Table S16. Pathogenicity assessment of more common pathogenic variants in the Norrin/β--catenin gene

Gene	Nucleotide change	Amino acid change	N. of families identified in this study	Minor allele frequency			*In-silico* prediction						Conserved domain	Known variant [reported in our earlier study]	Pathogenicity (evidenced criteria)*
				gnomAD [27]	HGVD [28]	TOMMO 3.5kJPN v2 [29]	GERP ++ [33]	SIFT [34]	M-CAP [35]	REVEL [36]	Polyphen 2 HumDIV [37]	CADD [38]			
FZD4	c.205C>T	p.H69Y	18¶	0.0004	0.0139	0.0096	4.80	0.020	0.125	0.663	0.197	24.2	(CDD:143557)	[21, 66]	Pathogenic (PS1+PS3+PS4+PM1+PP2+PP3)
LRP5	c.4619C>T	p.T1540M	8 §	0.0001	0.0142	0.0128	3.81	0.004	0.447	0.538	1.000	22.9	PPPSP motif	[22, 66]	Likely pathogenic (PS3+PM1+PP2+PP3)

* Based on the recommendation of the American College of Medical Genetics and Genomics (ACMG) standard and guidelines (2015) [37]. Underlined values are indicated as "not deleterious" according to the cutoff values.

¶ Found in 4 familial and 8 sporadic cases heterozygously, and in 6 probands through compound heterozygous transmission with variants in the *FZD4* or *LRP5* gene (including 2 p.T1540M variant).

§ Found in 2 familial and 2 sporadic FEVR cases, and in 4 families through compound heterozygous transmission with variants in the *LRP5* or *FZD4* gene (including 2 p.H69Y variant).

CDD, Conserved Domain Database (http://www.ncbi.nlm.nih.gov/RefSeq/, [38]).