Supplementary Table 1: Assessment of the missense variants using conservation algorithms

Gene	Nucleotide change	Amino acid change	Conservation scores* (Deleteriousness interpretation)†		
			GERP++	PhyloP	SiPhy
PCDH15	c.2885G>T	p.Arg962Leu	1.68 (Neutral)	0.548 (Neutral)	9.078 (Neutral)
CNGB1	c.2939A>T	p.Asn980Ile	5.2 (Deleterious)	1.968 (Deleterious)	8.876 (Neutral)
WDR19	c.2782A>T	p.Ile928Phe	5.49 (Deleterious)	2.075 (Deleterious)	15.595 (Deleterious)
EYS	c.8779T>C	p.Cys2927Arg	5.08 (Deleterious)	1.920 (Deleterious)	13.438 (Deleterious)

* The larger the score, the more conserved. Score ranges: GERP++ from -12.36 to 6.18; PhyloP from -14 to 3; SiPhy from 0 to 37.9718.

† According to Dong et al. (2015) deleterious thresholds are >4.4 for GERP++, >1.6 for PhyloP, >12.17 for SiPhy.[1]

Supplementary Table 2: Alignments and conservation across different species for the amino acid changes

PCDH15: p.Arg962Leu																							
Human	E	F	I	S	A	P	Y	P	F	Q	V	D	D	V	R	Y	R	V	**R**	S	A	P	L	G	intron
Chimp	D	F	I	S	A	P	Y	P	F	Q	V	D	D	V	R	Y	R	V	**R**	S	A	P	L	G	intron
Rhesus	D	F	I	S	A	P	Y	P	F	Q	V	D	D	V	R	Y	R	V	**R**	S	A	P	L	G	intron
Mouse	D	F	I	S	A	P	Y	P	F	Q	V	D	D	V	R	Y	R	V	**R**	S	A	P	M	G	intron
Rabbit	D	F	I	S	A	P	Y	P	F	Q	V	D	D	V	R	Y	R	V	**R**	S	A	P	L	G	intron
Pig	D	F	I	S	A	P	Y	P	F	Q	I	D	D	V	R	Y	R	V	**R**	S	A	P	L	G	intron
Elephant	D	F	I	S	A	P	Y	P	F	Q	V	D	D	V	R	Y	R	V	**R**	S	A	P	L	G	intron
Platypus	D	F	I	T	A	P	Y	P	Y	Q	I	D	D	V	K	Y	R	V	**R**	S	P	P	T	G	intron
Chicken																									
Lizard	D	F	I	S	A	S	Y	P	F	Q	V	V	D	V	K	Y	R	V	**R**	S	A	P	T	G	intron
Frog	D	F	I	S	A	S	Y	P	F	Q	V	V	D	V	K	Y	R	V	**K**	S	A	P	T	G	intron
Zebrafish	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=

CNGB1: p.Asn980Ile																							
Human	intron	K	K	C	V	Y	D	**N**	P	L	Y	V	V	S	R	L	R	K	L	M	D	F	I	M	Q
Chimp	intron	K	K	C	V	Y	D	**N**	P	L	Y	V	V	S	R	L	R	K	L	M	D	F	I	M	Q
Rhesus	intron	K	K	C	V	Y	D	**N**	P	L	Y	V	V	S	R	L	R	K	L	M	D	F	I	M	Q
Mouse	intron	K	K	C	V	Y	D	**N**	P	L	Y	V	V	S	R	L	R	K	L	M	D	F	I	M	Q
Rabbit	intron	K	K	C	V	Y	D	**N**	P	L	Y	V	V	S	R	L	R	K	L	M	D	F	I	M	Q
Pig	intron	K	K	C	V	Y	D	**N**	P	L	Y	V	V	S	R	L	R	K	L	M	D	F	I	M	Q
Elephant	intron	K	K	C	V	Y	D	**N**	P	L	Y	V	V	S	R	L	R	K	L	M	D	F	I	M	Q
Platypus	intron	K	K	C	V	Y	D	**N**	P	L	Y	V	V	S	R	L	R	K	L	M	D	F	I	M	Q
Chicken	intron	K	K	C	V	F	D	**N**	P	L	Y	V	V	S	R	L	R	K	L	M	D	F	I	M	Q
Lizard	intron	K	K	C	V	F	D	**G**	P	L	Y	V	I	S	K	L	R	L	L	M	D	C	I	M	Q
Frog	intron	K	K	C	V	Y	D	**G**	P	L	Y	V	V	S	R	L	R	K	L	M	D	Y	I	M	Q
Zebrafish	intron	K	E	C	V	F	D	**G**	P	L	Y	V	V	S	K	L	R	K	L	M	D	F	I	M	Q

WDR19: p.Ile928Phe																								
Human	V	A	Y	E	N	A	K	Q	W	Q	S	V	**I**	R	I	Y	L	D	H	L	N	N	P	E	K
Chimp	V	A	Y	E	N	A	K	Q	W	Q	S	V	**I**	R	I	Y	L	D	H	L	N	N	P	E	K
Rhesus	V	A	Y	E	N	A	K	Q	W	Q	S	V	**I**	R	I	Y	L	D	H	L	N	N	P	E	K
Mouse	V	A	Y	E	N	A	K	Q	W	N	S	V	**I**	R	I	Y	L	D	H	L	N	N	P	E	K
Rabbit	V	A	Y	E	N	A	K	Q	W	D	S	V	**I**	R	I	Y	L	D	H	L	N	N	P	E	K
Pig	V	A	Y	E	N	A	K	Q	W	N	S	V	**I**	R	I	Y	L	D	H	L	N	N	P	E	K
Elephant	A	A	Y	E	N	A	K	Q	W	N	S	V	**I**	R	I	Y	L	D	H	L	N	N	P	E	K
Platypus	V	A	Y	E	N	A	K	Q	W	D	S	V	**I**	R	I	Y	L	D	H	L	S	N	P	E	K
Chicken	V	A	Y	E	N	A	K	Q	W	D	S	V	**I**	R	L	C	L	D	H	L	N	N	P	E	R
Lizard	L	A	Y	E	N	A	K	Q	W	D	N	V	**I**	R	L	Y	L	D	H	L	N	N	P	E	K
Frog	L	A	Y	E	N	A	K	D	W	D	N	V	**I**	R	I	S	L	D	H	L	N	N	P	E	K
Zebrafish	M	A	Y	E	S	A	R	D	W	D	N	V	**I**	R	I	L	L	E	H	L	N	N	P	E	E

EYS: p.Cys2927Arg																									
Human	C	L	C	S	Y	S	F	S	Q	D	P	I	**C**	L	S	Q	H	L	C	L	N	N	L	C	S
Chimp	C	L	C	S	Y	S	F	S	Q	D	P	I	**C**	L	S	Q	H	L	C	L	N	N	L	C	S
Rhesus	C	L	C	S	Y	S	F	S	Q	D	P	I	**C**	L	S	Q	H	L	C	L	N	N	L	C	Y
Mouse	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=
Rabbit	C	L	C	S	Y	S	F	S	R	D	P	I	**C**	L	S	Q	H	P	C	P	N	N	L	Y	H
Pig	C	L	C	N	Y	S	F	A	Q	N	P	I	**C**	L	S	Q	H	L	C	L	N	N	L	C	Y
Elephant	C	L	C	S	Y	S	F	S	E	D	P	V	**C**	L	S	Q	H	L	C	L	N	N	L	C	Y
Platypus	C	A	C	S	Y	S	F	T	N	D	P	I	**C**	L	S	Q	H	Q	C	K	N	N	L	C	N
Chicken	C	V	C	T	Y	S	L	L	P	Q	P	I	**C**	L	A	Q	S	R	C	R	N	H	L	C	H
Lizard	C	M	C	T	Y	S	F	L	P	N	P	L	**C**	I	G	G	H	L	C	K	N	H	S	C	Y
Frog																									
Zebrafish	C	M	C	S	Y	S	A	S	T	N	H	I	**C**	V	S	N	H	Q	C	L	N	N	L	C	Q

Bold characters correspond to the amino acid affected by the missense variant.

Grey background highlights conservation of the amino acid in regards to the human species.

Double line (=): Such are the differences in the length and/or sequence composition for the species that alignment of one or more bases is not possible.

Species with blank alignments mean the sequence for the interval is not available.

Supplementary Table 3: Pathogenicity assessment of the novel variants according to ACMG guidelines[2]

Gene	Variant	Evidence for				Classification
		Very Strong	Strong	Moderate	Supporting	
ASIC5	c.58A>T	—	—	PM2	PP3	VUS
PCDH15	c.2885G>T	—	—	—	PP1	VUS
REEP6	c.598+1delG	PVS1	—	PM2, PM4	PP1, PP3, PP4	Pathogenic
WDR19	c.1983-2A>T	PVS1	—	PM2	PP3, PP4	Pathogenic
WDR19	c.2782A>T	—	—	PM2	PP3, PP4	VUS

Abbreviations:

PVS1, Pathogenic Very Strong criterion 1: Null variant (nonsense, frameshift, canonical ±1 or 2 splice sites, initiation codon, single or multiexon deletion) in a gene where LOF is a known mechanism of disease.

PM2, Pathogenic Moderate criterion 2: Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium.

PM4, Pathogenic Moderate criterion 4: Protein length changes as a result of in-frame deletions/insertions in a nonrepeat region or stop-loss variants.

PP1, Pathogenic Supporting criterion 1: Cosegregation with disease in multiple affected family members in a gene definitively known to cause the disease.

PP3, Pathogenic Supporting criterion 3: Multiple lines of computational evidence support a deleterious effect on the gene or gene product (conservation, evolutionary, splicing impact, etc.).

PP4, Pathogenic Supporting criterion 4: Patient's phenotype or family history is highly specific for a disease with a single genetic etiology

VUS, Variant of Unknown Significance.

References for Supplementary Material

1. Dong C, Wei P, Jian X, et al. Comparison and integration of deleteriousness prediction methods for nonsynonymous SNVs in whole exome sequencing studies. *Hum Mol Genet*. 2015;24(8):2125–2137. doi:10.1093/hmg/ddu733

2. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405–424. doi:10.1038/gim.2015.30