Supplementary Table 1: Pathogenicity classification of 615 variants listed as disease-causing variants in HGMD

Gene	hg19 location	rsID	ACMG	Function	cDNA position	Protein position	GERP Score	CADD Score	Total # Indiv's in EVS	Total EVS freq %	Meets disease specific cut off	Classification
ACVRL1	12:52314610	rs139142865	N	missense	NM_000020.2:c.1445C>T	p.482Ala>Val	3.52	16.87	30	0.231	N	Likely benign
ACVRL1	12:52306909	rs149664056	N	missense	NM_000020.2:c.88C>T	p.P30S	0.11	13.17	2	0.015	N	Likely benign
ACVRL1	12:52309928	rs141764916	N	missense	NM_000020.2:c.1157G>A	p.R386H	4.08	12.91	1	0.008	Y (1 indiv)	Likely pathogenic
ACVRL1	12:52309126	rs139380315	N	missense	NM_000020.2:c.890A>G	p.297His>Arg	2.69	4.41	3	0.023	N	Variant of Uncertain Significance
APC	5:112175528	rs141519952	Y	missense	NM_000038.5:c.4237A>G	p.M1413V	6.07	14.45	4	0.031	Y	Likely benign
APC	5:112178276	rs146048493	Y	missense	NM_000038.5:c.6985A>G	p.I2329V	5.70	2.49	2	0.015	Y	Likely benign
APC	5:112178690	rs372305287	Y	missense	NM_000038.5:c.7399C>A	p.P2467T	3.99	10.53	1	0.008	Y (1 indiv)	Likely benign
APC	5:112179069	rs367676584	Y	missense	NM_000038.5:c.7778A>G	p.N2593S	2.11	0.14	1	0.008	Y (1 indiv)	Likely benign
APC	5:112179674	rs369264968	Y	missense	NM_000038.5:c.8383G>A	p.A2795T	5.06	12.95	1	0.008	Y (1 indiv)	Likely benign
APC	5:112178112	rs34919187	N	missense	NM_000038.5:c.6821C>T	p.A2274V	6.02	10.47	14	0.108	N	Likely benign
APC	5:112102960	rs139196838	Y	missense	NM_000038.5:c.295C>T	p.99Arg>Trp	4.53	19.71	12	0.092	N	Variant of Uncertain Significance
APC	5:112174138	rs147394539	Y	missense	NM_000038.5:c.2847G>T	p.949Met>Ile	3.06	8.69	5	0.038	Y	Variant of Uncertain Significance
APC	5:112175627	rs146572883	Y	missense	NM_000038.5:c.4336G>A	p.1446Ala>Thr	4.39	2.36	5	0.038	Y	Variant of Uncertain Significance
APC	5:112175651	rs111866410	Y	missense	NM_000038.5:c.4360A>G	p.1454Lys>Glu	4.97	12.41	32	0.246	N	Variant of Uncertain Significance
APC	5:112175711	rs139387758	Y	missense	NM_000038.5:c.4420G>A	p.1474Ala>Thr	6.16	12.47	44	0.338	N	Variant of Uncertain Significance
APC	5:112176023	rs138367627	Y	missense	NM_000038.5:c.4732T>G	p.1578Cys>Gly	6.16	18.43	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
APC	5:112176209	rs0	Y	missense	NM_000038.5:c.4918C>T	p.1640Arg>Trp	4.34	11.01	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
APC	5:112176317	rs0	Y	missense	NM_000038.5:c.5026A>G	p.1676Arg>Gly	-0.312	7.20	2	0.015	Y	Variant of Uncertain Significance[1]
APC	5:112111352	rs371085910	Y	missense	NM_000038.5:c.449A>G	p.K150R	5.30	22.30	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
APC	5:112154969	rs137854567	Y	missense	NM_000038.5:c.1240C>T	p.R414C	5.94	29.70	5	0.038	Y	Variant of Uncertain Significance
APC	5:112174770	rs201004111	Y	missense	NM_000038.5:c.3479C>A	p.T1160K	5.76	12.87	3	0.023	Y	Variant of Uncertain Significance
APC	5:112176431	rs148275069	Y	missense	NM_000038.5:c.5140G>A	p.D1714N	6.16	13.47	2	0.015	Y	Variant of Uncertain Significance
APC	5:112176819	rs368080169	Y	missense	NM_000038.5:c.5528C>T	p.P1843L	6.07	17.93	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
APC	5:112179008	rs145444830	Y	missense	NM_000038.5:c.7717A>G	p.I2573V	5.97	11.51	4	0.031	Y	Variant of Uncertain Significance
APC	5:112179557	rs146115809	Y	missense	NM_000038.5:c.8266A>G	p.I2756V	-5.86	0.01	3	0.023	Y	Variant of Uncertain Significance[1]
ATP7B	13:52511706	rs121907990	N	missense	NM_000053.3:c.3809A>G	p.N1270S	4.73	12.66	3	0.024	NA (recessive)	Pathogenic (not returned, carrier status)
ATP7B	13:52542680	rs138427376	N	missense	NM_000053.3:c.1607T>C	p.V536A	1.67	8.16	28	0.222	NA (recessive)	Variant of Uncertain Significance[1]
ATP7B	13:52518387	rs74085882	N	missense	NM_000053.3:c.3101A>G	p.1034His>Arg	5.28	14.38	45	0.36	NA (recessive)	Variant of Uncertain Significance
ATP7B	13:52511629	rs0	N	missense	NM_000053.3:c.3886G>A	p.1296Asp>Asn	4.73	16.31	2	0.016	NA (recessive)	Variant of Uncertain Significance
BMPR1A	10:88681353	rs140592056	N	missense	NM_004329.2:c.1243G>A	p.E415K	5.63	37.00	6	0.046	N	Likely benign
BMPR1A	10:88681437	rs35619497	N	missense	NM_004329.2:c.1327C>T	p.443Arg>Cys	5.63	32.00	7	0.054	N	Variant of Uncertain Significance
BRCA1	17:41223240	rs56119278	Y	missense	NM_007294.3:c.4691T>C	p.1564Leu>Pro	3.71	6.67	6	0.046	Y	Likely benign
BRCA1	17:41223249	rs56158747	Y	missense	NM_007294.3:c.4682C>T	p.1561Thr>Ile	0.152	12.63	24	0.185	Y	Likely benign
BRCA1	17:41243800	rs28897686	Y	missense	NM_007294.3:c.3748G>A	p.1250Glu>Lys	1.01	10.03	4	0.031	Y	Likely benign
BRCA1	17:41219694	rs80357087	Y	missense	NM_007294.3:c.5005G>T	p.A1669S	5.24	15.51	1	0.008	Y (1 indiv)	Likely benign
BRCA1	17:41223048	rs4986854	Y	missense	NM_007294.3:c.4883T>C	p.M1628T	-2.25	0.66	4	0.031	Y	Likely benign
BRCA1	17:41243891	rs80356876	Y	missense	NM_007294.3:c.3657G>C	p.E1219D	2.29	17.45	1	0.008	Y (1 indiv)	Likely benign
BRCA1	17:41244982	rs80356892	Y	missense	NM_007294.3:c.2566T>C	p.Y856H	4.05	16.53	1	0.008	Y (1 indiv)	Likely benign
BRCA1	17:41245900	rs56012641	Y	missense	NM_007294.3:c.1648A>C	p.N550H	1.32	11.20	4	0.031	Y	Likely benign
BRCA1	17:41256266	rs28897673	Y	missense	NM_007294.3:c.314A>G	p.Y105C	4.22	14.18	1	0.008	Y (1 indiv)	Likely benign
BRCA1	17:41246411	rs56128296	Y	missense	NM_007294.3:c.1137T>G	p.I379M	3.77	15.62	28	0.215	Y	Likely benign
BRCA1	17:41244826	rs80356978	Y	stop-gained	NM_007294.3:c.2722G>T	p.908Glu>stop	2.63	38.00	1	0.008	Y (1 indiv)	Pathogenic
BRCA1	17:41243887	rs80357310	Y	stop-gained	NM_007294.3:c.3661G>T	p.E1221*	5.31	44.00	1	0.008	Y (1 indiv)	Pathogenic
BRCA1	17:41243941	rs62625308	Y	stop-gained	NM_007294.3:c.3607C>T	p.R1203*	4.13	38.00	1	0.008	Y (1 indiv)	Pathogenic
BRCA1	17:41247941	rs80358033	Y	splice-3	NA	NA	4.57	16.84	1	0.008	Y (1 indiv)	Pathogenic
BRCA1	17:41215948	rs55770810	Y	missense	NM_007294.3:c.5095C>T	p.1699Arg>Trp	4.83	21.80	1	0.008	Y (1 indiv)	Pathogenic
BRCA1	17:41209094	rs80357442	Y	missense	NM_007294.3:c.5252G>A	p.1751Arg>Gln	5.07	24.70	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
BRCA1	17:41215920	rs28897696	Y	missense	NM_007294.3:c.5123C>T	p.1708Ala>Val	5.83	27.10	3	0.023	Y	Variant of Uncertain Significance
BRCA1	17:41243840	rs28897687	Y	missense	NM_007294.3:c.3708T>G	p.1236Asn>Lys	-2.85	5.55	3	0.023	Y	Variant of Uncertain Significance[1]
BRCA1	17:41244526	rs56321129	Y	missense	NM_007294.3:c.3022A>G	p.1008Met>Val	-9.22	0.00	10	0.077	Y	Variant of Uncertain Significance[1]
BRCA1	17:41245233	rs80357467	Y	missense	NM_007294.3:c.2315T>C	p.772Val>Ala	3.17	15.49	2	0.015	Y	Variant of Uncertain Significance
BRCA1	17:41245381	rs4986845	Y	missense	NM_007294.3:c.2167A>G	p.723Asn>Asp	-3.95	9.85	32	0.246	Y	Variant of Uncertain Significance[1]
BRCA1	17:41246062	rs28897676	Y	missense	NM_007294.3:c.1486C>T	p.496Arg>Cys	-0.308	3.25	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]
BRCA1	17:41246812	rs28897675	Y	missense	NM_007294.3:c.736T>G	p.246Leu>Val	2.26	9.62	3	0.023	Y	Variant of Uncertain Significance
BRCA1	17:41249297	rs55688530	Y	missense	NM_007294.3:c.557C>A	p.186Ser>Tyr	4.96	20.30	30	0.231	Y	Variant of Uncertain Significance
BRCA1	17:41258486	rs80357102	Y	missense	NM_007294.3:c.199G>T	p.67Asp>Tyr	-1.4	15.10	2	0.015	Y	Variant of Uncertain Significance[1]
BRCA1	17:41199716	rs80356920	Y	missense	NM_007294.3:c.5411T>A	p.V1804D	1.52	29.80	2	0.015	Y	Variant of Uncertain Significance[1]
BRCA1	17:41223049	rs80357465	Y	missense	NM_007294.3:c.4882A>G	p.M1628V	-0.06	0.02	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]
BRCA1	17:41245071	rs28897683	Y	missense	NM_007294.3:c.2477C>A	p.T826K	1.68	11.61	3	0.023	Y	Variant of Uncertain Significance[1]
BRCA1	17:41245683	rs56039126	Y	missense	NM_007294.3:c.1865C>T	p.A622V	1.50	10.37	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]

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Gene	hg19 location	rsID	ACMG	Function	cDNA position	Protein position	GERP Score	CADD Score	Total # Indiv's in EVS	Total EVS freq %	Meets disease specific cut off	Classification
BRCA1	17:41246037	rs56272539	Y	missense	NM_007294.3:c.1511G>A	p.R504H	0.07	15.20	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]
BRCA1	17:41246164	rs80357221	Y	missense	NM_007294.3:c.1384G>A	p.G462R	4.57	14.22	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
BRCA1	17:41246167	rs62625300	Y	missense	NM_007294.3:c.1381T>C	p.F461L	4.57	14.75	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
BRCA2	13:32907407	rs28897710	Y	missense	NM_000059.3:c.1792A>G	p.598Thr>Ala	-2.76	8.66	19	0.146	Y	Likely benign
BRCA2	13:32913077	rs28897728	Y	missense	NM_000059.3:c.4585G>A	p.1529Gly>Arg	5.74	20.10	6	0.046	Y	Likely benign
BRCA2	13:32937521	rs28897749	Y	missense	NM_000059.3:c.8182G>A	p.2728Val>Ile	-7.77	0.15	43	0.331	Y	Likely benign
BRCA2	13:32953971	rs28897755	Y	missense	NM_000059.3:c.9038C>T	p.3013Thr>Ile	3.91	14.78	6	0.046	Y	Likely benign
BRCA2	13:32907277	rs80358451	Y	missense	NM_000059.3:c.1662T>G	p.C554W	4.32	9.73	2	0.015	Y	Likely benign
BRCA2	13:32907401	rs56328701	Y	missense	NM_000059.3:c.1786G>C	p.D596H	3.38	16.75	5	0.038	Y	Likely benign
BRCA2	13:32911524	rs80358548	Y	missense	NM_000059.3:c.3032C>G	p.T1011R	5.89	21.70	1	0.008	Y (1 indiv)	Likely benign
BRCA2	13:32911547	rs55638633	Y	missense	NM_000059.3:c.3055C>G	p.L1019V	3.07	7.47	2	0.015	Y	Likely benign
BRCA2	13:32971119	rs80359228	Y	missense	NM_000059.3:c.9586A>G	p.K3196E	3.56	9.23	1	0.008	Y (1 indiv)	Likely benign
BRCA2	13:32972695	rs80358387	Y	missense	NM_000059.3:c.10045A>G	p.T3349A	5.72	24.70	2	0.015	Y	Likely benign
BRCA2	13:32914132	rs11571657	Y	missense	NM_000059.3:c.5640T>G	p.N1880K	1.84	7.50	39	0.315	Y	Likely benign
BRCA2	13:32914839	rs55953736	Y	missense	NM_000059.3:c.6347A>G	p.H2116R	4.33	5.13	46	0.354	Y	Likely benign
BRCA2	13:32914174	rs41293497	Y	stop-gained	NM_000059.3:c.5682C>G	p.1894Tyr>stop	-3.92	42.00	1	0.008	Y (1 indiv)	Pathogenic
BRCA2	13:32930687	rs80358981	Y	stop-gained	NM_000059.3:c.7558C>T	p.R2520*	1.95	50.00	1	0.008	Y (1 indiv)	Pathogenic
BRCA2	13:32893369	rs28897701	Y	missense	NM_000059.3:c.223G>C	p.75Ala>Pro	5.59	24.70	4	0.031	Y	Variant of Uncertain Significance
BRCA2	13:32906593	rs28897706	Y	missense	NM_000059.3:c.978C>A	p.326Ser>Arg	-2.86	1.27	11	0.085	Y	Variant of Uncertain Significance[1]
BRCA2	13:32906766	rs41293475	Y	missense	NM_000059.3:c.1151C>T	p.384Ser>Phe	3.52	11.72	14	0.109	Y	Variant of Uncertain Significance
BRCA2	13:32907129	rs28897708	Y	missense	NM_000059.3:c.1514T>C	p.505Ile>Thr	4.13	5.26	10	0.077	Y	Variant of Uncertain Significance
BRCA2	13:32910630	rs55816687	Y	missense	NM_000059.3:c.2138A>T	p.713Gln>Leu	3.06	7.50	19	0.146	Y	Variant of Uncertain Significance
BRCA2	13:32911937	rs80358589	Y	missense	NM_000059.3:c.3445A>G	p.1149Met>Val	-1.41	0.04	4	0.031	Y	Variant of Uncertain Significance[1]
BRCA2	13:32912553	rs80358656	Y	missense	NM_000059.3:c.4061C>T	p.1354Thr>Met	-3.01	5.73	3	0.023	Y	Variant of Uncertain Significance[1]
BRCA2	13:32914202	rs55875643	Y	missense	NM_000059.3:c.5710C>G	p.1904Leu>Val	3.28	0.18	2	0.015	Y	Variant of Uncertain Significance
BRCA2	13:32914815	rs35029074	Y	missense	NM_000059.3:c.6323G>A	p.2108Arg>His	2.76	5.72	42	0.331	Y	Variant of Uncertain Significance
BRCA2	13:32929140	rs55977008	Y	missense	NM_000059.3:c.7150C>A	p.2384Gln>Lys	-4.01	0.04	24	0.185	Y	Variant of Uncertain Significance[1]
BRCA2	13:32930633	rs55716624	Y	missense	NM_000059.3:c.7504C>T	p.2502Arg>Cys	0.574	5.02	15	0.115	Y	Variant of Uncertain Significance[1]
BRCA2	13:32968922	rs56204128	Y	missense	NM_000059.3:c.9353T>C	p.3118Met>Thr	-1.34	2.18	3	0.023	Y	Variant of Uncertain Significance[1]
BRCA2	13:32905116	rs55854959	Y	missense	NM_000059.3:c.742G>A	p.A248T	-0.16	5.80	2	0.015	Y	Variant of Uncertain Significance[1]
BRCA2	13:32907378	rs373400041	Y	missense	NM_000059.3:c.1763A>G	p.N588S	0.56	14.15	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]
BRCA2	13:32937450	rs80359054	Y	missense	NM_000059.3:c.8111C>T	p.S2704F	3.60	11.13	2	0.015	Y	Variant of Uncertain Significance
BRCA2	13:32944558	rs80359076	Y	missense	NM_000059.3:c.8351G>A	p.R2784Q	5.33	34.00	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
CACNA1C	12:2794967	rs0	N	missense	NM_000719.6:c.5639G>A	p.1880Arg>Gln	1.36	2.84	7	0.057	N	Likely benign
CACNA1C	12:2797868	rs0	N	missense	NM_000719.6:c.6040G>A	p.2014Val>Ile	5.21	12.26	5	0.042	Y	Variant of Uncertain Significance
CACNA1S	1:201020165	rs145910245	Y	missense	NM_000069.2:c.4060A>T	p.1354Thr>Ser	4.43	4.03	48	0.369	N	Variant of Uncertain Significance
CACNA1S	1:201029944	rs80338782	Y	nissense-near-splic	NM_000069.2:c.3256C>T	p.R1086C	5.17	15.46	2	0.015	Y	Variant of Uncertain Significance
CACNB2	10:18787330	rs200367454	N	missense	NM_000724.3:c.215C>T	p.A72V	5.74	18.67	2	0.015	Y	Likely benign
CACNB2	10:18789874	rs150528041	N	missense	NM_000724.3:c.425C>T	p.142Ser>Phe	5.88	32.00	12	0.092	N	Variant of Uncertain Significance
CACNB2	10:18795447	rs149253719	N	missense	NM_000724.3:c.476G>C	p.159Ser>Thr	5.9	16.11	11	0.085	N	Variant of Uncertain Significance
CACNB2	10:18828181	rs143326262	N	missense	NM_000724.3:c.1346C>T	p.449Thr>Ile	3.56	17.08	19	0.146	N	Variant of Uncertain Significance
CACNB2	10:18828446	rs144182966	N	missense	NM_000724.3:c.1611C>A	p.537Asp>Glu	-11.3	12.42	4	0.031	Y	Variant of Uncertain Significance[1]
CACNB2	10:18823130	rs149793143	N	missense	NM_000724.3:c.1015G>A	p.V339I	5.54	28.60	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
CDH1	16:68855966	rs35187787	Y	missense	NM_004360.3:c.1774G>A	p.592Ala>Thr	5.56	15.26	59	0.454	N	Likely benign
CDH1	16:68863674	rs200894246	Y	missense	NM_004360.3:c.2413G>A	p.D805N	6.05	36.00	4	0.031	N	Likely benign
CDH1	16:68772239	rs139866691	Y	missense	NM_004360.3:c.88C>A	p.P30T	3.81	12.43	11	0.105	N	Likely benign
CDH1	16:68867247	rs35572355	Y	missense	NM_004360.3:c.2494G>A	p.832Val>Met	6.04	28.30	2	0.015	Y	Likely pathogenic
CDH1	16:68845646	rs142822590	Y	missense	NM_004360.3:c.892G>A	p.A298T	5.19	24.20	2	0.015	Y	Variant of Uncertain Significance
COL3A1	2:189855743	rs112185887	Y	missense	NM_000090.3:c.812G>A	p.271Arg>Gln	5.98	14.97	37	0.285	N	Likely benign
COL3A1	2:189851842	rs111391222	Y	missense	NM_000090.3:c.505C>T	p.169Leu>Phe	-6.53	1.00	7	0.054	N	Variant of Uncertain Significance[1]
COL3A1	2:189860458	rs142085247	Y	missense	NM_000090.3:c.1550C>T	p.517Pro>Leu	4.31	17.60	13	0.1	N	Variant of Uncertain Significance
COL3A1	2:189875018	rs111840783	Y	missense	NM_000090.3:c.3938A>G	p.1313Lys>Arg	5.93	18.95	23	0.177	N	Variant of Uncertain Significance
DMD	X:31222203	rs141392048	N	missense	NM_000109.3:c.9658T>C	p.3220Phe>Leu	4.19	16.45	13	0.18	N	Likely benign
DMD	X:31747837	rs151244052	N	missense	NM_000109.3:c.7547G>A	p.2516Arg>His	4.37	15.19	14	0.17	N	Likely benign
DMD	X:32591646	rs373286166	N	splice-5	NA	NA	4.97	11.28	1	0.009	Y (1 indiv)	Likely pathogenic
DMD	X:32591735	rs370644567	N	missense	NM_000109.3:c.1700T>C	p.L567P	5.15	20.50	1	0.009	Y (1 indiv)	Variant of Uncertain Significance
DMD	X:32662262	rs189143447	N	missense	NM_000109.3:c.1294G>A	p.E432K	5.83	33.00	1	0.009	Y (1 indiv)	Variant of Uncertain Significance
DSC2	18:28662951	rs368299411	Y	missense	NM_004949.3:c.1018A>G	p.T340A	1.67	19.00	1	0.008	Y (1 indiv)	Likely benign
DSC2	18:28672114	rs144799937	Y	missense	NM_004949.3:c.304G>A	p.E102K	3.28	12.53	10	0.077	Y	Likely benign
DSC2	18:28650748	rs151024019	Y	missense	NM_004949.3:c.2194T>G	p.732Leu>Val	-4.8	6.06	14	0.108	N	Variant of Uncertain Significance[1]

Supplementary Table 1: Pathogenicity classification of 615 variants listed as disease-causing variants in HGMD

Gene	hg19 location	rsID	ACMG	Function	cDNA position	Protein position	GERP Score	CADD Score	Total # Indiv's in EVS	Total EVS freq %	Meets disease specific cut off	Classification
DSC2	18:28648897	rs143413607	Y	missense	NM_004949.3:c.2471C>T	p.S824L	5.46	20.40	3	0.023	Y	Variant of Uncertain Significance
DSG2	18:29101156	rs0	Y	missense	NM_001943.3:c.473T>G	p.158Val>Gly	3.16	5.75	74	0.617	N	Likely benign
DSG2	18:29125783	rs121913010	Y	missense	NM_001943.3:c.2434G>T	p.812Gly>Cys	5.99	19.08	1	0.008	Y (1 indiv)	Likely pathogenic
DSG2	18:29099850	rs121913013	Y	missense	NM_001943.3:c.166G>A	p.56Val>Met	5.21	11.81	31	0.259	N	Variant of Uncertain Significance
DSG2	18:29111109	rs0	Y	missense	NM_001943.3:c.1174G>A	p.392Val>Ile	0.985	7.30	19	0.159	N	Variant of Uncertain Significance[1]
DSG2	18:29126108	rs142841727	Y	missense	NM_001943.3:c.2759T>G	p.920Val>Gly	2.5	4.38	47	0.386	N	Variant of Uncertain Significance
DSG2	18:29121188	rs201564919	Y	missense	NM_001943.3:c.1912G>A	p.G638R	5.77	17.82	2	0.017	Y	Variant of Uncertain Significance
DSP	6:7583008	rs377715841	Y	missense	NM_001008844.1:c.3716G>A	p.R1239H	4.33	18.40	3	0.023	Y	Likely benign
DSP	6:7542236	rs121912998	Y	missense	NM_001008844.1:c.88G>A	p.V30M	-7.34	0.004	16	0.124	N	Likely benign
DSP	6:7570791	rs148147581	Y	missense	NM_001008844.1:c.1696G>A	p.566Ala>Thr	5.68	21.00	5	0.038	Y	Variant of Uncertain Significance
DSP	6:7580795	rs28763965	Y	missense	NM_004415.2:c.4372C>G	p.1458Arg>Gly	4.76	7.81	22	0.169	N	Variant of Uncertain Significance
DSP	6:7575014	rs150339369	Y	missense	NM_001008844.1:c.2422C>T	p.R808C	5.82	22.50	2	0.015	Y	Variant of Uncertain Significance
DSP	6:7581747	rs34738426	Y	missense	NM_004415.2:c.5324G>T	p.R1775I	5.15	14.09	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
DSP	6:7584376	rs147000526	Y	missense	NM_001008844.1:c.5084C>G	p.A1695G	6.08	22.30	3	0.023	Y	Variant of Uncertain Significance
DSP	6:7584618	rs376923069	Y	missense	NM_001008844.1:c.5326G>C	p.G1776R	5.60	19.66	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
ENG	9:130578230	rs148002300	N	missense	NM_000118.2:c.1844C>T	p.615Ser>Leu	1.6	14.73	20	0.154	N	Likely benign
ENG	9:130581941	rs373842615	N	splice-3	NA	NA	3.44	8.26	1	0.008	Y (1 indiv)	Pathogenic
ENG	9:130581938	rs369997021	N	nissense-near-splic	NM_000118.2:c.1274C>T	p.A425V	2.29	0.02	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
ENG	9:130580575	rs116330805	N	missense	NM_000118.2:c.1510G>A	p.504Val>Met	2.12	8.92	48	0.369	N	Variant of Uncertain Significance
ENG	9:130588920	rs139398993	N	missense	NM_000118.2:c.392C>T	p.131Pro>Leu	-1.86	11.66	20	0.154	N	Variant of Uncertain Significance[1]
ENG	9:130588023	rs150932144	N	missense	NM_000118.2:c.640G>A	p.G214S	4.42	18.81	3	0.023	N	Variant of Uncertain Significance
EPCAM	2:47602372	rs373597944	N	splice-3	NA	NA	4.94	16.63	2	0.015	Y	Variant of Uncertain Significance
FBN1	15:48718025	rs143863014	Y	missense	NM_000138.4:c.7241G>A	p.R2414Q	4.30	12.43	1	0.008	Y (1 indiv)	Likely benign
FBN1	15:48776056	rs200283837	Y	missense	NM_000138.4:c.3797A>T	p.Y1266F	2.28	12.53	4	0.031	Y	Likely benign
FBN1	15:48782072	rs111801777	Y	missense	NM_000138.4:c.3058A>G	p.T1020A	5.66	13.35	3	0.023	Y	Likely benign
FBN1	15:48703309	rs0	Y	missense	NM_000138.4:c.8494A>G	p.2832Ser>Gly	5.04	10.22	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
FBN1	15:48704816	rs61746008	Y	missense	NM_000138.4:c.8176C>T	p.2726Arg>Trp	1.03	17.11	14	0.108	N	Variant of Uncertain Significance[1]
FBN1	15:48707938	rs143677764	Y	missense	NM_000138.4:c.7846A>G	p.2616Ile>Val	3.54	2.97	4	0.031	Y	Variant of Uncertain Significance
FBN1	15:48713001	rs138558987	Y	missense	NM_000138.4:c.7702G>A	p.2568Val>Met	5.99	15.61	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
FBN1	15:48717640	rs144189837	Y	missense	NM_000138.4:c.7379A>G	p.2460Lys>Arg	5.87	29.00	2	0.015	Y	Variant of Uncertain Significance
FBN1	15:48725102	rs112084407	Y	missense	NM_000138.4:c.6700G>A	p.2234Val>Met	1.64	12.44	8	0.062	N	Variant of Uncertain Significance[1]
FBN1	15:48779352	rs137854475	Y	missense	NM_000138.4:c.3509G>A	p.1170Arg>His	5.3	15.95	25	0.192	N	Variant of Uncertain Significance
FBN1	15:48704911	rs371375126	Y	missense	NM_000138.4:c.8081G>A	p.R2694Q	5.38	15.14	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
FBN1	15:48707932	rs141133182	Y	missense	NM_000138.4:c.7852G>A	p.G2618R	5.81	33.00	2	0.015	Y	Variant of Uncertain Significance
FBN1	15:48713794	rs369294972	Y	missense	NM_000138.4:c.7660C>T	p.R2554W	5.03	23.50	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
FBN1	15:48764814	rs201273753	Y	missense	NM_000138.4:c.4270C>G	p.P1424A	5.81	17.93	4	0.031	Y	Variant of Uncertain Significance
FBN1	15:48782203	rs140954477	Y	missense	NM_000138.4:c.2927G>A	p.R976H	5.66	36.00	2	0.015	Y	Variant of Uncertain Significance
FBN1	15:48796041	rs377621293	Y	missense	NM_000138.4:c.2056G>A	p.A686T	5.14	18.06	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
FBN1	15:48807707	rs139058991	Y	missense	NM_000138.4:c.1345G>A	p.V449I	0.35	7.77	2	0.015	Y	Variant of Uncertain Significance[1]
FBN1	15:48812976	rs146726731	Y	missense	NM_000138.4:c.1027G>A	p.G343R	5.65	35.00	2	0.015	Y	Variant of Uncertain Significance
FBN1	15:48936908	rs201309310	Y	missense	NM_000138.4:c.59A>G	p.Y20C	3.49	10.84	3	0.023	Y	Variant of Uncertain Significance
FH	1:241665852	rs200796606	N	missense	NM_000143.3:c.1127A>C	p.Q376P	5.96	22.80	1	0.008	Y (1 indiv)	Likely benign
FH	1:241675301	rs199822819	N	missense	NM_000143.3:c.521C>G	p.P174R	5.24	25.20	2	0.015	Y	Likely benign
FLCN	17:17125815	rs368778627	N	ɔp-gained-near-spli	NM_144606.5:c.779G>A	p.W260*	5.71	42.00	1	0.008	Y (1 indiv)	Pathogenic
FLCN	17:17118314	rs0	N	missense	NM_144997.5:c.1523A>G	p.508Lys>Arg	5.76	23.70	4	0.031	N	Variant of Uncertain Significance
FLCN	17:17125879	rs78683075	N	missense	NM_144606.5:c.715C>T	p.239Arg>Cys	5.71	25.90	6	0.046	N	Variant of Uncertain Significance
GCH1	14:55369176	rs56127440	N	missense	NM_000161.2:c.206C>T	p.P69L	4.58	18.74	6	0.046	N	Likely benign
GCH1	14:55312502	rs200891969	N	missense	NM_000161.2:c.610G>A	p.V204I	6.17	20.50	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
HMBS	11:118963982	rs144949995	N	missense	NM_000190.3:c.1075G>A	p.359Asp>Asn	4.99	32.00	6	0.046	Y	Likely benign
HMBS	11:118963869	rs150428209	Y	missense	NM_000190.3:c.962G>A	p.R321H	-0.632	9.653	25	0.192	N	Likely benign
HMBS	11:118962207	rs34413634	N	missense	NM_000190.3:c.583C>T	p.R195C	5.96	26.70	1	0.009	Y (1 indiv)	Likely pathogenic
HMBS	11:118962124	rs118204095	N	nissense-near-splic	NM_000190.3:c.500G>A	p.R167Q	5.59	37.00	1	0.009	Y (1 indiv)	Variant of Uncertain Significance
HMBS	11:118959973	rs150763621	N	missense	NM_000190.3:c.257A>T	p.86Glu>Val	5.96	27.30	10	0.077	N	Variant of Uncertain Significance
HMBS	11:118963136	rs142459647	N	missense	NM_000190.3:c.674G>A	p.225Arg>Gln	5.24	37.00	5	0.038	Y	Variant of Uncertain Significance
KCNE1	21:35821707	rs74315445	N	missense	NM_000219.4:c.226G>A	p.D76N	5.16	15.56	1	0.008	Y (1 indiv)	Likely pathogenic
KCNE1	21:35821559	rs142511345	N	missense	NM_000219.4:c.374C>T	p.T125M	-9.88	7.10	3	0.023	Y	Variant of Uncertain Significance[1]
KCNE1	21:35821608	rs77442996	N	missense	NM_000219.4:c.325G>A	p.V109I	-4.63	0.01	2	0.015	Y	Variant of Uncertain Significance[1]
KCNE1	21:35821904	rs144917638	N	missense	NM_000219.4:c.29C>T	p.T10M	-9.65	9.24	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]
KCNE1	21:35821910	rs199473348	N	missense	NM_000219.4:c.23C>T	p.A8V	0.94	12.81	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]
KCNE1	21:35821733	rs79654911	N	missense	NM_000219.4:c.200G>A	p.R67H	5.16	27.70	3	0.023	Y	Variant of Uncertain Significance

Supplementary Table 1: Pathogenicity classification of 615 variants listed as disease-causing variants in HGMD

Gene	hg19 location	rsID	ACMG	Function	cDNA position	Protein position	GERP Score	CADD Score	Total # Indiv's in EVS	Total EVS freq %	Meets disease specific cut off	Classification
KCNE2	21:35742938	rs74315447	N	missense	NM_172201.1:c.161T>C	p.M54T	5.66	16.00	3	0.023	Y	Likely pathogenic
KCNE2	21:35742817	rs142153692	N	missense	NM_172201.1:c.40G>A	p.14Val>Ile	4.65	2.93	11	0.085	N	Variant of Uncertain Significance
KCNE2	21:35742857	rs148968498	N	missense	NM_172201.1:c.80G>A	p.27Arg>His	5.53	14.83	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
KCNE2	21:35742947	rs74315448	N	missense	NM_172201.1:c.170T>C	p.57Ile>Thr	5.66	23.70	5	0.038	Y	Variant of Uncertain Significance
KCNE2	21:35743006	rs141423405	N	missense	NM_172201.1:c.229C>T	p.R77W	5.66	18.21	2	0.015	Y	Variant of Uncertain Significance
KCNE2	21:35743007	rs199473365	N	missense	NM_172201.1:c.230G>A	p.R77Q	-4.35	7.88	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]
KCNH2	7:150645571	rs143512106	Y	missense	NM_000238.3:c.2653C>T	p.885Arg>Cys	3.22	16.63	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
KCNH2	7:150646000	rs0	Y	missense	NM_000238.3:c.2536C>G	p.846Pro>Ala	3.95	25.90	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
KCNH2	7:150654468	rs138776684	Y	missense	NM_000238.3:c.1039C>T	p.347Pro>Ser	4.83	14.54	6	0.046	Y	Variant of Uncertain Significance
KCNH2	7:150656690	rs139544114	Y	missense	NM_000238.3:c.442C>T	p.148Arg>Trp	3.8	17.43	16	0.123	N	Variant of Uncertain Significance
KCNH2	7:150656789	rs150988911	Y	missense	NM_000238.3:c.343G>A	p.115Val>Met	4.71	26.40	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
KCNH2	7:150644071	rs199473028	Y	missense	NM_000238.3:c.3224C>T	p.P1075L	4.01	23.50	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
KCNH2	7:150644429	rs377095107	Y	missense	NM_000238.3:c.3139C>T	p.R1047C	2.73	17.36	1	0.009	Y (1 indiv)	Variant of Uncertain Significance
KCNH2	7:150644711	rs149955375	Y	missense	NM_000238.3:c.2948C>T	p.T983I	4.75	18.47	3	0.023	Y	Variant of Uncertain Significance
KCNH2	7:150644756	rs199473432	Y	missense	NM_000238.3:c.2660G>A	p.R887H	4.11	22.00	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
KCNH2	7:150644756	rs199473017	Y	missense	NM_000238.3:c.2903C>T	p.P968L	1.64	11.73	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]
KCNH2	7:150645564	rs199473432	Y	missense	NM_000238.3:c.2660G>A	p.R887H	4.11	22	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
KCNH2	7:150647283	rs138498207	Y	missense	NM_000238.3:c.2371C>T	p.R791W	4.91	25.40	3	0.023	Y	Variant of Uncertain Significance
KCNH2	7:150647399	rs121912512	Y	missense	NM_000238.3:c.2255G>A	p.R752Q	4.84	34.00	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
KCNH2	7:150648023	rs199473532	Y	missense	NM_000238.3:c.2131A>G	p.I711V	4.36	16.71	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
KCNH2	7:150648878	rs375872367	Y	missense	NM_000238.3:c.1603G>A	p.V535M	4.08	21.00	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
KCNH2	7:150656710	rs199472864	Y	missense	NM_000238.3:c.422C>T	p.P141L	3.82	11.45	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
KCNJ2	17:68171457	rs147750704	N	missense	NM_000891.2:c.277G>A	p.V93I	3.48	2.50	3	0.023	Y	Variant of Uncertain Significance
KCNJ2	17:68172133	rs367560052	N	missense	NM_000891.2:c.953A>G	p.N318S	5.77	0.01	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
KCNJ2	17:68172379	rs144022753	N	missense	NM_000891.2:c.1199C>T	p.T400M	6.07	14.00	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
KCNQ1	11:2608850	rs12720457	Y	missense	NM_000218.2:c.1179G>T	p.393Lys>Asn	0.592	6.56	9	0.069	N	Likely benign
KCNQ1	11:2591915	rs199473394	Y	missense	NM_000218.2:c.535G>A	p.G179S	4.40	34.00	1	0.008	Y (1 indiv)	Likely benign
KCNQ1	11:2608860	rs199472776	Y	missense	NM_000218.2:c.1189C>T	p.R397W	4.72	16.48	5	0.038	Y	Likely benign
KCNQ1	11:2594115	rs199472728	Y	missense	NM_000218.2:c.820A>G	p.I274V	3.74	19.91	1	0.008	Y (1 indiv)	Likely pathogenic
KCNQ1	11:2592563	rs151344631	Y	missense	NM_000218.2:c.613G>A	p.V205M	4.46	23.10	1	0.008	Y (1 indiv)	Pathogenic
KCNQ1	11:2790111	rs17215500	Y	stop-gained	NM_000218.2:c.1552C>T	p.R518*	-0.65	37.00	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
KCNQ1	11:2549229	rs143709408	Y	missense	NM_000218.2:c.458C>T	p.153Thr>Met	3.53	14.01	6	0.046	Y	Variant of Uncertain Significance
KCNQ1	11:2610043	rs0	Y	missense	NM_000218.2:c.1352G>A	p.451Arg>Gln	2.93	2.94	2	0.015	Y	Variant of Uncertain Significance
KCNQ1	11:2610045	rs140452381	Y	missense	NM_000218.2:c.1354C>T	p.452Arg>Trp	0.941	11.65	2	0.015	Y	Variant of Uncertain Significance[1]
KCNQ1	11:2869001	rs34516117	Y	missense	NM_000218.2:c.1799C>T	p.600Thr>Met	0.914	7.96	7	0.054	N	Variant of Uncertain Significance[1]
KCNQ1	11:2591912	rs120074177	Y	missense	NM_000218.2:c.532G>A	p.A178T	4.40	29.70	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
KCNQ1	11:2591963	rs150172393	Y	missense	NM_000218.2:c.583C>T	p.R195W	1.15	19.78	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]
KCNQ1	11:2594172	rs199472737	Y	missense	NM_000218.2:c.877C>T	p.R293C	3.90	14.03	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
KCNQ1	11:2610069	rs199472783	Y	missense	NM_000218.2:c.1378G>A	p.G460S	-0.78	3.81	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]
KCNQ1	11:2790112	rs145974930	Y	missense	NM_000218.2:c.1553G>A	p.R518Q	4.26	17.19	2	0.015	Y	Variant of Uncertain Significance
KCNQ1	11:2790135	rs199472792	Y	missense	NM_000218.2:c.1576A>G	p.K526E	4.26	21.90	2	0.015	Y	Variant of Uncertain Significance
KCNQ1	11:2869033	rs147445322	Y	missense	NM_000218.2:c.1831G>A	p.D611N	2.94	13.42	4	0.031	Y	Variant of Uncertain Significance
KIT	4:55564644	rs115585711	N	missense	NM_000222.2:c.532G>A	p.178Ala>Thr	-0.807	2.47	44	0.338	N	Variant of Uncertain Significance[1]
KIT	4:55573290	rs143388949	N	missense	NM_000222.2:c.952A>G	p.M318V	-1.02	0.08	2	0.015	Y	Variant of Uncertain Significance[1]
LDLR	19:11217303	rs150673992	Y	missense	NM_000527.4:c.757C>T	p.R253W	4.02	16.43	5	0.038	Y	Likely benign
LDLR	19:11222214	rs138315511	Y	missense	NM_000527.4:c.1085A>C	p.D362A	3.34	15.44	3	0.023	Y	Likely benign
LDLR	19:11223989	rs137943601	Y	missense	NM_000527.4:c.1222G>A	p.E408K	4.87	22.10	1	0.008	Y (1 indiv)	Likely benign
LDLR	19:11233991	rs138477254	Y	missense	NM_000527.4:c.2282C>T	p.T761M	4.39	18.64	1	0.008	Y (1 indiv)	Likely benign
LDLR	19:11221357	rs72658860	Y	missense	NM_000527.4:c.970G>A	p.G324S	4.37	18.83	62	0.477	N	Likely benign
LDLR	19:11227645	rs72658865	Y	missense	NM_000527.4:c.1816G>T	p.606Ala>Ser	4.44	11.81	3	0.023	Y	Likely pathogenic
LDLR	19:11217328	rs121908040	Y	missense	NM_000527.4:c.782G>T	p.C261F	5.10	19.56	1	0.008	Y (1 indiv)	Likely pathogenic
LDLR	19:11218160	rs121908030	Y	missense	NM_000527.4:c.910G>A	p.D304N	5.33	28.00	1	0.008	Y (1 indiv)	Likely pathogenic
LDLR	19:11240274	rs374045590	Y	missense	NM_000527.4:c.2475C>G	p.N825K	2.22	16.98	2	0.015	Y	Likely pathogenic
LDLR	19:11213450	rs144172724	Y	missense	NM_000527.4:c.301G>A	p.E101K	4.60	18.08	1	0.008	Y (1 indiv)	Likely pathogenic
LDLR	19:11223968	rs146200173	Y	missense	NM_000527.4:c.1201C>G	p.L401V	4.87	16.53	3	0.023	Y	Likely pathogenic
LDLR	19:11218112	rs368657165	Y	missense	NM_000527.4:c.862G>A	p.E288K	5.33	20.90	1	0.008	Y (1 indiv)	Likely pathogenic
LDLR	19:11213445	rs0	Y	stop-gained	NM_000527.4:c.296C>G	p.99Ser>stop	4.62	17.25	1	0.008	Y (1 indiv)	Pathogenic
LDLR	19:11224319	rs370777955	Y	stop-gained	NM_000527.4:c.1467C>G	p.Y489*	4.72	37.00	1	0.008	Y (1 indiv)	Pathogenic
LDLR	19:11224210	rs139617694	Y	splice-3	NA	NA	4.55	16.18	1	0.008	Y (1 indiv)	Pathogenic
LDLR	19:11227604	rs137929307	Y	missense	NM_000527.4:c.1775G>A	p.G592E	5.48	17.62	3	0.023	Y	Pathogenic

Supplementary Table 1: Pathogenicity classification of 615 variants listed as disease-causing variants in HGMD

Gene	hg19 location	rsID	ACMG	Function	cDNA position	Protein position	GERP Score	CADD Score	Total # Indiv's in EVS	Total EVS freq %	Meets disease specific cut off	Classification
LDLR	19:11200282	rs147509697	Y	missense	NM_000527.4:c.58G>A	p.20Gly>Arg	0.318	12.02	9	0.069	Y	Variant of Uncertain Significance[1]
LDLR	19:11210979	rs137853960	Y	missense	NM_000527.4:c.148G>T	p.50Ala>Ser	-5.68	8.95	7	0.054	Y	Variant of Uncertain Significance[1]
LDLR	19:11211016	rs0	Y	missense	NM_000527.4:c.185C>T	p.62Thr>Met	5.37	13.74	2	0.015	Y	Variant of Uncertain Significance
LDLR	19:11221411	rs139361635	Y	missense	NM_000527.4:c.1024G>A	p.342Asp>Asn	-0.687	7.03	28	0.215	N	Variant of Uncertain Significance[1]
LDLR	19:11221444	rs0	Y	missense	NM_000527.4:c.1057G>A	p.353Glu>Lys	3.03	16.30	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
LDLR	19:11224005	rs0	Y	missense	NM_000527.4:c.1238C>T	p.413Thr>Met	4.87	14.12	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
LDLR	19:11224284	rs144614838	Y	missense	NM_000527.4:c.1432G>A	p.478Gly>Arg	4.72	29.90	2	0.015	Y	Variant of Uncertain Significance
LDLR	19:11240240	rs5928	Y	missense	NM_000527.4:c.2441G>A	p.814Arg>Gln	4.78	15.56	13	0.1	Y	Variant of Uncertain Significance
LDLR	19:11240278	rs137853964	Y	missense	NM_000527.4:c.2479G>A	p.827Val>Ile	4.78	21.80	10	0.077	Y	Variant of Uncertain Significance
LDLR	19:11217352	rs143992984	Y	missense	NM_000527.4:c.806G>A	p.G269D	5.10	11.28	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
LDLR	19:11218109	rs375495026	Y	missense	NM_000527.4:c.859G>A	p.G287S	5.33	22.80	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
LDLR	19:11218157	rs151207122	Y	missense	NM_000527.4:c.907C>T	p.R303W	3.05	16.53	2	0.015	Y	Variant of Uncertain Significance
LDLR	19:11221354	rs373869746	Y	missense	NM_000527.4:c.967G>A	p.G323S	5.40	21.20	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
LDLR	19:11222295	rs149227308	Y	missense	NM_000527.4:c.1166C>T	p.T389M	4.51	14.89	2	0.015	Y	Variant of Uncertain Significance
LDLR	19:11224296	rs139624145	Y	missense	NM_000527.4:c.1444G>A	p.D482N	4.72	35.00	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
LDLR	19:11224326	rs373646964	Y	missense	NM_000527.4:c.1474G>A	p.D492N	4.72	29.90	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
LDLR	19:11233961	rs200142970	Y	missense	NM_000527.4:c.2252G>A	p.R751Q	-3.79	2.97	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]
LDLR	19:11217344	rs139043155	Y	missense	NM_000527.4:c.798T>A	p.D266E	-3.77	14.91	2	0.015	Y	Variant of Uncertain Significance[1]
LDLR	19:11227666	rs148181903	Y	missense	NM_000527.4:c.1837G>A	p.V613I	1.13	0.93	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]
LDLR	19:11213381	rs370860696	Y	missense	NM_000527.4:c.232C>T	p.R78C	5.65	27.20	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
LDLR	19:11227612	rs373371572	Y	missense	NM_000527.4:c.1783C>T	p.R595W	3.24	14.46	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
LMNA	1:156100408	rs41313880	Y	nonymous-near-spl	NM_001257374.1:c.21C>T	p.119	4.68	11.48	35	0.269	N	Likely benign
LMNA	1:156108511	rs368386019	Y	missense	NM_001257374.1:c.1595G>A	p.R532H	4.69	12.99	3	0.023	Y	Likely benign
LMNA	1:156106776	rs11575937	Y	missense	NM_001257374.1:c.1109G>A	p.R370Q	5.40	18.89	1	0.008	Y (1 indiv)	Pathogenic
LMNA	1:156108384	rs60662302	Y	missense	NM_001257374.1:c.1468G>A	p.602Gly>Ser	-2	1.94	12	0.092	N	Variant of Uncertain Significance[1]
LMNA	1:156108510	rs142000963	Y	missense	NM_001257374.1:c.1594C>T	p.644Arg>Cys	4.69	21.00	14	0.108	N	Variant of Uncertain Significance
LMNA	1:156104245	rs267607626	Y	missense	NM_001257374.1:c.229C>T	p.R77W	3.30	16.07	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
LMNA	1:156105062	rs150924946	Y	missense	NM_001257374.1:c.559A>G	p.I187V	5.60	8.61	5	0.038	Y	Variant of Uncertain Significance
LMNA	1:156105756	rs370656306	Y	missense	NM_001257374.1:c.665G>A	p.S222N	5.87	13.92	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
LMNA	1:156106150	rs150840924	Y	missense	NM_001257374.1:c.967C>T	p.R323C	5.74	20.90	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
LMNA	1:156106995	rs57520892	Y	missense	NM_001257374.1:c.1244G>A	p.R415H	5.59	16.57	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
LMNA	1:156108450	rs140455668	Y	missense	NM_001257374.1:c.1534C>T	p.R512C	4.69	23.70	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
LMNA	1:156108472	rs267607648	Y	missense	NM_001257374.1:c.1556G>A	p.G519D	4.69	24.60	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MEN1	11:64575506	rs143329068	Y	missense	NM_000244.3:c.526C>T	p.R176W	2.83	16.18	4	0.031	N	Likely benign
MEN1	11:64575454	rs199706698	Y	missense	NM_000244.3:c.578C>T	p.P193L	4.76	20.60	2	0.015	Y	Variant of Uncertain Significance
MET	7:116339209	rs180985111	N	missense	NM_000245.2:c.71G>A	p.G24E	5.14	11.97	4	0.033	N	Likely benign
MLH1	3:37090074	rs55907433	Y	missense	NM_000249.3:c.1963A>G	p.655Ile>Val	0.59	13.02	42	0.323	N	Likely benign
MLH1	3:37059009	rs63750650	Y	missense	NM_000249.3:c.803A>G	p.E268G	5.61	29.00	3	0.023	Y	Likely benign
MLH1	3:37061893	rs63751049	Y	missense	NM_000249.3:c.977T>C	p.326Val>Ala	5.76	25.30	11	0.085	N	Variant of Uncertain Significance
MLH1	3:37067410	rs63750365	Y	missense	NM_000249.3:c.1321G>A	p.441Ala>Thr	2.19	11.80	4	0.031	Y	Variant of Uncertain Significance
MLH1	3:37089131	rs63750449	Y	missense	NM_000249.3:c.1853A>C	p.618Lys>Thr	5.35	23.00	49	0.377	N	Variant of Uncertain Significance
MLH1	3:37092125	rs140195825	Y	missense	NM_000249.3:c.2252A>G	p.751Lys>Arg	1.72	15.74	2	0.015	Y	Variant of Uncertain Significance[1]
MLH1	3:37061929	rs63751467	Y	missense	NM_000249.3:c.1013A>G	p.N338S	4.08	15.78	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MLH1	3:37067237	rs141344760	Y	missense	NM_000249.3:c.1148T>C	p.M383T	4.52	15.25	2	0.015	Y	Variant of Uncertain Significance
MLH1	3:37090075	rs63751225	Y	missense	NM_000249.3:c.1964T>C	p.I655T	5.81	15.99	2	0.015	Y	Variant of Uncertain Significance
MLH1	3:37090471	rs63750702	Y	missense	NM_000249.3:c.2066A>G	p.Q689R	5.93	14.38	3	0.023	Y	Variant of Uncertain Significance
MLH3	14:75513910	rs143278116	N	missense	NM_001040108.1:c.2449A>G	p.817Ser>Gly	0.067	0.43	5	0.038	Y	Likely benign
MLH3	14:75485594	rs138006166	N	missense	NM_001040108.1:c.4180G>A	p.A1394T	5.55	34.00	8	0.062	Y	Variant of Uncertain Significance
MLH3	14:75513418	rs377337763	N	missense	NM_001040108.1:c.2941G>A	p.G981S	-5.64	0.00	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]
MSH2	2:47637301	rs63750124	Y	missense	NM_000251.2:c.435T>G	p.I145M	3.36	8.78	5	0.038	Y	Likely benign
MSH2	2:47637365	rs63750255	Y	missense	NM_000251.2:c.499G>C	p.D167H	5.73	28.30	2	0.015	Y	Likely benign
MSH2	2:47690201	rs63751403	Y	missense	NM_000251.2:c.1418C>T	p.S473L	5.40	34.00	1	0.008	Y (1 indiv)	Likely benign
MSH2	2:47630468	rs33946261	Y	missense	NM_000251.2:c.138C>G	p.46His>Gln	4.61	26.70	3	0.023	Y	Variant of Uncertain Significance
MSH2	2:47641430	rs34136999	Y	missense	NM_000251.2:c.815C>T	p.272Ala>Val	5.04	32.00	5	0.038	Y	Variant of Uncertain Significance
MSH2	2:47641528	rs63751454	Y	missense	NM_000251.2:c.913G>A	p.A305T	4.23	28.50	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MSH2	2:47643460	rs63750732	Y	missense	NM_000251.2:c.968C>G	p.S323C	4.75	20.70	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MSH2	2:47643537	rs267607939	Y	missense	NM_000251.2:c.1045C>G	p.P349A	5.62	22.30	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MSH2	2:47698190	rs201118107	Y	missense	NM_000251.2:c.1748A>G	p.N583S	5.86	10.31	2	0.015	Y	Variant of Uncertain Significance
MSH2	2:47702331	rs374840361	Y	missense	NM_000251.2:c.1927G>A	p.E643K	5.96	36.00	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MSH2	2:47703703	rs2229061	Y	missense	NM_000251.2:c.2203A>G	p.I735V	6.17	19.42	3	0.023	Y	Variant of Uncertain Significance

Supplementary Table 1: Pathogenicity classification of 615 variants listed as disease-causing variants in HGMD

Gene	hg19 location	rsID	ACMG	Function	cDNA position	Protein position	GERP Score	CADD Score	Total # Indiv's in EVS	Total EVS freq %	Meets disease specific cut off	Classification
MSH2	2:47705637	rs63749841	Y	missense	NM_000251.2:c.2437A>G	p.M813V	5.30	17.19	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MSH2	2:47710051	rs146421227	Y	missense	NM_000251.2:c.2768T>A	p.V923E	5.40	21.90	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MSH2	2:47702191	rs41295288	Y	missense	NM_000251.2:c.1787A>G	p.N596S	5.61	13.77	3	0.023	Y	Variant of Uncertain Significance
MSH6	2:48018236	rs3211299	Y	missense	NM_000179.2:c.431G>T	p.144Ser>Ile	2.34	19.82	13	0.1	N	Likely benign
MSH6	2:48026648	rs63751005	Y	missense	NM_000179.2:c.1526T>C	p.509Val>Ala	5.35	18.88	11	0.085	N	Likely benign
MSH6	2:48027755	rs2020912	Y	missense	NM_000179.2:c.2633T>C	p.878Val>Ala	1.99	0.24	71	0.546	N	Likely benign
MSH6	2:48027853	rs63751017	Y	stop-gained	NM_000179.2:c.2731C>T	p.R911*	2.84	43.00	1	0.008	Y (1 indiv)	Pathogenic (reduced penetrance)
MSH6	2:48033750	rs41295278	Y	missense	NM_000179.2:c.3961A>G	p.1321Arg>Gly	6.03	14.00	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MSH6	2:48010431	rs63750664	Y	missense	NM_000179.2:c.59C>T	p.A20V	2.14	14.54	3	0.023	Y	Variant of Uncertain Significance
MSH6	2:48025976	rs63750878	Y	missense	NM_000179.2:c.854G>T	p.S285I	4.27	11.67	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MSH6	2:48026525	rs41295268	Y	missense	NM_000179.2:c.1403G>A	p.R468H	4.27	19.36	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MSH6	2:48027520	rs61748083	Y	missense	NM_000179.2:c.2398G>C	p.V800L	3.85	10.99	2	0.015	Y	Variant of Uncertain Significance
MSH6	2:48027530	rs63751450	Y	missense	NM_000179.2:c.2408A>G	p.D803G	5.65	9.19	2	0.015	Y	Variant of Uncertain Significance
MSH6	2:48027683	rs34374438	Y	missense	NM_000179.2:c.2561A>T	p.K854M	4.48	14.99	5	0.039	Y	Variant of Uncertain Significance
MSH6	2:48030645	rs63750998	Y	missense	NM_000179.2:c.3259C>T	p.P1087S	3.54	17.25	4	0.031	Y	Variant of Uncertain Significance
MYBPC3	11:47357479	rs35078470	Y	missense	NM_000256.3:c.2686G>A	p.896Val>Met	2.21	15.71	46	0.375	N	Likely benign
MYBPC3	11:47364189	rs11570082	Y	missense	NM_000256.3:c.1564G>A	p.522Ala>Thr	1.35	2.04	22	0.171	N	Likely benign
MYBPC3	11:47359047	rs0	Y	missense	NM_000256.3:c.2497G>A	p.833Ala>Thr	4.6	29.30	15	0.117	N	Likely benign
MYBPC3	11:47371449	rs201012766	Y	missense	NM_000256.3:c.530G>A	p.R177H	2.88	16.14	43	0.343	N	Likely benign
MYBPC3	11:47369031	rs368121566	Y	splice-3	NA	NA	4.51	15.82	1	0.008	Y (1 indiv)	Likely pathogenic
MYBPC3	11:47373058	rs376395543	Y	splice-3	NA	NA	4.27	11.87	1	0.008	Y (1 indiv)	Likely pathogenic
MYBPC3	11:47359280	rs187830361	Y	missense	NM_000256.3:c.2374T>C	p.W792R	3.99	19.29	1	0.008	Y (1 indiv)	Likely pathogenic
MYBPC3	11:47355161	rs371061770	Y	missense	NM_000256.3:c.3137C>T	p.T1046M	4.28	11.77	1	0.008	Y (1 indiv)	Likely pathogenic
MYBPC3	11:47364129	rs121909374	Y	nissense-near-splic	NM_000256.3:c.1624G>C	p.E542Q	4.63	19.02	1	0.008	Y (1 indiv)	Pathogenic
MYBPC3	11:47364249	rs0	Y	missense	NM_000256.3:c.1504C>T	p.502Arg>Trp	4.63	22.20	1	0.008	Y (1 indiv)	Pathogenic
MYBPC3	11:47360070	rs112738974	Y	splice-5	NA	NA	5.40	27.50	1	0.008	Y (1 indiv)	Pathogenic (reduced penetrance)
MYBPC3	11:47356628	rs0	Y	missense	NM_000256.3:c.2870C>G	p.957Thr>Ser	0.79	7.54	11	0.09	N	Variant of Uncertain Significance[1]
MYBPC3	11:47361234	rs0	Y	missense	NM_000256.3:c.2035C>T	p.679Pro>Ser	4.9	24.70	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYBPC3	11:47362731	rs0	Y	missense	NM_000256.3:c.1855G>A	p.619Glu>Lys	3.87	22.00	8	0.065	Y	Variant of Uncertain Significance
MYBPC3	11:47364234	rs35736435	Y	missense	NM_000256.3:c.1519G>A	p.507Gly>Arg	4.63	24.90	17	0.132	N	Variant of Uncertain Significance
MYBPC3	11:47364285	rs0	Y	missense	NM_000256.3:c.1468G>A	p.490Gly>Arg	4.63	25.10	4	0.031	Y	Variant of Uncertain Significance
MYBPC3	11:47364465	rs0	Y	missense	NM_000256.3:c.1373G>A	p.458Arg>His	3.61	9.16	2	0.016	Y	Variant of Uncertain Significance
MYBPC3	11:47364637	rs0	Y	missense	NM_000256.3:c.1286C>T	p.429Ala>Val	4.72	18.87	5	0.039	Y	Variant of Uncertain Significance
MYBPC3	11:47370065	rs0	Y	missense	NM_000256.3:c.682G>A	p.228Asp>Asn	5.12	13.71	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYBPC3	11:47371333	rs0	Y	missense	NM_000256.3:c.646G>A	p.216Ala>Thr	-1.14	2.74	7	0.056	Y	Variant of Uncertain Significance[1]
MYBPC3	11:47372898	rs0	Y	missense	NM_000256.3:c.184A>C	p.62Thr>Pro	0.403	7.32	3	0.023	Y	Variant of Uncertain Significance[1]
MYBPC3	11:47374186	rs0	Y	missense	NM_000256.3:c.13G>C	p.5Gly>Arg	4.48	21.50	10	0.082	N	Variant of Uncertain Significance
MYBPC3	11:47353695	rs202147520	Y	missense	NM_000256.3:c.3742G>A	p.G1248R	3.60	14.76	3	0.025	Y	Variant of Uncertain Significance
MYBPC3	11:47353755	rs201312636	Y	missense	NM_000256.3:c.3682C>T	p.R1228C	5.46	24.20	7	0.058	Y	Variant of Uncertain Significance
MYBPC3	11:47354443	rs377171707	Y	missense	NM_000256.3:c.3412C>T	p.R1138C	5.38	24.70	2	0.016	Y	Variant of Uncertain Significance
MYBPC3	11:47355249	rs368180702	Y	missense	NM_000256.3:c.3049G>A	p.E1017K	2.86	7.87	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYBPC3	11:47356616	rs373056282	Y	missense	NM_000256.3:c.2882C>T	p.P961L	4.24	17.18	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYBPC3	11:47356625	rs376504548	Y	missense	NM_000256.3:c.2873C>T	p.T958I	5.16	6.71	2	0.016	Y	Variant of Uncertain Significance
MYBPC3	11:47357547	rs371401403	Y	missense	NM_000256.3:c.2618C>A	p.P873H	5.28	29.70	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYBPC3	11:47359115	rs375675796	Y	missense	NM_000256.3:c.2429G>A	p.R810H	4.60	33.00	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYBPC3	11:47359334	rs368104687	Y	missense	NM_000256.3:c.2320G>A	p.A774T	-5.52	17.18	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]
MYBPC3	11:47359343	rs371488302	Y	missense	NM_000256.3:c.2311G>A	p.V771M	3.75	21.20	2	0.017	Y	Variant of Uncertain Significance
MYBPC3	11:47360110	rs369790992	Y	missense	NM_000256.3:c.2269G>A	p.V757M	4.50	25.10	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYBPC3	11:47362758	rs371564200	Y	missense	NM_000256.3:c.1828G>A	p.D610N	4.60	29.40	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYBPC3	11:47364602	rs193922377	Y	missense	NM_000256.3:c.1321G>A	p.E441K	3.79	17.02	5	0.039	Y	Variant of Uncertain Significance
MYBPC3	11:47364677	rs371513491	Y	missense	NM_000256.3:c.1246G>A	p.G416S	4.72	21.90	3	0.024	Y	Variant of Uncertain Significance
MYBPC3	11:47367887	rs200119454	Y	missense	NM_000256.3:c.961G>A	p.V321M	4.70	30.00	5	0.039	Y	Variant of Uncertain Significance
MYBPC3	11:47369217	rs375774648	Y	missense	NM_000256.3:c.836G>C	p.G279A	3.55	7.96	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYBPC3	11:47371355	rs202139499	Y	missense	NM_000256.3:c.624G>C	p.Q208H	4.80	23.60	5	0.039	Y	Variant of Uncertain Significance
MYBPC3	11:47371450	rs193922385	Y	missense	NM_000256.3:c.529C>T	p.R177C	4.80	19.26	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYBPC3	11:47371592	rs193068692	Y	missense	NM_000256.3:c.478C>T	p.R160W	1.46	15.78	2	0.016	Y	Variant of Uncertain Significance[1]
MYBPC3	11:47371609	rs373946195	Y	missense	NM_000256.3:c.461T>C	p.I154T	3.33	0.05	2	0.016	Y	Variant of Uncertain Significance
MYBPC3	11:47369411	rs376461745	Y	missense	NM_000256.3:c.818G>A	p.R273H	4.58	20.50	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYBPC3	11:47372859	rs375471260	Y	missense	NM_000256.3:c.223G>A	p.D75N	4.27	18.24	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYBPC3	11:47364468	rs370538243	Y	missense	NM_000256.3:c.1370C>T	p.T457M	2.64	12.87	1	0.008	Y (1 indiv)	Variant of Uncertain Significance

Supplementary Table 1: Pathogenicity classification of 615 variants listed as disease-causing variants in HGMD

Gene	hg19 location	rsID	ACMG	Function	cDNA position	Protein position	GERP Score	CADD Score	Total # Indiv's in EVS	Total EVS freq %	Meets disease specific cut off	Classification
MYBPC3	11:47369442	rs373730381	Y	missense	NM_000256.3:c.787G>A	p.G263R	4.64	15.24	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYH11	16:15812194	rs142546324	Y	missense	NM_001040113.1:c.5294G>A	p.R1765Q	4.70	33.00	3	0.023	Y	Likely benign
MYH11	16:15872688	rs150759461	Y	missense	NM_001040113.1:c.760C>T	p.R254C	5.1	23.6	32	0.246	N	Likely benign
MYH11	16:15814019	rs369409348	Y	missense	NM_001040113.1:c.4963C>T	p.R1655C	3.99	20.40	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYH11	16:15844048	rs111404182	Y	missense	NM_001040113.1:c.2026C>T	p.R676C	4.43	21.50	3	0.023	Y	Variant of Uncertain Significance
MYH7	14:23894525	rs3218716	Y	missense	NM_000257.2:c.2389G>A	p.A797T	0.75	12.81	1	0.008	Y (1 indiv)	Likely pathogenic[1]
MYH7	14:23896042	rs371898076	Y	missense	NM_000257.2:c.1988G>A	p.R663H	3.98	26.60	1	0.008	Y (1 indiv)	Likely pathogenic
MYH7	14:23883310	rs372381770	Y	nissense-near-splic	NM_000257.2:c.5561C>T	p.T1854M	5.07	22.10	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYH7	14:23885257	rs141122361	Y	missense	NM_000257.2:c.4909G>A	p.1637Ala>Thr	2.67	10.36	6	0.046	Y	Variant of Uncertain Significance
MYH7	14:23886807	rs145213771	Y	missense	NM_000257.2:c.4258C>T	p.1420Arg>Trp	4.07	20.30	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYH7	14:23892910	rs145532615	Y	missense	NM_000257.2:c.2945T>C	p.982Met>Thr	5.06	19.63	22	0.169	N	Variant of Uncertain Significance
MYH7	14:23895007	rs121913644	Y	missense	NM_000257.2:c.2183C>T	p.728Ala>Val	4.88	15.95	3	0.023	Y	Variant of Uncertain Significance
MYH7	14:23884227	rs12590294	Y	missense	NM_000257.2:c.5536C>T	p.R1846C	4.51	18.22	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYH7	14:23884269	rs201865159	Y	missense	NM_000257.2:c.5494C>T	p.R1832C	4.34	13.03	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYH7	14:23884458	rs139222507	Y	missense	NM_000257.2:c.5305C>A	p.L1769M	4.36	17.79	2	0.015	Y	Variant of Uncertain Significance
MYH7	14:23885010	rs370328209	Y	missense	NM_000257.2:c.4985G>A	p.R1662H	4.28	9.70	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYH7	14:23886504	rs201307101	Y	missense	NM_000257.2:c.4377G>T	p.K1459N	1.31	18.07	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]
MYH7	14:23887536	rs370403289	Y	missense	NM_000257.2:c.4052C>T	p.T1351M	4.97	14.56	2	0.015	Y	Variant of Uncertain Significance
MYH7	14:23887607	rs141764279	Y	missense	NM_000257.2:c.3981C>A	p.N1327K	-0.39	18.04	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]
MYH7	14:23890202	rs367546859	Y	missense	NM_000257.2:c.3301G>A	p.G1101S	5.55	13.78	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYH7	14:23894049	rs138049878	Y	missense	NM_000257.2:c.2608C>T	p.R870C	4.73	19.98	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYH7	14:23894554	rs376754645	Y	missense	NM_000257.2:c.2360G>A	p.R787H	4.60	14.33	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYH7	14:23894555	rs145677314	Y	missense	NM_000257.2:c.2359C>T	p.R787C	2.69	12.35	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYH7	14:23899792	rs372731424	Y	missense	NM_000257.2:c.976G>C	p.A326P	-3.02	13.04	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]
MYH7	14:23899810	rs376897125	Y	missense	NM_000257.2:c.958G>A	p.V320M	3.41	15.43	2	0.015	Y	Variant of Uncertain Significance
MYH7	14:23902827	rs376160714	Y	missense	NM_000257.2:c.115G>A	p.V39M	3.42	18.60	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYH7	14:23902865	rs186964570	Y	missense	NM_000257.2:c.77C>T	p.A26V	2.36	20.20	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYL2	12:111356964	rs104894363	Y	missense	NM_000432.3:c.37G>A	p.13Ala>Thr	3.23	16.11	6	0.046	Y	Variant of Uncertain Significance
MYL2	12:111353547	rs199474808	Y	missense	NM_000432.3:c.141C>A	p.N47K	-5.06	16.32	5	0.038	Y	Variant of Uncertain Significance[1]
MYL2	12:111350901	rs143139258	Y	nissense-near-splic	NM_000432.3:c.401A>C	p.134Glu>Ala	5.09	27.90	5	0.038	Y	Likely pathogenic
MYL3	3:46902238	rs150634297	Y	missense	NM_000258.2:c.235G>A	p.V79I	4.36	17.69	1	0.008	Y (1 indiv)	Likely pathogenic
MYL3	3:46899903	rs193922391	Y	missense	NM_000258.2:c.530A>G	p.E177G	3.77	24.10	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYL3	3:46900980	rs199474707	Y	missense	NM_000258.2:c.466G>A	p.V156M	4.26	20.70	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
MYL3	3:46900986	rs143852164	Y	missense	NM_000258.2:c.460C>T	p.R154C	4.26	18.24	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
OTC	X:38240681	rs140046498	N	nissense-near-splic	NM_000531.5:c.385C>T	p.129Arg>Cys	5.02	19.46	2	0.019	Y	Variant of Uncertain Significance
OTC	X:38226606	rs67939655	N	missense	NM_000531.5:c.140A>C	p.N47T	5.39	14.07	1	0.009	Y (1 indiv)	Variant of Uncertain Significance
OTC	X:38240670	rs72554356	N	missense	NM_000531.5:c.374C>T	p.T125M	-2.96	9.28	1	0.009	Y (1 indiv)	Variant of Uncertain Significance[1]
PAH	12:103260383	rs77554925	N	missense	NM_000277.1:c.500A>G	p.N167S	-4.01	11.16	72	0.554	NA (recessive)	Likely benign
PAH	12:103246615	rs142934616	N	missense	NM_000277.1:c.820A>G	p.K274E	5.73	15.83	72	0.554	NA (recessive)	Likely benign
PAH	12:103246701	rs76212747	N	missense	NM_000277.1:c.734T>C	p.245Val>Ala	5.92	28.80	7	0.054	NA (recessive)	Variant of Uncertain Significance
PKP2	12:33049590	rs143004808	Y	missense	NM_001005242.2:c.76G>A	p.26Asp>Asn	4.07	33.00	60	0.486	N	Likely benign
PKP2	12:32994073	rs146882581	Y	missense	NM_001005242.2:c.1445C>T	p.T482M	2.01	3.327	48	0.369	N	Likely benign
PKP2	12:33003841	rs372827156	Y	stop-gained	NM_001005242.2:c.1237C>T	p.R413*	0.09	33.00	1	0.008	Y (1 indiv)	Likely pathogenic
PKP2	12:32955491	rs193922674	Y	splice-3	NA	NA	4.75	19.27	2	0.015	Y	Likely pathogenic
PKP2	12:32977026	rs146102241	Y	missense	NM_001005242.2:c.1627G>A	p.543Val>Ile	5.32	23.60	42	0.323	N	Variant of Uncertain Significance
PKP2	12:33031309	rs139139859	Y	missense	NM_001005242.2:c.505A>G	p.169Ser>Gly	-1.54	14.27	21	0.162	N	Variant of Uncertain Significance[1]
PKP2	12:33031395	rs150821281	Y	missense	NM_001005242.2:c.419C>T	p.140Ser>Phe	2.38	11.56	26	0.2	N	Variant of Uncertain Significance
PKP2	12:32949101	rs139734328	Y	missense	NM_001005242.2:c.2299C>A	p.R767S	5.06	17.80	5	0.038	Y	Variant of Uncertain Significance
PKP2	12:32974373	rs144601090	Y	missense	NM_001005242.2:c.1930T>C	p.S644P	4.88	21.20	2	0.015	Y	Variant of Uncertain Significance
PKP2	12:32996161	rs111450489	Y	missense	NM_004572.3:c.1465G>A	p.G489R	-0.52	4.02	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]
PKP2	12:33049482	rs199601548	Y	missense	NM_001005242.2:c.184C>A	p.Q62K	4.06	18.51	3	0.024	Y	Variant of Uncertain Significance
PMS2	7:6026469	rs63751422	Y	stop-gained	NM_000535.5:c.1927C>T	p.Q643*	4.92	28.00	1	0.008	Y (1 indiv)	Pathogenic
PMS2	7:6031649	rs200640585	Y	stop-gained	NM_000535.5:c.943C>T	p.R315*	5.39	27.90	1	0.008	Y (1 indiv)	Pathogenic
PMS2	7:6045549	rs121434629	Y	missense	NM_000535.5:c.137G>T	p.46Ser>Ile	5.67	32.00	1	0.014	Y (1 indiv)	Pathogenic
PMS2	7:6038824	rs374704824	Y	missense	NM_000535.5:c.620G>A	p.G207E	4.77	22.10	2	0.015	Y	Variant of Uncertain Significance
PRKAG2	7:151478406	rs79474211	Y	missense	NM_001040633.1:c.166G>A	p.G56S	4.08	15.21	11	0.085	N	Likely benign
PRKAR1A	17:66518939	rs137853303	N	missense	NM_002734.3:c.220C>T	p.R74C	5.96	28.70	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
PROC	2:128183756	rs28933986	N	missense	NM_000312.3:c.631C>T	p.R211W	0.63	10.66	1	0.008	Y (1 indiv)	Likely pathogenic[1]
PROC	2:128178913	rs369504169	N	missense	NM_000312.3:c.125G>A	p.R42H	5.20	21.60	1	0.008	Y (1 indiv)	Likely pathogenic
PROC	2:128186337	rs142742242	N	missense	NM_000312.3:c.1201G>A	p.D401N	3.92	23.90	1	0.008	Y (1 indiv)	Pathogenic

Supplementary Table 1: Pathogenicity classification of 615 variants listed as disease-causing variants in HGMD

Gene	hg19 location	rsID	ACMG	Function	cDNA position	Protein position	GERP Score	CADD Score	Total # Indiv's in EVS	Total EVS freq %	Meets disease specific cut off	Classification
PROC	2:128180669	rs0	N	missense	NM_000312.3:c.322C>A	p.108His>Asn	2.08	8.48	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
PROC	2:128186370	rs139741458	N	missense	NM_000312.3:c.1234G>A	p.412Gly>Ser	4.84	16.69	3	0.023	Y	Variant of Uncertain Significance
PROC	2:128177570	rs146793243	N	missense	NM_000312.3:c.52G>A	p.G18S	-8.27	1.32	3	0.023	Y	Variant of Uncertain Significance[1]
PROC	2:128178948	rs376049280	N	missense	NM_000312.3:c.160A>T	p.S54C	5.20	16.95	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
PROC	2:128183705	rs371071104	N	missense	NM_000312.3:c.580C>T	p.R194C	2.13	15.52	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
PROC	2:128186146	rs369881972	N	missense	NM_000312.3:c.1010C>T	p.T337I	1.20	11.31	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]
PROC	2:128180687	rs374476971	N	missense	NM_000312.3:c.340G>C	p.G114R	3.16	18.35	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
PROC	2:128183690	rs146922325	N	missense	NM_000312.3:c.565C>T	p.R189W	-0.86	10.19	2	0.015	Y	Variant of Uncertain Significance[1]
PROS1	3:93598123	rs138925964	N	missense	NM_000313.3:c.1528G>A	p.V510M	2.11	9.335	51	0.392	N	Likely benign
PROS1	3:93595918	rs142846443	N	missense	NM_000313.3:c.1762A>G	p.588Thr>Ala	4.64	8.97	12	0.092	N	Variant of Uncertain Significance
PROS1	3:93615439	rs0	N	missense	NM_000313.3:c.946C>T	p.316Arg>Cys	3.27	16.14	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
PROS1	3:93619677	rs41267007	N	missense	NM_000313.3:c.698G>A	p.233Arg>Lys	-0.333	1.63	26	0.2	N	Variant of Uncertain Significance[1]
PROS1	3:93624903	rs146366248	N	missense	NM_000313.3:c.431C>A	p.144Thr>Asn	0.129	6.67	5	0.038	Y	Variant of Uncertain Significance[1]
PROS1	3:93593213	rs368173480	N	missense	NM_000313.3:c.1907A>G	p.Y636C	3.10	16.43	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
PROS1	3:93595933	rs139479630	N	missense	NM_000313.3:c.1747A>C	p.N583H	-3.10	9.53	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]
PROS1	3:93598057	rs371028997	N	missense	NM_000313.3:c.1594A>G	p.T532A	0.23	0.64	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]
PROS1	3:93603733	rs369244777	N	missense	NM_000313.3:c.1331C>T	p.P444L	3.78	22.90	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
PROS1	3:93611837	rs199469491	N	missense	NM_000313.3:c.1095T>G	p.N365K	0.65	11.43	2	0.015	Y	Variant of Uncertain Significance[1]
PROS1	3:93619699	rs370855515	N	missense	NM_000313.3:c.676T>A	p.C226S	4.08	21.30	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
PROS1	3:93629525	rs144526169	N	missense	NM_000313.3:c.284G>A	p.G95E	3.42	11.94	4	0.031	Y	Variant of Uncertain Significance
PTCH1	9:98220308	rs138911275	N	missense	NM_000264.3:c.3155C>T	p.1052Thr>Met	5.87	25.10	15	0.115	N	Likely benign
PTCH1	9:98215787	rs376844749	N	missense	NM_000264.3:c.3422C>T	p.A1141V	5.35	26.70	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
PTCH1	9:98220518	rs145924695	N	missense	NM_000264.3:c.2945G>A	p.R982Q	3.38	15.94	2	0.015	Y	Variant of Uncertain Significance
PTCH1	9:98240450	rs370354759	N	missense	NM_000264.3:c.1234G>T	p.A412S	-0.07	11.22	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]
PTEN	10:89720741	rs0	Y	missense	NM_000314.4:c.892C>G	p.298Gln>Glu	5.13	10.98	3	0.023	Y	Variant of Uncertain Significance
RBM20	10:112572302	rs375798246	N	missense	NM_001134363.1:c.2147G>A	p.R716Q	5.75	27.60	1	0.022	Y (1 indiv)	Variant of Uncertain Significance
RBM20	10:112544125	rs0	N	missense	NM_001134363.1:c.1364C>T	p.455Ser>Leu	5.54	15.92	33	0.723	N	Variant of Uncertain Significance
RET	10:43595999	rs145633958	Y	missense	NM_020630.4:c.166C>A	p.56Leu>Met	3.41	8.18	48	0.369	N	Likely benign
RET	10:43613908	rs77724903	Y	missense	NM_020630.4:c.2372A>T	p.791Tyr>Phe	5.34	19.83	15	0.123	N	Likely benign
RET	10:43609994	rs148935214	Y	missense	NM_020630.4:c.1946C>T	p.S649L	4.34	24.10	7	0.054	N	Likely benign
RET	10:43610044	rs143795581	Y	missense	NM_020630.4:c.1996A>G	p.K666E	4.75	17.55	1	0.008	Y (1 indiv)	Likely benign
RET	10:43610046	rs146646971	Y	missense	NM_020630.4:c.1998G>T	p.K666N	1.59	14.67	6	0.046	N	Likely benign
RET	10:43614996	rs79658334	Y	missense	NM_020630.4:c.2410G>A	p.V804M	5.36	18.29	1	0.008	Y (1 indiv)	Pathogenic
RET	10:43600559	rs139790943	Y	missense	NM_020630.4:c.785T>C	p.262Val>Ala	3.64	21.80	3	0.023	Y	Variant of Uncertain Significance
RET	10:43601917	rs0	Y	missense	NM_020630.4:c.961G>A	p.321Gly>Arg	-1.32	11.54	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]
RET	10:43607555	rs0	Y	missense	NM_020630.4:c.1531G>A	p.511Glu>Lys	4.77	12.42	3	0.023	Y	Variant of Uncertain Significance
RET	10:43607555	rs0	Y	missense	NM_020630.4:c.1531G>A	p.511Glu>Lys	4.77	12.42	3	0.023	Y	Variant of Uncertain Significance
RET	10:43615108	rs149891333	Y	missense	NM_020630.4:c.2522C>T	p.841Pro>Leu	4.46	23.10	5	0.038	Y	Variant of Uncertain Significance
RET	10:43606815	rs138624658	Y	missense	NM_020630.4:c.1424G>A	p.R475Q	-0.33	11.67	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]
RET	10:43609990	rs77711105	Y	missense	NM_020630.4:c.1942G>A	p.V648I	-2.96	3.67	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]
RET	10:43610129	rs141185224	Y	missense	NM_020630.4:c.2081G>A	p.R694Q	2.90	15.17	2	0.015	Y	Variant of Uncertain Significance
RET	10:43615038	rs377767420	Y	missense	NM_020630.4:c.2452G>A	p.E818K	5.36	15.27	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
RET	10:43622099	rs79853121	Y	missense	NM_020630.4:c.3116C>T	p.P1039L	5.09	24.40	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
RET	10:43623563	rs149513065	Y	missense	NM_020975.4:c.3191T>C	p.M1064T	5.34	18.05	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
RET	10:43615577	rs146838520	Y	missense	NM_020630.4:c.2656C>T	p.R886W	2.53	19.96	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
RET	10:43597991	rs370736139	Y	missense	NM_020630.4:c.539G>A	p.R180Q	-1.05	15.94	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1]
RYR1	19:38987106	rs200563280	Y	stop-gained	NM_000540.2:c.6721C>T	p.R2241*	4.91	49.00	1	0.008	Y (1 indiv)	Likely benign
RYR1	19:39034060	rs377178986	Y	stop-gained	NM_000540.2:c.11763C>A	p.Y3921*	2.01	53.00	1	0.008	Y (1 indiv)	Likely benign
RYR1	19:39057626	rs150396398	Y	nissense-near-splic	NM_000540.2:c.13513G>C	p.4505Asp>His	3.93	8.18	43	0.331	N	Likely benign
RYR1	19:39026638	rs140616359	Y	nissense-near-splic	NM_000540.2:c.11518G>A	p.V3840I	4.38	9.32	2	0.015	Y	Likely benign
RYR1	19:38954162	rs147336515	Y	missense	NM_000540.2:c.2677G>A	p.893Gly>Ser	4	18.12	22	0.169	N	Likely benign
RYR1	19:38955289	rs148623597	Y	missense	NM_000540.2:c.2797G>A	p.933Ala>Thr	4.23	19.72	17	0.131	N	Likely benign
RYR1	19:38973933	rs146429605	Y	missense	NM_000540.2:c.4711A>G	p.1571Ile>Val	3.99	10.29	12	0.093	N	Likely benign
RYR1	19:38976331	rs146504767	Y	missense	NM_000540.2:c.5036G>A	p.1679Arg>His	4.07	20.70	12	0.092	N	Likely benign
RYR1	19:39009932	rs137932199	Y	missense	NM_000540.2:c.10097G>A	p.3366Arg>His	3.54	10.13	11	0.085	N	Likely benign
RYR1	19:39016132	rs143987857	Y	missense	NM_000540.2:c.10616G>A	p.3539Arg>His	3.07	15.28	24	0.185	N	Likely benign
RYR1	19:39034191	rs147136339	Y	missense	NM_000540.2:c.11798A>G	p.3933Tyr>Cys	4.11	12.67	11	0.085	N	Likely benign
RYR1	19:38948887	rs138874610	Y	missense	NM_000540.2:c.2122G>A	p.D708N	5.02	23.10	4	0.031	Y	Likely benign
RYR1	19:38956987	rs111272095	Y	missense	NM_000540.2:c.3127C>T	p.R1043C	2.94	15.25	1	0.008	Y (1 indiv)	Likely benign
RYR1	19:39008026	rs200950673	Y	missense	NM_000540.2:c.9713A>G	p.E3238G	4.16	11.83	2	0.015	Y	Likely benign

Supplementary Table 1: Pathogenicity classification of 615 variants listed as disease-causing variants in HGMD

Gene	hg19 location	rsID	ACMG	Function	cDNA position	Protein position	GERP Score	CADD Score	Total # Indiv's in EVS	Total EVS freq %	Meets disease specific cut off	Classification
RYR1	19:39057618	rs139647387	Y	missense	NM_000540.2:c.13505A>G	p.E4502G	2.91	6.71	2	0.015	Y	Likely benign
RYR1	19:38964306	rs112105381	Y	missense	NM_000540.2:c.4055C>G	p.A1352G	1.45	10.09	43	0.369	N	Likely benign
RYR1	19:38965975	rs137933390	Y	missense	NM_000540.2:c.4178A>G	p.K1393R	4.6	16.05	56	0.431	N	Likely benign
RYR1	19:39076780	rs146876145	Y	missense	NM_000540.2:c.14918C>T	p.P4973L	4.21	10.79	2	0.015	Y	Likely pathogenic
RYR1	19:38946103	rs111888148	Y	missense	NM_000540.2:c.1589G>A	p.R530H	4.01	15.90	2	0.015	Y	Pathogenic
RYR1	19:38948185	rs28933996	Y	missense	NM_000540.2:c.1840C>T	p.R614C	3.76	15.96	1	0.008	Y (1 indiv)	Pathogenic
RYR1	19:38990295	rs193922802	Y	missense	NM_000540.2:c.7048G>A	p.A2350T	3.82	19.17	1	0.008	Y (1 indiv)	Pathogenic
RYR1	19:38976478	rs193922781	Y	missense	NM_000540.2:c.5183C>T	p.S1728F	3.77	12.37	1	0.008	Y (1 indiv)	Pathogenic
RYR1	19:38946112	rs144336148	Y	missense	NM_000540.2:c.1598G>A	p.533Arg>His	4.01	16.65	7	0.054	Y	Variant of Uncertain Significance
RYR1	19:38956816	rs150993059	Y	missense	NM_000540.2:c.2956C>T	p.986Arg>Cys	2.74	15.47	4	0.031	Y	Variant of Uncertain Significance
RYR1	19:38989817	rs34390345	Y	missense	NM_000540.2:c.6961A>G	p.2321Ile>Val	4.11	8.54	11	0.085	N	Variant of Uncertain Significance
RYR1	19:38989881	rs147213895	Y	missense	NM_000540.2:c.7025A>G	p.2342Asn>Ser	3.69	11.42	13	0.1	N	Variant of Uncertain Significance
RYR1	19:39038899	rs144685735	Y	missense	NM_000540.2:c.12121C>T	p.4041Arg>Trp	3.07	12.42	2	0.015	Y	Variant of Uncertain Significance
RYR1	19:38931470	rs139161723	Y	missense	NM_000540.2:c.131G>A	p.R44H	3.81	15.23	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
RYR1	19:38945887	rs147723844	Y	missense	NM_000540.2:c.1453A>G	p.M485V	-2.06	5.99	2	0.015	Y	Variant of Uncertain Significance[1]
RYR1	19:38948884	rs376526576	Y	missense	NM_000540.2:c.2119G>A	p.G707S	5.02	18.89	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
RYR1	19:38949893	rs147320363	Y	missense	NM_000540.2:c.2275A>G	p.N759D	4.36	16.01	2	0.015	Y	Variant of Uncertain Significance
RYR1	19:38964051	rs150495044	Y	missense	NM_000540.2:c.3800C>G	p.P1267R	5.07	15.24	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
RYR1	19:38968456	rs145573319	Y	missense	NM_000540.2:c.4400A>G	p.K1467R	5.41	14.79	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
RYR1	19:38968461	rs200546266	Y	missense	NM_000540.2:c.4405C>T	p.R1469W	3.26	15.64	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
RYR1	19:38976415	rs371566475	Y	missense	NM_000540.2:c.5120G>A	p.R1707H	3.98	14.93	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
RYR1	19:38985195	rs143398211	Y	missense	NM_000540.2:c.6478G>A	p.G2160S	2.38	13.69	3	0.023	Y	Variant of Uncertain Significance
RYR1	19:38986946	rs193922795	Y	missense	NM_000540.2:c.6640G>A	p.V2214I	4.59	13.30	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
RYR1	19:38990346	rs146306934	Y	missense	NM_000540.2:c.7099G>A	p.A2367T	3.99	21.50	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
RYR1	19:38990624	rs193922810	Y	missense	NM_000540.2:c.7291G>A	p.D2431N	3.99	15.92	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
RYR1	19:39008071	rs375626634	Y	missense	NM_000540.2:c.9758T>C	p.I3253T	4.16	8.83	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
RYR1	19:39016137	rs376338203	Y	missense	NM_000540.2:c.10621G>A	p.A3541T	4.15	12.96	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
RYR1	19:39026677	rs145087576	Y	missense	NM_000540.2:c.11557G>A	p.E3853K	4.38	15.81	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
RYR1	19:39061260	rs118192130	Y	missense	NM_000540.2:c.13673G>A	p.R4558Q	5.10	18.09	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
RYR1	19:39062672	rs143520367	Y	missense	NM_000540.2:c.13760C>T	p.P4587L	5.76	14.22	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
RYR1	19:39070725	rs148540135	Y	missense	NM_000540.2:c.14468C>T	p.T4823M	4.57	15.15	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
RYR1	19:39071022	rs193922879	Y	missense	NM_000540.2:c.14524G>A	p.V4842M	4.57	15.17	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
RYR1	19:39075653	rs118192153	Y	missense	NM_000540.2:c.14717C>T	p.A4906V	5.08	17.17	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
RYR1	19:38990457	rs111364296	Y	missense	NM_000540.2:c.7210G>A	p.E2404K	3.74	13.85	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
RYR2	1:237811894	rs374191985	Y	missense	NM_001035.2:c.7493C>T	p.A2498V	4.73	31.00	2	0.017	Y	Likely benign
RYR2	1:237711862	rs149514924	Y	missense	NM_001035.2:c.3038G>A	p.1013Arg>Gln	5.73	12.39	11	0.091	N	Variant of Uncertain Significance
RYR2	1:237540715	rs201211033	Y	missense	NM_001035.2:c.556G>A	p.V186M	5.17	15.94	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
RYR2	1:237617794	rs376612295	Y	missense	NM_001035.2:c.1396C>G	p.P466A	5.80	14.13	2	0.017	Y	Variant of Uncertain Significance
RYR2	1:237955507	rs189345192	Y	missense	NM_001035.2:c.13666G>A	p.A4556T	2.12	7.57	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
SCN5A	3:38592012	rs41315493	Y	missense	NM_000335.4:c.5848G>T	p.1950Val>Leu	-0.527	7.06	24	0.191	N	Likely benign
SCN5A	3:38592152	rs150264233	Y	missense	NM_000335.4:c.5708C>T	p.1903Ser>Leu	4.86	24.40	10	0.079	N	Likely benign
SCN5A	3:38592503	rs199473316	Y	missense	NM_000335.4:c.5357G>A	p.1786Ser>Asn	4.82	21.70	9	0.069	N	Likely benign
SCN5A	3:38603947	rs41313031	Y	missense	NM_000335.4:c.3919C>T	p.1307Leu>Phe	3.17	12.31	17	0.134	N	Likely benign
SCN5A	3:38639408	rs45553235	Y	missense	NM_000335.4:c.2074C>A	p.692Gln>Lys	1.95	10.67	2	0.016	Y	Likely benign
SCN5A	3:38645241	rs45488304	Y	missense	NM_000335.4:c.1852C>T	p.618Leu>Phe	4.18	16.91	27	0.215	N	Likely benign
SCN5A	3:38591990	rs199473331	Y	missense	NM_000335.4:c.5870G>A	p.R1957Q	-0.29	2.54	2	0.016	Y	Likely benign
SCN5A	3:38607905	rs199473341	Y	missense	NM_000335.4:c.3832G>A	p.V1278I	3.92	17.85	1	0.008	Y (1 indiv)	Likely benign
SCN5A	3:38655327	rs370438420	Y	splice-3	NA	NA	4.30	20.30	1	0.008	Y (1 indiv)	Likely pathogenic
SCN5A	3:38603958	rs199473603	Y	missense	NM_000335.4:c.3908C>T	p.1303Thr>Met	4.04	16.01	5	0.04	Y	Likely pathogenic
SCN5A	3:38591960	rs199473639	Y	missense	NM_000335.4:c.5900T>G	p.1967Ile>Ser	3.78	7.39	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
SCN5A	3:38592356	rs45563942	Y	missense	NM_000335.4:c.5504T>C	p.1835Ile>Thr	4.82	16.43	11	0.086	N	Variant of Uncertain Significance
SCN5A	3:38592386	rs137854610	Y	missense	NM_000335.4:c.5474G>A	p.1825Arg>His	4.82	22.50	2	0.016	Y	Variant of Uncertain Significance
SCN5A	3:38592527	rs199473634	Y	missense	NM_000335.4:c.5333C>T	p.1778Thr>Met	4.82	19.84	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
SCN5A	3:38595989	rs199473618	Y	missense	NM_000335.4:c.4591G>A	p.1531Val>Ile	3.69	9.76	7	0.056	N	Variant of Uncertain Significance
SCN5A	3:38620916	rs0	Y	missense	NM_000335.4:c.3296C>T	p.1099Ala>Val	3.16	9.87	4	0.032	Y	Variant of Uncertain Significance
SCN5A	3:38622706	rs0	Y	missense	NM_000335.4:c.2944T>C	p.982Cys>Arg	2.57	12.78	5	0.041	Y	Variant of Uncertain Significance
SCN5A	3:38639416	rs0	Y	missense	NM_000335.4:c.2066G>A	p.689Arg>His	2.01	10.80	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
SCN5A	3:38645249	rs12720452	Y	missense	NM_000335.4:c.1844G>A	p.615Gly>Glu	4.18	11.96	5	0.04	Y	Variant of Uncertain Significance
SCN5A	3:38645379	rs0	Y	missense	NM_000335.4:c.1714G>T	p.572Ala>Ser	-3.04	2.91	4	0.032	Y	Variant of Uncertain Significance[1]
SCN5A	3:38647498	rs0	Y	missense	NM_000335.4:c.1282G>A	p.428Glu>Lys	4.67	14.73	2	0.016	Y	Variant of Uncertain Significance

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Gene	hg19 location	rsID	ACMG	Function	cDNA position	Protein position	GERP Score	CADD Score	Total # Indiv's in EVS	Total EVS freq %	Meets disease specific cut off	Classification
SCN5A	3:38655243	rs45471994	Y	missense	NM_000335.4:c.694G>A	p.232Val>Ile	4.01	24.70	3	0.025	Y	Variant of Uncertain Significance
SCN5A	3:38655278	rs45620037	Y	missense	NM_000335.4:c.659C>T	p.220Thr>Ile	4.3	24.50	4	0.032	Y	Variant of Uncertain Significance
SCN5A	3:38591902	rs199473335	Y	missense	NM_000335.4:c.5958C>A	p.N1986K	4.95	6.37	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
SCN5A	3:38592174	rs45465995	Y	missense	NM_000335.4:c.5686C>T	p.R1896W	3.97	15.83	3	0.024	Y	Variant of Uncertain Significance
SCN5A	3:38627472	rs45475899	Y	missense	NM_000335.4:c.2497G>A	p.G833R	4.44	26.00	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
SCN5A	3:38645238	rs199473133	Y	missense	NM_000335.4:c.1855C>T	p.L619F	4.12	15.08	2	0.016	Y	Variant of Uncertain Significance
SCN5A	3:38646354	rs199473572	Y	missense	NM_000335.4:c.1384G>A	p.E462K	5.33	34.00	2	0.016	Y	Variant of Uncertain Significance
SCN5A	3:38647444	rs199473339	Y	missense	NM_000335.4:c.1336G>A	p.E446K	5.54	34.00	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
SCN5A	3:38651294	rs199473084	Y	missense	NM_000335.4:c.865G>A	p.G289S	5.10	6.91	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
SCN5A	3:38655264	rs199473072	Y	missense	NM_000335.4:c.673C>T	p.R225W	4.30	20.10	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
SCN5A	3:38663959	rs199473060	Y	missense	NM_000335.4:c.414G>A	p.M138I	3.99	19.39	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
SDHB	1:17371286	rs35962811	Y	missense	NM_003000.2:c.170A>G	p.H57R	-5.43	1.93	37	0.284	N	Likely benign
SDHB	1:17380483	rs111430410	Y	missense	NM_003000.2:c.32G>A	p.11Arg>His	4.19	12.56	30	0.231	N	Variant of Uncertain Significance
SDHB	1:17349152	rs201098090	Y	missense	NM_003000.2:c.716C>G	p.S239C	5.62	28.10	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
SDHB	1:17371377	rs74315369	Y	missense	NM_003000.2:c.79C>G	p.R27G	3.72	10.80	2	0.015	Y	Variant of Uncertain Significance
SDHC	1:161284203	rs142139022	Y	missense	NM_001035511.1:c.8C>T	p.A3V	4.32	16.11	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
SDHD	11:111958686	rs149516118	Y	missense	NM_003002.2:c.158C>T	p.P53L	4.90	16.46	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
SERPINA1	14:94844950	rs143370956	N	missense	NM_000295.4:c.1093G>A	p.D365N	2.98	18.19	7	0.054	NA (recessive)	Likely benign
SERPINA1	14:94849388	rs28931570	N	missense	NM_000295.4:c.187C>T	p.R63C	2.83	15.29	21	0.161	NA (recessive)	Likely pathogenic (in combination with a severe null or Pi Z)
SERPINA1	14:94847286	rs28929472	N	missense	NM_000295.4:c.839A>T	p.D280V	5.05	18.72	8	0.062	NA (recessive)	Likely pathogenic (in combination with a severe null or Pi Z)
SERPINA1	14:94844947	rs28929474	N	missense	NM_000295.4:c.1096G>A	p.E366K	2.95	21.90	155	1.23	NA (recessive)	Pathogenic
SERPINA1	14:94847262	rs17580	N	missense	NM_000295.4:c.863A>T	p.E288V	5.18	20.30	389	3.06	NA (recessive)	Pathogenic
SERPINA1	14:94847386	rs28929470	N	missense	NM_000295.4:c.739C>T	p.R247C	4.09	18.96	40	0.308	NA (recessive)	Variant of Uncertain Significance
SERPINA1	14:94849558	rs140814100	N	missense	NM_000295.4:c.17C>T	p.S6L	3.79	10.05	3	0.023	NA (recessive)	Variant of Uncertain Significance
SERPINC1	1:173883863	rs121909552	N	missense	NM_000488.3:c.236G>A	p.R79H	5.67	24.30	4	0.031	Y	Likely benign
SERPINC1	1:173883881	rs121909551	N	missense	NM_000488.3:c.218C>T	p.P73L	5.67	32.00	5	0.038	Y	Likely benign
SERPINC1	1:173873166	rs121909568	N	missense	NM_000488.3:c.1256C>T	p.419Ala>Val	-6.85	9.17	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1.]
SERPINC1	1:173873176	rs121909548	N	missense	NM_000488.3:c.1246G>T	p.416Ala>Ser	5.74	21.70	15	0.115	N	Variant of Uncertain Significance
SERPINC1	1:173878957	rs372820797	N	missense	NM_000488.3:c.886G>C	p.A296P	3.32	11.61	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
SERPINC1	1:173881079	rs121909563	N	missense	NM_000488.3:c.482G>A	p.R161Q	5.66	33.00	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
SGCD	5:155935644	rs376659221	N	missense	NM_000337.5:c.226G>T	p.G76C	5.49	26.90	1	0.008	Y (1 indiv)	Likely benign
SLC7A9	19:33353427	rs79389353	N	missense	NM_001126335.1:c.544G>A	p.A182T	5.54	11.31	43	0.338	NA (recessive)	Likely pathogenic (not returned, carrier status)
SLC7A9	19:33334847	rs201618022	N	missense	NM_001126335.1:c.988G>A	p.V330M	5.37	17.39	1	0.008	NA (recessive)	Variant of Uncertain Significance
SMAD4	18:48604751	rs149755320	N	missense	NM_005359.5:c.1573A>G	p.I525V	6.08	12.34	11	0.085	N	Likely benign
STK11	19:1223034	rs0	Y	missense	NM_000455.4:c.971C>T	p.324Pro>Leu	3.79	13.70	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
TGFBR1	9:101911508	rs141259922	Y	missense	NM_001130916.1:c.1202A>G	p.401Asn>Ser	5.66	14.73	6	0.046	Y	Variant of Uncertain Significance
TGFBR2	3:30733044	rs112215250	Y	missense	NM_001024847.2:c.1732T>A	p.S578T	6.01	22.4	18	0.138	N	Likely benign
TGFBR2	3:30713660	rs148665451	Y	missense	NM_001024847.2:c.1060G>A	p.354Ala>Thr	1.71	12.74	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1.]
TGFBR2	3:30713834	rs35766612	Y	missense	NM_001024847.2:c.1234G>A	p.412Val>Met	4.15	17.28	30	0.231	N	Variant of Uncertain Significance
TMEM127	2:96930903	rs121908820	N	missense	NM_001193304.2:c.217G>C	p.G73R	4.62	24.70	2	0.015	Y	Likely benign
TMEM127	2:96920712	rs121908823	N	missense	NM_001193304.2:c.268G>A	p.V90M	5.91	18.79	36	0.277	N	Likely benign
TNNI3	19:55665463	rs368861241	Y	missense	NM_000363.4:c.484C>T	p.R162W	3.67	19.61	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
TNNI3	19:55663249	rs104894727	Y	missense	NM_000363.4:c.586G>A	p.D196N	4.42	29.50	1	0.008	Y (1 indiv)	Likely pathogenic (Harvard LMM calls VUS)
TNNT2	1:201328373	rs121964857	Y	missense	NM_000364.2:c.853C>T	p.285Arg>Cys	3.05	16.14	6	0.046	Y	Likely pathogenic (Harvard LMM calls VUS)
TNNT2	1:201328348	rs141121678	Y	missense	NM_000364.2:c.878G>A	p.R293H	3.98	24.90	1	0.008	Y (1 indiv)	Likely pathogenic
TNNT2	1:201337340	rs0	Y	missense	NM_000364.2:c.113C>T	p.23Ala>Val	-1.3	6.76	4	0.031	Y	Variant of Uncertain Significance[1.]
TNNT2	1:201330455	rs45466197	Y	missense	NM_000364.2:c.753G>T	p.E251D	1.77	17.02	1	0.008	Y (1 indiv)	Variant of Uncertain Significance[1.]
TNNT2	1:201334772	rs144900708	Y	missense	NM_000364.2:c.260C>T	p.P87L	4.68	16.58	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
TP53	17:7577090	rs371409680	Y	missense	NM_000546.5:c.848G>A	p.R283H	4.02	19.28	1	0.008	Y (1 indiv)	Likely benign
TP53	17:7577094	rs28934574	Y	missense	NM_000546.5:c.844C>T	p.R282W	1.49	20.80	1	0.015	Y (1 indiv)	Likely benign
TP53	17:7578184	rs146340390	Y	missense	NM_000546.5:c.665C>T	p.P222L	3.03	14.69	2	0.015	Y	Likely benign
TP53	17:7578463	rs371524413	Y	missense	NM_000546.5:c.467G>A	p.R156H	3.45	14.28	1	0.008	Y (1 indiv)	Likely benign
TP53	17:7577548	rs28934575	Y	missense	NM_000546.5:c.733G>A	p.G245S	4.62	33.00	1	0.008	Y (1 indiv)	Likely pathogenic
TP53	17:7577091	rs149633775	Y	missense	NM_000546.5:c.847C>T	p.283Arg>Cys	4.01	13.04	5	0.038	Y	Likely pathogenic
TP53	17:7577538	rs11540652	Y	missense	NM_000546.5:c.743G>A	p.R248Q	3.65	27.30	1	0.008	Y (1 indiv)	Pathogenic
TP53	17:7577069	rs55819519	Y	missense	NM_000546.5:c.869G>A	p.290Arg>His	-1.23	8.23	4	0.031	Y	Variant of Uncertain Significance[1.]
TP53	17:7577577	rs144340710	Y	missense	NM_000546.5:c.704A>G	p.235Asn>Ser	4.62	16.94	2	0.015	Y	Variant of Uncertain Significance
TPM1	15:63353090	rs199476312	Y	missense	NM_000366.5:c.515T>C	p.I172T	5.80	20.10	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
TSC2	16:2124321	rs45517238	Y	missense	NM_000548.3:c.2476C>A	p.826Leu>Met	2.38	15.75	11	0.085	N	Likely benign
TSC2	16:2103409	rs372321790	Y	missense	NM_000548.3:c.292C>T	p.R98W	4.79	20.80	1	0.008	Y (1 indiv)	Likely benign

Supplementary Table 1: Pathogenicity classification of 615 variants listed as disease-causing variants in HGMD

Gene	hg19 location	rsID	ACMG	Function	cDNA position	Protein position	GERP Score	CADD Score	Total # Indiv's in EVS	Total EVS freq %	Meets disease specific cut off	Classification
TSC2	16:2112989	rs137854154	Y	missense	NM_000548.3:c.1378G>A	p.A460T	5.24	15.92	9	0.08	N	Likely benign
TSC2	16:2114403	rs45457694	Y	missense	NM_000548.3:c.1574A>G	p.525Asn>Ser	5.57	9.75	2	0.015	Y	Variant of Uncertain Significance
TSC2	16:2115598	rs141631268	Y	missense	NM_000548.3:c.1678G>A	p.560Val>Met	5.3	18.33	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
TSC2	16:2130189	rs45505895	Y	missense	NM_000548.3:c.3421G>A	p.1141Ala>Thr	4.74	11.45	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
TSC2	16:2130198	rs45517294	Y	missense	NM_000548.3:c.3430G>A	p.1144Val>Met	-9.47	11.94	2	0.015	Y	Variant of Uncertain Significance[1.]
TSC2	16:2138570	rs45517423	Y	missense	NM_000548.3:c.5383C>T	p.1795Arg>Cys	4.64	15.06	17	0.131	N	Variant of Uncertain Significance
TSC2	16:2100429	rs144165984	Y	missense	NM_000548.3:c.167A>G	p.N56S	3.64	10.59	2	0.015	Y	Variant of Uncertain Significance
TSC2	16:2121610	rs45509392	Y	missense	NM_000548.3:c.1939G>A	p.D647N	5.45	34.00	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
TSC2	16:2138565	rs45506695	Y	missense	NM_000548.3:c.5378G>A	p.R1793Q	4.64	23.70	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
TSC2	16:2106732	rs137854123	Y	missense	NM_000548.3:c.736A>G	p.T246A	5.05	19.80	1	0.008	Y (1 indiv)	Variant of Uncertain Significance
TSC2	16:2100485	rs145470784	Y	missense	NM_000548.3:c.223G>A	p.E75K	4.77	19.50	3	0.023	Y	Variant of Uncertain Significance
VHL	3:10183766	rs200885420	Y	missense	NM_000551.3:c.235C>T	p.R79C	4.56	25.90	1	0.008	Y (1 indiv)	Likely benign
VHL	3:10183772	rs5030806	Y	missense	NM_000551.3:c.241C>T	p.P81S	3.24	28.60	5	0.039	N	Likely benign
VHL	3:10191545	rs377715747	Y	missense	NM_000551.3:c.538A>G	p.I180V	4.97	21.80	1	0.008	Y (1 indiv)	Likely benign
VHL	3:10191605	rs28940298	Y	missense	NM_000551.3:c.598C>T	p.R200W	4.03	22.40	2	0.015	Y	Likely benign
VHL	3:10183685	rs0	Y	missense	NM_000551.3:c.154G>A	p.52Glu>Lys	0.645	16.91	3	0.024	N	Variant of Uncertain Significance[1.]
VHL	3:10191563	rs367545984	Y	missense	NM_000551.3:c.556G>A	p.E186K	4.97	26.60	1	0.008	Y (1 indiv)	Variant of Uncertain Significance

1. Consideration of GERP score may reduce pathogenicity classification

Supplemental Table 2. Pathogenic actionable variants listed as disease-causing in HGMD

Gene	Associated Phenotype (s)	Inheritance	Genomic coordinate (hg19)	Function	Nucleotide change	Protein Change	rsID	Ancestry (n)[5]
ATP7B[2] *[MIM 606882]*	Wilson disease [MIM 277900]	AR	13:52511706	missense	NM_000053.3:c.3809A>G,	p.Asn1270Ser	121907990	NA
BRCA1 [MIM 113705]	Hereditary breast and ovarian cancer [MIM 604370]	AD	17:41244826	stop gain	NM_007294.3:c.2722G>T	p.Glu908*	80356978	E (1)
			17:41243887	stop gain	NM_007294.3:c.3661G>T	p.Glu1221*	80357310	E (1)
			17:41215948	missense	NM_007294.3:c.5095C>T,	p.Arg1699Trp	55770810	E (1)
			17:41243941	stop gain	NM_007294.3:c.3607C>T	p.Arg1203*	62625308	A (1)
			17:41247941	splice-3	NM_007300.3: c.594-2A>C	NA	80358033	E (1)
BRCA2 [MIM 600185]	Hereditary breast and ovarian cancer [MIM 612555]	AD	13:32914174	stop gain	NM_000059.3:c.5682C>G	p.Tyr1894*	41293497	E (1)
			13:32930687	stop gain	NM_000059.3:c.7558C>T	p.Arg2520*	80358981	E (1)
ENG [MIM 131195]	Hereditary hemorrhagic telangiectasias [MIM 187300]	AD	9:130581941	splice-3	NM_001114753.1 : c.1273-2A>G	NA	373842615	E (1)
FLCN [MIM 607273]	Birt-Hogg-Dube syndrome [MIM 136150]	AD	17:17125815	stop gain - near-splice	NM_144606.5:c.779G>A	p.Trp260*[6]	368778627	E (1)
KCNQ1 [MIM 607542]	Long QT syndrome [MIM 192500]	AD	11:2592563	missense	NM_000218.2:c.613G>A	p.Val205Met	151344631	A (1)
LDLR [MIM 606945]	Familial hypercholesterolemia [MIM 143890]	AD	19:11213445	stop gain	NM_000527.4:c.296C>G	p.Ser99*	-	E (1)
			19:11224319	stop gain	NM_000527.4:c.1467C>G	p.Tyr489*	370777955	E (1)
			19:11224210	splice-3	NM_000527.4:c.1359-1G>A	NA	139617694	E (1)
			19:11227604	missense	NM_000527.4:c.1775G>A	p.Gly592Glu	137929307	E (3)
LMNA [MIM 150330]	Dilated cardiomyopathy [MIM 115200]	AD	1:156106776	missense	NM_001257374.1 :c.1109G>A	p.Arg370Gln	11575937	E (1)
MSH6 [MIM 600678]	Lynch syndrome [MIM 614337]	AD	2:48027853	stop gain	NM_000179.2:c.2731C>T	p.Arg911*[4]	63751017	E (1)

MYBPC3 [MIM 600958]	Hypertrophic cardiomyopathy [MIM 115197]	AD	11:47364129	missense-near-splice	NM_000256.3:c.1624G>C	p.Glu542Gln	121909374	A (1)
			11:47364249	missense	NM_000256.3:c.1504C>T	p.Arg502Trp	-	E (1)
			11:47360070	splice-5[4]	NM_000256.3: c.2308+1G>A	NA	112738974	E (1)
PMS2 [MIM 600259]	Lynch syndrome [MIM 614337]	AD	7:6026469	stop gain	NM_000535.5:c.1927C>T	p.Gln643*	63751422	A (1)
			7:6031649	stop gain	NM_000535.5:c.943C>T	p.Arg315*	200640585	E (1)
			7:6045549	missense	NM_000535.5:c.137G>T	p.Ser46Ile	121434629	E (1)
PROC [MIM 612283]	Protein C deficiency [MIM 612283]	AD	2:128186337	missense	NM_000312.3:c.1201G>A	p.Asp401Asn	142742242	E (1)
RET [MIM 164761]	Multiple endocrine neoplasia, type 2 [MIM 171400]	AD	10:43614996	missense	NM_020630.4:c.2410G>A	p.Val804Met	79658334	E (1)
RYR1 [MIM 180901]	Malignant Hyperthermia [MIM 145600]	AD	19:38946103	missense	NM_000540.2:c.1589G>A,	p.Arg530His	111888148	E (1) A (1)
			19:38948185	missense	NM_000540.2:c.1840C>T	p.Arg614Cys	28933996	E (1)
			19:38990295	missense	NM_000540.2:c.7048G>A	p.Arg2350Thr	193922802	E (1)
			19:38976478	missense	NM_000540.2:c.5183C>T	p.Ser1728Phe	193922781	E (1)
SERPINA1 [MIM 107400]	Alpha 1 Antitrypsin deficiency (Z allele) [MIM 613490]	AR	14:94844947	missense	NM_000295.4:c.1096G>A	p.Glu366Lys	28929474	E (3)[3] A (1)[3]
			14:94847262	missense	NM_000295.4:c.863A>T	p.Glu288Val	17580	
TP53 [MIM 191170]	Li-Fraumeni syndrome [MIM 151623]	AD	17:7577538	missense	NM_000546.5:c.743G>A	p.Arg248Gln	11540652	E (1)

1. Bolded genes are on the ACMG list
2. Carrier status. Was not included in counts of participants that would have results returned
3. Found in the same individual. All cases compound heterozygous.
4. Reduced penetrance variant
5. E = European-ancestry; A = African-ancestry; AR = autosomal recessive; AD = autosomal dominant
6. In the first 90% of the transcript, however is in the last coding exón or last 50bp, so may be subjected to nonsense mediated decay

Supplementary Table 3. Disruptive variants not in HGMD annotated as disease-causing

Gene	Associated Phenotype (s)	Inheritance	Genomic Coordinate (hg19)	Function	Nucleotide Change	Protein Change	Amino Acid Length	rsID	Ancestry (n)[4.]
BRCA1 [MIM 113705]	Hereditary breast and ovarian cancer [MIM 612555]	AD	17:41228521	stop gain	c.4468G>T	p.Glu1490*	1836	138608489	E (1)
			17:41231417	splice-3	c.4358-1G>A	NA	1836	374435098	E (1)
BRCA2 [MIM 600185]	Hereditary breast and ovarian cancer [MIM 612555]	AD	13:32914347	stop gain	c.5855T>A	p.Leu1952*[2]	3419	-	A (1)
DSC2 [MIM 125645]	Arrhythmogenic right ventricular dysplasia [MIM 610476]	AD	18:28667744	stop gain	c.663A>T	p.Tyr221*	848, 902	145476705	A (1)
DSP [MIM 125647]	Arrhythmogenic right ventricular dyplasia [MIM 607450]	AD	6:7580603	stop gain	c.4180C>T	p.Gln1394*	2871	140474226	E (1)
MSH6 [MIM 600678]	Lynch syndrome [MIM 614337]	AD	2:48026014	stop gain	c.892C>T	p.Arg298*[3]	1360	146816935	A (1)
MYBPC3 [MIM 600958]	Hypertrophic cardiomyopathy [MIM 115197]	AD	11:47353795	stop gain	c.3642G>A	p.Trp1214*		368765949	E (1)
MYH7 [MIM 160760]	Dilated and hypertrophic cardiomyopathy [MIM 613426; 192600]	AD	14:23889431	stop gain	c.3349G>T	p.Glu1117*	1935	141735183	A (1)
PMS2 [MIM 600259]	Lynch syndrome [MIM 614337]	AD	7:6029430	splice-5	c.1144+1G>A	NA	862	373885654	A (2)
PROS1 [MIM 176880]	Protein S deficiency [MIM 612336]	AD	3:93617414	splice-3	c.728-1G>A	NA	676	368074804	E (1)
PTCH1 [MIM 601309]	Basal cell nevus syndrome [MIM 109400]	AD	9:98248157	splice-3	c.395-1G>A	NA	1447	368869806	E (1)

1. Bolded genes are on the ACMG list
2. Listed as pathogenic in ClinVar, submission accession RCV000031583.1
3. Listed as pathogenic in the InSiGHT database
4. E = European-ancestry; A = African-ancestry

Supplemental Table 4. Discrepant variants from Partners' LMM review

Gene	Associated phentoype	Protein change	DNA change	rsID	Partners LMM		EVS Reviewer	
					Evidence	Classification	Evidence	Classification
TNNI3 [MIM 191044]	Hypertrophic cardiomyopathy [MIM 613690]	p.Asp196 Asn	c.586G>A	104894727	• Allele frequency below disease specific cut off • Literature: reported in 3 affected unrelated individuals, 1 family with 2 segregations • LMM database: seen in 2 affected individuals with other variants • Weak support from computational analyses	VUS	• Allele frequency below disease specific cut off • Literature: reported in 3 affected unrelated individuals, 1 family with 2 segregations	Likely pathogenic
TNNT2 [MIM 191045]	Hypertrophic cardiomyopathy [MIM 115195]	p.Arg285 Cys	c.853G>A	121964857	• Allele frequency below disease specific cut off • Literature: reported in >10 affected individuals, segregation with disease • LMM database: detected in >15 probands, 7 of which carried a variant in another gene • Poorly conserved region • Functional studies: may effect muscle contraction in vitro	VUS[1.]	• Allele frequency below disease specific cut off • Literature: reported in 17 affected unrelated individuals	Likely pathogenic

1. This variant probably has a milder effect when present in isolation and should be interpreted carefully in the context of the individual's age at onset

Supplemental Table 5: List of 112 medically actionable gene-disease associations

GENE [a]	INHERITANCE PATTERN	DISEASE	% OF GENE COVERED[g]
ACTA2[b]	Dominant	Aortic aneurysm, familial thoracic	100%
ACTC1	Dominant	Cardiomyopathy, dilated; Cardiomyopathy, familial hypertrophic; Left ventricular noncompaction	99.90%
ACVRL1	Dominant	Telangiectasia, hereditary hemorrhagic	99.70%
APC	Dominant	Familial adenomatous polyposis	98%
ATP7B	Recessive	Wilson disease	99.90%
BCHE[c]	Recessive	Pseudocholinesterase deficiency	100%
BLM	Recessive	Bloom syndrome	99.90%
BMPR1A	Dominant	Juvenile polyposis syndrome	99.90%
BRCA1	Dominant	Hereditary breast and ovarian cancer	98.70%
BRCA2	Dominant	Hereditary breast and ovarian cancer	99.90%
CACNA1C	Dominant	Short QT syndrome	99.20%
CACNA1S	Dominant	Malignant hyperthermia susceptibility	99.90%
CACNB2	Dominant	Short QT syndrome	100%
CASQ2	Recessive	Ventricular tachycardia, catecholaminergic polymorphic	100%
CDC73	Dominant	Hyperparathyroidism-jaw tumor syndrome	100%
CDH1	Dominant	Hereditary diffuse gastric cancer	98.20%
CNBP	Dominant	Myotonic dystrophy	100%
COL3A1	Dominant	Ehlers-Danlos syndrome	99.90%
COQ2	Recessive	Coenzyme Q10 deficiency	73.5%[h]
COQ9	Recessive	Coenzyme Q10 deficiency	92.40%
CPT2	Recessive	CPT deficiency, hepatic, type II	92.20%
DMD	X-Linked	Cardiomyopathy, dilated	99.90%
DMPK	Dominant	Myotonic dystrophy	94.30%
DSC2	Dominant	Arrhythmogenic right ventricular dysplasia	97.40%
DSG2	Dominant	Arrhythmogenic right ventricular dysplasia; Cardiomyopathy, dilated	99.60%
DSP	Dominant	Arrhythmogenic right ventricular dysplasia	99.90%
EMD	X-Linked	Emery-Dreifuss muscular dystrophy	100%
ENG	Dominant	Hereditary Hemorrhagic Telangiectasia	98.10%
EPCAM	Dominant	Hereditary nonpolyposis colorectal cancer/Lynch syndrome	96.70%
F5[d]	Recessive	Factor V deficiency	100%
FBN1	Dominant	Marfan syndrome	100%
FH	Dominant	Leiomyomatosis and renal cell cancer	99.10%
FLCN	Dominant	Birt-Hogg-Dube syndrome	99.90%
GAA	Recessive	Glycogen storage disease II	99.80%
GCH1	Dominant	Dystonia, DOPA-responsive, with or without hyperphenylalaninemia	84.90%
GLA	X-Linked	Fabry disease	99.90%
HAMP	Recessive	Hemochromatosis, type 2B	100%
HFE2	Recessive	Hemochromatosis, type 2A	99.90%
HFE[e]	Recessive	HFE associated hemochromatosis	99.80%
HMBS	Dominant	Porphyria, acute intermittent	99.90%
IDUA	Recessive	Mucopolysaccharidosis	69%[h]
KCNE1	Dominant	Long QT syndrome	100%
KCNE2	Dominant	Long QT syndrome	100%
KCNH2	Dominant	Long QT syndrome, short QT syndrome	77.9%[h]
KCNJ2	Dominant	Short QT syndrome	100%
KCNQ1	Dominant	Long QT syndrome, short QT syndrome	86.30%
KIT	Dominant	Gastrointestinal stromal tumor	100%
LDLR	Dominant	Hypercholesterolemia, familial	99.90%
LDLRAP1	Recessive	Hypercholesterolemia, familial	90.50%
LMNA	Dominant	Cardiomyopathy	95.40%
MAX[f]	Dominant	Susceptibility to pheochromocytoma	100%
MEN1	Dominant	Multiple endocrine neoplasia, type 1	97.90%
MET	Dominant	Renal cell carcinoma, papillary, familial	99.90%
MLH1	Dominant	Hereditary nonpolyposis colorectal cancer/Lynch syndrome	100%
MLH3	Dominant	Hereditary nonpolyposis colorectal cancer/Lynch syndrome	100%
MSH2	Dominant	Hereditary nonpolyposis colorectal cancer/Lynch syndrome	99.80%
MSH6	Dominant	Hereditary nonpolyposis colorectal cancer/Lynch syndrome	96.80%
MUTYH	Dominant	MUTYH Associated polyposis	99.90%
MYBPC3	Dominant	Cardiomyopathy, familial hypertrophic	99.60%
MYH11	Dominant	Aortic aneurysm, familial thoracic	100%
MYH7	Dominant	Cardiomyopathy, dilated; Cardiomyopathy, familial hypertrophic	99%
MYL2	Dominant	Cardiomyopathy, familial hypertrophic	100%
MYL3	Dominant	Cardiomyopathy, familial hypertrophic	100%
MYLK	Dominant	Aortic aneurysm, familial thoracic	99.90%
NF2	Dominant	Neurofibromatosis, type 2	99.90%
OTC	X-Linked	Ornithine transcarbamylase deficiency	100%
PAH	Recessive	Phenylketonuria	100%
PCBD1	Recessive	Hyperphenylalaninemia, BH4-deficient	99%
PDGFRA	Dominant	Gastrointestinal stromal tumor	100%
PKP2	Dominant	Arrhythmogenic right ventricular dysplasia	95.80%
PLN	Dominant	Cardiomyopathy, dilated; Cardiomyopathy, familial hypertrophic	100%
PMS2	Dominant	Hereditary nonpolyposis colorectal cancer/Lynch syndrome	94.80%
PRKAG2	Dominant	Wolff-Parkinson-White syndrome; Cardiomyopathy, hypertrophic	99.90%
PRKAR1A	Dominant	Carney complex, type 1	96.50%
PROC	Dominant	Thrombophilia due to protein C deficiency	98.60%
PROS1	Dominant	Thrombophilia due to protein S deficiency	99.90%
PTCH1	Dominant	Basal cell nevus syndrome	97.80%
PTEN	Dominant	Cowden syndrome	100%
PTS	Recessive	Hyperphenylalaninemia, BH4-deficient	99.80%
QDPR	Recessive	Hyperphenylalaninemia, BH4-deficient	99.90%
RBM20	Dominant	Cardiomyopathy, dilated	0%[h]
RET	Dominant	Multiple endocrine neoplasia Type 2	97.60%

Supplemental Table 5: List of 112 medically actionable gene-disease associations

GENE [a]	INHERITANCE PATTERN	DISEASE	% OF GENE COVERED[g]
RYR1	Dominant	Malignant hyperthermia susceptibility	94.40%
RYR2	Dominant	Arrhythmogenic right ventricular dysplasia	99.90%
SCN5A	Dominant	Long QT syndrome, Brugada syndrome	99.80%
SDHAF2	Dominant	Hereditary paragangliomas and pheochromocytomas	100%
SDHB	Dominant	Hereditary paragangliomas and pheochromocytomas	99.80%
SDHC	Dominant	Hereditary paragangliomas and pheochromocytomas	99.80%
SDHD	Dominant	Hereditary paragangliomas and pheochromocytomas	79.9%[h]
SERPINA1	Recessive	Alpha-1-Antitrypsin Deficiency	100%
SERPINC1	Dominant	Thrombophilia due to antithrombin III deficiency	100%
SGCD	Dominant	Cardiomyopathy, dilated	100%
SLC25A13	Recessive	Citrullinemia, adult-onset type II	99.20%
SLC37A4	Recessive	Glycogen storage disease Ib; Glycogen storage disease Ic	94.80%
SLC7A9	Recessive	Cystinuria	100%
SMAD3	Dominant	Loeys-Dietz syndrome	94.50%
SMAD4	Dominant	Juvenile polyposis syndrome	99.90%
SMARCB1	Dominant	Schwannomatosis	100%
STK11	Dominant	Peutz-Jeghers syndrome	94.20%
TGFB2[f]	Dominant	Loeys-Dietz syndrome	100%
TGFB3	Dominant	Arrhythmogenic right ventricular dysplasia	100%
TGFBR1	Dominant	Loeys-Dietz syndrome	93.60%
TGFBR2	Dominant	Loeys-Dietz syndrome	99.90%
TMEM127[f]	Dominant	Susceptibility to pheochromocytoma	85.80%
TMEM43	Dominant	Arrhythmogenic right ventricular dysplasia	100%
TNNI3	Dominant	Cardiomyopathy, dilated; Cardiomyopathy, familial hypertrophic	99.80%
TNNT2	Dominant	Cardiomyopathy, dilated; Cardiomyopathy, familial hypertrophic	99.90%
TP53	Dominant	Li-Fraumeni syndrome	96.80%
TPM1	Dominant	Cardiomyopathy, dilated; Cardiomyopathy, familial hypertrophic	97.90%
TSC1	Dominant	Tuberous sclerosis complex	100%
TSC2	Dominant	Tuberous sclerosis complex	99.10%
VHL	Dominant	von Hippel-Lindau syndrome	97.50%

(a) Does not include the 5 genes removed from the gene list after Dorschner et al., 2013 publication (*GPD1L, HCN4, KCNE3, SCN1B* and *SCN3B*)

(b) **Bolded** genes are recommended for return by the ACMG guidelines.

(c) Only homozygotes for null alleles

(d) Only homozygotes for the *F5* c.1601 G>A, pArg534Gln, Factor V Leiden mutation are deemed actionable

(e) Only homozygotes for the *HFE* c.845G>A, p.Cys282Tyr mutation are deemed actionable

(f) Added to the gene list after Dorschner et al., 2013 publication

(g) The number of coding locations for which the number of individuals covered was > 3251 (half of 6503) and the average depth for those covered was >= 8, divided by the total number of coding locations (x100).

(h) Less than 80% of the gene covered