The American Journal of Human Genetics, Volume *98*

Supplemental Data

Mutations in *SMG9*, Encoding an Essential Component of Nonsense-Mediated Decay Machinery, Cause a Multiple Congenital Anomaly Syndrome in Humans and Mice

Ranad Shaheen, Shams Anazi, Tawfeg Ben-Omran, Mohammed Zain Seidahmed, L. Brianna Caddle, Kristina Palmer, Rehab Ali, Tarfa Alshidi, Samya Hagos, Leslie Goodwin, Mais Hashem, Salma M. Wakil, Mohamed Abouelhoda, Dilek Colak, Stephen A. Murray, and Fowzan S. Alkuraya

'Supplemental Note: Case Reports'

Family 1: IV:5 (the index) had a birth weight of 2.130 kg (5^{th} centile), length of 44 cm (-2.4SD), and head circumference of 31.5 cm (-2.2SD). Antenatal ultrasound scan had revealed polyhydramnios, abnormal umbilical artery Doppler (absent diastolic flow), splaying of the cerebellum and VSD. Apgar scores were 6 and 8 at one and five minutes respectively. Physical examination showed craniofacial abnormalities consisting of prominent forehead and occiput, low set malformed ears, wide anterior fontanelle, depressed nasal bridge and anteverted nares, microphthalmia, high arched palate, clenched hands with camptodactyly. Central nervous system involvement included Dandy-Walker malformation, cerebellar vermis hypoplasia and hypoplastic corpus callosum on CT brain (Figure 1B). Cardiac evaluation revealed interrupted aortic arch, hypoplastic tricuspid and aortic valves, and large muscular VSD. She developed seizures and sepsis, and was mechanically ventilated. Despite aggressive management, she died at the age of 7 weeks. Laboratory investigations included normal hematologic indices, liver functions and renal functions. Her karyotype was 46,XX. Plasma amino acids, carnitine and acylcarnitines were normal. TORCH serology for congenital infections was negative. Renal ultrasound was normal.

Family 2: V:1 (the index) had a birth weight of 2.26 kg, length (-2.2SD) was 47 cm (15^{th} centile) and head circumference was 32 cm (-1.8SD). She was found to have right-sided cleft lip, and a large ventricular septal defect (VSD). Additional dysmorphic features included narrow forehead, prominent metopic suture, widow's peak, hypertelorism, posteriorly rotated ears with attached lobules, broad nasal bridge, full and everted lower lip, small eyes, and syndactyly between 2^{nd} and 3^{rd} toes (Figure 1C and D). She underwent VSD closure at 1 year of age and repair of cleft

lip at 18 months of age. She showed features of global developmental delay. At 3 years of age, she was only able to roll over, but not sit independently. Examination at 14 months of age revealed weight of 6 kg (-4.3SD), length of 67 cm (-3SD) and head circumference of 40 cm (-4.4SD). Neurological examination revealed truncal hypotonia and exaggerated deep tendon reflexes with clonus. Ophthalmological examination was significant for poor vision necessitating corrective glasses. Laboratory investigations showed normal electrolytes, renal and hepatic functions and the hematologic indices. Creatine kinase (CK) was normal. Tandem mass spectrometry (TMS) for metabolic disorders screen was unremarkable. Serum ammonia, lactate, plasma sterol profile and transferrin isoelectric focusing–CDG screening were normal. Array CGH and clinical exome sequencing were negative. Abdominal ultrasound revealed no abnormalities. Her most recent echocardiography showed status post VSD closure, otherwise unremarkable study. Brain MRI performed at 15 months revealed brain atrophy, decreased myelination and Dandy-Walker malformation. IV:3: The first cousin of the index was also found to have a similar phenotype. She was born at term after an uneventful pregnancy and delivery. She was found to have ventricular septal defect (VSD) and dysmorphic features. She underwent VSD closure at 13 months of age. She was also found to have major gastroesophageal reflux and recurrent aspiration necessitating NG feeding, bronchial stenosis and laryngeal cleft type 1. She showed features of global developmental delay. At 2 years of age, there was no eye contact, and she was only able to roll over, but not sit independently. Examination at 2 years of age revealed weight of 6.3 kg (-5.2SD), length of 69 cm (-4.8SD) and head circumference of 39 cm (-6SD). Neurological examination showed truncal hypotonia with peripheral hypertonia, brisk deep tendon reflexes and adductor spasm in both lower limbs. Laboratory investigations showed normal array CGH, plasma sterol profile and lysosomal

studies. Abdominal ultrasound revealed no abnormalities. Her most recent echocardiography showed status post VSD closure, and mild tricuspid regurgitation. Brain MRI performed at 7 months revealed generalized brain atrophy, prominent ventricular system and thin corpus

Figure S1

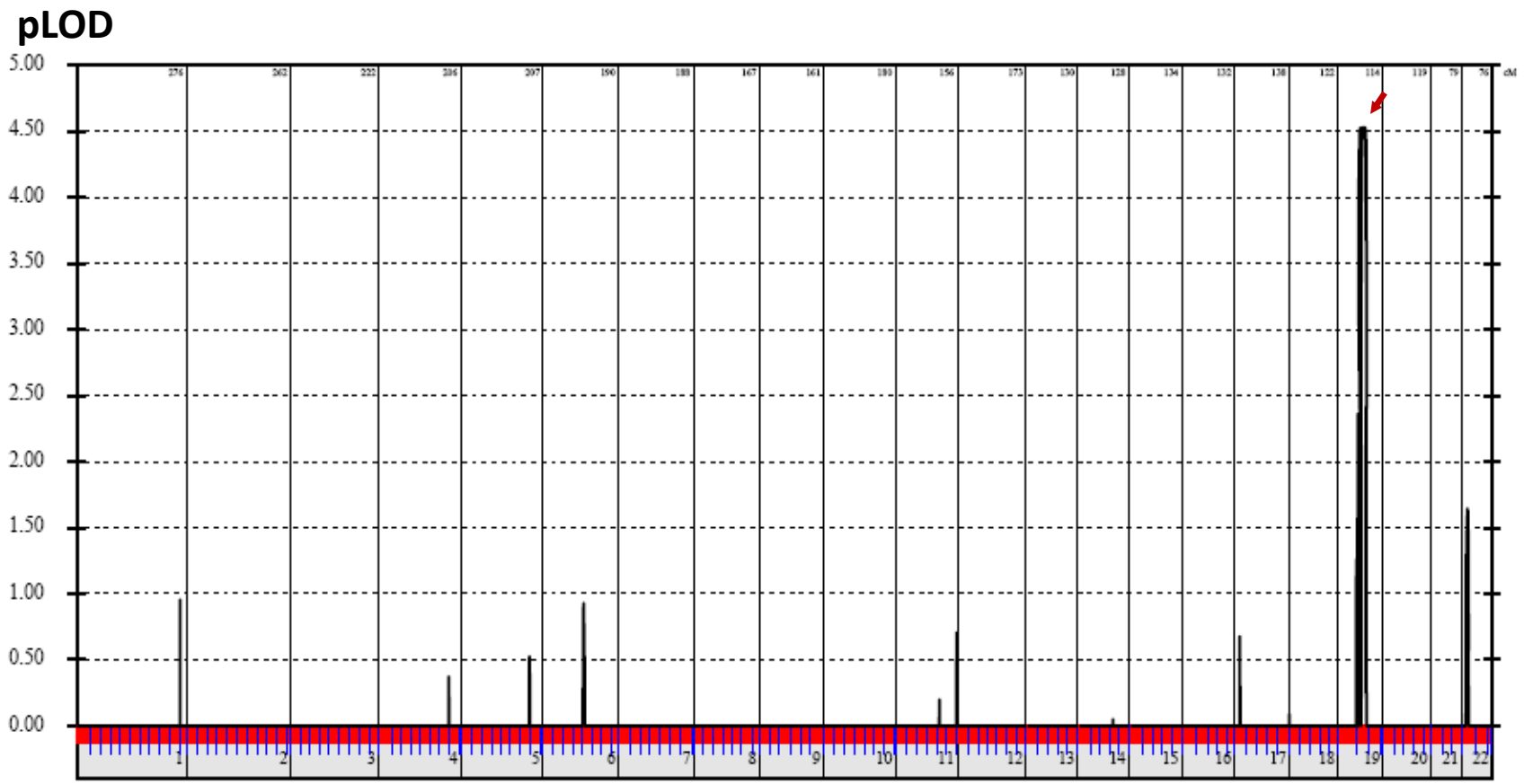

pLOD
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22

Figure S1. Genome-wide linkage analysis revealed a single maximal peak with a LOD score of ~4.5 on chromosome 19.

Figure S2

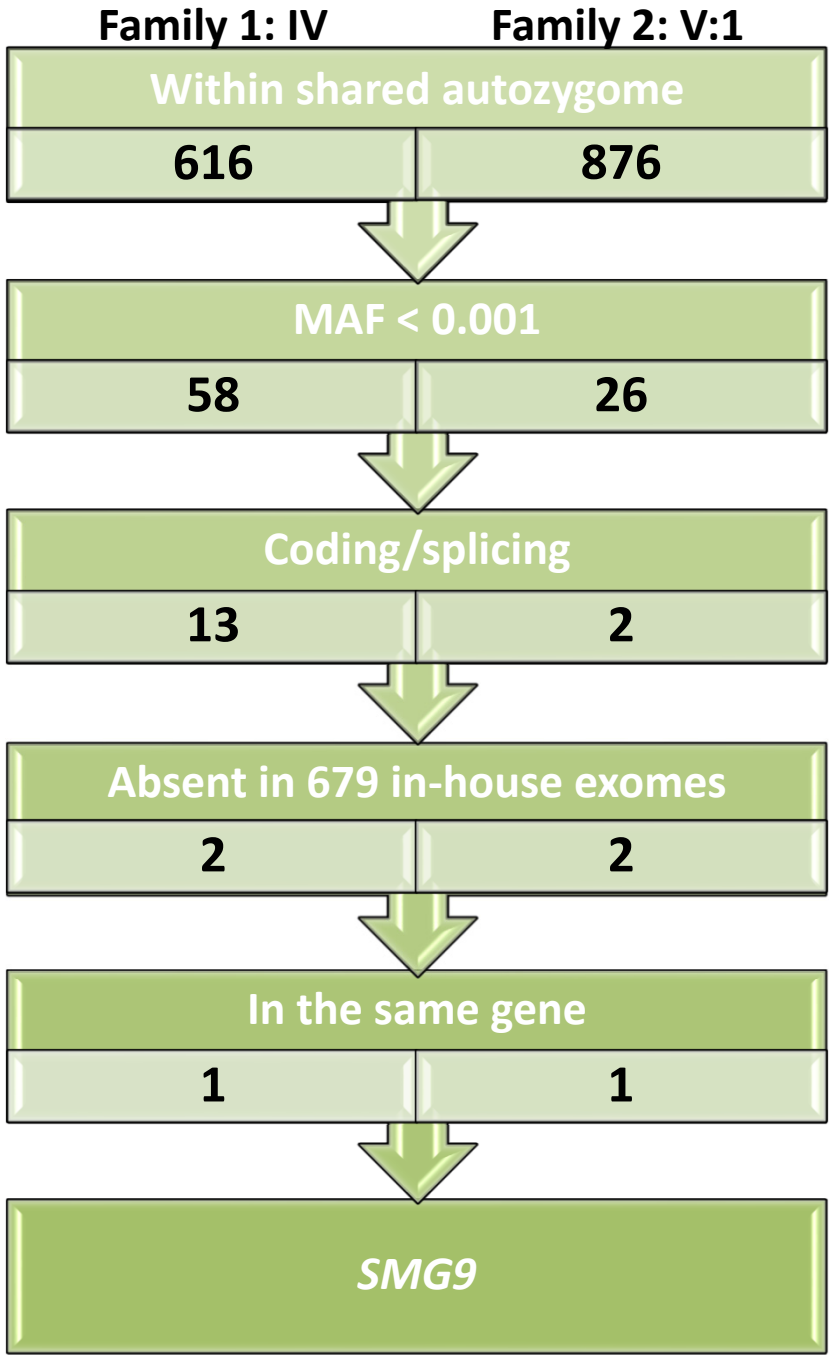

Family 1: IV
Family 2: V:1
Within shared autozygome
616
876
MAF < 0.001
58
26
Coding/splicing
13
2
Absent in 679 in-house exomes
2
2
In the same gene
1
1
SMG9

Figure S2. Illustration of the exome filtering scheme and the number of survived variants in each step in both families.

Figure S3

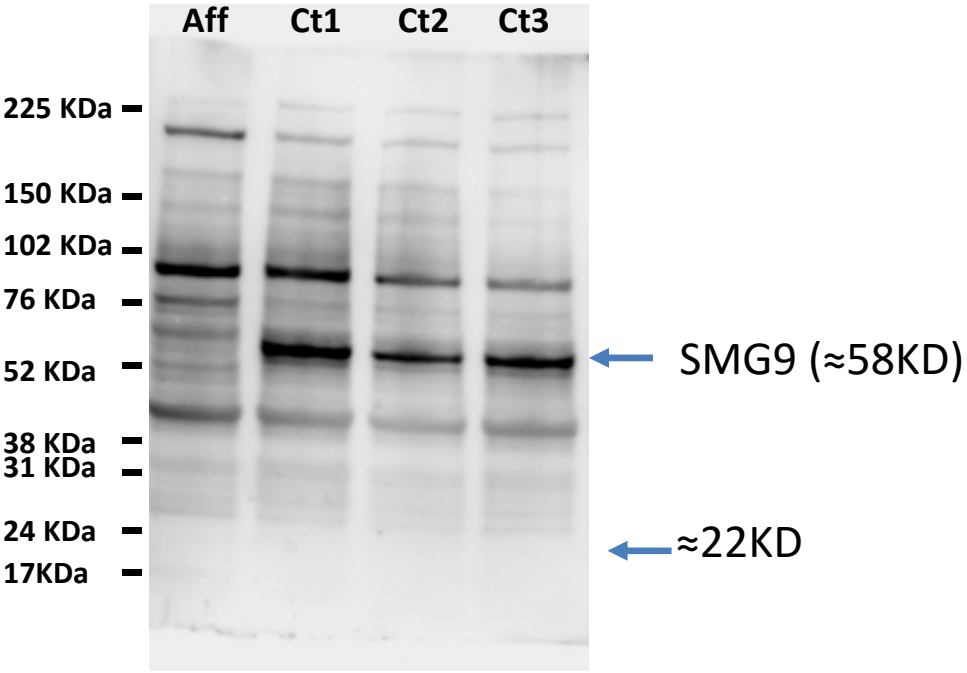
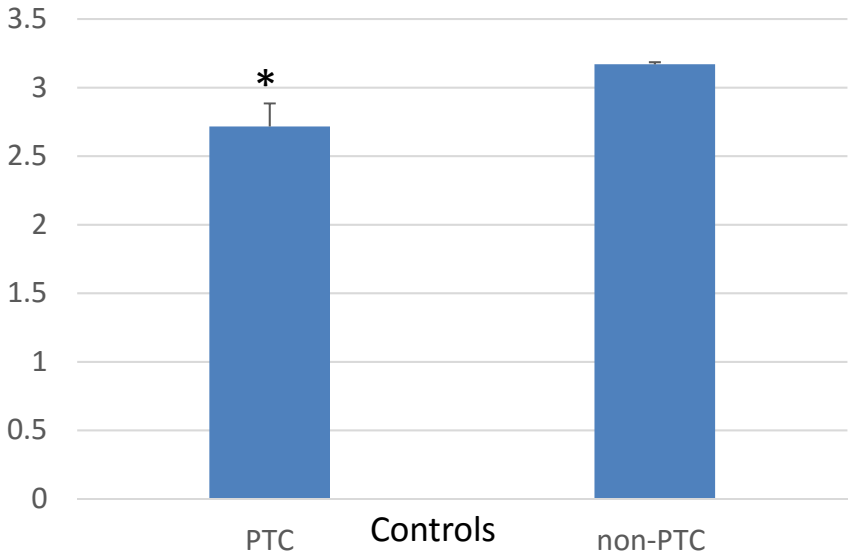

Aff
Ct1
Ct2
Ct3
225 KDa
150 KDa
102 KDa
76 KDa
52 KDa
38 KDa
31 KDa
24 KDa
17KDa
SMG9 (≈58KD)
≈22KD

Figure S3. Immunobloting using antibody against the N terminal of SMG9 antibody (SAB2107730). The image shows no detectable band from cells derived from affected individual (V:1) as compared with the three normal controls (Ct1, Ct2, Ct3) at the target mass (57.7-54.8) kDa as well as from the truncated transcript (predicted mass approximately 22KDa).

Figure S4

A


3.5
3
2.5
2
1.5
1
0.5
0
*
PTC
Controls
non-PTC

B

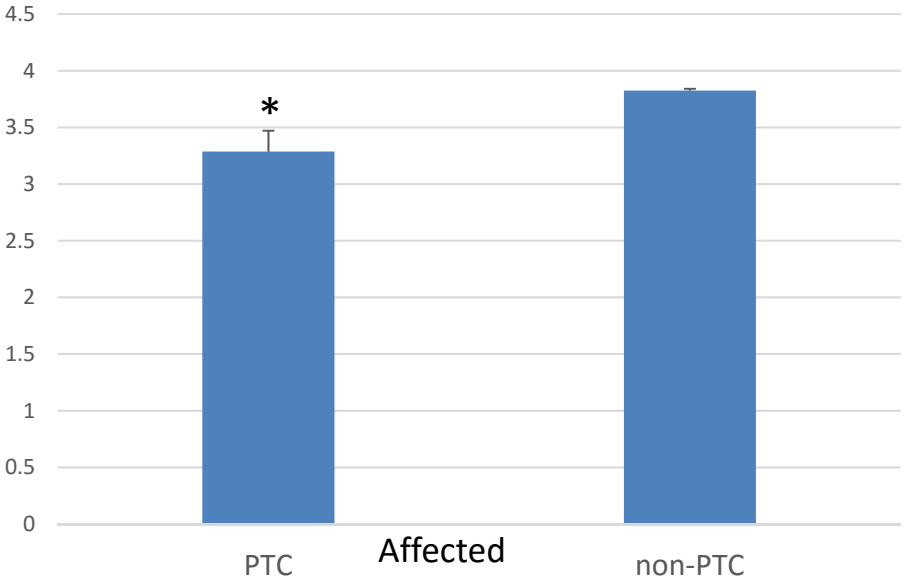
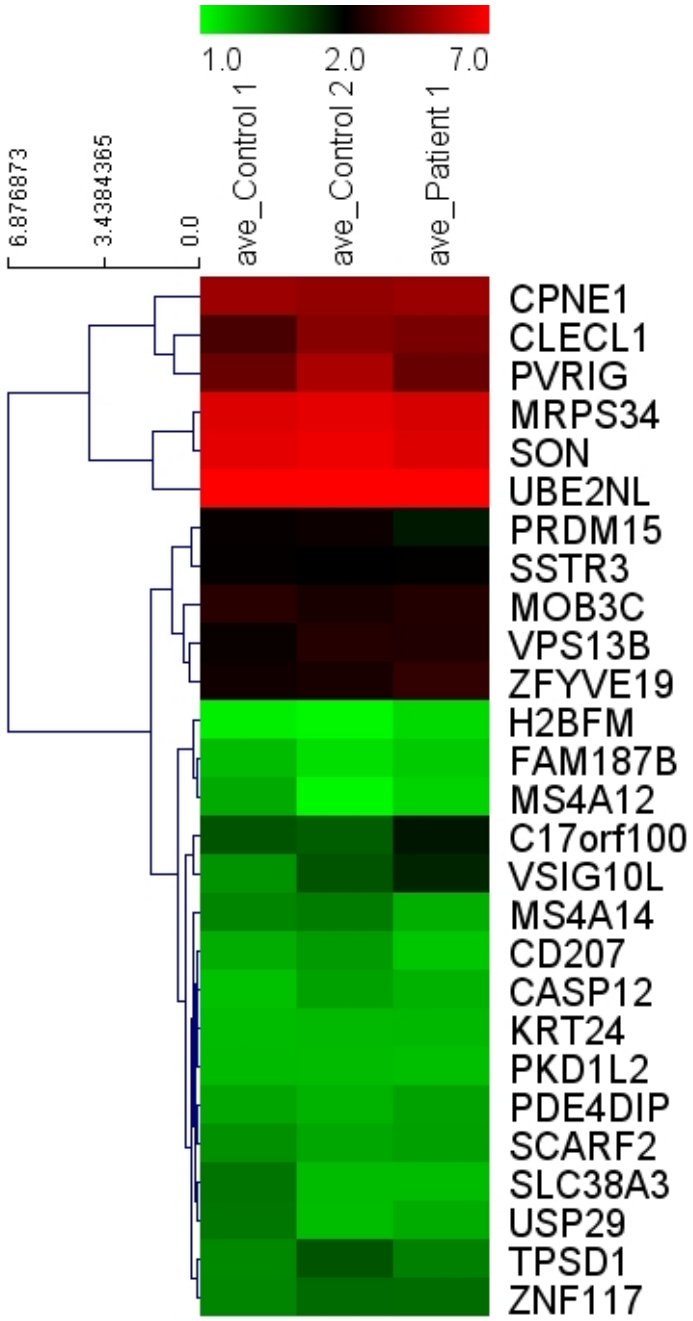

4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
*
PTC
Affected
non-PTC

Figure S4. Comparison of PTC-containing transcripts to other transcripts in controls and affected individual obtained from the expression microarray. Transcripts with PTC are significantly lower than other transcripts in general in controls (averaged) (A) and affected individual (B) ($p < 0.01$). Data shown represent mean ± SEM.

Figure S5



p_value (C1,C2)	0.918
p_value (C2,P1)	0.827
p_value (P1,C1)	0.758
p_value (P1,Cntrls)	0.986

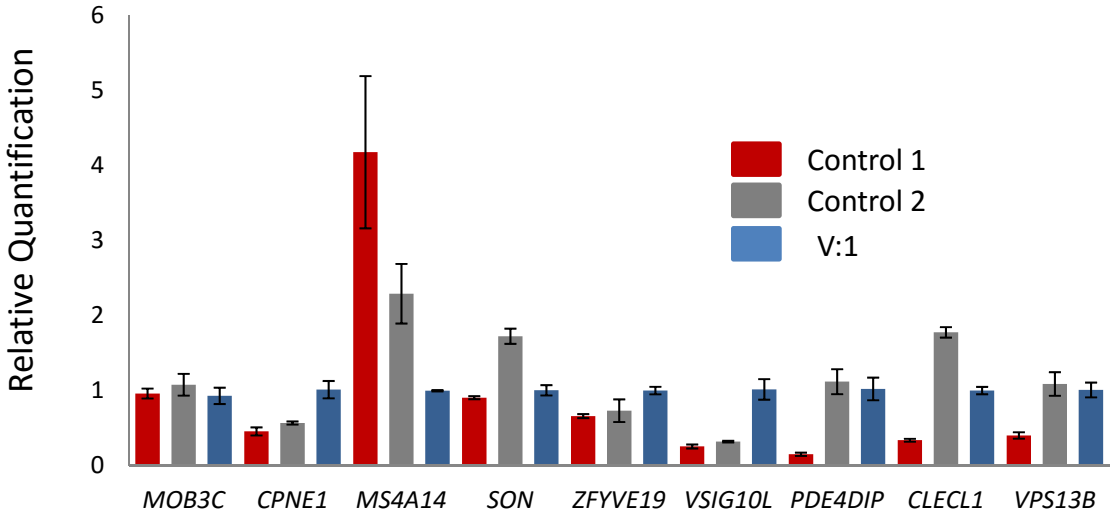


Figure S5. Heat-map and Venn diagram of common PTC-containing genes in controls and patient. There was no significant difference between in mRNA expression in affected individual and controls for the 27 shared PTC containing genes (p value >0.05). Purple circle in the Venn diagram represents affected individual (V:1), light pink represents control 1 and light green represents control 2.

Figure S6

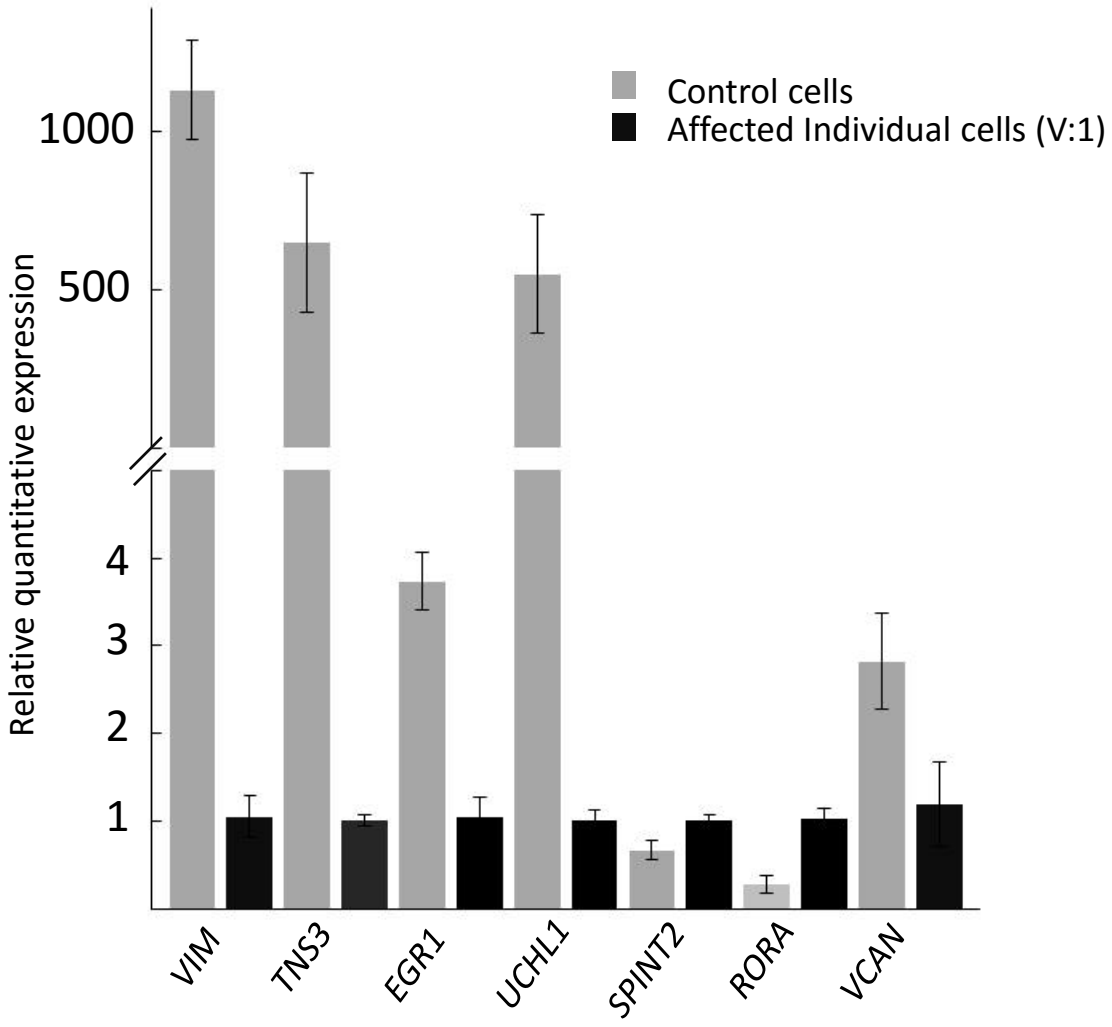

Control cells
Affected Individual cells (V:1)
Relative quantitative expression
1000
500
4
3
2
1
VIM
TNS3
EGR1
UCHL1
SPINT2
RORA
VCAN

Figure S6. Relative quantification Real time PCR result for selected genes found to be dysregulated in the microarray in affected individual (V:1) compared to control. Result is the average of triplicate experiments.

Figure S7

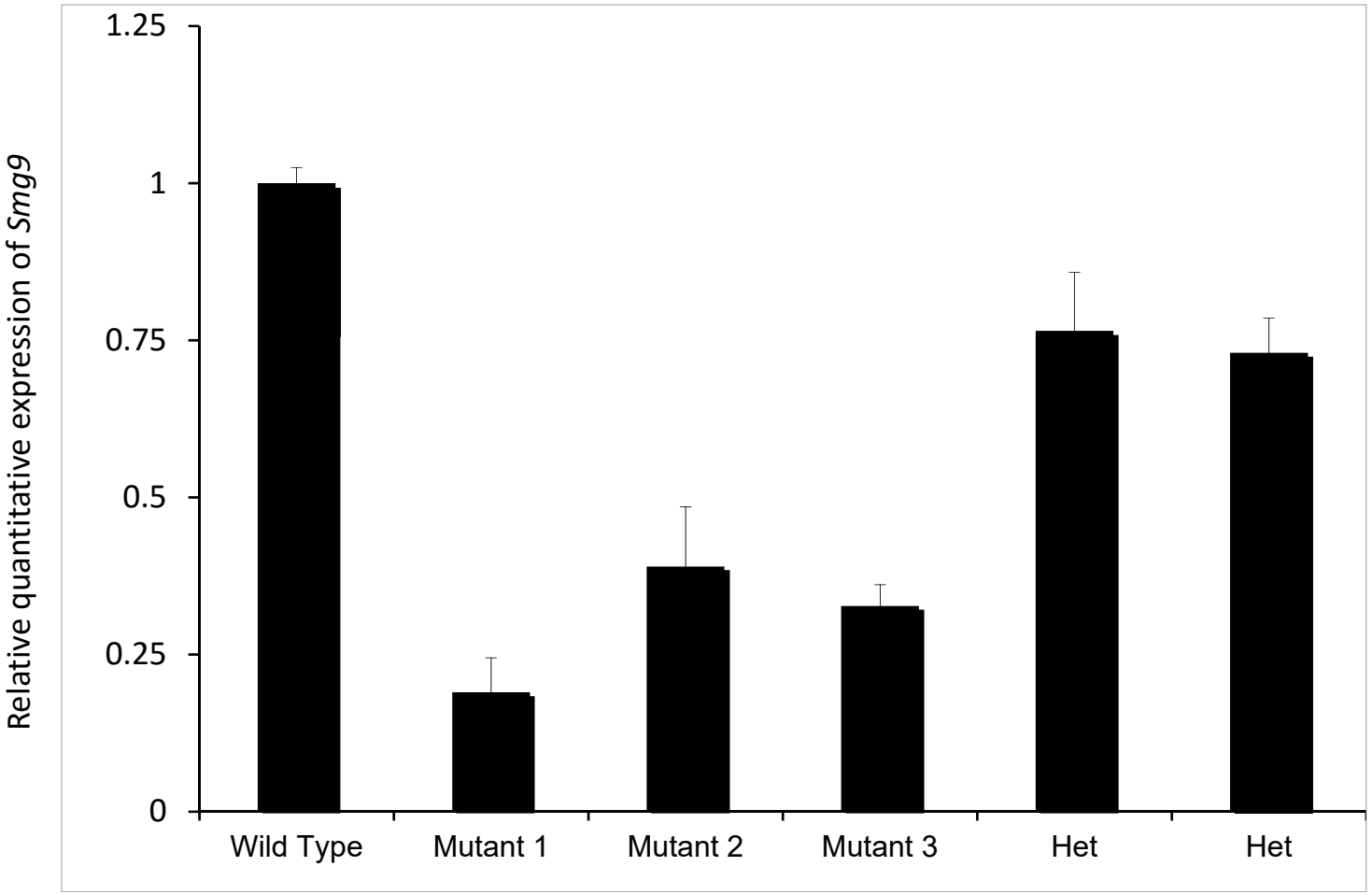

Relative quantitative expression of *Smg9*
1.25
1
0.75
0.5
0.25
0
Wild Type
Mutant 1
Mutant 2
Mutant 3
Het
Het

Figure S7. Relative quantification Real time PCR of *Smg9* shows 60-80% reduction in *Smg9* transcripts in mutant mouse compare to wild type. Each biological replicate is represented on the bar graphs.

Supplementary Table 1A. Significantly up-regulated genes in SMG9 deficient individual compared to controls.

Gene Symbol	Gene Title	FC[a]
CCL20	chemokine (C-C motif) ligand 20	38.3
IGKC	immunoglobulin kappa constant	26.7
DSC2	desmocollin 2	22.4
CRYBB2 /// CRYBB2P1	crystallin, beta B2 /// crystallin, beta B2 pseudogene 1	20.0
HLA-DRB4	major histocompatibility complex, class II, DR beta 4	19.0
TMPRSS3	transmembrane protease, serine 3	16.2
SERPINB2	serpin peptidase inhibitor, clade B (ovalbumin), member 2	15.7
ADAMDEC1	ADAM-like, decysin 1	15.3
RORA	RAR-related orphan receptor A	14.3
CXCL9	chemokine (C-X-C motif) ligand 9	14.3
CRNDE	colorectal neoplasia differentially expressed (non-protein coding)	13.2
CASP1	caspase 1, apoptosis-related cysteine peptidase	12.3
DSC3	desmocollin 3	11.3
TACSTD2	tumor-associated calcium signal transducer 2	10.2
PRRX1	paired related homeobox 1	8.9
CMTM7	CKLF-like MARVEL transmembrane domain containing 7	8.5
TAGAP	T-cell activation RhoGTPase activating protein	6.8
LOC100506548 /// RPL37	uncharacterized LOC100506548 /// ribosomal protein L37	6.8
VCAN	versican	6.7
TCFL5	transcription factor-like 5 (basic helix-loop-helix)	6.7
PHF16	PHD finger protein 16	6.6
GLUL	glutamate-ammonia ligase	6.5
CMAHP	cytidine monophospho-N-acetylneuraminic acid hydroxylase, pseudogene	6.3

SPINT2	serine peptidase inhibitor, Kunitz type, 2	6.0
PIEZO2	piezo-type mechanosensitive ion channel component 2	6.0
CARD16 /// CASP1	caspase recruitment domain family, member 16 /// caspase 1, apoptosis-related cysteine	5.8
NOTCH2	notch 2	5.8
HSPA6	heat shock 70kDa protein 6 (HSP70B')	5.8
UXS1	UDP-glucuronate decarboxylase 1	5.6
C12orf79	chromosome 12 open reading frame 79	5.5
UGT8	UDP glycosyltransferase 8	5.4
LOC101060315 //NOTCH2 /// NOTCH2NL	neurogenic locus notch homolog protein 2-like /// neurogenic locus notch homolog protei	5.4
LOC389906	zinc finger protein 839 pseudogene	5.4
KRT7	keratin 7	5.2
SETD7	SET domain containing (lysine methyltransferase) 7	5.2
SOCS2	suppressor of cytokine signaling 2	5.1
CARD16	caspase recruitment domain family, member 16	5.0
APLP2	amyloid beta (A4) precursor-like protein 2	4.8
CR2	complement component (3d/Epstein Barr virus) receptor 2	4.7
OTTHUMG00000168533 /// RP11-277P12.20	NULL /// NULL	4.6
LINC00888	long intergenic non-protein coding RNA 888	4.4
NIPAL4	NIPA-like domain containing 4	4.3
LOC100506453	uncharacterized LOC100506453 /// zinc finger protein 839 pseudogene /// uncharacterized	4.3
NUDT12	nudix (nucleoside diphosphate linked moiety X)-type motif 12	4.3
ITM2A	integral membrane protein 2A	4.2
BAG3	BCL2-associated athanogene 3	4.2
JAK1	Janus kinase 1	4.2
CBS	cystathionine-beta-synthase	4.2

TBC1D1	TBC1 (tre-2/USP6, BUB2, cdc16) domain family, member 1	4.1
ZAK	sterile alpha motif and leucine zipper containing kinase AZK	4.0
PGAP1	post-GPI attachment to proteins 1	4.0
LOC100996457	uncharacterized LOC100996457	4.0
RASA4 /// RASA4B /// RASA4CP	RAS p21 protein activator 4 /// RAS p21 protein activator 4B /// RAS p21 protein activa	3.9
JUN	jun proto-oncogene	3.9
FOXO3	forkhead box O3	3.8
KLF3	Kruppel-like factor 3 (basic)	3.8
ANKDD1A	ankyrin repeat and death domain containing 1A	3.8
DHRS7	dehydrogenase/reductase (SDR family) member 7	3.7
IFRD1	interferon-related developmental regulator 1	3.7
CD44	CD44 molecule (Indian blood group)	3.7
SPIN3	spindlin family, member 3	3.6
DNAJC18	DnaJ (Hsp40) homolog, subfamily C, member 18	3.6
IL1R2	interleukin 1 receptor, type II	3.5
CR1	complement component (3b/4b) receptor 1 (Knops blood group)	3.5
KCNN2	potassium intermediate/small conductance calcium-activated channel, subfamily N, member	3.4
PSPC1	paraspeckle component 1	3.4
ERAP2	endoplasmic reticulum aminopeptidase 2	3.4
BAG1	BCL2-associated athanogene	3.3
GOLM1	golgi membrane protein 1	3.3
---	---	3.2
TSC22D1	TSC22 domain family, member 1	3.2
GLB1L3	galactosidase, beta 1-like 3	3.2
CD55	CD55 molecule, decay accelerating factor for complement (Cromer blood group)	3.2

TMEM173	transmembrane protein 173	3.2
NFKBIZ	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, zeta	3.1
AZI2	5-azacytidine induced 2	3.1
LOC100507581	uncharacterized LOC100507581	3.1
FNDC3B	fibronectin type III domain containing 3B	3.1
GAS5 /// SNORD44 ///	growth arrest-specific 5 (non-protein coding) /// small nucleolar RNA, C/D box 44 /// s	3.1
SNHG12 /// SNORA16A /// SNORA44 /// SNORA61	small nucleolar RNA host gene 12 (non-protein coding) /// small nucleolar RNA, H/ACA bo	3.0
TET2	tet methylcytosine dioxygenase 2	3.0
GADD45B	growth arrest and DNA-damage-inducible, beta	3.0
MAN1A1	mannosidase, alpha, class 1A, member 1	3.0
CXCR4	chemokine (C-X-C motif) receptor 4	3.0
EPB41L4A-AS1	EPB41L4A antisense RNA 1	3.0
RASA4 /// RASA4B	RAS p21 protein activator 4 /// RAS p21 protein activator 4B	3.0
ZBTB10	zinc finger and BTB domain containing 10	3.0
MAP3K7CL	MAP3K7 C-terminal like	2.9
PLAU	plasminogen activator, urokinase	2.9
SNHG15 /// SNORA9	small nucleolar RNA host gene 15 (non-protein coding) /// small nucleolar RNA, H/ACA bo	2.9
C17orf58	chromosome 17 open reading frame 58	2.9
C6orf48	chromosome 6 open reading frame 48	2.9
GPR55	G protein-coupled receptor 55	2.9
IL2RA	interleukin 2 receptor, alpha	2.9
CBLB	Cbl proto-oncogene, E3 ubiquitin protein ligase B	2.8
BZW2	basic leucine zipper and W2 domains 2	2.8
LOC152225	uncharacterized LOC152225	2.8
TFDP2	transcription factor Dp-2 (E2F dimerization partner 2)	2.8

TP53BP2	tumor protein p53 binding protein, 2	2.8
THAP9-AS1	THAP9 antisense RNA 1	2.8
FAM189A1	family with sequence similarity 189, member A1	2.8
CCR7	chemokine (C-C motif) receptor 7	2.7
RAB27A	RAB27A, member RAS oncogene family	2.7
ZFAS1	ZNFX1 antisense RNA 1	2.7
EXOSC7	exosome component 7	2.7
UPF3B	UPF3 regulator of nonsense transcripts homolog B (yeast)	2.7
SNHG6 /// SNORD87	small nucleolar RNA host gene 6 (non-protein coding) /// small nucleolar RNA, C/D box 8	2.6
HNRNPA2B1	heterogeneous nuclear ribonucleoprotein A2/B1	2.6
ARSK	arylsulfatase family, member K	2.6
RGPD3 /// RGPD4 /// RGPD5 /// RGPD6 /// RGPD8	RANBP2-like and GRIP domain containing 3 /// RANBP2-like and GRIP domain containing 4 /	2.6
GADD45A	growth arrest and DNA-damage-inducible, alpha	2.6
BMP4	bone morphogenetic protein 4	2.6
POLR2J2 /// POLR2J3 /// POLR2J4 /// UPK3BL	polymerase (RNA) II (DNA directed) polypeptide J2 /// polymerase (RNA) II (DNA directed	2.6
GAB1	GRB2-associated binding protein 1	2.5
DOCK9	dedicator of cytokinesis 9	2.5
ERCC8	excision repair cross-complementing rodent repair deficiency, complementation group 8	2.5
DNAJB2	DnaJ (Hsp40) homolog, subfamily B, member 2	2.5
SARNP	SAP domain containing ribonucleoprotein	2.5
HNRNPA1	heterogeneous nuclear ribonucleoprotein A1	2.5
CD274	CD274 molecule	2.5
CD86	CD86 molecule	2.5
PIK3R5	phosphoinositide-3-kinase, regulatory subunit 5	2.5
DENND1A	DENN/MADD domain containing 1A	2.5

CCL5	chemokine (C-C motif) ligand 5	2.5
CLYBL	citrate lyase beta like	2.5
CFP	complement factor properdin	2.4
TIGIT	T cell immunoreceptor with Ig and ITIM domains	2.4
GALNT1	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 1 (Gal	2.4
UFM1	ubiquitin-fold modifier 1	2.3
LOC728613	programmed cell death 6 pseudogene	2.3
F11R	F11 receptor	2.3
MBNL3	muscleblind-like splicing regulator 3	2.3
RBMX /// SNORD61	RNA binding motif protein, X-linked /// small nucleolar RNA, C/D box 61	2.3
OARD1	O-acyl-ADP-ribose deacylase 1	2.3
RASSF1	Ras association (RalGDS/AF-6) domain family member 1	2.3
MDM2	MDM2 oncogene, E3 ubiquitin protein ligase	2.3
GPATCH2L	G patch domain containing 2-like	2.3
LOC100506453	uncharacterized LOC100506453 /// zinc finger protein 839 pseudogene /// uncharacterized	2.3
IL6	interleukin 6 (interferon, beta 2)	2.2
MICU3	mitochondrial calcium uptake family, member 3	2.2
PTBP2	polypyrimidine tract binding protein 2	2.2
RC3H1	ring finger and CCCH-type domains 1	2.2
ATP2B4	ATPase, Ca++ transporting, plasma membrane 4	2.2
COA1	cytochrome c oxidase assembly factor 1 homolog (S. cerevisiae)	2.2
C5orf56	chromosome 5 open reading frame 56	2.2
LETMD1	LETM1 domain containing 1	2.2
LRRC37B	leucine rich repeat containing 37B	2.2
ZNF79	zinc finger protein 79	2.2
TESPA1	thymocyte expressed, positive selection associated 1	2.2

TTC38	tetratricopeptide repeat domain 38	2.2
UHRF1BP1L	UHRF1 binding protein 1-like	2.2
LOC100996400 /// NOL4	uncharacterized LOC100996400 /// nucleolar protein 4	2.2
HSDL2	hydroxysteroid dehydrogenase like 2	2.2
RABEP1	rabaptin, RAB GTPase binding effector protein 1	2.2
VDR	vitamin D (1,25- dihydroxyvitamin D3) receptor	2.1
TTF2	transcription termination factor, RNA polymerase II	2.1
PRMT2	protein arginine methyltransferase 2	2.1
SNHG8 /// SNORA24	small nucleolar RNA host gene 8 (non-protein coding) /// small nucleolar RNA, H/ACA box	2.1
ISG20	interferon stimulated exonuclease gene 20kDa	2.1
LARP1B	La ribonucleoprotein domain family, member 1B	2.1
CRYBB2P1	crystallin, beta B2 pseudogene 1	2.1
RFX3	regulatory factor X, 3 (influences HLA class II expression)	2.1
FAM188A	family with sequence similarity 188, member A	2.1
LOC645513	uncharacterized LOC645513	2.1
NBN	nibrin	2.0
C7orf31	chromosome 7 open reading frame 31	2.0
MIR155 /// MIR155HG	microRNA 155 /// MIR155 host gene (non-protein coding)	2.0
ARNTL2	aryl hydrocarbon receptor nuclear translocator-like 2	2.0
SNHG1 /// SNORD22	small nucleolar RNA host gene 1 (non-protein coding) /// small nucleolar RNA, C/D box 2	2.0
IL10RB	interleukin 10 receptor, beta	2.0
BTG3	BTG family, member 3	2.0

[a]FC was calculated between the mean values of control and patient

Supplementary Table 1B. Significantly down-regulated genes in SMG9 deficient individual compared to controls.

Gene Symbol	Gene Title	FC[a]
HLA-DQA1	major histocompatibility complex, class II, DQ alpha 1	-39.2
IGHG1 /// IGHG2 /// IGHM /// IGHV4-31	immunoglobulin heavy constant gamma 1 (G1m marker) /// immunoglobulin heavy constant ga	-20.3
VIM	vimentin	-15.5
UCHL1	ubiquitin carboxyl-terminal esterase L1 (ubiquitin thiolesterase)	-10.0
SLC12A8	solute carrier family 12 (potassium/chloride transporters), member 8	-7.8
DUSP4	dual specificity phosphatase 4	-6.1
MB21D2	Mab-21 domain containing 2	-5.6
CECR1	cat eye syndrome chromosome region, candidate 1	-5.1
COL5A1	collagen, type V, alpha 1	-4.8
LCK	lymphocyte-specific protein tyrosine kinase	-4.8
BIN1	bridging integrator 1	-4.7
ARL4C	ADP-ribosylation factor-like 4C	-4.6
CRIM1	cysteine rich transmembrane BMP regulator 1 (chordin-like)	-4.5
PLD6	phospholipase D family, member 6	-4.5
TNS3	tensin 3	-4.5
TSPO	translocator protein (18kDa)	-4.2
KDM4C	lysine (K)-specific demethylase 4C	-4.1
WARS2	tryptophanyl tRNA synthetase 2, mitochondrial	-3.5
CAPG	capping protein (actin filament), gelsolin-like	-3.3
SLC8A3	solute carrier family 8 (sodium/calcium exchanger), member 3	-3.1
NFIL3	nuclear factor, interleukin 3 regulated	-3.1

LILRB4	leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member	-3.1
RNASET2	ribonuclease T2	-3.0
RHOB	ras homolog family member B	-3.0
ALOX5	arachidonate 5-lipoxygenase	-3.0
S100A11	S100 calcium binding protein A11	-3.0
EGR1	early growth response 1	-2.8
PMEPA1	prostate transmembrane protein, androgen induced 1	-2.7
TNFRSF1B	tumor necrosis factor receptor superfamily, member 1B	-2.6
TMC8	transmembrane channel-like 8	-2.6
TCF4	transcription factor 4	-2.5
KIAA1551	KIAA1551	-2.5
LOC285972	uncharacterized LOC285972	-2.4
PPAT	phosphoribosyl pyrophosphate amidotransferase	-2.4
MS4A1	membrane-spanning 4-domains, subfamily A, member 1	-2.3
LHFPL2	lipoma HMGIC fusion partner-like 2	-2.3
HLA-DPB1	major histocompatibility complex, class II, DP beta 1	-2.3
PSTPIP1	proline-serine-threonine phosphatase interacting protein 1	-2.3
GATM	glycine amidinotransferase (L-arginine:glycine amidinotransferase)	-2.2
RAPGEF5	Rap guanine nucleotide exchange factor (GEF) 5	-2.2
MBP	myelin basic protein	-2.2
ADD3	adducin 3 (gamma)	-2.2
LOC100996752 /// LOC101060261 /// NUDT4	uncharacterized LOC100996752 /// uncharacterized LOC101060261 /// nudix (nucleoside dip	-2.2
SMG9	smg-9 homolog, nonsense mediated mRNA decay factor (C. elegans)	-2.2

KCNN3	potassium intermediate/small conductance calcium-activated channel, subfamily N, member	-2.2
COTL1	coactosin-like 1 (Dictyostelium)	-2.1
NAPSB	napsin B aspartic peptidase, pseudogene	-2.1
MGC70870	C-terminal binding protein 2 pseudogene	-2.1
ANXA11	annexin A11	-2.0
KYNU	kynureninase	-2.0
KIAA0930	KIAA0930	-2.0
MAST3	microtubule associated serine/threonine kinase 3	-2.0
BTN3A3	butyrophilin, subfamily 3, member A3	-2.0
NEK6	NIMA-related kinase 6	-2.0

[a]FC was calculated between the mean values of control and patient

Table S2: List of PTC-containing genes

Gene Symbol	Gene Title	Affymetrix	Type	zygosity	refGene functio	refGene exonic function	Patient1a	Patient1b	Average Expr
PLEKHA2	pleckstrin homo	225136_at	NMD	hom	exonic;splicing	frameshift deletion	8.469	8.474	8.471
SON	SON DNA binding	214988_s_	NMD	hom	exonic	frameshift deletion	8.398	8.472	8.435
SLAIN1	SLAIN motif fam	225619_at	NMD	hom	exonic	frameshift insertion	8.323	8.438	8.381
EFTUD2	elongation fact	222398_s_	NMD	het	exonic;splicing	frameshift insertion	8.124	8.153	8.139
NOP16	NOP16 nucleolar	214011_s_	NMD	hom	exonic	frameshift insertion	8.101	8.042	8.072
UBE2NL	ubiquitin-conju	217393_x_	NMD	hom	exonic	stopgain	8.064	8.001	8.033
CLECL1	C-type lectin-l	244413_at	NMD	het	exonic	frameshift insertion	8.097	7.933	8.015
RRM2B	ribonucleotide	223342_at	NMD	het	exonic	frameshift insertion	7.207	7.655	7.431
DCAF7	DDB1 and CUL4 a	224748_at	NMD	hom	exonic;splicing	frameshift deletion	7.215	7.280	7.248
P2RX5	purinergic rece	210448_s_	NMD	het	exonic	frameshift deletion	7.160	7.222	7.191
MRPS34	mitochondrial r	218112_at	NMD	het	exonic;splicing	frameshift insertion	6.814	6.773	6.794
KMT2C	lysine (K)-spec	222415_at	NMD	het	exonic	stopgain	6.629	6.858	6.743
SENP3	SUMO1/sentrin/S	203871_at	NMD	hom	exonic;splicing	frameshift deletion	6.213	6.271	6.242
CPNE1	copine I	206918_s_	NMD	het	exonic	frameshift insertion	6.029	6.075	6.052
HEY1	hes-related fam	44783_s_a	NMD	hom	exonic	frameshift deletion	5.795	5.861	5.828
CASP7	caspase 7, apop	207181_s_	NMD	het	exonic	frameshift deletion	5.804	5.677	5.740
IQSEC1	IQ motif and Se	203907_s_	NMD	hom	exonic;splicing	frameshift deletion	5.478	5.660	5.569
SLC37A4	solute carrier	202830_s_	NMD	hom	exonic;splicing	frameshift deletion	5.628	5.499	5.564
ZNF598	zinc finger pro	225104_at	NMD	hom	exonic;splicing	frameshift deletion	5.650	5.384	5.517
EML3	echinoderm micr	203442_x_	NMD	hom	exonic	stopgain	5.260	5.260	5.260
IL17RB	interleukin 17	224156_x_	NMD	hom	exonic	stopgain	5.445	4.932	5.188
VPS13B	vacuolar protei	213243_at	NMD	het	exonic	stopgain	4.846	5.297	5.072
KMT2B	lysine (K)-spec	203419_at	NMD	hom	exonic;splicing	frameshift insertion	5.040	4.792	4.916
NEIL2	nei endonucleas	226585_at	NMD	het	exonic;splicing	frameshift deletion	4.866	4.853	4.860
PVRIG	poliovirus rece	219812_at	NMD	hom	exonic	stopgain	4.948	4.743	4.846
SLC41A3	solute carrier	224931_at	NMD	het	exonic	frameshift deletion	4.655	4.918	4.787
ZFPM1	zinc finger pro	242282_at	NMD	hom	exonic	frameshift deletion	4.764	4.764	4.764
NOP9	NOP9 nucleolar	225514_at	NMD	het	exonic	stopgain	4.614	4.724	4.669
ZBTB7B	zinc finger and	235145_at	NMD	het	exonic	stopgain	4.670	4.598	4.634
BTN3A3	butyrophilin, s	204821_at	NMD	het	exonic	stopgain	4.559	4.663	4.611
ZNF211	zinc finger pro	205437_at	NMD	het	exonic	frameshift deletion	4.464	4.623	4.544
ZFYVE19	zinc finger, FY	225843_at	NMD	het	exonic	frameshift insertion	4.574	4.505	4.539
PRDM15	PR domain conta	230777_s_	NMD	hom	exonic;splicing	frameshift insertion	4.493	4.349	4.421
MOB3C	MOB kinase acti	227066_at	NMD	hom	exonic	stopgain	4.306	4.306	4.306
CRIPAK	cysteine-rich P	228318_s_	NMD	het	exonic	frameshift deletion	3.838	4.035	3.936
SARM1	sterile alpha a	213259_s_	NMD	hom	exonic	frameshift insertion	3.757	3.337	3.547
TMEM80	transmembrane p	65630_at	NMD	het	exonic	frameshift deletion	3.515	3.515	3.515

EBLN2	endogenous Born	219906_at	NMD	het	exonic	frameshift insertion	3.266	3.266	3.266
MAPK12	mitogen-activat	206106_at	NMD	het	exonic	frameshift insertion	3.482	2.928	3.205
SSTR3	somatostatin re	1553178_a	NMD	hom	exonic	frameshift insertion	3.211	3.097	3.154
LCN10	lipocalin 10	238071_at	NMD	het	exonic;splicing	stopgain	2.920	3.388	3.154
ZNF516	zinc finger pro	203604_at	NMD	hom	exonic;splicing	frameshift deletion	2.919	3.321	3.120
ZNF117	zinc finger pro	235408_x_	NMD	het	exonic	stopgain	3.070	3.070	3.070
NLRC3	NLR family, CAR	236295_s_	NMD	hom	exonic;splicing	frameshift deletion	2.684	3.316	3.000
ZNF480	zinc finger pro	222283_at	NMD	hom	exonic	frameshift deletion	3.091	2.876	2.983
PDE4DIP	phosphodiestera	205872_x_	NMD	het	exonic	stopgain	2.916	3.002	2.959
C17orf100	chromosome 17 o	229071_at	NMD	hom	exonic	frameshift insertion	2.648	2.981	2.814
NCAM1	neural cell adh	209968_s_	NMD	hom	exonic;splicing	frameshift deletion	2.795	2.795	2.795
TUT1	terminal uridyl	218965_s_	NMD	het	exonic	frameshift deletion	2.814	2.655	2.735
SLC46A1	solute carrier	1552279_a	NMD	hom	exonic;splicing	frameshift deletion	2.634	2.746	2.690
KHDC1	KH homology dom	230055_at	NMD	het	exonic	stopgain	2.543	2.814	2.679
FUT2	fucosyltransfer	208505_s_	NMD	het	exonic	stopgain	2.683	2.526	2.604
NEK3	NIMA-related ki	213116_at	NMD	hom	exonic;splicing	frameshift insertion	2.432	2.543	2.488
GAB4	GRB2-associated	1563816_a	NMD	het	exonic;splicing	stopgain	2.424	2.504	2.464
KCNMB3	potassium large	221125_s_	NMD	het	exonic	frameshift deletion	2.336	2.411	2.373
RHPN2	rhophilin, Rho	227196_at	NMD	het	exonic	stopgain	2.283	2.384	2.334
DNAH11	dynein, axonema	1553159_a	NMD	het	exonic	stopgain	2.317	2.317	2.317
EFCAB13	EF-hand calcium	231651_at	NMD	het	exonic	stopgain	2.206	2.363	2.284
VSIG10L	V-set and immun	238654_at	NMD	hom	exonic;splicing	frameshift insertion	2.055	2.486	2.270
SRRM3	serine/arginine	235880_at	NMD	hom	exonic;splicing	frameshift insertion	2.313	2.206	2.260
PKD1L2	polycystic kidn	1559261_a	NMD	hom	exonic	frameshift deletion	2.144	2.313	2.228
CC2D2A	coiled-coil and	234936_s_	NMD	het	exonic	stopgain	2.126	2.326	2.226
GGT6	gamma-glutamylt	236225_at	NMD	hom	exonic;splicing	stopgain	2.083	2.299	2.191
APOC3	apolipoprotein	205820_s_	NMD	het	exonic;splicing	stopgain	2.205	2.130	2.168
ZNF519	zinc finger pro	1564190_x	NMD	het	exonic	stopgain	2.219	2.111	2.165
LFNG	LFNG O-fucosylp	228762_at	NMD	het	exonic	stopgain	2.303	2.027	2.165
TPSD1	tryptase delta	214568_at	NMD	het	exonic	frameshift deletion	2.141	2.141	2.141
DDIT4L	DNA-damage-indu	228057_at	NMD	het	exonic	frameshift deletion	2.006	2.264	2.135
SSPO	SCO-spondin	234349_at	NMD	hom	exonic;splicing	frameshift insertion	2.079	2.150	2.115
ATRNL1	attractin-like	1569796_s	NMD	hom	exonic	frameshift insertion	1.921	2.248	2.085
ZNF283	zinc finger pro	243188_at	NMD	het	exonic	frameshift deletion	2.079	2.079	2.079
OPRM1	opioid receptor	211359_s_	NMD	het	exonic	stopgain	2.017	2.125	2.071
GRIA3	glutamate recep	1569290_s	NMD	hom	exonic	frameshift insertion	2.012	2.113	2.063
C14orf105	chromosome 14 o	1569434_a	NMD	het	exonic	stopgain	2.177	1.893	2.035
KRTAP7-1	keratin associa	1564960_a	NMD	hom	exonic;splicing	frameshift deletion	1.913	2.122	2.018
SCARF2	scavenger recep	227557_at	NMD	hom	exonic;splicing	frameshift insertion	2.201	1.826	2.014

P2RY4	pyrimidinergic	221466_at	NMD	het	exonic	stopgain	1.862	2.165	2.014
NR2E3	nuclear recepto	208385_at	NMD	hom	exonic;splicing	frameshift deletion	2.116	1.911	2.014
P4HA3	prolyl 4-hydrox	228703_at	NMD	het	exonic	stopgain	2.138	1.886	2.012
ACTN2	actinin, alpha	203864_s_	NMD	het	exonic	frameshift deletion	2.095	1.916	2.006
ADRA2C	adrenoceptor al	206128_at	NMD	het	exonic	frameshift insertion	2.117	1.849	1.983
DHDH	dihydrodiol deh	231416_at	NMD	het	exonic	frameshift insertion	2.123	1.838	1.981
RETNLB	resistin like b	223969_s_	NMD	het	exonic	frameshift insertion	1.889	1.951	1.920
ROBO3	roundabout, axo	219550_at	NMD	het	exonic	frameshift insertion	1.858	1.972	1.915
DCHS2	dachsous cadher	220373_at	NMD	het	exonic	frameshift deletion	1.884	1.884	1.884
FAM187B	family with seq	242259_at	NMD	hom	exonic	stopgain	1.908	1.825	1.866
KRT24	keratin 24	220267_at	NMD	het	exonic	frameshift deletion	1.892	1.820	1.856
TCEB3B	transcription e	220844_at	NMD	het	exonic	stopgain	1.788	1.876	1.832
SLC38A3	solute carrier	205972_at	NMD	hom	exonic;splicing	frameshift insertion	1.995	1.654	1.825
SPATA8	spermatogenesis	231006_at	NMD	het	exonic;splicing	stopgain	1.879	1.770	1.825
KRT37	keratin 37	207649_at	NMD	het	exonic	stopgain	1.935	1.702	1.819
ALLC	allantoicase	220365_at	NMD	het	exonic	stopgain	1.747	1.817	1.782
MS4A14	membrane-spanni	229510_at	NMD	hom	exonic	frameshift deletion	1.875	1.676	1.776
ZNF233	zinc finger pro	230919_at	NMD	het	exonic	frameshift deletion	1.844	1.707	1.776
TGM4	transglutaminas	206260_at	NMD	het	exonic	stopgain	1.896	1.592	1.744
CASP12	caspase 12 (gen	1564736_a	NMD	hom	exonic	stopgain	1.691	1.774	1.733
TRPM4	transient recep	219360_s_	NMD	het	exonic	stopgain	1.809	1.657	1.733
SLC22A24	solute carrier	1553923_a	NMD	het	exonic	stopgain	1.613	1.852	1.733
C11orf40	chromosome 11 o	1553086_a	NMD	het	exonic	frameshift insertion	1.689	1.764	1.727
PRM3	protamine 3	231758_at	NMD	hom	exonic	stopgain	1.633	1.731	1.682
USP29	ubiquitin speci	220895_at	NMD	hom	exonic	stopgain	1.587	1.691	1.639
PTTG2	pituitary tumor	214557_at	NMD	het	exonic	frameshift deletion	1.638	1.638	1.638
IDO2	indoleamine 2,3	1568638_a	NMD	hom	exonic	stopgain	1.753	1.495	1.624
ZNF852	zinc finger pro	1564662_a	NMD	hom	exonic;splicing	frameshift deletion	1.556	1.639	1.598
MS4A12	membrane-spanni	220834_at	NMD	hom	exonic	stopgain	1.598	1.598	1.598
CHST15	carbohydrate (N	203066_at	NMD	hom	exonic;splicing	frameshift deletion	1.553	1.636	1.595
COL6A5	collagen, type	1553835_a	NMD	het	exonic	stopgain	1.614	1.500	1.557
H2BFM	H2B histone fam	234899_at	NMD	het	exonic	stopgain	1.553	1.553	1.553
A2ML1	alpha-2-macrogl	1553505_a	NMD	het	exonic	frameshift deletion	1.555	1.483	1.519
CD207	CD207 molecule,	220428_at	NMD	hom	exonic;splicing	frameshift insertion	1.607	1.419	1.513
SLC7A13	solute carrier	238287_at	NMD	hom	exonic	frameshift deletion	1.537	1.445	1.491
GRP	gastrin-releasi	206326_at	NMD	het	exonic;splicing	frameshift deletion	1.527	1.455	1.491
CPN2	carboxypeptidas	216223_at	NMD	het	exonic	stopgain	1.311	1.388	1.350
VWDE	von Willebrand	239552_at	NMD	het	exonic	stopgain	1.382	1.250	1.316
MAL2	mal, T-cell dif	224650_at	NMD	hom	exonic;splicing	frameshift deletion	1.269	1.355	1.312

ZNF80	zinc finger pro	207272_at	NMD	hom	exonic	stopgain		1.350	1.066	1.208

Supplemental Table 3: List of RTPCR primers used in this study

Gene name	Forward	Reverse
SMG9	GAATTGGTGTGACAGTGCCA	GCAGTTTGCGGTCATTATTGA
VIM	TCA AGGGCCAAGGCA A	ATCTGAGCCTGCAGCTCC
TNS3	ACCAGGCCCTTG ACAGG	ATG ACA TCTCCC TTC AGA AGC
EGR1	ACCTTCAACCCTCAGGCG	CTA GGCCACTGA CCA AGCTG
UCHL1	CAG TGGCCA ATAATCAAGACA	CTT CAGCAGGGTGTC CTCT
SPINT2	CCATGC CTA GGTGGTGGT	GGAGTGGTCTTCAGA ATCCTG
RORA	GTAGAAACCGCTGCCAAC A	TGGTCTGGGGAAGGCTG
VCAN	GCC TTCCAA GTTATGTTG GTG	GCC AAATGATTA CAACACAGTCTT