Table S1. Pathogenic variants in *FZD4* gene

Nucleotide change	Amino acid change	N. of families identified in this study	Minor allele frequency			*In-silico* prediction						Conserved domain	Associated phenotype	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]	Polyphen2 HumDIV [37]	CADD [38]				
c.9G>A	p.W3*	1	NL	NL	NL	3.33	NA	NA	NA	NA	35.0	NA	FEVR §	No	Pathogenic (PVS1+PM2+PP1)
c.80dupT	p.L27Ffs*103	1	NL	NL	NL	NL	NA	NA	NA	NA	NA	NA	FEVR(AD)	No	Pathogenic (PVS1+PM2+PP1)
c.173A>C	p.Y58S	2	NL	NL	NL	4.80	0.000	0.431	0.970	1.000	31.0	(CDD: 143557)	FEVR(AD)	No	Likely pathogenic (PM1+PM2+PM5+PP1+PP2+PP3)
c.173A>G	p.Y58C	1	NL	NL	NL	4.80	0.000	0.429	0.928	1.000	32.0	(CDD: 143557)	FEVR(DI)	Yes	Pathogenic (PS1+PM1+PM2+PP2+PP3)
c.265G>T	p.G89C	1	NL	NL	NL	5.03	0.029	0.279	0.809	1.000	32.0	(CDD: 143557)	FEVR(AD)	No	Likely pathogenic (PM1+PM2+PP2+PP3)
c.313A>G	p.M105V	5	NL	NL	0.0001	5.82	0.000	0.020	0.551	0.793	24.9	(CDD: 143557)	FEVR(AD)	[21]	Pathogenic (PS1+PS3+PM1+PM2+PM5+PP1+PP2+PP3)
c.326_328del	p.K109del	1	NL	NL	NL	NL	NA	NA	NA	NA	NA	(CDD: 143557)	FEVR(SP)	No	Likely pathogenic (PM1+PM2+PM4+PP2)
c.341T>C	p.I114T	1	NL	NL	NL	5.82	0.000	1.000	0.851	1.000	26.1	(CDD: 143557)	FEVR(SP)	No	Likely pathogenic (PM1+PM2+PM5+PP2+PP3)
c.380G>A	p.R127H	1	NL	0.0004	0.0015	5.82	0.00	0.132	0.559	0.984	25.5	(CDD::	FEVR(AD)	YES: ROP	Pathogenic

							7					143557)			(PS1+PM1+PM2+PP2+PP3)
c.430A>C	p.N144H	1	NL	NL	NL	5.82	0.000	1.000	0.449	0.843	24.1	(CDD: 143557)	FEVR(AD)	No	Likely pathogenic (PM1+PM2+PP2+PP3)
c.678G>T	p.W226C	1	NL	NL	NL	5.74	0.010	1.000	0.832	1.000	32.0	(CDD: 144942)	FEVR(DI)	No	Likely pathogenic (PM1+PM2+PM3+PM5+PP2+PP3)
c.836_942del	p.R279Sfs*24	1	NL	NL	NL	NL	NA	NA	NA	NA	NA	NA	FEVR(AD)	No	Pathogenic (PVS1+PM2+PP1)
c.845G>A	p.C282Y	1	NL	NL	NL	5.72	0.000	0.430	0.919	1.000	29.2	(CDD: 144942)	FEVR(AD)	No	Likely pathogenic (PM1+PM2+PP1+PP2+PP3)
c.957G>A	p.W319*	1	NL	NL	NL	5.59	NA	NA	NA	NA	37.0	NA	FEVR(SP)	[21]	Pathogenic (PVS1+PS2+PS3+PM2)
c.1005G>C	p.W335C	2	NL	NL	NL	5.59	0.000	0.170	0.755	1.000	32.0	(CDD: 144942)	FEVR(AD)	[22]	Likely pathogenic (PM1+PM2+PP1+PP2+PP3)
c.1024A>G	p.M342V	7	NL	0.0023	0.0001	5.59	0.170	0.045	0.157	0.636	22.3	(CDD: 144942)	FEVR(AD/SP)	[22]	Likely pathogenic (PM1+PM2+PM5+PP1+PP2+PP3)
c.1159delC	p.L387Sfs*44	3	NL	NL	NL	NL	NA	NA	NA	NA	NA	NA	FEVR(AD)	No	Pathogenic (PVS1+PM2+PP1+PP3)
c.1250G>A	p.R417Q	5	NL	NL	NL	5.77	0.010	0.214	0.933	1.000	32.0	(CDD: 144942)	FEVR(AD)	[21]	Pathogenic (PS1+PS3+PM1+PM2+PM5+PP1+PP2+PP3)
c.1282_1285del	p.D428Sfs*2	2	NL	NL	NL	NL	NA	NA	NA	NA	NA	NA	FEVR(AD)	Yes	Pathogenic (PVS1+PS1+PM2)
c.1400A>G	p.Y467C	1	NL	NL	NL	3.46	0.17	0.099	0.492	0.837	19.9	(CDD:	FEVR(AD)	No	Likely pathogenic

							0					144942)			(PM1+PM2+PP1+PP2+PP3)
c.1423G>C	p.A475P	1	NL	NL	0.0003	6.06	0.070	0.055	0.396	0.020	23.0	(CDD: 144942)	FEVR(AD)	[41]	Likely pathogenic (PM1+PM2+PP1+PP2)
c.1463G>A	p.G488D	1	NL	NL	NL	5.91	0.000	0.380	0.967	1.000	29.4	(CDD: 144942)	FEVR(AD)	[21]	Pathogenic (PS3+PM1+PM2+PM5+PP1+PP2+PP3)
c.1488G>C	p.W496C	1	NL	NL	NL	6.06	0.030	0.164	0.437	0.987	32.0	(CDD: 144942)	FEVR(AD)	No	Likely pathogenic (PM1+PM2+PP1+PP2+PP3)
c.1511G>A	p.W504*	1	NL	NL	NL	5.27	NA	NA	NA	NA	39.0	NA	FEVR(AD)	No	Pathogenic (PVS1+PM2+PP1)

Underlined values are indicated as "not deleterious" according to the cutoff values ([33]-[37]), AD, autosomal dominant; CDD, Conserved Domain Database (http://www.ncbi.nlm.nih.gov/RefSeq/, [31]); DI, digenic inheritance; FEVR, familial exudative vitreoretinopathy; NA, not applicable; NL, not listed; ROP, retinopathy of prematurity; SP, sporadic.

* Based on the recommendation of the American College of Medical Genetics and Genomics (ACMG) standard and guidelines [32].

§ Affected sibs without parents' genotype and phenotype.