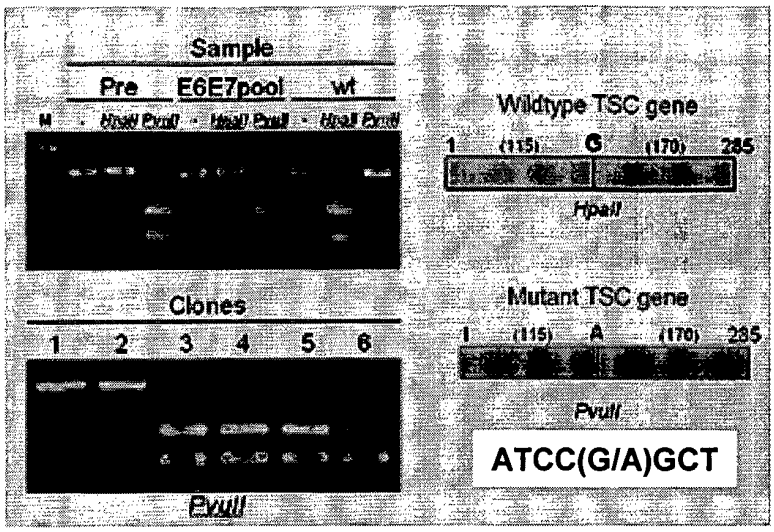
thereby identifying a therapeutic agent appropriate for said subject.

27. A method of identifying an agent that inhibits the expression or activity of a TSC-associated gene, comprising contacting a test cell expressing said TSC associated gene with a test agent and determining the expression level of said TSC associated gene, wherein a decrease of said level compared to a level of said gene in the absence of said test agent indicates that said test agent is an inhibitor of said TSC-associated gene.

28. A kit comprising a detection reagent which binds to two or more nucleic acid sequences selected from the group consisting of TSC 1-26

29. An array comprising a nucleic acid which binds to two or more nucleic acid sequences selected from the group consisting of TSC 1-26.

A.


Sample
Pre
E6E7pool
wt
M
HpaII PvuII
HpaII PvuII
HpaII PvuII
Clones
1 2 3 4 5 6
PvuII
Wildtype TSC gene
1 (115) G (170) 285
HpaII
Mutant TSC gene
1 (115) A (170) 285
PvuII
ATCC(G/A)GCT

B.

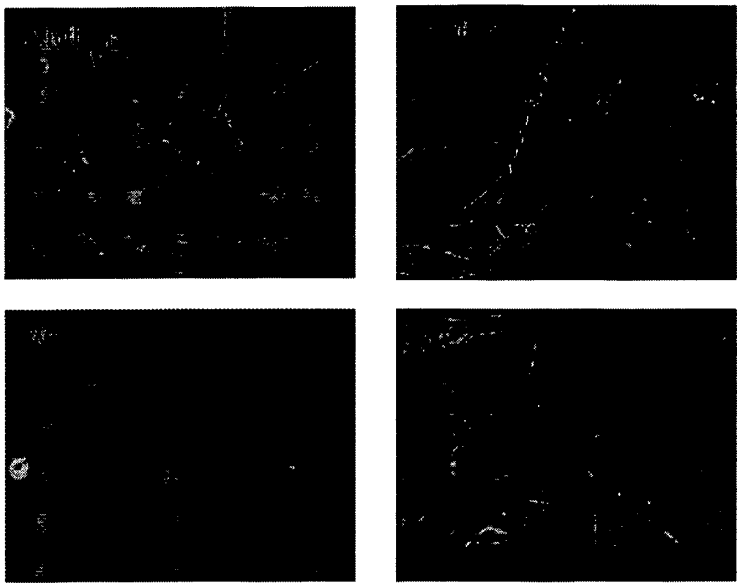


Figure 1

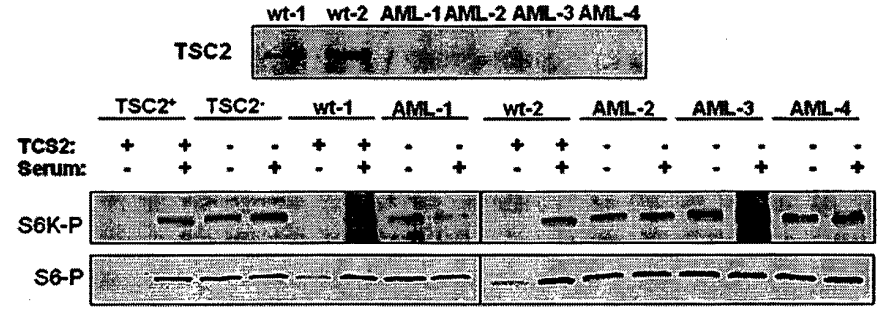

wt-1
wt-2
AML-1
AML-2
AML-3
AML-4
TSC2
TSC2+
TSC2-
wt-1
AML-1
wt-2
AML-2
AML-3
AML-4
TCS2:
Serum:
S6K-P
S6-P

Figure 2.

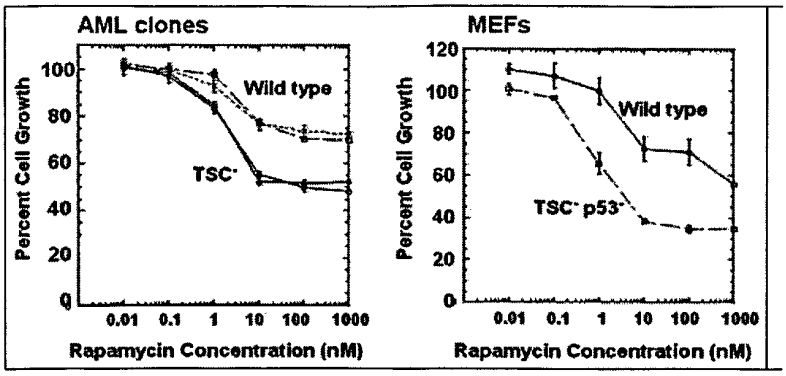
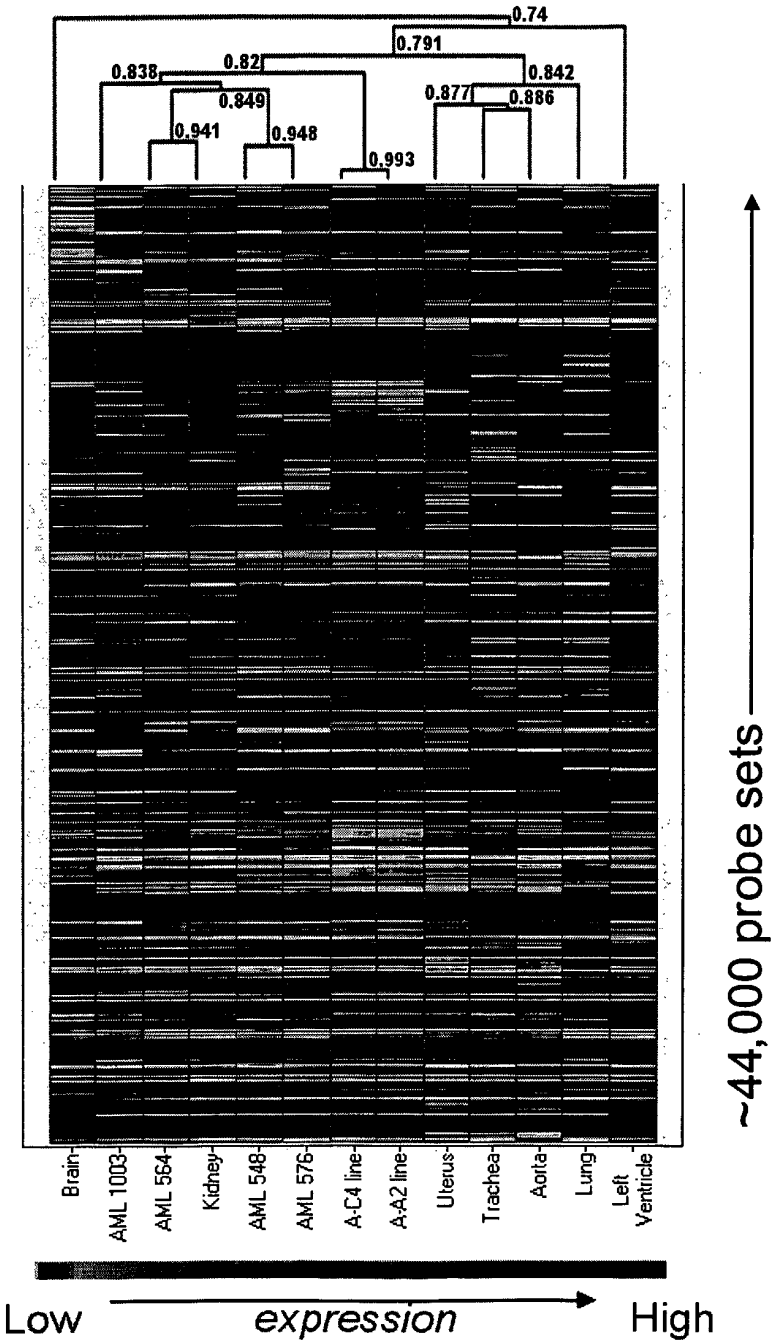

AML clones
Percent Cell Growth
100
80
60
40
20
0
Wild type
TSC-
0.01
0.1
1
10
100
1000
Rapamycin Concentration (nM)
MEFs
Percent Cell Growth
120
100
80
60
40
20
0
Wild type
TSC- p53-
0.01
0.1
1
10
100
1000
Rapamycin Concentration (nM)

Figure 3.

Figure 4.


0.74
0.791
0.838
0.82
0.842
0.849
0.877
0.886
0.941
0.948
0.993
~44,000 probe sets
Brain
AML 1003
AML 564
Kidney
AML 548
AML 576
A-C4 line
A-A2 line
Uterus
Trachea
Aorta
Lung
Left Ventricle
Low
expression
High

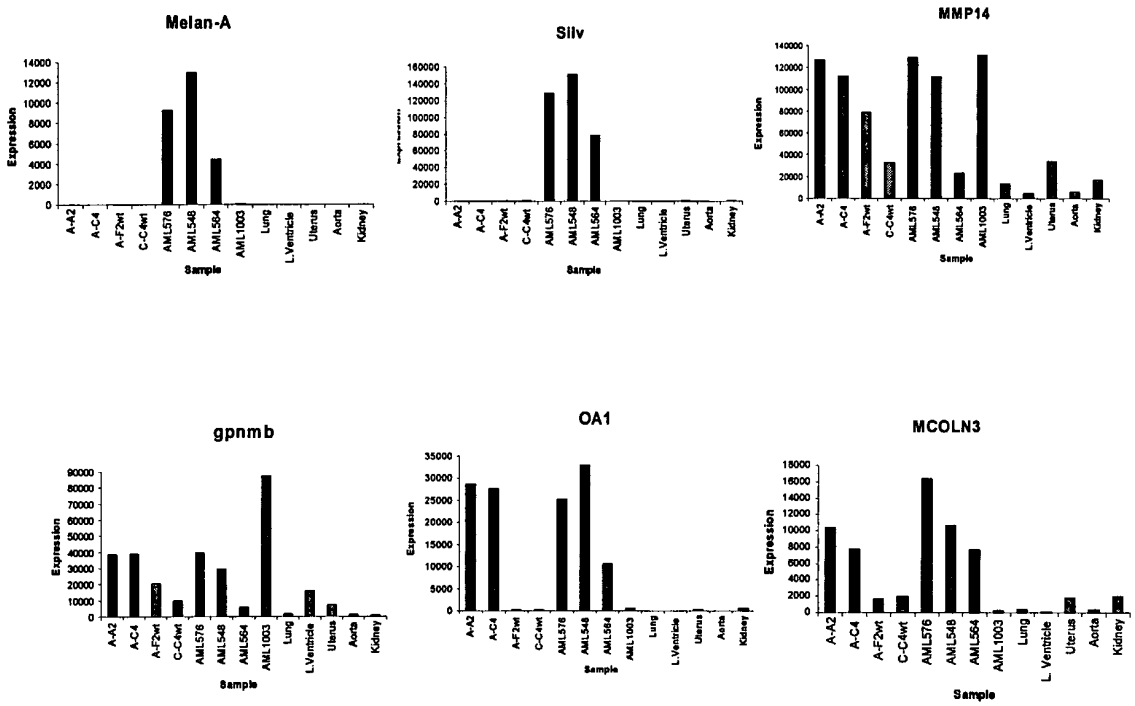

Melan-A
Silv
MMP14
gpnmb
OA1
MCOLN3
Expression
Sample
A-A2
A-C4
A-F2wt
C-C4wt
AML576
AML548
AML564
AML1003
Lung
L.Ventricle
Uterus
Aorta
Kidney

Figure 5.

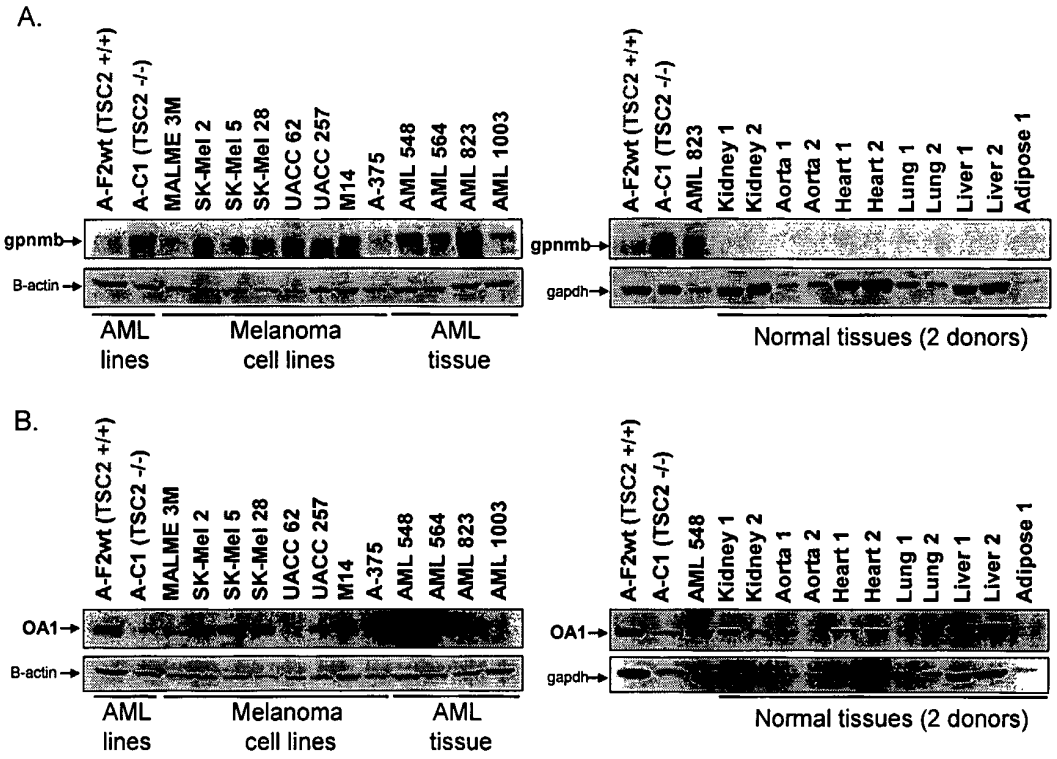

A.
A-F2wt (TSC2 +/+)
A-C1 (TSC2 -/-)
MALME 3M
SK-Mel 2
SK-Mel 5
SK-Mel 28
UACC 62
UACC 257
M14
A-375
AML 548
AML 564
AML 823
AML 1003
gpnmb
B-actin
AML lines
Melanoma cell lines
AML tissue
A-F2wt (TSC2 +/+)
A-C1 (TSC2 -/-)
AML 823
Kidney 1
Kidney 2
Aorta 1
Aorta 2
Heart 1
Heart 2
Lung 1
Lung 2
Liver 1
Liver 2
Adipose 1
gpnmb
gapdh
Normal tissues (2 donors)
B.
A-F2wt (TSC2 +/+)
A-C1 (TSC2 -/-)
MALME 3M
SK-Mel 2
SK-Mel 5
SK-Mel 28
UACC 62
UACC 257
M14
A-375
AML 548
AML 564
AML 823
AML 1003
OA1
B-actin
AML lines
Melanoma cell lines
AML tissue
A-F2wt (TSC2 +/+)
A-C1 (TSC2 -/-)
AML 548
Kidney 1
Kidney 2
Aorta 1
Aorta 2
Heart 1
Heart 2
Lung 1
Lung 2
Liver 1
Liver 2
Adipose 1
OA1
gapdh
Normal tissues (2 donors)

Figure 6. .

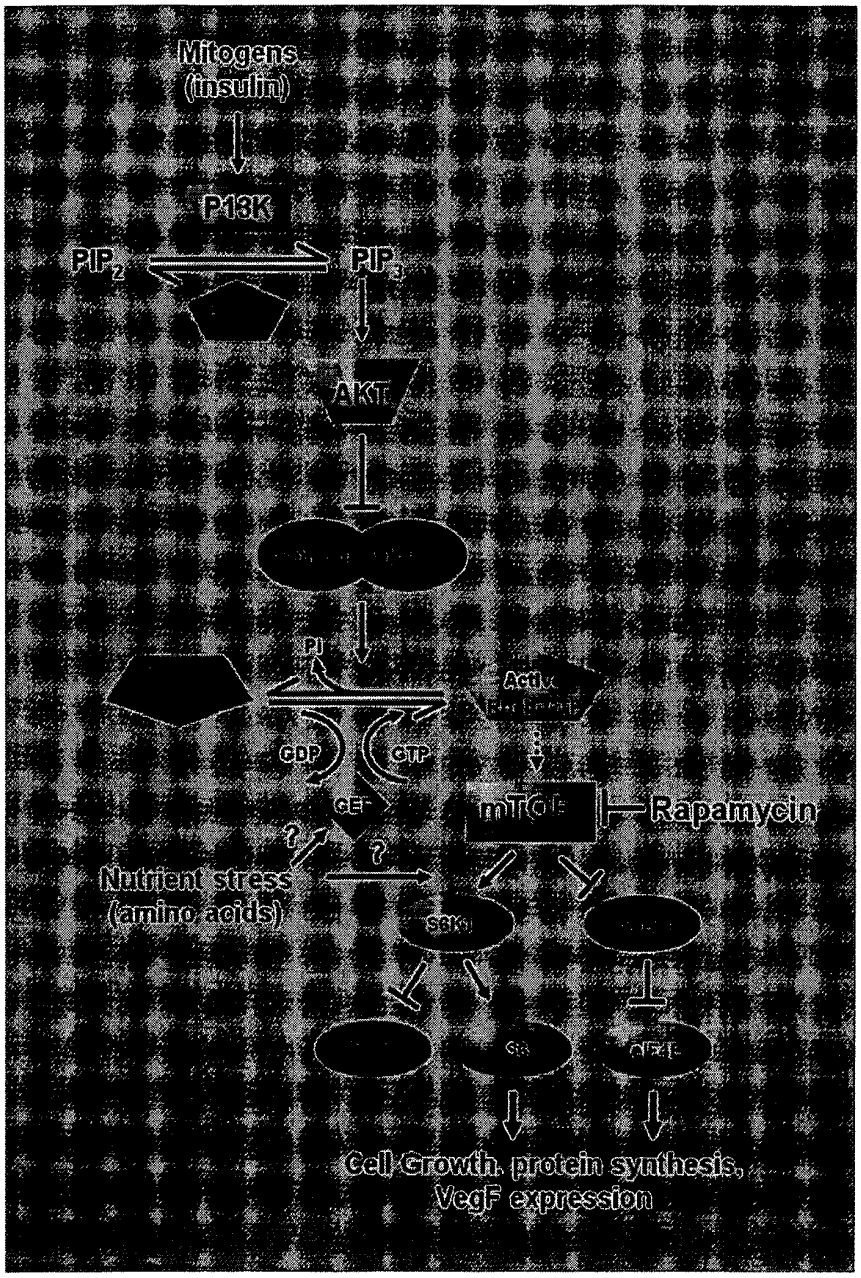

Mitogens
(insulin)
P13K
PIP2
PIP3
AKT
PI
GDP
GTP
GEF
mTOR
Rapamycin
Nutrient stress
(amino acids)
S6K1
4E-BP1
Cell Growth, protein synthesis,
VegF expression

Figure 7