

Supplementary Data

Molecular Psychiatry

Transcriptome profiling of UPF3B/NMD deficient lymphoblastoid cells from patients with various forms of intellectual disability.

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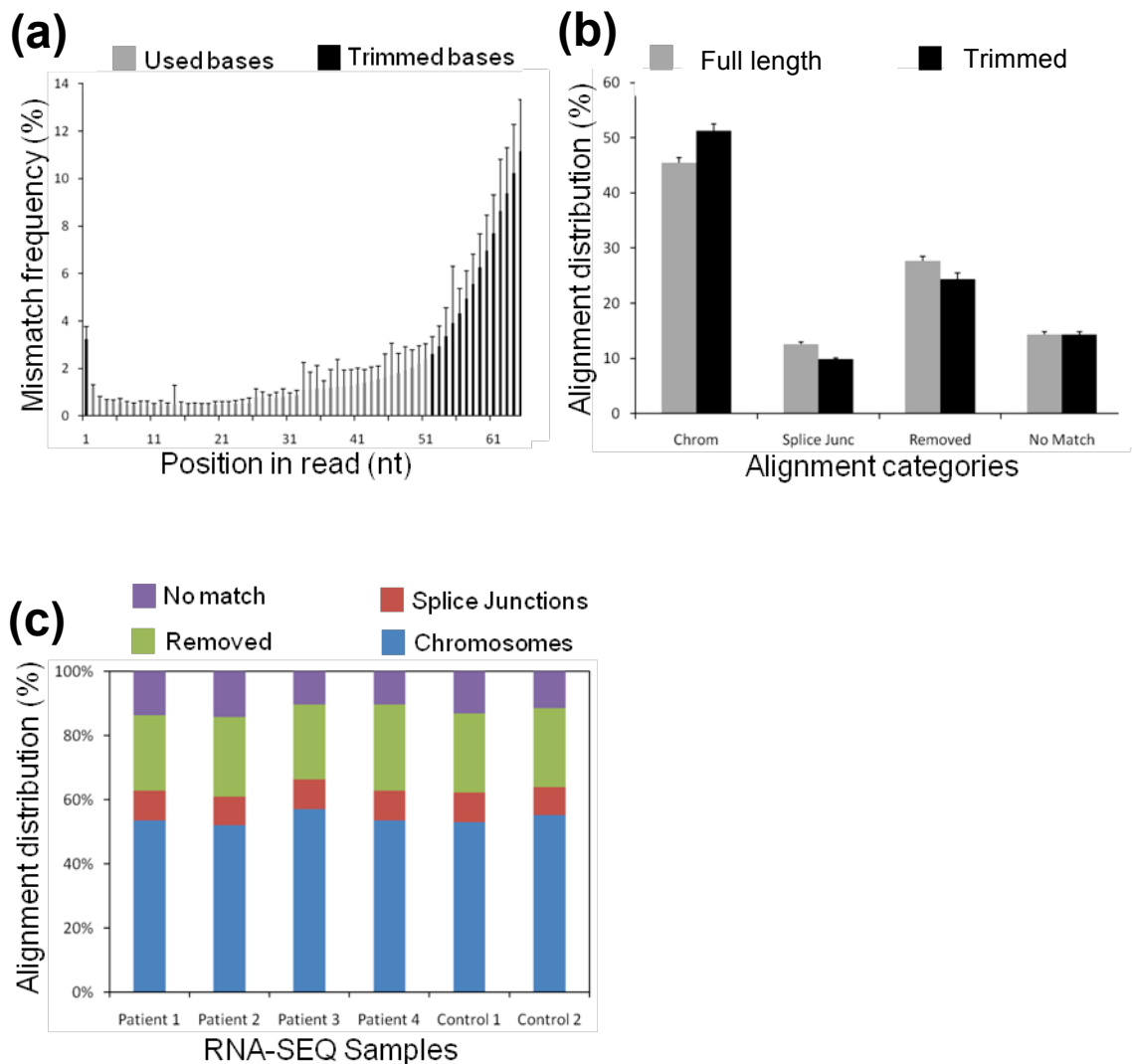
Supplementary Table S5: Summary of CNV and overlapping DEGs detected in *UPF3B* patients.

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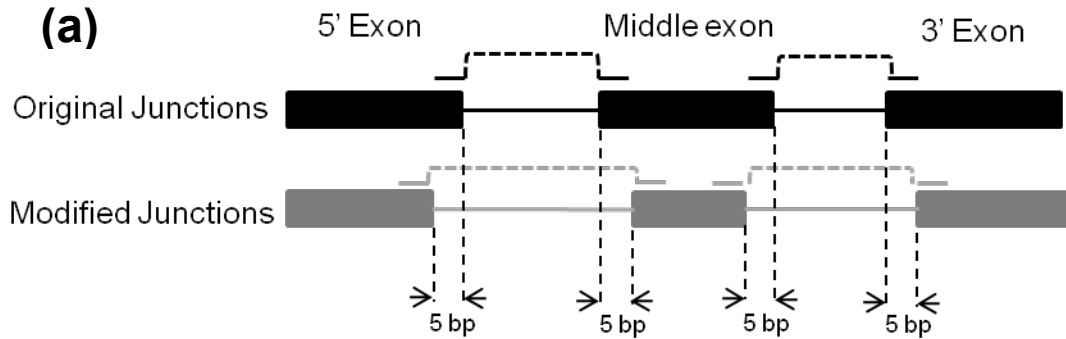
Supplementary Table S8: List of all primers used in this study.

Supplementary Table S9: List of all antibodies used in this study.



Supplementary Figure S1: Mapping of RNA-SEQ reads to the transcriptome. **(a)** Mis-mapping frequency at each position in the 65 bp reads in all samples. The first and the last 14 bases (black bar) were trimmed to reduce mapping error; the middle 50 bases (gray bar) were used for final alignment. **(b)** Trimming improved the total number of aligned reads. The distribution of reads mapped to the chromosome, splice junctions or reads that were removed (mapped to rRNA, mtDNA or multiple matches) and reads that have no match were compared when using the full length 65 bp (gray bar) or trimmed 50 bp reads (black bar) for mapping. Trimming increased the total number of mapped reads by >3%. **(c)** Distribution of mapped reads is similar across all samples despite the difference in the total number of starting reads (see Supplementary Table S2). Reads were mapped to the chromosome (blue

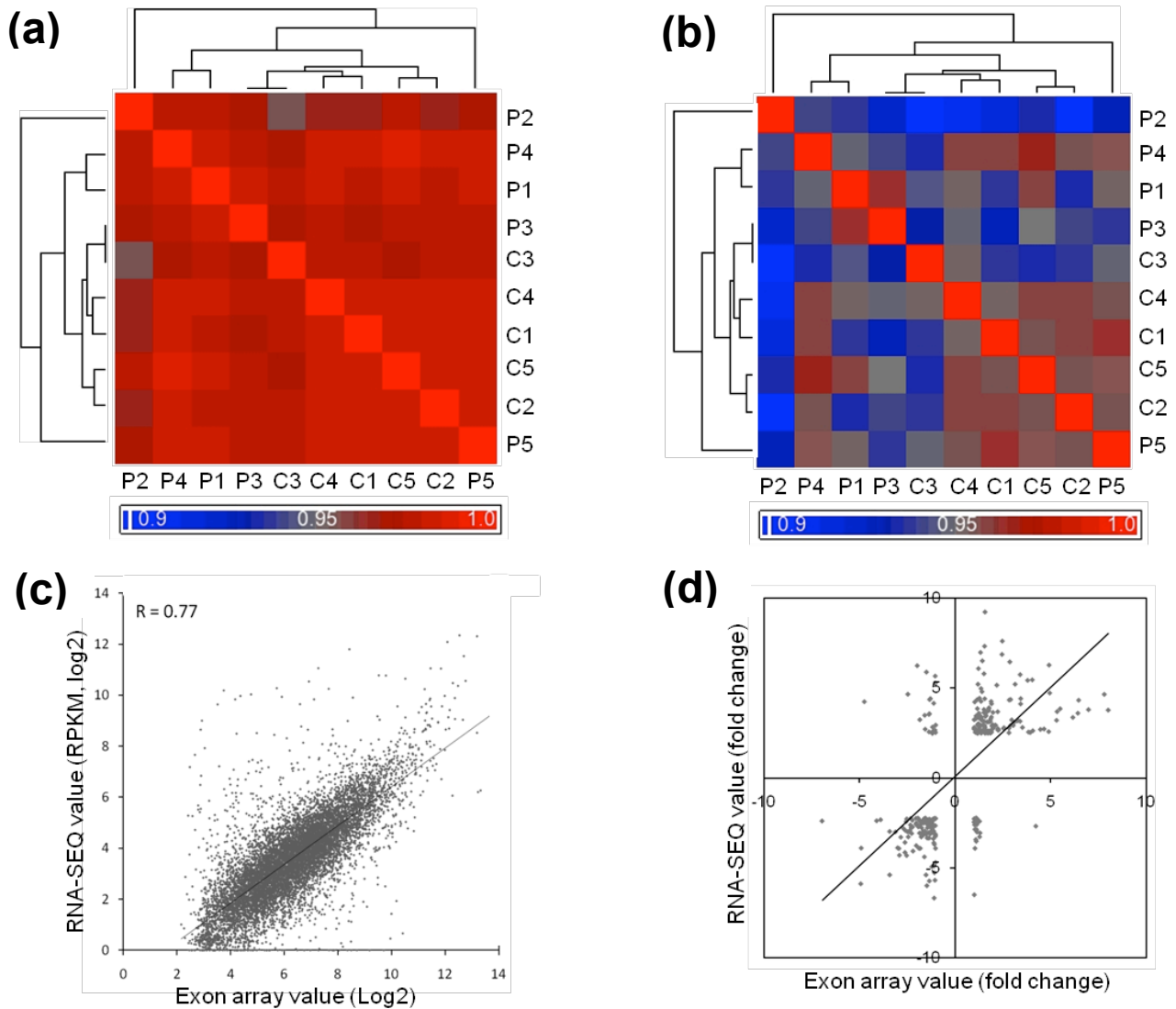
bar), splice junction (red bar); reads were removed from downstream analysis (green bar) or have no match (purple bar).



(b)

Sample	Original Junctions		Modified Junctions	
	Aligned Reads	Junctions > 2 reads	Aligned Reads	Junctions > 2 reads
P 2	203093	15145	200	19
C 1	212442	14654	248	16

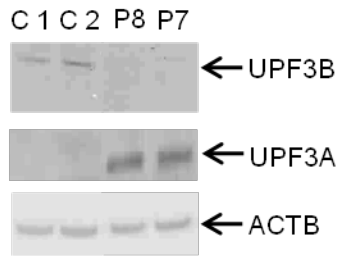
Supplementary Figure S2: Estimation of the rate of mis-mapping. **(a)** Design of the junctions and modified junctions. The exons were shortened by 5 bp on each side of the exon-exon junction. A set of ~75 k modified junctions were created. **(b)** Number of reads mapped to the authentic junctions and the modified junctions. Reads from patient 2 and control 1 were mapped to either the authentic or modified junctions. Data indicate that the rate of mis-mapping is very low, less than 0.2 %.



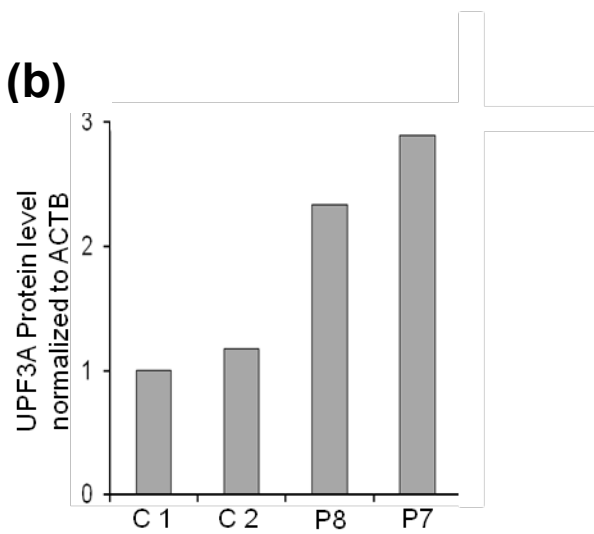
Supplementary Figure S3: Comparison between RNA-SEQ and exon array. **(a)** Heat map and hierarchical clustering showing Pearson's correlation efficiency between exon array samples. All core probesets were included in this analysis. **(b)** Heat map and hierarchical clustering showing Pearson's correlation efficiency between exon array samples. Only core probesets targeting confident genes that can be detected by RNA-SEQ (RPKM >3) were included in this analysis. Slight reduction in expression correlation is the result of having fewer values for comparison. **(c)** Absolute expression correlation. Values from RNA-SEQ and exon array of the same sample (Patient 1 shown as representative) were compared directly by Pearson correlation. To reduce false positive due to background noise, only core

probesets targeting genes that can be confidently detected by RNA-SEQ (RPKM >3) were included in this analysis and further downstream analysis. **(d)** Expression fold change comparison. Values were calculated using only samples that were subjected to both RNA-SEQ and exon array (Patient 1, 2 & 3 and control 1 & 2, see Supplementary Table S3). DEGs in the patients with the same trend of de-regulation (85%) are shown in top right and bottom left of the graph. DEGs in the patients with a different trend of de-regulation (15%) are shown in the top left and bottom right of the graph. Only the top 300 DEGs by at least 2 folds as determined by RNA-SEQ were included in this analysis.

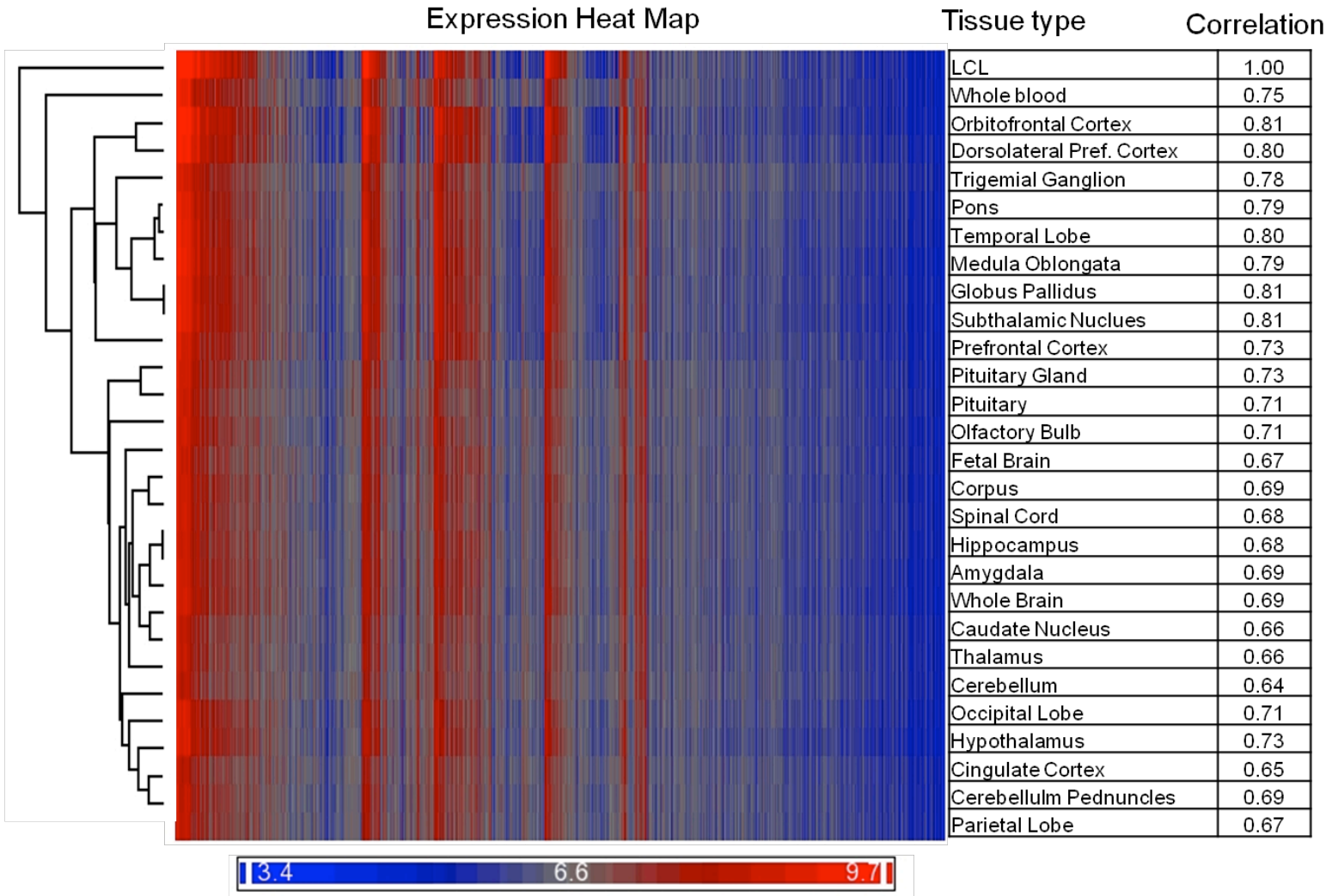
(a)



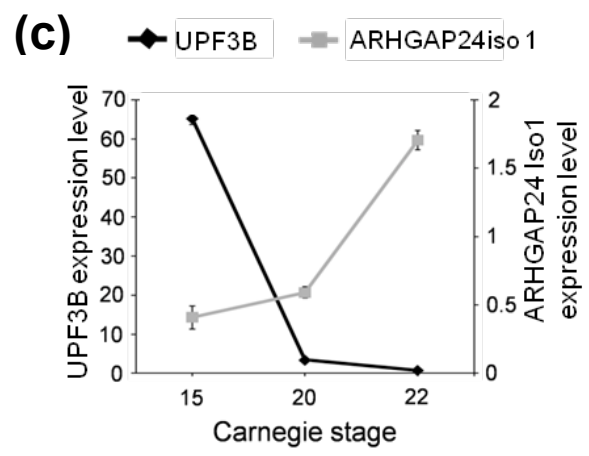
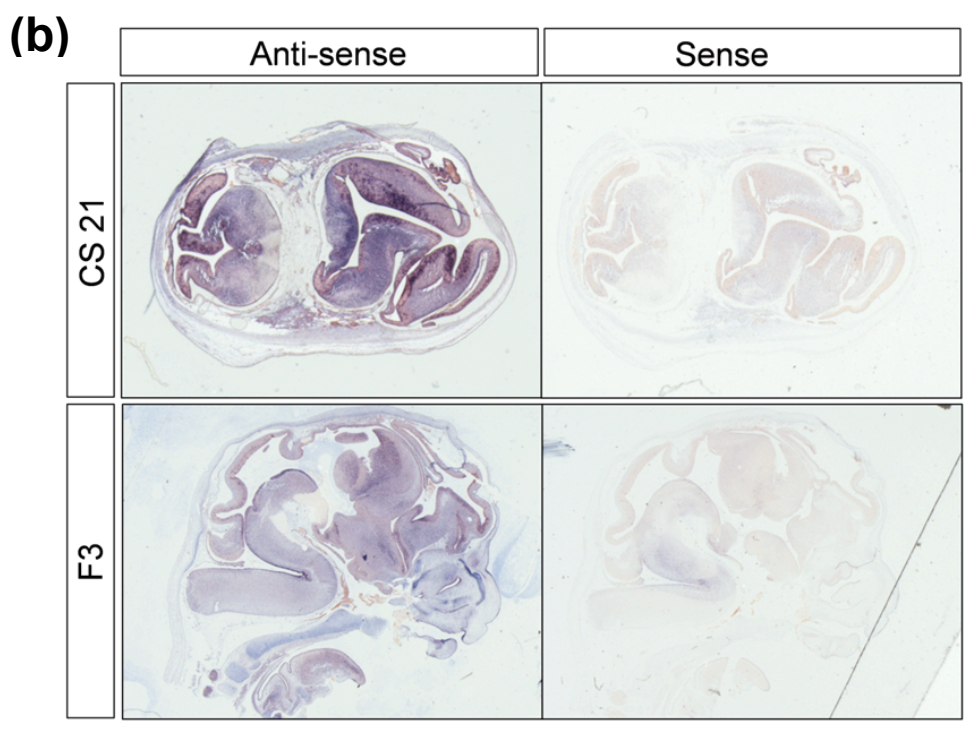
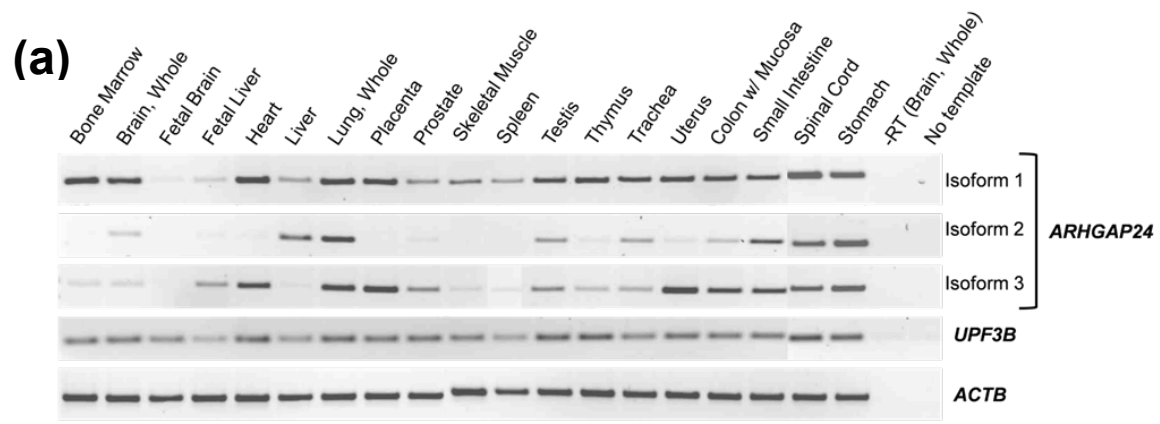
(b)



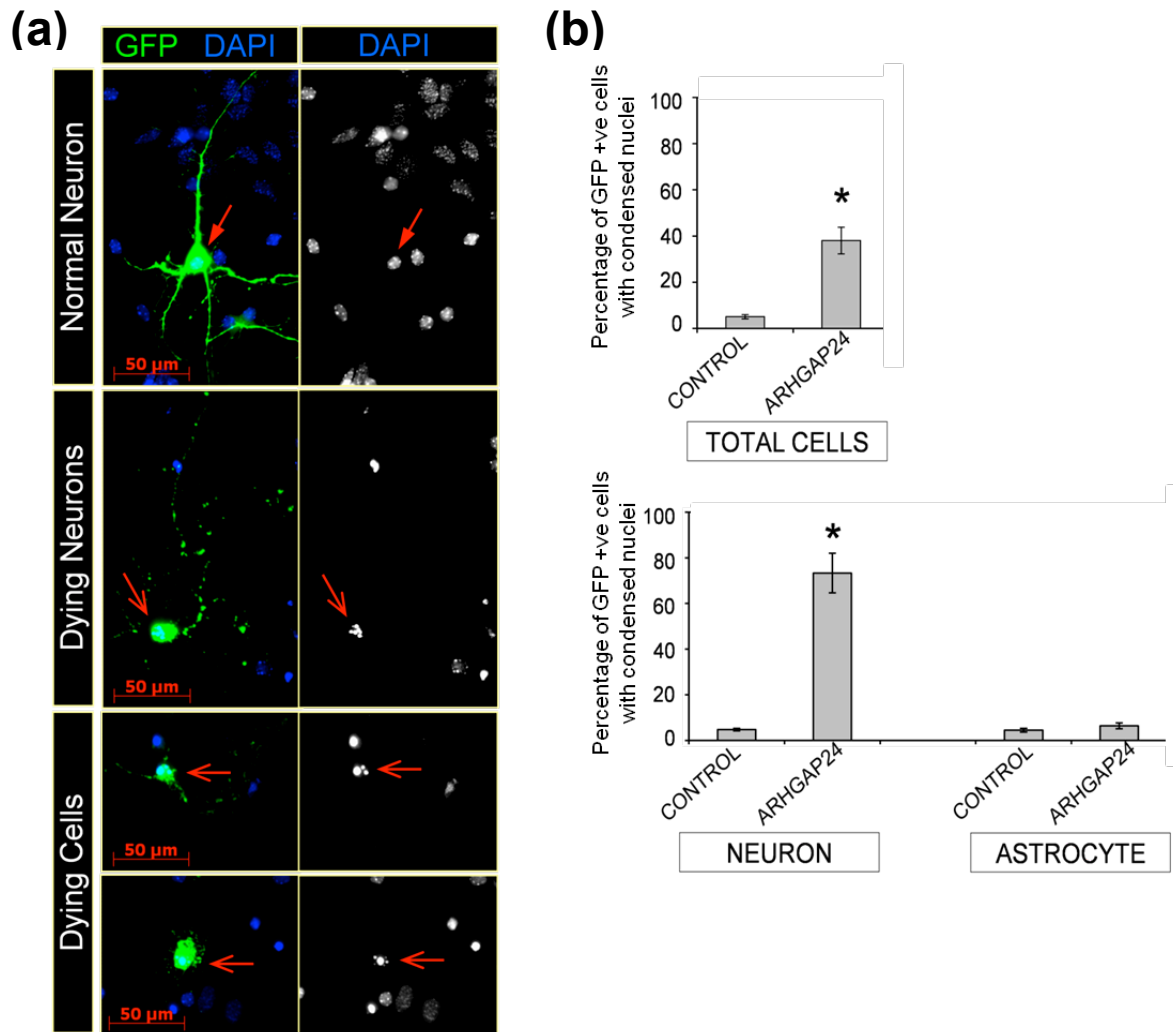
Supplementary Figure S4: Upregulation of UPF3A in newly identified patients with *UPF3B* mutations. **(a)** Protein blot analysis of UPF3B and UPF3A in two recently identified ID patients (Addington et al, 2011). When UPF3B-NMD is compromised, UPF3A is stabilised in the patients. **(b)** UPF3A is stabilized at the same level in these two patients (brothers). Densitometry was performed directly on images captured with low exposure time and normalized against the level of ACTB in the same sample. Value was averaged from two images, and is representative of two independent experiments.



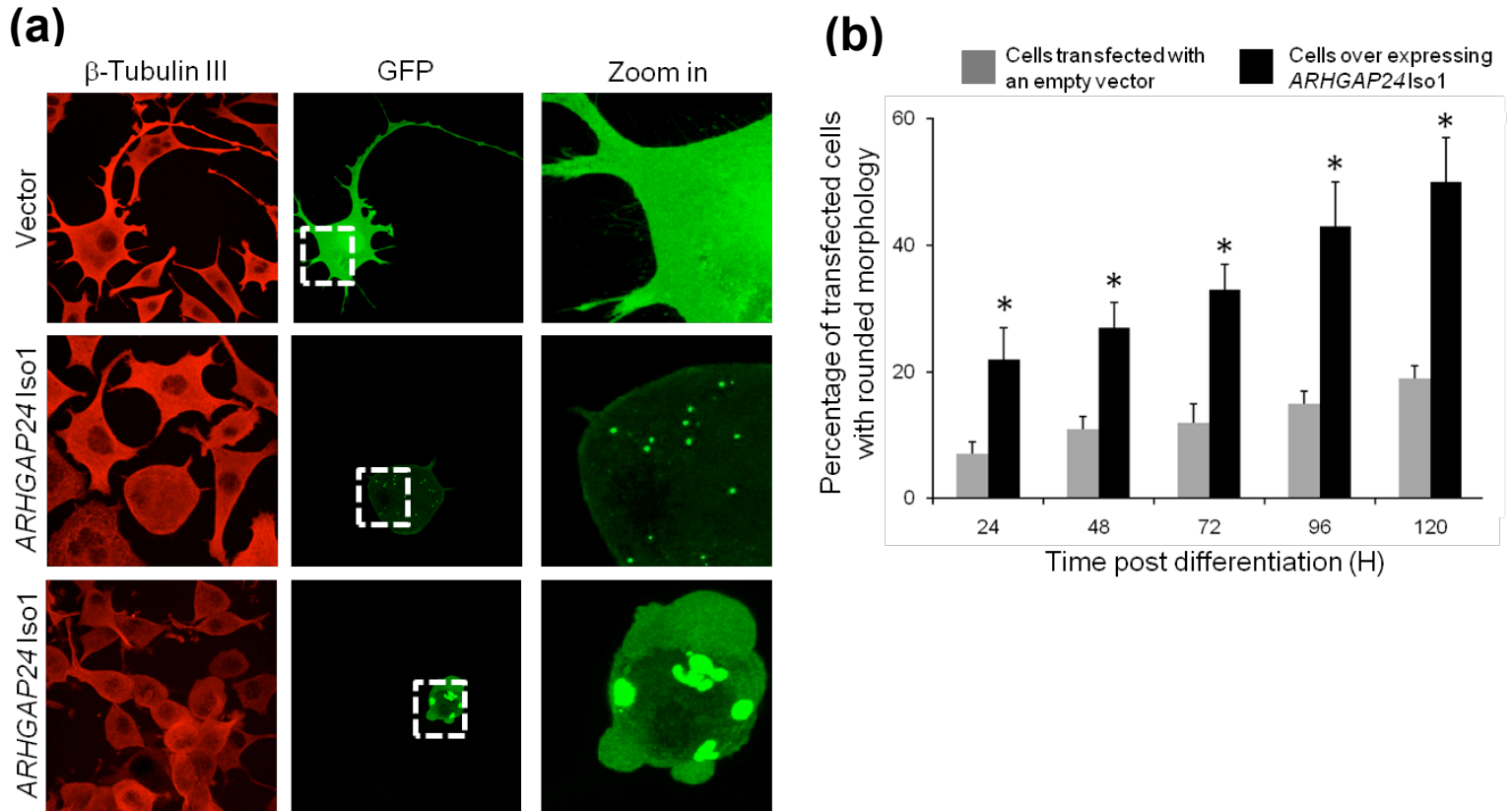
Supplementary Figure S5: Gene expression of the LCL transcriptome correlates well with that of different parts of human brain. Heat map and Pearson's correlation efficiency (right column) show similar expression pattern of probesets detected in LCLs (top panel) and various parts of the brain (lower panels).



Supplementary Figure S6: Expression profile of *ARHGAP24*. **(a)** Tissue expression profile of human *ARHGAP24* isoforms 1, 2 and 3 and *UPF3B*. Selected RNAs from the Total Human RNA Master Panel II (Clontech) were subjected to reverse transcription. The no reverse transcriptase (-RT) sample with whole brain RNA was used as a negative control. The efficiency of the reaction was tested by PCR using primers specific to the ubiquitously expressed *ACTB* gene (bottom panel). The expressions of the three isoforms of *ARHGAP24* were assessed by semi-quantitative RT-PCR using isoform specific forward primers ARHGAP24 E1.3F, ARHGAP24 E2.1F and ARHGAP24 E3.1F for isoforms 1, 2 and 3 (top, second and third panel respectively) and reverse primer targeting common region in all three isoforms ARHGAP24 E2R, respectively. *UPF3B* expression was assessed using primers UPF3B qPCR F and UPF3B qPCR R, which target both isoforms of *UPF3B*. **(b)** *ARHGAP24* isoform1 expression during human embryonic/foetal brain development. *In-situ* hybridization of *ARHGAP24* isoform1 mRNA. Coronal sections of human Carnegie stage 21 (CS21) (upper panels) and sagittal sections of human foetal day 3 (F3) (lower panels) probed with anti-sense and sense DIG-labelled RNA probes. **(c)** Inverse temporal relationship between *UPF3B* and *ARHGAP24* isoform 1 mRNA expression during development of the nervous system. RT-qPCR analysis of mRNA expression across three different Carnegie stages of human embryonic brain development (Upper panel). Mean expression of technical replicates (\pm s.d.) of *UPF3B* (black line) and *ARHGAP24* isoform 1 (gray line). Expression was measured from two independent real time PCRs (only one shown as representative). Values were normalised to the *ACTB* level in the same sample using relative standard curve method.



Supplementary Figure S7: Ectopic expression of *ARHGAP24* isoform 1 at high concentration results in neurotoxicity. Primary hippocampal neurons exogenously expressing GFP alone (Control), or together with *ARHGAP24* isoform1 for 8 days of culture were scored for viability using nuclear condensation/fragmentation as a marker of cell death. **(a)** Examples of images used to define the scoring system applied. Cells were defined as neuronal or astrocyte only if overt morphology was present. Cells were defined as alive or dying based on DAPI staining, which revealed normal (closed arrow heads) or condensed/fragmented (open arrow heads) nuclear material respectively. **(b)** Cultures ectopically expressing high amount of *ARHGAP24* isoform 1 contain more cells in total with condensed nuclear material (right panel) that was largely restricted to the neuronal, but not astrocyte, populations (left panel). Experiments were done in triplicate with at least 100 cells scored each experiment. * $P < 0.0001$ by Student's paired two-tailed t-test.



Supplementary Figure S8: Transient ectopic expression of *ARHGAP24* isoform 1 blocks nerve growth factor (NGF) stimulated differentiation of PC12 cells. **(a)** Sub-cellular localisation of an empty vector (upper panel) and *ARHGAP24* isoform 1 ectopically expressed in PC12 cells (middle and bottom panels) following 72 hrs of 50ng/ml of NGF stimulation. Microtubules stained with B-Tubulin III (left), GFP-tagged vector or *ARHGAP24* isoform 1 (centre) with a zoomed image of the transfected cell (right). **(b)** Percentage of transfected PC12 cells with rounded morphology after 50 ng/ml NGF stimulation in empty vector (gray bar) and *ARHGAP24* (black bar) transfected cells. Results shown are averaged from 2 independent experiments; over 1000 cells were counted per transfection. * $P < 0.0001$ by Student's paired two-tailed t-test.

Supplementary Table S1: Spectrum of UPF3B associated phenotypes in patients with ID. This table only contains summarized clinical features of *UPF3B* patients included in this study. For full description of other *UPF3B* patients, please refer to the original publications.

Patient ID	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Original Pedigree	Fam 1, III-1	Fam 2, III-4	Fam 2, III-5	Fam 3, IV-1	Fam 4, II-3	MRX62, III-7
Mutation	c.674_677delGAAA, p.R225fs*20	c.867_868delAG, p.G290fs*2	c.867_868delAG, p.G290fs*2	c.1288C>T, p.R430*	c.478T>G, p.Y160D	c.1081C>T, p.R361*
Reference	Nguyen et al (2007)	Nguyen et al (2007)	Nguyen et al (2007)	Nguyen et al (2007)	Nguyen et al (2007)	Laumonnier et al (2009)
Diagnosed disorder	FG	Lujan-Fryns	Lujan-Fryns	Lujan-Fryns	Non-syndromic	Non-syndromic
ID level	Severe	Severe	Mild	Moderate	Mild	Severe
Height	~25P	182 cm (92-97P)	193 cm (>97P)		~10P	158 cm (-2.6 SD)
Neurological or brain features	- dysgenesis of corpus callosum	- autistic	- no	- no	- high functioning autism	- no
Seizures	- yes	- no	- no	- no	- no	- no
Facial dysmorphic features	- OFC >97P - midface hypoplasia - long thin face - widow's peak - slightly upslanting palpebral fissures - bulbous distal nose	- OFC = 54cm (25-50P) - long thin face - high arched palate - high nasal bridge	-OFC = 58cm (90-98P) - long thin face - high arched palate - large ears (>97P)	- long thin face - prominent forehead - facial asymmetry - high nasal bridge - prominent chin - high arched palate	- OFC ~80P - interpupillary > 75P	- OFC = 58cm (+0.9 SD) - short forehead - absent teeth - widow's peak - dysmorphic prominent ears
Vision	- normal	- normal	- normal	- normal	- normal	- bilateral divergent strabismus
Physical features	- pectus excavatum - long hands and fingers (>98P) - broad thumb	- poor musculature - slender build - mild thoracic scoliosis - mild pectus carinatum - long arm, feet, palm and fingers (>97P) - small left testis (5cm)	- long hands, palm and fingers (>97P) - pes cavus - marked thoracic kyphosis - narrow chest - lower pectus excavatum - minimal gynecomastia	- slender build - ataxic gait		- knee and elbow valgus - pronounced kyphosis and scoliosis - unilateral macroorchidism
Behaviours	- shy	- withdrawn - bizarre psychotic - hyperactive when young		- temper tantrums - affectionate and humorous		- jovial
Other features	- constipation	- poor suck as child - never cried		- hypernasal speech		

Legend: OFC – Orbital Frontal Cortex; P – Percentile; SD – Standard deviation

Patient ID	Patient 7	Patient 8
Original Pedigree	PED 0057, II-1 (NSB1442)	PED 0057, II-2 (NSB1438)
Mutation	c.683_686delAAGA, p.Q228fs*18	c.683_686delAAGA, p.Q228fs*18
Reference	Addington et al (2011)	Addington et al (2011)
Diagnosed disorder	COS	ADHD
ID level	Borderline (IQ=79)	Normal (IQ =87)
Height		
Neurological or brain features	- ADHD, COS and autistic	- ADHD, autistic. - language, fine motor and social delay, and mixed pervasive disorder.
Seizures		
Facial dysmorphic features		
Vision		
Physical features		
Behaviours	- Aggression towards peers	
Other features	- product of uneventful pregnancy and delivery	- born with congenital pulmonary stenosis

Legend: COS – Childhood onset schizophrenia, ADHD – Attention deficit hyperactivity disorder

Supplementary Table S2: RNA-SEQ sample processing information.

	Sample	Sequencer	Basecalls Software	# Reads	Read length
Lot 1	Patient 2	GAI	IPAR-1.3	~9.5 M	65 bp
	Patient 3	GAI	IPAR-1.3	~10 M	65 bp
	Control 1	GAI	IPAR-1.3	~9.6 M	65 bp
Lot 2	Patient 1	GAI	RTA	~20 M	65 bp
	Patient 6	GAI	RTA	~20 M	65 bp
	Control 2	GAI	RTA	~20 M	65 bp

Supplementary Table S3: Samples analyzed on the Affymetrix Human Exon 1.0 ST array.

	Batch 1	Batch 2
Sample ID	Patient 1	Patient 1
	Patient 2	Patient 2
	Patient 3	Patient 3
		Patient 4
		Patient 5
	Control 1	Control 1
	Control 2	Control 2
	Control 3	Control 3
	Control 4	Control 4
	Control 5	Control 5
Total	8	10

Supplementary Table S4: DEGs in *UPF3B* patients as determined by RNA-SEQ and exon array. Genes that were up or down regulated by at least 2-fold in either platforms, as well as having the same trend of de-regulation in both platforms were considered to be differently expressed in the patients. n.a. – genes do not have corresponding probesets in the core probesets or probesets did not pass quality control analysis.

Platform	Gene Symbol	Transcript ID	RefSeq	Exon Array Value		RNA-SEQ Value	
				P Value	Fold Change	P Value	Fold Change
Both platform	ADAM23	2524653	NM_003812	0.023637	-2.40	0.132194	-5.92
Both platform	APOL1	3944404	NM_145343	0.002747	3.28	0.039855	6.33
Both platform	ARHGAP24	2734421	NM_001025616	0.000571	3.02	0.281842	2.41
Both platform	BAIAP2L1	3062868	NM_018842	0.029725	-2.47	0.182571	-3.27
Both platform	BEND4	2767295	NM_207406	0.004997	2.78	0.127014	4.43
Both platform	BTBD3	3876645	NM_014962	0.019940	3.20	0.003749	4.40
Both platform	C14orf105	3566383	NM_018168	0.001405	5.69	0.334146	3.78
Both platform	C3orf59	2711034	NM_178496	0.001094	-2.25	0.26336	-2.14
Both platform	CAPN2	2382117	NM_001748	0.001730	-4.05	0.024473	-5.89
Both platform	CD38	2719656	NM_001775	0.008621	2.96	0.240116	5.77
Both platform	CD96	2635741	NM_198196	0.022763	2.39	0.342591	2.52
Both platform	CHL1	2607568	NM_006614	0.013115	3.53	0.313007	3.15
Both platform	CHST2	2646125	NM_004267	0.000176	-2.44	0.087794	-2.13
Both platform	CLEC2B	3443891	NM_005127	0.011165	2.61	0.346243	2.52
Both platform	CLECL1	3443857	NM_172004	0.007947	2.00	0.178414	6.50
Both platform	CLIC6	3919278	NM_053277	0.012542	-2.19	0.205385	-3.25
Both platform	CNKSR3	2980516	NM_173515	0.002737	2.29	0.291206	2.09
Both platform	CNR2	4044363	NM_001841	0.012931	-2.82	0.174446	-2.36
Both platform	CR2	2377283	NM_001006658	0.016299	-2.26	0.13625	-2.71
Both platform	CXCL10	2773958	NM_001565	0.033329	2.43	0.063699	4.44
Both platform	CYP7B1	3138204	NM_004820	0.000115	3.28	0.028466	4.80
Both platform	DAPK1	3177880	NM_004938	0.027444	-2.07	0.03676	-2.33
Both platform	DBNDD1	3705151	NM_024043	0.003953	2.16	0.323029	2.47
Both platform	DPP4	2584018	NM_001935	0.000490	3.46	0.230861	2.48
Both platform	EPS8	3445908	NM_004447	0.001284	3.44	0.164094	3.89
Both platform	F13A1	2940202	NM_000129	0.044337	3.67	0.459993	2.92
Both platform	FAM13A	2777564	NM_014883	0.019029	3.49	0.312712	2.00
Both platform	FCRL5	2438892	NM_031281	0.010436	2.75	0.259374	5.83
Both platform	FLT1	3507282	NM_002019	0.003039	2.39	0.326561	2.20
Both platform	FXYD2	3393446	NM_001127489	0.001787	4.90	0.327833	2.36
Both platform	FYN	2969886	NM_002037	0.180272	-2.13	0.268465	-2.78
Both platform	GAB1	2745547	NM_207123	0.001224	2.28	0.004772	2.40
Both platform	GAS2	3323891	NM_005256	0.003559	2.88	0.214071	3.29
Both platform	GAS8	3674659	NR_023348	0.000789	2.79	0.078457	2.98
Both platform	GBP4	2421995	NM_052941	0.042098	2.25	0.043775	2.18
Both platform	GBP5	2422035	NM_052942	0.007315	3.16	0.282009	2.71
Both platform	GIMAP5	3031573	NM_018384	0.016743	-2.53	0.214599	-4.25
Both platform	GIMAP6	3079103	NM_024711	0.066243	-2.05	0.162455	-2.97
Both platform	GIMAP7	3031517	NM_153236	0.001452	-3.27	0.120316	-2.95
Both platform	GPC4	4022370	NM_001448	0.010332	2.91	0.317883	2.54
Both platform	GSTM1	2350981	NM_000561	0.015622	3.58	0.116499	4.64

Both platform	GSTT1	3955102	NM_000853	0.021707	2.99	0.002754	12.77
Both platform	HGSNAT	3096575	NM_152419	0.047396	-2.15	0.108591	-2.15
Both platform	HLA-DQA1	2903219	NM_002122	0.157384	-3.02	0.137269	-2.16
Both platform	HNF1B	3754797	NM_000458	0.007840	4.07	0.444833	3.40
Both platform	HOXB2	3761291	NM_002145	0.000186	3.05	0.116535	5.46
Both platform	IGFBP2	2527253	NM_000597	0.096385	2.57	0.159149	10.41
Both platform	INPP5F	3267382	NM_014937	0.048239	-2.17	0.354142	-4.24
Both platform	IPCEF1	2980449	NM_001130699	0.117110	2.47	0.034277	7.63
Both platform	IRAK3	3420442	NM_007199	0.079674	2.02	0.337153	2.02
Both platform	ITGB8	2991860	NM_002214	0.002362	3.42	0.041849	3.24
Both platform	LAG3	3402757	NM_002286	0.009951	2.75	0.167702	4.33
Both platform	LCP2	2886595	NM_005565	0.012329	-2.01	0.195963	-2.61
Both platform	LEPREL1	2710474	NM_018192	0.004183	-5.89	0.365239	-3.90
Both platform	LGALS3BP	3772719	NM_005567	0.007445	3.30	0.185741	2.77
Both platform	LYPD6B	2509988	NM_177964	0.086238	-2.00	0.060343	-5.41
Both platform	MAN2A1	2823551	NM_002372	0.002138	2.17	0.06179	2.36
Both platform	MAP7D2	4002081	NM_152780	0.008650	3.09	0.33194	2.39
Both platform	MCTP2	3609592	NM_018349	0.001450	4.33	0.139075	3.61
Both platform	MGC39372	2939014	BC025340	0.022913	2.09	0.33553	2.03
Both platform	MMP7	3388673	NM_002423	0.012887	3.37	0.469798	2.56
Both platform	MUC13	2692883	NM_033049	0.083737	2.98	0.550491	2.58
Both platform	NFIL3	3214451	NM_005384	0.004187	3.23	0.094243	2.87
Both platform	PLOD2	2699564	NM_182943	0.013129	4.70	0.257012	3.81
Both platform	PRSS21	3645338	NM_006799	0.091720	2.79	0.483007	2.25
Both platform	PTK2	3156307	NM_153831	0.055111	-2.00	0.288927	-2.74
Both platform	RAB31	3778504	NM_006868	0.004905	-3.82	0.499725	-2.10
Both platform	RALGPS2	2369339	NM_152663	0.007081	2.43	0.338341	2.33
Both platform	RASSF6	2773222	NM_201431	0.031328	2.52	0.200422	5.21
Both platform	RBPMS	3092415	NM_001008711	0.007117	3.90	0.302038	2.64
Both platform	SAMD10	3914273	NM_080621	0.019005	-2.01	0.247985	-2.31
Both platform	SERINC2	2328273	NM_178865	0.000961	4.12	0.502287	2.62
Both platform	SLC12A7	2845699	NM_006598	0.000841	2.51	0.002682	10.70
Both platform	SLC12A8	2693014	NM_024628	0.007899	-2.13	0.371185	-2.71
Both platform	SLC23A2	3896078	NM_005116	0.004378	-2.94	0.278395	-3.87
Both platform	SPARC	2882098	NM_003118	0.019636	-2.38	0.02064	-2.73
Both platform	STEAP1	3011838	NM_012449	0.003515	3.08	0.352101	3.05
Both platform	STEAP2	3011861	NM_152999	0.000010	4.10	0.179174	2.39
Both platform	STS	3967689	NM_000351	0.023707	2.57	0.159301	2.24
Both platform	TGFBR3	2422722	NM_003243	0.001644	-3.24	0.120189	-3.55
Both platform	TMEM176A	3031624	NM_018487	0.060507	3.33	0.347443	3.69
Both platform	TMEM176B	3079172	NM_014020	0.035596	2.78	0.361807	2.53
Both platform	TMEM2	3209384	NM_013390	0.040346	2.08	0.17779	2.39
Both platform	TMEM45A	2633691	NM_018004	0.004999	2.54	0.000844	2.81
Both platform	TNFRSF11A	3791254	NM_003839	0.002569	2.42	0.351173	2.05
Both platform	TNFRSF21	2956052	NM_014452	0.020510	2.42	0.409962	3.21
Both platform	TNFSF11	3487299	NM_003701	0.002597	-3.32	0.053093	-4.07
Both platform	UST	2930418	NM_005715	0.015123	-2.99	0.388295	-2.37
Both platform	ZNF595	2713789	NM_182524	0.001106	2.61	0.121121	2.81
Exon Array only	ADM	3320123	NM_001124	0.025374	2.70	0.899037	1.19
Exon Array only	ASCL1	3429008	NM_004316	0.016186	2.06	0.758782	1.44
Exon Array only	CACNB2	3237396	NM_201571	0.008960	2.07	0.54147	1.44
Exon Array only	CASK	4005859	NM_003688	0.015132	2.33	0.42559	1.68

Exon Array only	CDCP1	2671728	NM_022842	0.054734	2.10	0.810256	1.26
Exon Array only	CMKLR1	3470193	NM_001142343	0.053699	-2.00	0.790147	-1.33
Exon Array only	CYBRD1	2515240	NM_024843	0.001681	-2.07	0.637883	-1.25
Exon Array only	DNASE1L3	2678298	NM_004944	0.141855	2.52	0.39583	1.95
Exon Array only	ECE1	2400518	NM_001113349	0.022184	-2.04	0.536016	-1.90
Exon Array only	EFR3B	2473376	NM_014971	0.054249	-2.16	0.825249	-1.26
Exon Array only	EPB41L5	2503109	NM_020909	0.018625	2.47	0.512014	1.44
Exon Array only	FOXP1	2681753	NM_032682	0.033835	2.14	0.245829	1.85
Exon Array only	FUT8	3540552	NM_178155	0.004788	-2.18	0.220873	-1.60
Exon Array only	GPR174	3982612	NM_032553	0.029775	2.09	0.615977	1.39
Exon Array only	HLA-DOB	2950145	NM_002120	0.031808	-2.46	0.422967	-1.34
Exon Array only	HLA-DRB1	4048265	NM_002124	0.512018	-2.27	0.017569	-1.84
Exon Array only	HLA-DRB5	4048241	NM_002125	0.536585	-2.62	0.470412	-1.65
Exon Array only	HNF4G	3103818	NM_004133	0.014723	2.41	0.869684	1.17
Exon Array only	IGF1	3468345	NM_001111283	0.035097	-2.62	0.089511	-1.66
Exon Array only	JAM2	3916527	NM_021219	0.005201	-2.33	0.6261	-1.72
Exon Array only	JUP	3757329	NM_002230	0.031439	-2.44	0.776382	-1.35
Exon Array only	KCNIP2	3304073	NM_014591	0.000581	-2.04	0.88435	-1.14
Exon Array only	KIAA1324L	3059942	NM_001142749	0.068207	2.61	0.925632	1.10
Exon Array only	LAPTM4B	3108489	NM_018407	0.047668	-2.42	0.812657	-1.36
Exon Array only	LRRC16A	2898746	NM_017640	0.051800	2.24	0.596663	1.50
Exon Array only	MACC1	3040518	NM_182762	0.000713	2.26	0.447682	1.64
Exon Array only	NEUROD1	2590491	NM_002500	0.067931	3.32	0.54147	1.48
Exon Array only	NFATC2	3909553	NM_012340	0.014298	-2.70	0.475913	-1.95
Exon Array only	NFATC4	3529908	NM_001136022	0.007574	2.00	0.404438	1.98
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Exon Array only	PAG1	3142217	NM_018440	0.015750	-2.09	0.813315	-1.32
Exon Array only	PEX5L	2707045	NM_016559	0.000351	2.13	0.54147	1.53
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Exon Array only	RNASE6	3527662	NM_005615	0.094328	-2.01	0.216795	-1.77
Exon Array only	RORA	3627422	NM_134260	0.022874	2.47	0.494055	1.84
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Exon Array only	SMARCA2	3159946	NM_003070	0.000545	-2.29	0.421704	-1.48
Exon Array only	SNTB1	3150844	NM_021021	0.002137	2.97	0.313527	1.75
Exon Array only	SSTR3	3960042	NM_001051	0.007195	2.15	0.589578	1.39
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Exon Array only	SYNE2	3539724	NM_182914	0.000682	2.51	0.31796	1.81
Exon Array only	TEX9	3594986	NM_198524	0.015451	-2.08	0.898365	-1.07
Exon Array only	TMTC1	3449068	NM_175861	0.121314	2.10	0.45148	1.68
Exon Array only	TP63	2657665	NM_003722	0.016732	-2.14	0.839582	-1.25
Exon Array only	TSPAN12	3069955	NM_012338	0.021349	2.01	0.181873	2.00
Exon Array only	TSPAN7	3974019	NM_004615	0.206801	2.09	0.54147	1.94
Exon Array only	WWTR1	2700404	NM_015472	0.004408	2.19	0.320713	1.74
RNA-SEQ only	ABCA12	2598145	NM_173076	0.590694	-1.36	0.317469	-2.44
RNA-SEQ only	ABCC9	3446919	NM_020297	0.071296	1.07	0.463291	2.17
RNA-SEQ only	ABLIM1	3307939	NM_002313	0.064277	-1.45	0.214565	-2.15
RNA-SEQ only	ACADS	3434594	NM_000017	0.057666	1.32	0.130966	3.01
RNA-SEQ only	ACER2	3164312	NM_001010887	0.104148	-1.11	0.027811	-2.21
RNA-SEQ only	ACOT4	3543714	NM_152331	0.435507	-1.07	0.033486	-2.18

RNA-SEQ only	ACTN1	3569814	NM_001130004	0.091556	1.61	0.064209	9.24
RNA-SEQ only	ACY3	3379063	NM_080658	0.036045	-1.61	0.120531	-2.44
RNA-SEQ only	ADARB1	3924041	NM_001033049	0.022610	-1.38	0.458873	-2.31
RNA-SEQ only	ADCY6	3453252	NM_015270	0.000838	1.70	0.331331	2.23
RNA-SEQ only	ADRB1	3265140	NM_000684	0.839097	-1.04	0.177808	-2.07
RNA-SEQ only	AIF1	2902444	NM_004847	0.683892	1.13	0.496102	2.27
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RNA-SEQ only	AK093002	n.a.				0.215159	-2.82
RNA-SEQ only	AK128525	n.a.				0.012931	55.04
RNA-SEQ only	ALDH1L2	n.a.				0.3077	2.22
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RNA-SEQ only	ALOX5AP	3484060	NM_001629	0.017337	-1.70	0.214593	-2.97
RNA-SEQ only	AMICA1	3393670	NM_001098526	0.120620	1.45	0.422317	2.26
RNA-SEQ only	ANK1	3132940	NM_020476	0.019934	1.30	0.395329	2.41
RNA-SEQ only	ANKRD24	n.a.				0.316769	-2.25
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RNA-SEQ only	ARHGEF17	3339812	NM_014786	0.049998	1.33	0.028194	3.54
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RNA-SEQ only	ARMC9	2531779	NM_025139	0.024400	-1.82	0.080787	-2.45
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RNA-SEQ only	AUTS2	3006572	NM_015570	0.027454	-1.50	0.23364	-2.63
RNA-SEQ only	BAG3	3267314	NM_004281	0.017693	-1.30	0.308343	-2.45
RNA-SEQ only	BC031259	n.a.				0.123391	4.11
RNA-SEQ only	BEX4	n.a.				0.582396	2.03
RNA-SEQ only	BHLHE22	3101153	NM_152414	0.072040	1.87	0.462269	2.25
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RNA-SEQ only	BLK	3085990	NM_001715	0.127713	-1.45	0.140785	-2.25
RNA-SEQ only	BMP4	3565206	NM_001202	0.145530	1.56	0.36879	2.18
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RNA-SEQ only	C10orf10	3286776	NM_007021	0.113118	1.36	0.045317	2.06
RNA-SEQ only	C10orf11	3252690	NM_032024	0.224626	1.65	0.219255	2.92
RNA-SEQ only	C10orf99	3255284	NM_207373	0.439134	1.18	0.199019	2.53
RNA-SEQ only	C11orf41	3326067	NM_012194	0.162163	-1.31	0.067094	-5.73
RNA-SEQ only	C11orf63	3353441	NM_024806	0.007334	-1.13	0.083804	-2.06
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RNA-SEQ only	C17orf91	3740664	NM_032895	0.651263	1.09	0.208583	2.09
RNA-SEQ only	C20orf103	3876084	NM_012261	0.892203	1.09	0.224962	7.15
RNA-SEQ only	C21orf7	3917204	NM_020152	0.046104	-1.70	0.035102	-2.03
RNA-SEQ only	C3orf34	2713016	NM_032898	0.233797	-1.10	0.035693	-2.14
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RNA-SEQ only	CCL3	n.a.				0.208848	2.42
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RNA-SEQ only	EBI3	3817380	NM_005755	0.016864	-1.34	0.03795	-2.23
RNA-SEQ only	ECHDC2	2413032	NM_018281	0.956972	1.01	0.262639	2.11
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RNA-SEQ only	EMILIN1	2474223	NM_007046	0.276560	1.19	0.192153	2.75
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RNA-SEQ only	GAS6	3502829	NM_000820	0.251411	1.08	0.185218	2.42
RNA-SEQ only	GBGT1	3228523	NM_021996	0.140431	1.35	0.009053	3.74
RNA-SEQ only	GBP1	2421883	NM_002053	0.173599	1.57	0.05735	5.45
RNA-SEQ only	GBP2	n.a.				0.077684	6.18
RNA-SEQ only	GBP3	2421843	NM_018284	0.012991	1.46	0.289786	2.52
RNA-SEQ only	GHR	2807949	NM_000163	0.404478	-1.27	0.178917	-5.26
RNA-SEQ only	GIMAP1	3031544	NM_130759	0.064405	-1.33	0.116071	-2.98
RNA-SEQ only	GIMAP4	3031533	NM_018326	0.027509	-1.40	0.177808	-3.01
RNA-SEQ only	GIMAP8	3031466	NM_175571	0.540747	-1.11	0.027491	-2.11
RNA-SEQ only	GLT1D1	3437500	NM_144669	0.821752	1.09	0.499917	2.69
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RNA-SEQ only	GNA15	3816815	NM_002068	0.143405	1.48	0.209265	3.93
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RNA-SEQ only	GPR153	2394608	NM_207370	0.644722	-1.07	0.071437	-2.04
RNA-SEQ only	GPR98	2819779	NM_032119	0.635926	-1.16	0.499102	-2.17
RNA-SEQ only	GPX7	2336439	NM_015696	0.448057	1.37	0.155923	4.31
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RNA-SEQ only	GRAP2	3946095	NM_004810	0.856948	-1.07	0.517855	-2.36

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RNA-SEQ only	HDGFRP3	3636522	NM_016073	0.012457	-1.98	0.20088	-2.12
RNA-SEQ only	HECW2	n.a.				0.352727	-2.49
RNA-SEQ only	HERC5	2735409	NM_016323	0.035166	1.64	0.017514	3.66
RNA-SEQ only	HES1	2658595	NM_005524	0.047029	-1.36	0.085382	-3.02
RNA-SEQ only	HIST1H2BC	2946268	NM_003526	0.722548	1.05	0.225949	2.91
RNA-SEQ only	HIST1H2BE	2899194	NM_003523	0.180798	1.07	0.138929	2.02
RNA-SEQ only	HIST1H4H	2946383	NM_003543	0.467492	1.10	0.106512	2.34
RNA-SEQ only	HLA-DQB1	n.a.				0.18122	-2.43
RNA-SEQ only	HLA-DQB2	2950125	NR_003937	0.451514	1.16	0.668621	2.10
RNA-SEQ only	HLA-G	n.a.				0.152604	4.52
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RNA-SEQ only	HSPC159	2485406	NM_014181	0.020083	-1.65	0.157252	-2.15
RNA-SEQ only	ID3	2401493	NM_002167	0.003186	-1.96	0.260279	-2.31
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RNA-SEQ only	IGFBP4	3721010	NM_001552	0.064374	1.58	0.157154	2.79
RNA-SEQ only	IGJ	2772566	NM_144646	0.030608	1.77	0.146708	4.43
RNA-SEQ only	IGL1	n.a.				0.301691	-3.59
RNA-SEQ only	IL10	2452948	NM_000572	0.401382	1.23	0.414031	2.29
RNA-SEQ only	IL13RA1	3988538	NM_001560	0.249864	-1.24	0.219571	-3.24
RNA-SEQ only	IL17RB	2624565	NM_018725	0.287528	1.65	0.220508	4.09
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RNA-SEQ only	INHBE	3418111	NM_031479	0.051049	1.61	0.414854	2.08
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RNA-SEQ only	KMO	2388085	NM_003679	0.129382	1.34	0.218872	2.43
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RNA-SEQ only	LHX2	3188656	NM_004789	0.125362	-1.54	0.3744	-2.22
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RNA-SEQ only	LNP1	n.a.				0.019711	2.18
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RNA-SEQ only	LOC284551	n.a.				0.395978	3.25
RNA-SEQ only	LOC374443	n.a.				0.122682	2.68

RNA-SEQ only	LOC654433	2501317	NR_015377	0.105227	1.39	0.438617	2.39
RNA-SEQ only	LOC678655	n.a.				0.016609	2.45
RNA-SEQ only	LOC728392	n.a.				0.057617	2.23
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RNA-SEQ only	MEIS2	3618333	NM_172316	0.002010	-1.96	0.390903	-2.56
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RNA-SEQ only	MGST1	3406589	NM_145791	0.801367	1.10	0.57061	2.17
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RNA-SEQ only	MST150	2835662	NM_032947	0.658305	1.06	0.312256	2.50
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RNA-SEQ only	NCKAP1	2590736	NM_013436	0.056556	1.62	0.266329	2.22
RNA-SEQ only	NCOA1	2473149	NM_147223	0.278110	1.24	0.36103	2.05
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RNA-SEQ only	NEDD4L	3789947	NM_001144967	0.142037	-1.66	0.32578	-2.93
RNA-SEQ only	NIACR2	3475794	NM_006018	0.165705	-1.78	0.299918	-2.01
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RNA-SEQ only	NOMO2	n.a.				0.020738	2.37
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RNA-SEQ only	NRCAM	3067478	NM_001037132	0.192923	-1.71	0.275646	-2.84
RNA-SEQ only	NRN1	2940145	NM_016588	0.506810	1.47	0.383167	2.19
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RNA-SEQ only	P2RX1	3741769	NM_002558	0.005417	1.67	0.158671	3.66
RNA-SEQ only	PAPLN	3543539	NM_173462	0.341038	-1.14	0.185608	-2.11
RNA-SEQ only	PARD3	3284596	NM_019619	0.235549	1.56	0.494016	2.75
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RNA-SEQ only	PCYOX1L	2835021	NM_024028	0.000022	-1.65	0.013507	-2.10
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RNA-SEQ only	PHGDH	2354634	NM_006623	0.182981	1.80	0.068531	4.48
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RNA-SEQ only	PLAG1	3136178	NM_002655	0.018299	-1.56	0.297105	-2.05
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RNA-SEQ only	PRR18	2984543	NM_175922	0.499414	-1.07	0.182357	-2.89
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RNA-SEQ only	PTPRK	2973376	NM_001135648	0.271173	1.28	0.424209	2.00
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RNA-SEQ only	SDC1	2542795	NM_001006946	0.600101	1.22	0.403408	2.74
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RNA-SEQ only	SELS	3642137	NM_203472	0.110034	1.19	0.017356	2.06
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RNA-SEQ only	SYNJ2	2933392	NM_003898	0.416589	1.12	0.33583	2.36
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RNA-SEQ only	TNFRSF19	3481410	NM_148957	0.215737	-1.79	0.494951	-2.50
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RNA-SEQ only	TNFSF10	2705706	NM_003810	0.325898	1.22	0.474691	2.25
RNA-SEQ only	TNFSF12	n.a.				0.120099	2.29
RNA-SEQ only	TNFSF13	n.a.				0.54147	2.21
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RNA-SEQ only	TRIB1	3115008	NM_025195	0.111124	1.60	0.021513	3.86
RNA-SEQ only	TRIB2	2470165	NM_021643	0.003112	-1.64	0.017391	-2.47
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RNA-SEQ only	TSC22D3	4017381	NM_198057	0.007773	1.40	0.048982	2.64
RNA-SEQ only	TSNARE1	3156848	NM_145003	0.565581	-1.06	0.038312	-2.39
RNA-SEQ only	TSPAN4	3316375	NM_001025237	0.133308	1.36	0.13749	2.56
RNA-SEQ only	TSPYL5	3145801	NM_033512	0.220363	1.47	0.203086	2.93
RNA-SEQ only	TUBA8	3936515	NM_018943	0.518341	1.21	0.143885	3.18
RNA-SEQ only	TUBB6	3779579	NM_032525	0.758701	1.08	0.071947	6.55
RNA-SEQ only	TXNDC11	3680479	NM_015914	0.202674	1.18	0.092059	2.16

RNA-SEQ only	UBTD2	2887128	NM_152277	0.036634	-1.52	0.167847	-2.04
RNA-SEQ only	UGT2B17	2772088	NM_001077	0.410868	1.47	0.351415	2.43
RNA-SEQ only	UNC13B	3167731	NM_006377	0.014538	-1.67	0.358786	-2.20
RNA-SEQ only	UPF3B	4019570	NM_080632	0.000441	-1.59	0.000384	-3.14
RNA-SEQ only	VIM	3236958	NM_003380	0.283037	1.30	0.415541	3.23
RNA-SEQ only	VPREB3	3954879	NM_013378	0.953203	-1.02	0.044147	-3.03
RNA-SEQ only	WBP5	3985523	NM_016303	0.890561	1.04	0.148029	2.02
RNA-SEQ only	WFDC2	3886938	NM_006103	0.270036	1.20	0.19729	7.49
RNA-SEQ only	XBPI	3956589	NM_005080	0.431607	1.13	0.325237	2.25
RNA-SEQ only	XRRA1	3382061	NM_182969	0.465130	1.15	0.051195	2.31
RNA-SEQ only	ZBP1	3911177	NM_030776	0.981417	1.00	0.285309	2.17
RNA-SEQ only	ZMAT1	4016001	NM_001011657	0.680663	-1.04	0.051247	-2.83
RNA-SEQ only	ZNF334	3907934	NM_199441	0.570776	1.11	0.073482	2.66
RNA-SEQ only	ZNF362	2329266	NM_152493	0.004557	-1.77	0.25946	-2.88
RNA-SEQ only	ZNF439	3821479	NM_152262	0.710320	1.03	0.294405	2.03
RNA-SEQ only	ZNF503	3295376	NM_032772	0.119184	1.40	0.314158	2.05
RNA-SEQ only	ZNF711	3983154	NM_021998	0.014583	-1.35	0.281224	-2.16

Supplementary Table S5: Summary of CNV and overlapping DEGs detected in *UPF3B* patients.

(-) : deletion, (+) : amplification.

Sample ID	Total CNVs	-	+	Average CNV Size (kb)	Overlapping DEGs	Fold change exon array	Fold change RNA-SEQ
Patient 1	77	54	23	68	<i>FNDC3B</i> (+) <i>QPDP</i> (+) <i>SIX3</i> (-)	1.6 1.4 1.4	2.7 2.1 2.4
Patient 2	95	47	48	90	<i>GBP5</i> (+)	3.2	2.7
Patient 3	130	78	52	326	<i>TMEM140</i> (+)	1.5	2.3
Patient 4	97	59	38	65	<i>ELL2</i> (+)	1.3	2.1
Patient 5	68	41	27	61	<i>SYNJ2</i> (+)	1.1	2.4
Patient 6	82	48	34	116	<i>EVC</i> (-)	-1.0	-5.7

Supplementary Table S6: Sequence variation detection by RNA-SEQ and validation with Illumina Human Omni Express Chip.

Sample	Variants Called	Known SNPs (db130)	Presented in Omin Express Chip	Number of SNP validated	% Validated
Patient 1	14316	9927	3857	3697	96
Patient 2	6288	4819	1894	1777	94
Patient 3	6163	4856	1925	1805	94
Patient 6	14124	10164	3815	3653	96
Control 1	6673	4665	1724	1621	94
Control 2	15061	10679	4024	3841	96

Supplementary Table S7: Variants with possible deleterious effects.

Sample	Nonsynonymous SNP with damaging effect	Genes with naturally occurring SNPs that introduce PTCs	Gene expression change
Patient 1	89	8 - <i>PHB2, C4ORF41, CMAS, FAM104B, TCP11L1, TLK2, WDR26, ZNF117</i>	Nil
Patient 2	66	9 - <i>CARD8, PHB2, ALG12, B4GALT1, GON4L, MACF1, MRPL33, POLA2, PSD4</i>	Nil
Patient 3	62	4 - <i>CARD8, PHB2, CDC123, UBR5</i>	Nil
Patient 6	102	6 - <i>PHB2, ARFGEF1, GPS1, LASP1, TCP11L1, TFDP2</i>	Nil
Control 1	61	3 - <i>CDC123, PHB2, HMG20B</i>	Nil
Control 2	106	11 - <i>CARD8, PHB2, CDC123, CMAS, HMG20B, MAN1B1, MLL, MPV17L2, NT5C3L, SLFN13, WDR26</i>	Nil

Supplementary Table S8: List of all primers used in this study.

Use	Primer Name	Primer Sequence (5' → 3')	Tm (°C)	Expected length (bp)
RNA-SEQ and exon array validation				
RT-qPCR	UPF3B qPCR F	CTT CAG GGC AAA GAA TAG AGA GA	60	77
	UPF3B qPCR R	TTG ACA CAA GAC TTA CTC CTC TG		
	ARHGAP24 Iso1 E1.3 F	CTG CAA TGA AGA GAA CCC AG	60	209
	ARHGAP24 Ex2 R	CAT AAC GAA CAG TAT CCT CCA G		
	SLC23A2 qPCR F	TTT GCC TGT AGA GTG TTG TAA AAT A	60	139
	SLC23A2 qPCR R	CCC ACA CAA ATG CTT TCT TTC A		
	BHLHE22 qPCR F	GCT GCG GCT TAA CAT CAA TGC	60	210
	BHLHE22 qPCR R	TGG TTG AGG TAG GCG ACT AGG		
	SYNE2 qPCR F	GCA CTG TCA GGT AAA TCC ATT TC	60	118
	SYNE2 qPCR R	GGG GAA CAG GTG GAA CAT TC		
	SERINC2 qPCR F	TGG GTG CCT TCT ACA TTC CT	60	90
	SERINC2 qPCR R	GCT GGA TGA GGA TGA AGA GGA		
	ASPH qPCR F	TGA AAT GGT ACA CGC AGA ACA	60	130
	ASPH qPCR R	CAG GGT CTC AAA TCT ATC ATC TAC A		
	HNF1B qPCR F	TGG CGA TCA TGG CAA GTT AG	60	133
HNF1B qPCR R	AGG GGA GTT TCA CAA GCA AAA			
GAB1 qPCR F	GTG AAG AAC TGG ATG AAA ATT ACG	60	115	
GAB1 qPCR R	CCT GGA GTC ATT GGC ACA TAA			
ETV5 qPCR F	GCT GTC GTC TTG TAG CCA TGA	60	151	
ETV5 qPCR R	GGG ATT CTG ATG GGT GGG T			
ARHGAP24 profiling				
RT-PCR	ARHGAP24 Iso1 E1.3 F	CTG CAA TGA AGA GAA CCC AG	60	209
	ARHGAP24 Ex2 R	CAT AAC GAA CAG TAT CCT CCA G		
	ARHGAP24 Iso2 E2.1 F	ATG CCT GAA GAC CGG AAT TC	60	151
	ARHGAP24 Ex2 R	CAT AAC GAA CAG TAT CCT CCA G		
	ARHGAP24 Iso3 E3.1 F	CAG TGG ACA GTT AAA CAA GAG	60	230
ARHGAP24 Ex2 R	CAT AAC GAA CAG TAT CCT CCA G			
RT-qPCR	Arhgap24 F (Mouse)	AAG GGC GGC AGA ACA CCA AGT G	60	134
	Arhgap24 R (Mouse)	CTG ATC CCC CTT AAG CAC AA		
	Upf3b F (Mouse)	GCG TTC TGA TGT CGA ACT GA	60	111
	Upf3b R (Mouse)	ATC ATG CGC TCC TGA TCT CT		
	Actb F (Mouse)	CTG CCT GAC GGC CAG G	60	89
Actb R (Mouse)	GAT TCC ATA CCC AAG AAG GAA GG			
Insitu probe	ARHGAP24 F	ACC TTT CCA TGC AGC TGT GG	n/a	458
	ARHGAP24 R1	TCC TGG GTT TTC TTC ATT GC		

Supplementary Table S9: List of all antibodies used in this study.

Protein	Expected Size (kDa)	Primary Antibody		Secondary Antibody	
		Source	Concentration used (ng/ml)	Source	Dilution
Western Blot					
UPF3B	~58	UPF3B-901 Sheep Ab (inhouse)	75	HRP-Conjugated Donkey anti Sheep IgG (Chemicon)	1:10,000
UPF3A	~55	Rent3A C-17 Goat Ab (SCB)	1000	HRP-Conjugated Rabbit anti Goat IgG (DAKO)	1:4,000
UPF2	~148	Rent2 C-18 Goat Ab (SCB)	400	HRP-Conjugated Rabbit anti Goat IgG (DAKO)	1:4,000
MAGOH	~17	MAGOH 21B12 Mouse Ab (SCB)	200	HRP-Conjugated Goat anti Mouse IgG (DAKO)	1:4,000
RBM8A	~20	Y14 (4C4) Mouse Ab (SCB)	400	HRP-Conjugated Goat anti Mouse IgG (DAKO)	1:4,000
ACTB	~42	AC-74 Mouse Ab (Sigma)	0.0125	HRP-Conjugated Goat anti Mouse IgG (DAKO)	1:20,000
Immuno-fluorescent analysis					
MAP2	n/a	MAP2 Chicken Ab (Millipore)	1:2000 (Dilution)	Cy3-Conjugated Donkey anti Chicken (Jackson Lab)	1:400
Tau1	n/a	Tau1 Mouse Ab (Millipore)	1:2000 (Dilution)	Alexa Fluor 647 Conjugated Donkey anti Mouse (Invitrogen)	1:800
β III-tubulin	n/a	β III-tubulin Rabbit (Sigma)	1:200 (Dilution)	Alex Fluor 555 Conjugated Donkey anti Rabbit (Invitrogen)	1:800