Table S2. Pathogenic variants in the *LRP5* 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]	Polyphen 2 HumDIV [37]	CADD [38]				
c.121C>T	p.R41W	1	NL	NL	NL	3.31	0.023	0.427	0.717	1.000	23.6	BP1	FEVR(AR)	Yes	Likely pathogenic (PM1+PM2+PM3+PP2+PP3)
c.362A>G	p.K121R	3	NL	NL	NL	3.71	0.005	0.238	0.760	1.000	24.9	(CDD: 158893)	FEVR(AD)	No	Likely pathogenic (PM1+PM2+PM3+PP1+PP2+PP3)
c.433C>T	p.L145F	4	NL	NL	NL	3.71	0.002	0.587	0.853	0.999	23.2	BP1	FEVR(AD/AR)	[22]	Likely pathogenic (PM1+PM2+PM3+PP1+PP2+PP3)
c.556C>T	p.R186W	1	NL	NL	NL	3.56	0.000	0.805	0.852	1.000	27.6	(CDD: 158893)	FEVR(SP)	No	Likely pathogenic (PM1+PM2+PP2+PP3)
c.803_812del	p.G269Rfs*4	1	NL	NL	NL	NL	NL	NL	NL	NL	NA	NL	FEVR(AD/AR)	[22]	Pathogenic (PVS1+PM2+PM3)
c.871C>T	p.R291W	1	NL	NL	NL	NL	0.003	0.702	0.785	1.000	26.8	adjacent to LDL-receptor class B5	FEVR(SP)	Yes	Pathogenic (PS1+PM1+PM2+PP2+PP3)
c.961T>C	p.C321R	1	NL	NL	NL	3.85	0.000	1.000	0.905	1.000	23.6	NA	FEVR(AR)	No	Likely pathogenic (PM2+PM3+PP2+PP3)
c.1021G>A	p.E341K	1	NL	NL	NL	3.85	0.207	1.000	0.000	0.077	22.7	BP2	FEVR(AR)	No	Likely pathogenic

														(PM1+PM2+PM3+PP2)
c.1145C>T	p.P382L	3	NL	0.0008	0.0001	3.81	0.002	0.964	0.936	0.998	25.8	(CDD: 158893)	FEVR(AD/AR)	Yes	Pathogenic (PS1+PM1+PM2+PM3+PP1+PP2+PP3)
c.1270G>A	p.D424N	1	NL	NL	NL	3.85	0.000	1.000	0.952	1.000	25.4	(CDD: 158893)	FEVR(AR)	Yes	Pathogenic (PS1+PM1+PM2+PM3+PM5+PP2+PP3)
c.1282C>T	p.R428*	1	NL	NL	NL	2.94	NA	NA	NA	NA	38.0	NA	FEVR(AD)	Yes: OPPG	Pathogenic (PVS1+PS1+PM2+PP1)
c.1321G>A	p.E441K	1	0.0000	NL	NL	2.99	0.005	0.603	0.844	0.999	26.3	(CDD: 158893)	FEVR(AD)	Yes	Pathogenic (PS1+PM1+PM2+PP1+PP2+PP3)
c.1330C>T	p.R444C	1	NL	NL	NL	3.94	0.000	0.773	0.800	0.882	24.5	(CDD: 158893)	FEVR(DI)	[22]	Pathogenic (PS1+PS3+PM1+PM2+PM5+PP1+PP2+PP3)
c.1333C>T	p.L445F	1	NL	NL	NL	3.94	0.002	1.000	0.779	1.000	24.9	(CDD: 158893)	FEVR(AR)	Yes	Likely pathogenic (PM1+PM2+PM3+PP2+PP3)
c.1412+1G>A	-	1	NL	NL	NL	3.94	NA	NA	NA	NA	33.0	NA	FEVR(AR)	No	Likely pathogenic (PVS1+PM2)
c.1433G>A	p.W478*	1	NL	NL	NL	3.3	NA	NA	NA	NA	42.0	NA	FEVR(AR)	Yes	Pathogenic (PVS1+PS1+PM2+PP1)

c.1564G>A	p.A522T	1	NL	NL	NL	3.28	0.002	0.706	0.906	0.997	27.1	(CDD:: 158893)	FEVR(AD)	[22]	Pathogenic (PS1+PS3+PM1+PM2+PM5+PP1+PP2+PP3)
c.1604C>T	p.T535M	1	NL	NL	0.0040	4.13	0.001	0.530	0.769	1.000	24.2	(CDD: 158893)	FEVR(AR)	[22]	Pathogenic (PS1+PM1+PM2+PM3+PP2+PP3)
c.1828G>A	p.G610R	1	NL	NL	NL	4.11	0.000	0.784	0.962	1.000	24.5	NA	FEVR(AR)	[22]	Likely pathogenic (PM2+PM3+PM5+PP2+PP3)
c.1850T>G	p.F617C	1	NL	NL	NL	4.11	0.001	0.856	0.958	0.966	27.5	NA	FEVR(AR)	[22]	Likely pathogenic (PM2+PM3+PP2+PP3)
c.1873T>C	p.C625R	1	NL	NL	NL	4.11	0.000	1.000	0.979	1.000	26.3	NA	FEVR(AR)	No	Likely pathogenic (PM2+PM3+PP2+PP3)
c.1888G>A	p.G630S	1	NL	NL	NL	4.11	0.009	0.750	0.961	1.000	27.5	NA	FEVR(AR)	No	Likely pathogenic (PM2+PM3+PP2+PP3)
c.1985C>T	p.T662I	1	NL	NL	NL	4.11	0.009	0.421	0.726	0.641	23.8	BP3	FEVR(DI)	No	Likely pathogenic (PM1+PM2+PM3+PP2+PP3)
c.1994A>G	p.N665S	1	NL	0.0013	0.0003	2.97	0.020	0.118	0.333	0.000	18.5	BP3	FEVR(SP)	No	Likely pathogenic (PM1+PM2+PP2+PP3)
c.2227G>A	p.E743K	1	NL	NL	NL	4.53	0.002	1.000	0.834	1.000	32.0	(CDD: 158893)	FEVR(AR)	No	Likely pathogenic (PM1+PM2+PM3+PP2+PP3)

c.2254C>T	p.R752W	1	NL	NL	NL	3.54	0.000	1.000	0.996	1.000	31.0	(CDD: 158893)	FEVR(AD)	Yes	Pathogenic (PS1+PM1+PM2+ PM5+PP2+PP3)
c.2392A>G	p.T798A	2	NL	0.0014	0.0006	4.5	0.063	0.144	0.784	0.074	22.4	BP3	FEVR(AR/SP)	[22]	Likely pathogenic (PM1+PM2+PP2+ PP3)
c.2783G>A	p.C928Y	1	NL	NL	NL	5.02	0.000	0.644	0.953	1.000	27.4	-	FEVR(AR)	No	Likely pathogenic (PM2+PM3+PP2+ PP3)
c.2973C>G	p.I991M	2	NL	0.0014	0.0008	3.76	0.003	0.202	0.421	0.003	22.8	(CDD: 158893)	FEVR(AD/SP)	No	Likely pathogenic (PM1+PM2+PP1+ PP2+PP3)
c.3232C>T	p.R1078*	1	NL	0.0034	NL	2.74	NA	NA	NA	NA	40.0	NA	FEVR(AD)	Yes	Pathogenic (PVS1+PS1+PM2+ PP1)
c.3280G>A	p.E1094K	1	NL	NL	NL	4.93	0.066	1.000	0.825	1.000	26.1	BP4	FEVR(AR)	Yes: OPPG	Pathogenic (PS1+PM1+PM2+ PM3+PP2+PP3)
c.3361A>G	p.N1121D	4	0.0004	0.0046	0.0041	4.93	0.163	NA	0.608	0.415	22.6	(CDD: 158893)	FEVR(AD/DI)	[22]	Pathogenic (PS1+PM1+PM2+ PM3+PP1+PP2)
c.3569G>A	p.R1190H	1	NL	NL	NL	3.72	0.070	0.180	0.468	0.896	17.3	BP4	FEVR(AR)	No	Likely pathogenic (PM1+PM2+PM3+ PP2+PP3)
c.3877G>A	p.E1293K	1	NL	NL	NL	4.39	0.810	0.126	0.300	0.001	22.1	(CDD: 29012)	FEVR(AR)	No	Likely pathogenic (PM1+PM2+PM3+ PP2)
c.4042T>C	p.C1348R	2	0.0000	NL	NL	4.37	0.001	0.925	0.981	1.000	29.0	(CDD:	FEVR(AR)	No	Likely pathogenic

											29012)			(PM1+PM2+PM3+PP2)
c.4001-1G>C	-	1	NL	NL	NL	4.37	NA	NA	NA	NA	35.0	NA	FEVR(SP)	No	Likely pathogenic (PVS1+PM2)
c.4148A>C	p.H1383P	1	NL	0.0021	0.0011	4.53	0.367	0.380	0.476	0.001	19.2	NA	FEVR(AD/SP)	Yes: ROP	Likely pathogenic (PS1+PM2+PP1+PP2+PP4)
c.4454_4465del	p.S1485_S1488del	1	NL	NL	NL	NL	NA	NA	NA	NA	NA	NA	FEVR(AD)	No	Likely pathogenic (PM2+PM4+PP1+PP2)
c.4457C>A	p.S1486*	1	NL	NL	NL	4.76	NA	NA	NA	NA	51.0	NA	FEVR(AR)	No	Pathogenic (PVS1+PM2+PM3+PP1)
c.4488G>A	p.P1496=	1	NL	NL	NL	3.84	NA	NA	NA	NA	24.9	NA	FEVR(SP)	No	Likely pathogenic (PVS1+PM2)
c.4643G>T	p.C1548F	1	0.0002	0.0040	0.0008	4.73	0.050	0.295	0.842	0.999	25.1	NA	FEVR(AD)	Yes	Likely pathogenic (PS3+PM2+PP2+PP3)
c.4835C>A	p.T1612K	1	NL	NL	NL	4.53	0.000	0.741	0.600	1.000	24.5	PPPSP motif	FEVR(AR)	No	Likely pathogenic (PM1+PM2+PM3+PP2+PP3)

Underlined values are classified as "not deleterious" according to the cutoff values ([33]-[37]), AD, autosomal dominant; AR, autosomal recessive; BP, beta-propeller; 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; OPPG, osteoporosis-pseudoglioma syndrome; ROP, retinopathy of prematurity; SP, sporadic.

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