SUPPLEMENTARY DATA

Supplementary Table 1. PCR amplification and sequencing primers used for Sanger sequencing of human *PPP1R15B* gene

Region amplified	Chromosome 1 map position[a]		PCR amplification and sequencing primer (5'-3')			Product Size (bp)
	Start	End	Forward	Reverse	Internal sequencing primers	
Promoter	204380800	204381633	CTCGACGCTTCAACACCA	GGGCATTCAACCTTCCAT		834
Exon 1	204380426	204381021	CGTCGGGAACTTAGAAGAGC	GACGTAGACGCCCAACAGTC		596
Exon 1	204379845	204380621	GGAAAGCAGTCCAGGTAGGA	TCTGTAGGCTTCCTCCGAAT		777
Exon 1	204379186	204379984	CTTCCTCATCCCAATCCTCA	TTGCCCAGTAGCCTTCAATC		799
Exon 1	204378537	204379351	AAGCCTCCAAAGTCATGCTG	GGAGAGGGCCGAATAAGTGT		815
Intron[b]	204376192	204377016	AATAACCACTATATCCCTGGAAGTC	CCTTTGACTACCTGCCATTG		825
Exon 2	204375199	204375499	CTAGGACTACAGGCTGCCAAC	CCTCAATGCTGATTGTAAGATCC		301
Exon 2	204374565	204375305	TTGTGGCAGTCCTTGGAAAT	GCTTGACATTTGAACACAGAGA		741
Exon 2	204374234	204374967	TGACAGTGCTGAGGCATGAT	ATGTCCTTTGCCTGCATGA		734
Exon 2	204373791	204374484	CCCTGTAAGCACTTCTGATGA	TTTGAAGAGGGTTCTGTGTACG		694
Exon 2	204372956	204373998	TCCTTTCTGTCCTTCTTATCACC	GCATTGACTGTTTGTGTTTGG	CAGCTTGGAGTGCAGTGG	1043
Exon 2	204372325	204373064	AAAGCTAGGGCCAATTTCAG	TGGGATTCTAACCTCACTACCAA		740

[a]Map position on hg19 reference sequence. [b]This intronic region was selected as potentially functionally relevant to PPP1R15B because it shows species conservation and includes non-spliced human ESTs.

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Supplementary Table 2. siRNA sequences

siRNA	Sequence	Company	Validated in
P1R15B 1	GACUUACUGUUGUACAGCATT	Invitrogen	
P1R15B 2	AAGGGAUGGAUGCAGGUUCCA		(1)
DP5	UCACAGUUUCUUGGUGCUAAGUGUA	Invitrogen	(2)
PUMA	ACGAGCGGCGGAGACAAGAAGAGCA	Invitrogen	(3)
Bim	CGAGGAGGGCGUUUGCAAACGAUUA	Invitrogen	(3)

Supplementary Table 3. Primer sequences used for mRNA expression studies

Gene	STD/RT[a]	Forward	Reverse	Size
PPP1R15B	STD	AGGCAGTCAGGCATCCTCT	TCAAGTAAGAGATGGAGTGGG	431
	RT	TGGGTGAGGCACTTTCTGG	TGGCGACTTCTGTTTCCTG	177
GAPDH	STD	ATGACTCTACCCACGGCAA	TGTGAGGGAGATGCTCAGTG	930
	RT	AGTTCAACGGCACAGTCAA	TACTCAGCACCAGCATCACC	136
DP5	STD	GCACCCTGTGACCTTCCTA	TCACATGCACGAACACACAC	550
	RT	GCCGTGGTGTTACTTGGAC	GATTGTGCCAGAGCTTCACA	125
PUMA	STD	TGGGTGCACTGATGGAGA	AACCTATGCAATGGGATGGA	497
	RT	AGTGCGCCTTCACTTTGG	CAGGAGGCTAGTGGTCAGGT	109

[a] STD: Standard, RT: Real time

Supplementary Table 4. Filtering of variants identified by whole exome sequencing of patient 1 (index patient)

Filter	Patient 1
All variants	55298
Homozygous variants[a]	19591
Coding-affecting variants[b]	3934
Rare Variants[c]	18

Counts are the number of autosomal variants (SNVs and insertion/deletion variants (indels)) identified by Whole Exome Sequencing of the patient compared to the Human Reference Genome on UCSC build hg19. The successive filters applied after quality filtering are shown: [a]homozygous variants, [b]nonsynonymous variants including missense and nonsense, splice-site variants and exonic indels (frameshift and non-shifted), [c]variants that were absent in the homozygous status in an in-house database, in Exome Variant Server (EVS) and in Exome Aggregation Consortium (ExAC) and with a MAF < 0.005 in these databases and in dbSNP.

SUPPLEMENTARY DATA

Supplementary Table 5. Description of the 18 rare variants identified by whole exome sequencing in patient 1, and complementary genotyping of these variants in patient 2

Map position	Gene	cDNA RefSeq	cDNA change	Protein RefSeq	Protein change	rs number	EVS heterozygous count/total (frequency)	EVS MAF	ExAC heterozygous count/total (frequency)	ExAC MAF	Genotype Patients 1	2
chr1:150532595G>A	**ADAMTSL4**	**NM_019032**	**c.3384G>A**	**NP_061905**	**p.Val1050Ile**	**rs201941243**	**Absent**	**0**	**9/60664 (0.00015)**	**0.00007**	**2/2**	**2/2**
chr1:152285138A>G	**FLG**	**NM_002016**	**c.2262T>C**	**NP_002007**	**p.Ser742Pro**	**NA**	**Absent**	**0**	**2/60705 (0.00003)**	**0.00002**	**2/2**	**2/2**
chr1:200972760C>A	**KIF21B**	**NM_017596**	**c.1485G>T**	**NP_060066**	**p.Arg389Leu**	**NA**	**Absent**	**0**	**Absent**	**0**	**2/2**	**2/2**
chr1:204375390G>A	**PPP1R15B**	**NM_032833**	**c.2379C>T**	**NP_116222**	**p.Arg658Cys**	**NA**	**Absent**	**0**	**Absent**	**0**	**2/2**	**2/2**
chr1:205632155G>A	**SLC45A3**	**NM_033102**	**c.1105C>T**	**NP_149093**	**p.Ala255Val**	**rs142713511**	**3/6492 (0.00046)**	**0.00023**	**19/57327 (0.00033)**	**0.00017**	**2/2**	**2/2**
chr10:79601934T>C	DLG5	NM_004747	c.1214A>G	NP_004738	p.His381Arg	rs150885638	9/6503 (0.0014)	0.00069	68/60227 (0.0011)	0.00056	2/2	1/2
chr11:6646598C>T	DCHS1	NM_003737	c.7380G>A	NP_003728	p.Arg2326His	NA	Absent	0	1/60150 (0.00002)	0.00001	2/2	1/2
chr16:1719068C>T	CRAMP1L	NM_020825	c.3401C>T	NP_065876	p.Pro1134Leu	NA	Absent	0	2/55044 (0.00004)	0.00002	2/2	1/2
chr16:1967936T>C	HS3ST6	NM_001009606	c.298A>G	NP_001009606	p.Thryr99Cys	NA	Absent	0	Absent	0	2/2	1/2
chr16:2816615 G>A	SRRM2	NM_016333	c.6635G>A	NP_057417	p.Arg2029His	NA	Absent	0	6/60547 (0.00010)	0.00005	2/2	1/2
chr18:8784555C>T	MTCL1	NM_015210	c.1587C>T	NP_056025	p.Ala482Val	rs115077293	13/6502 (0.0020)	0	57/56978 (0.0010)	0.00050	2/2	1/2
chr19:2807595C>T	THOP1	NM_003249	c.1197C>T	NP_003240	p.Arg348Cys	NA	Absent	0	3/58471 (0.00005)	0.00003	2/2	1/2
chr19:2851553C>T	ZNF555	NM_152791	c.356C>T	NP_001166246	p.Thr73Met	rs369544612	2/6503 (0.00031)	0	8/60476 (0.00013)	0.00007	2/2	1/2
chr2:210742714G>C	**UNC80**	**NM_032504**	**c.3963G>C**	**NP_115893**	**p.Glu1295Gln**	**rs187089611**	**Absent**	**0**	**4/10840 (0.00037)**	**0.00018**	**2/2**	**2/2**
chr3:133474254A>G	TF	NM_001063	c.858A>G	NP_001054	p.Thr184Ala	rs139768770	3/6503 (0.00046)	0.00023	14/60704 (0.00023)	0.00012	2/2	1/2
chr3:133647257A>G	C3orf36	NM_025041	c.1402T>C	NP_079317	p.Ser131Pro	rs149002991	1/6503 (0.00015)	0.00008	4/60232 (0.00007)	0.00003	2/2	1/2
chr5 :169310284C>A	FAM196B	NM_001129891	c.2003G>T	NP_001123363	p.Asp207Tyr	rs200832892	Absent	0	15/10832 (0.0014)	0.00069	2/2	1/2
chr8 :23560457A>G	NKX2-6	NM_001136271	c.226T>C	NP_001129743	p.Leu56Pro	NA	Absent	0	Absent	0	2/2	1/2

Genomic map position is on UCSC hg19. Description of the consequences on cDNA and protein follows the Human Genome Variation Society (HGVS) recommendations (4). Heterozygotes and total genotype counts, heterozygotes frequencies, and minor allele frequencies (MAF) are given for EVS and ExAC. All the variants were absent in the homozygous status in these databases. The genotype of the two affected siblings is shown as 2/2 (homozygous for the rare allele), 1/2 (heterozygous) and 1/1 (homozygous for the frequent allele, none found). Variants homozygous in both patients are shown in bold. NA: not available.

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Supplementary Table 6. Functional predictions of the variants compatible with mutation status and human mutations and knockout mouse phenotypes of the corresponding genes

Gene	Name	Protein RefSeq	Protein change	Polyphen (score)	Provean (score)	SIFT (score)	Monogenic disease (mode of inheritance)	Knockout mouse model (homozygous)	Human islet expression (RPKM)[a]
ADAMTSL4	ADAMTS-like 4	NP_061905	p.Val1050Ile	Probably damaging (1)	Neutral (-0.69)	Damaging (0.014)	Ectopia lentis (autosomal recessive) (5)	NA	1.6
FLG	filaggrin	NP_002007	p.Ser742Pro	Benign (0.018)	Neutral (-1.77)	Tolerated (0.201)	Atopic dermatitis, ichtyosis vulgaris (semi-dominant) (6)	Atopic dermatitis (7)	0.9
KIF21B	kinesin family member 21B	NP_060066	p.Arg389Leu	Probably damaging (0.998)	Deleterious (-6.29)	Damaging (0.001)	Not reported	Cellular phenoype : chromosome instability[a]	0.7
PPP1R15B	protein phosphatase 1, regulatory subunit 15B	NP_116222	p.Arg658Cys	Probably damaging (1)	Deleterious (-7.48)	Damaging (0.000)	Not reported	Post-natal lethal, extremely small size (4)	12.1
SLC45A3	solute carrier family 45, member 3	NP_149093	p.Ala255Val	Benign (0.015)	Neutral (-1.11)	Tolerated (0.169)	Not reported	NA	3.1
UNC80	Unc-80 homolog (C. elegans)	NP_115893	p.Glu1295Gln	Possibly damaging (0.844)	Neutral (-1.61)	Damaging (0.041)	Not reported	NA	7.9

In silico prediction of the impact and severity of mutation on protein function was performed using Polyphen-2 (8), SIFT and Provean (9), using recommended parameters. Polyphen-2 predictions were made based on the HumDiv model. aHuman islet expression is based on (10) and our unpublished data (M.C.) and is given in RPKM (reads per kilobase of exon model per million mapped reads) units. bKnockout mouse model phenotype information is according to the Mouse Genome informatics (MGI) and the Wellcome Trust Sanger Institute (WTSI) databases. NA: not available.

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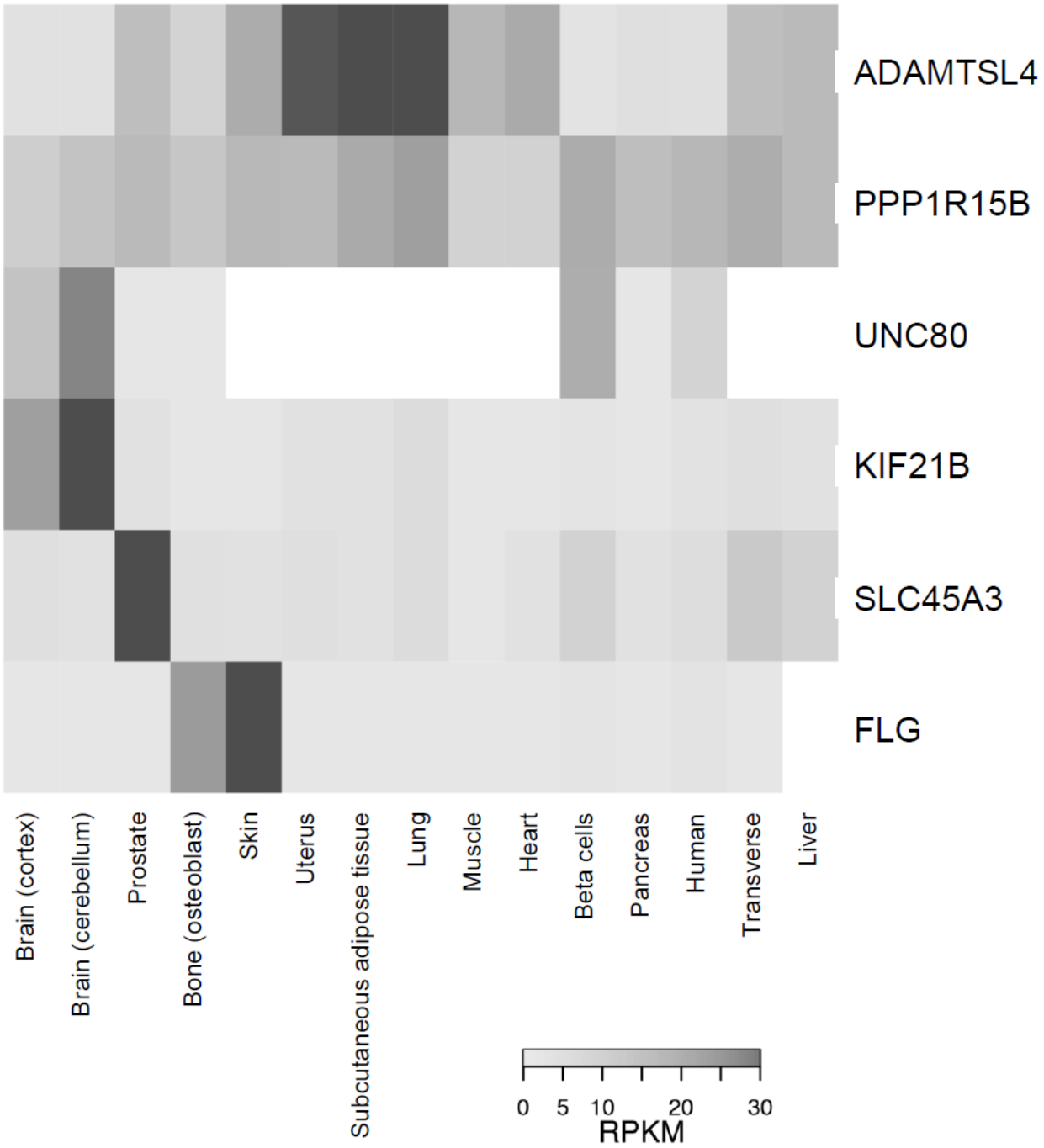
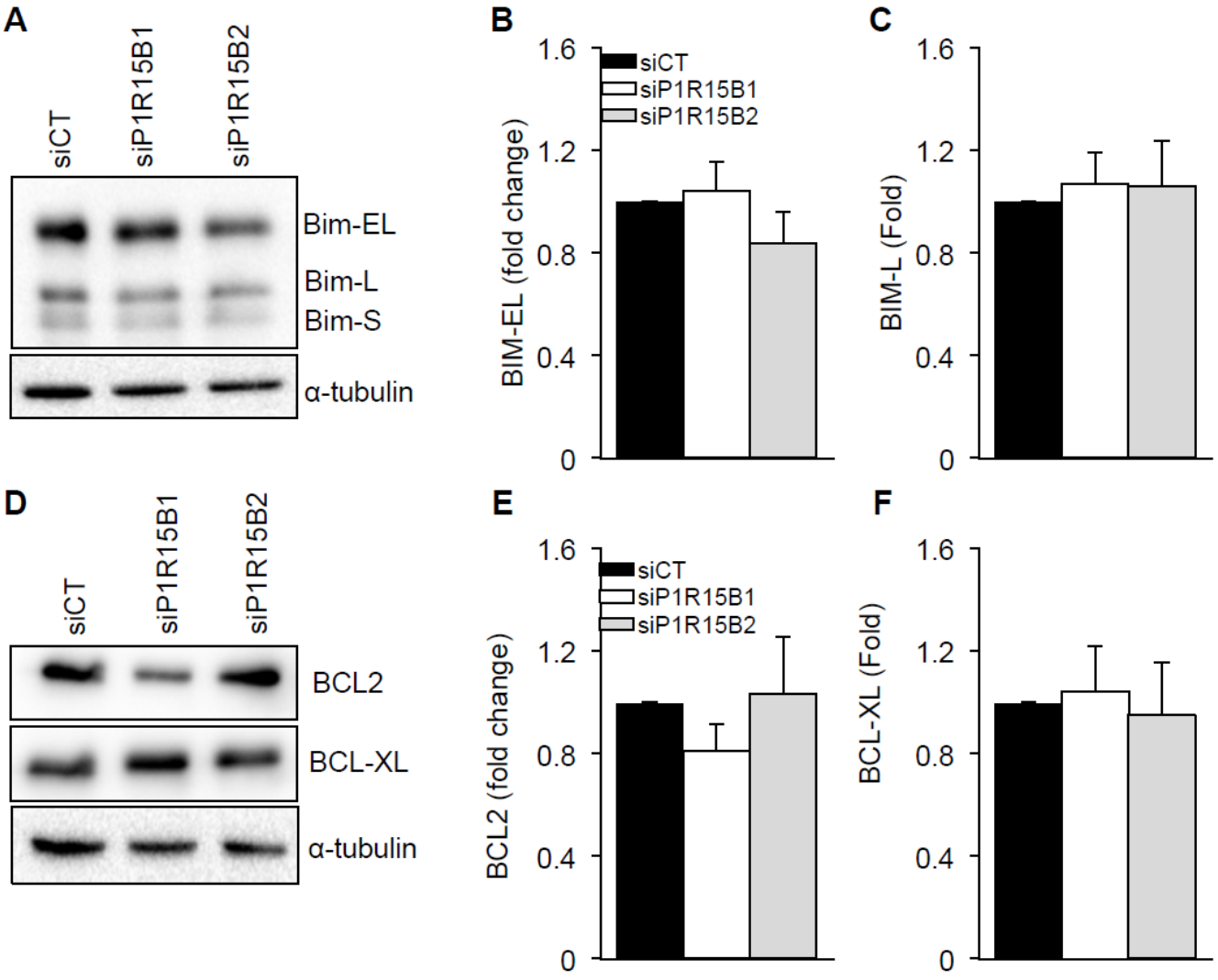
Supplementary Figure 1. Heatmap of gene expression in human tissues. RNAseq values (in RPKM) from the indicated human tissues were obtained from GTEx (v4.pl). RNA-seq data of FACS-purified human islet β-cells were from Nica et al (11). Human islet RNA-seq data (24 in total) were from Eizirik et al and Cnop et al (10; 12) (and unpublished data). Bone (osteoblast) gene expression was obtained from GEO dataset accession number GSE57925 (unpublished data). The median RPKM value of the samples is represented, with the maximum set at 30. The heatmap was made in R (function heatmap.2).



SUPPLEMENTARY DATA

Supplementary Figure 2. PPP1R15B silencing does not modify expression of the pro-apoptotic Bim splice variants Bim-EL and Bim-L or the anti-apoptotic proteins BCL2 and BCL-XL. INS-1E cells were transfected with control siRNA (siCT) or two different siRNAs targeting PPP1R15B (siP1R15B1 and siP1R15B2). 48h after transfection the Bim-EL and Bim-L (A, B, C) and BCL2 and BCL-XL (D, E, F) expression was examined by Western blot. A and D are representative blots of 5 experiments. B, C, E and F are densitometric quantifications of protein expression corrected for α-tubulin, and expressed as fold of siCT.



SUPPLEMENTARY DATA

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