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Resources for Genetics Professionals — Genetic Disorders Associated with Founder Variants Common in the Ashkenazi Jewish Population

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A founder variant is a pathogenic variant observed at high frequency in a specific population due to the presence of the variant in a single ancestor or small number of ancestors. The presence of a founder variant can affect the approach to molecular genetic testing. When one or more founder variants account for a large percentage of all pathogenic variants found in a population, testing for the founder variant(s) may be performed first.

The table below includes common founder variants – here defined as **three or fewer variants that account for >50% of the pathogenic variants identified in a single gene in individuals of a specific ancestry** – in individuals of Ashkenazi Jewish ancestry. Note: (1) Pathogenic variants that are common worldwide due to a DNA sequence hot spot are not considered founder variants and thus are not included. (2) Disorders with a carrier frequency ≤1/200 are not included.

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Table. Genetic Disorders Associated with Founder Variants Common in the Ashkenazi Jewish Population

Gene	Disorder	MOI	DNA Nucleotide Change	Predicted Protein Change	Proportion of Pathogenic Variants in Gene [1]	Carrier Frequency	Reference Sequences	References [2]
ABCC8	Familial hyperinsulinism	AR	c.3989-9G>A	--	93%	1/83	NM_000352.6	Zlotogora et al [2018]
ACADS	Short chain acyl-CoA dehydrogenase deficiency	AR	c.319C>T	p.Arg107Cys	70%	1/15 to 1/26	NM_000017.4 NP_000008.1	Tein et al [2008], Zlotogora et al [2018]
ACSF3	Combined malonic & methylmalonic aciduria (OMIM 614265)	AR	c.1411C>T	p.Arg471Trp	~100% [3]	1/69	NM_174917.5 NP_777577.2	Zlotogora et al [2018]
ADAMTS2	Ehlers-Danlos syndrome, dermatosparaxis type (OMIM 225410)	AR	c.673C>T	p.Gln225Ter	95%	1/159 to 1/187	NM_014244.5 NP_055059.2	Shi et al [2017], Zlotogora et al [2018]
APC	Colorectal cancer (See *APC*-Associated Polyposis Conditions.)	AD	c.3920T>A	p.Ile1307Lys	92%	NA	NM_000038.6 NP_000029.2	Ukaegbu et al [2021]
ASPA	Canavan disease	AR	c.854A>C	p.Glu285Ala	83%	1/55	NM_000049.4 NP_000040.1	Kaul et al [1994], Lazarin et al [2013], Zlotogora et al [2018]
			c.693C>A	p.Tyr231Ter	15%			
ATP7B	Wilson disease	AR	c.3191A>C	p.Glu1064Ala	85%	1/67	NM_000053.4 NP_000044.2	Shi et al [2017]
			c.3207C>A	p.His1069Gln				
			c.1934T>G	p.Met645Arg				
BBS2	Bardet-Biedl syndrome	AR	c.311A>C	p.Asp104Ala	25%	1/139	NM_031885.5 NP_114091.4	Shi et al [2017], Zlotogora et al [2018]
			c.1895G>C	p.Arg632Pro	75%			
BCKDHB	Maple syrup urine disease	AR	c.548G>C	p.Arg183Pro	81%	1/97	NM_183050.4 NP_898871.1	Zlotogora et al [2018]
			c.832G>A	p.Gly278Ser	19%			

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Gene	Disorder	MOI	DNA Nucleotide Change	Predicted Protein Change	Proportion of Pathogenic Variants in Gene [1]	Carrier Frequency	Reference Sequences	References [2]
BLM	Bloom syndrome	AR	c.2207_2212delATCTGAinsTAGATTC	p.Tyr736LeufsTer5	98%-99%	1/104 to 1/134	NM_000057.4 NP_000048.1	German et al [2007], Scott et al [2010], Lazarin et al [2013], Zlotogora et al [2018]
BRCA1	*BRCA1*- and *BRCA2*-associated hereditary breast and ovarian cancer	AD	c.68_69delAG	p.Glu23ValfsTer17	72%	NA	NM_007294.4 NP_009225.1	Bahar et al [2001], Frank et al [2002], Phelan et al [2002], Ferla et al [2007], Cox et al [2018]
			c.5266dupC	p.Gln1756ProfsTer74	26%			
BRCA2			c.5946delT	p.Ser1982ArgfsTer22	95%		NM_000059.4 NP_000050.3	
CCDC65	Primary ciliary dyskinesia	AR	c.877_878delAT	p.Ile293ProfsTer2	~100% [3]	1/118 to 1/344	NM_033124.5 NP_149115.2	Austin-Tse et al [2013], Horani et al [2013]
CCM2	Cerebral cavernous malformation	AD	c.30+5_30+6delGCinsTT	--	>70%	NA	NM_031443.4	Gallione et al [2011]
CFTR	Cystic fibrosis	AR	c.3846G>A	p.Trp1282Ter	45%-50%	1/55	NM_000492.4 NP_000483.3	Scott et al [2010], Lazarin et al [2013], Zlotogora et al [2018]
			c.1521_1523delCTT	p.Phe508del	27%-34%	1/88		
			c.3454G>C	p.Asp1152His	7%-14%	1/175		
CHEK2	Hereditary breast and ovarian cancer (OMIM 114480)	AD	c.1283C>T	p.Ser428Phe	67%	NA	NM_007194.4 NP_009125.1	Leedom et al [2016], Nielsen et al [2016], Walsh et al [2017], Cox et al [2018]
			c.1100delC	p.Thr367MetfsTer15	17%			
			c.470T>C	p.Ile157Thr	11%			
CHRNE	Congenital myasthenic syndrome	AR	c.1353dupG	p.Asn452GlufsTer4	85%	1/182 to 1/200	NM_000080.4 NP_000071.1	Zlotogora et al [2018]
CLRN1	Usher syndrome type 3A (OMIM 276902)	AR	c.144T>G	p.Asn48Lys	~100% [3]	1/92 to 1/120	NM_174878.3 NP_777367.1	Scott et al [2010], Zlotogora et al [2018]
CNGA3	Achromatopsia	AR	c.1669G>A	p.Gly557Arg	<100% [4]	1/169	NM_001298.3 NP_001289.1	Zlotogora et al [2018]

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Gene	Disorder	MOI	DNA Nucleotide Change	Predicted Protein Change	Proportion of Pathogenic Variants in Gene [1]	Carrier Frequency	Reference Sequences	References [2]
COL4A3	Alport syndrome	AR	c.40_63del24	p.Leu14_Leu21del	95%	1/192	NM_000091.5 NP_000082.2	Shi et al [2017], Zlotogora et al [2018]
COQ4	Mitochondrial encephalomyopathy (See Primary Coenzyme Q_{10} Deficiency.)	AR	c.718C>T	p.Arg240Cys	~100% [3]	1/149 to 1/161	NM_016035.5 NP_057119.3	Zlotogora et al [2018]
CPT2	Carnitine palmitoyltransferase II deficiency	AR	c.338C>T	p.Ser113Leu	40%	1/51	NM_000098.3 NP_000089.1	Shi et al [2017], Zlotogora et al [2018]
			c.1239_1240delGA	p.Lys414ThrfsTer7	25%			
			c.1342T>C	p.Phe448Leu	25%			
CRB2	Ventriculomegaly w/ cystic kidney disease (OMIM 219730)	AR	c.2400C>G	p.Asn800Lys	68%	1/66	NM_173689.7 NP_775960.4	Zlotogora et al [2018]
			c.1928A>C	p.Glu643Ala	32%			
DCXR	Pentosuria (OMIM 260800)	AR	c.583delC	p.His195ThrfsTer7	80%	1/29	NM_016286.4 NP_057370.1	
DGAT1	Protein-losing enteropathy (OMIM 615863)	AR	c.751+2T>C	--	~100% [3]	1/90	NM_012079.6	
DHCR7	Smith-Lemli-Opitz syndrome	AR	c.964-1G>C	--	93%	1/40	NM_001360.3	Shi et al [2017], Zlotogora et al [2018]
DHDDS	Retinitis pigmentosa, nonsyndromic	AR	c.124A>G	p.Lys42Glu	<100% [4]	1/90 to 1/118	NM_024887.4 NP_079163.2	Zelinger et al [2011], Shi et al [2017], Zlotogora et al [2018]
DLD	Dihydrolipoamide dehydrogenase deficiency	AR	c.685G>T	p.Gly229Cys	72%	1/61 to 1/108	NM_000108.5 NP_000099.2	Shaag et al [1999], Scott et al [2010], Zlotogora et al [2018]
			c.104dupA	p.Tyr35Ter	28%			

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Gene	Disorder	MOI	DNA Nucleotide Change	Predicted Protein Change	Proportion of Pathogenic Variants in Gene [1]	Carrier Frequency	Reference Sequences	References [2]
DNAH5	Primary ciliary dyskinesia	AR	c.7502G>C	p.Arg2501Pro	86%	1/143 to 1/172	NM_001369.3 NP_001360.1	Fedick et al [2015], Baskovich et al [2016], Zlotogora et al [2018]
DNAI2			c.1304G>A	p.Trp435Ter	~100% [3]	1/145 to 1/200	NM_023036.6 NP_075462.3	Knowles et al [2013], Zlotogora et al [2018]
ELP1	Familial dysautonomia	AR	c.2204+6T>C	--	>99%	1/31 to 1/43	NM_003640.5	Scott et al [2010], Lazarin et al [2013]
EYS	Retinitis pigmentosa	AR	c.9286_9295delGTAAATATCG	p.Val3096LeufsTer28	<100% [4]	1/189	NM_001142800.2 NP_001136272.1	Zlotogora et al [2018]
F11	Factor XI deficiency (OMIM 612416)	AD AR	c.403G>T	p.Glu135Ter	42%	1/12	NM_000128.4 NP_000119.1	
			c.901T>C	p.Phe301Leu	57%			
FAH	Tyrosinemia type 1	AR	c.782C>T	p.Pro261Leu	>99%	1/132 to 1/143	NM_000137.4 NP_000128.1	Elpeleg et al [2002], Shi et al [2017], Zlotogora et al [2018]
			c.1062+5G>A	--			NM_000137.4	
FANCC	Fanconi anemia	AR	c.456+4A>T	--	>99%	1/83 to 1/100	NM_000136.3	Scott et al [2010], Lazarin et al [2013], Zlotogora et al [2018]
FKTN	Fukuyama congenital muscular dystrophy	AR	c.1167dupA	p.Phe390IlefsTer14	~100% [3]	1/63 to 1/90	NM_001079802.2 NP_001073270.1	Zlotogora et al [2018]
G6PC	Glycogen storage disease type 1A	AR	c.247C>T	p.Arg83Cys	~100% [3]	1/64 to 1/75	NM_000151.4 NP_000142.2	Scott et al [2010], Zlotogora et al [2018]
GALT	Galactosemia	AR	c.-1039_+789del5573ins129 [5] (5458-bp del; whole-gene del)	--	80%	1/160	NG_009029.2	Coffee et al [2006], Shi et al [2017]
			c.563A>G	p.Gln188Arg	<10%		NM_000155.4 NP_000146.2	
			c.855G>T	p.Lys285Asn	<10%			

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Gene	Disorder	MOI	DNA Nucleotide Change	Predicted Protein Change	Proportion of Pathogenic Variants in Gene [1]	Carrier Frequency	Reference Sequences	References [2]
GBA1 (*GBA*)	Gaucher disease	AR	c.1226A>G	p.Asn409Ser	88%	1/15	NM_001005741.3 NP_001005741.1	Scott et al [2010], Lazarin et al [2013], Zlotogora et al [2018]
GBE1	Glycogen storage disease type IV	AR	c.986A>C	p.Tyr329Ser	95%	1/68	NM_000158.4 NP_000149.4	Hussain et al [2012], Zlotogora et al [2018]
GJB2	*GJB2*-related autosomal recessive nonsyndromic hearing loss	AR	c.167delT	p.Leu56ArgfsTer26	58%	1/31	NM_004004.6 NP_003995.2	Zlotogora et al [2018]
			c.109G>A	p.Val37Ile	28%	1/63		
			c.35delG	p.Gly12ValfsTer2	13%	1/133		
GMPPB	Muscular dystrophy & epilepsy (See Congenital Myasthenic Syndromes Overview.)	AR	c.860G>A	p.Arg287Gln	<100% [4]	1/112	NM_013334.4 NP_037466.3	
GREM1	Colorectal cancer (OMIM 601228)	AD	40-kb dup incl *GREM1* upstream region & *SCG5* exons 2-5 [5]	--	~100% [3]	NA	NG_033791.1	Jaeger et al [2012]
HEXA	Tay-Sachs disease	AR	c.1274_1277dupTATC	p.Tyr427IlefsTer5	80%-81%	1/27	NM_000520.6 NP_000511.2	Kaback et al [1993], Scott et al [2010], Lazarin et al [2013], Zlotogora et al [2018]
			c.1421+1G>C	--	9%-15%		NM_000520.6	
HIKESHI	Leukodystrophy, early-onset spastic paraparesis, acquired microcephaly (OMIM 616881)	AR	c.160G>C	p.Val54Leu	~100% [3]	1/189 to 1/200	NM_016401.4 NP_057485.2	Edvardson et al [2016], Zlotogora et al [2018]
HOGA1	Primary hyperoxaluria type 3	AR	c.944_946delAGG	p.Glu315del	66%	Unknown	NM_138413.4 NP_612422.2	Belostotsky et al [2010], Zlotogora et al [2018]
			c.107C>T	p.Ala36Val	22%			

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Gene	Disorder	MOI	DNA Nucleotide Change	Predicted Protein Change	Proportion of Pathogenic Variants in Gene [1]	Carrier Frequency	Reference Sequences	References [2]
IDH3A	Retinitis pigmentosa & pseudocoloboma (OMIM 619007)	AR	c.938T>C	p.Met313Thr	~100% [3]	1/103	NM_005530.3 NP_005521.1	Zlotogora et al [2018]
KIFBP	Goldberg-Shprintzen syndrome (OMIM 609460)	AR	c.1516dupA	p.Ile506AsnfsTer3	~100% [3]	1/196	NM_015634.4 NP_056449.1	
LCA5	Leber congenital amaurosis	AR	c.835C>T	p.Gln279Ter	~100% [3]	1/100 to 1/222	NM_181714.4 NP_859065.2	
LDLR	Familial hypercholesterolemia	AD	c.655_657delGGC	p.Gly219del	35%-100%	NA	NM_000527.5 NP_000518.1	Durst et al [2001]
LOXHD1	Nonsyndromic hearing loss (See Hereditary Hearing Loss and Deafness Overview.)	AR	c.4714C>T	p.Arg1572Ter	~100% [3]	1/167 to 1/180	NM_144612.7 NP_653213.6	Edvardson et al [2011], Zlotogora et al [2018]
MAK	Retinitis pigmentosa, nonsyndromic	AR	c.1297_1298ins353 [5] (c.1297ins(Alu))	--	99%	1/90	NG_030040.1	Kimchi et al [2018]
MCOLN1	Mucolipidosis IV	AR	c.406-2A>G	--	78%	1/89 to 1/133	NM_020533.3	Bach et al [2005], Scott et al [2010], Lazarin et al [2013]
			c.-1015_789del6434 [5] (g.511_6943del; exon 1-7 del)	--	22%			
MECR	*MECR*-related neurologic disorder	AR	c.830+2_830+3insT	p.Glu303del	69%	1/97	NM_016011.4 NP_057095.4	Zlotogora et al [2018]
			c.695G>A	p.Gly232Glu	31%			
MEFV	Familial Mediterranean fever	AR	c.442G>C	p.Glu148Gln	47%-59%	1/5	NM_000243.3 NP_000234.1	Aksentijevich et al [1999], Zlotogora et al [2018]
			c.1105C>T	p.Pro369Ser	20%			
			c.2177T>C	p.Val726Ala	18%-41%			
			c.2084A>G	p.Lys695Arg	12%			
MPL	Congenital amegakaryocytic thrombocytopenia (OMIM 604498)	AR	c.79+2T>A	--	95%	1/57 to 1/62	NM_005373.3	Shi et al [2017], Zlotogora et al [2018]

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Gene	Disorder	MOI	DNA Nucleotide Change	Predicted Protein Change	Proportion of Pathogenic Variants in Gene [1]	Carrier Frequency	Reference Sequences	References [2]
MSH2	Lynch syndrome	AD	c.1906G>C	p.Ala636Pro	74%	NA	NM_000251.3 NP_000242.1	Goldberg et al [2014]
MSH6			c.3984_3987dupGTCA	p.Leu1330ValfsTer12	66%		NM_000179.3 NP_000170.1	
			c.3959_3962delCAAG	p.Ala1320GlufsTer6	33%			
MTTP	Abetalipoproteinemia	AR	c.2593G>T	p.Gly865Ter	95%	1/131 to 1/185	NM_000253.4 NP_000244.2	Benayoun et al [2007], Shi et al [2017], Zlotogora et al [2018]
			c.2212delT	p.Ser738fs				
NEB	Nemaline myopathy 2 (OMIM 256030)	AR	c.7431+1919_7536+374del2502 [5] (2.5-kb del of exon 55)	p.Arg2478_Asp2512 del	>95%	1/168	NM_001271208.2 NP_001258137.2	Scott et al [2010], Zlotogora et al [2018]
			c.9619-2A>G	--			NM_001271208.2	
NR2E3	Enhanced S-cone syndrome (OMIM 268100)	AR	c.932G>A	p.Arg311Gln	~80%	Unknown	NM_014249.4 NP_055064.1	Zlotogora et al [2018]
OTOF	Deafness	AR	c.5332G>T	p.Val1778Phe	~100% [3]	1/78 to 1/106	NM_194248.3 NP_919224.1	
OPTN	Amyotrophic lateral sclerosis	AD AR	c.381_382insAG	p.Asp128ArgfsTer22	~100% [3]	1/100	NM_021980.4 NP_068815.2	Goldstein et al [2016], Zlotogora et al [2018]
PAH	Phenylalanine hydroxylase deficiency	AR	c.898G>T	p.Ala300Ser	24%	1/18	NM_000277.3 NP_000268.1	Zlotogora et al [2018]
			c.506G>A	p.Arg169His	24%			
			c.1208C>T	p.Ala403Val	18%			
PCDH15	Usher syndrome type 1	AR	c.733C>T	p.Arg245Ter	66%	1/147	NM_033056.4 NP_149045.3	Scott et al [2010], Zlotogora et al [2018]
			c.5557A>C	p.Met1855Leu	34%			
PEX2	Zellweger spectrum disorder	AR	c.355C>T	p.Arg119Ter	~100% [3]	1/196 to 1/227	NM_000318.3 NP_000309.2	Zlotogora et al [2018]

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Gene	Disorder	MOI	DNA Nucleotide Change	Predicted Protein Change	Proportion of Pathogenic Variants in Gene [1]	Carrier Frequency	Reference Sequences	References [2]
PKHD1	Polycystic kidney disease, autosomal recessive	AR	c.3761_3762delCCinsG	p.Ala1254GlyfsTer49	90%	1/105	NM_138694.4 NP_619639.3	Shi et al [2017]
			c.107C>T	p.Thr36Met				
PMM2	PMM2-CDG	AR	c.422G>A	p.Arg141His	90%	1/61	NM_000303.3 NP_000294.1	
RTEL1	Dyskeratosis congenita	AR	c.3791G>A [6]	p.Arg1264His	78%	1/165	NM_001283009.2 NP_001269938.1	Zlotogora et al [2018]
RTEL1			c.1548G>T	p.Met516Ile	22%		NM_032957.5 NP_116575.3	
SACS	ARSACS	AR	c.7140T>A	p.Asn2380Lys	<100% [4]	1/141	NM_014363.6 NP_055178.3	
SAMHD1	Aicardi-Goutières syndrome	AR	8984-bp del of exon 1 [5]	--	75%	1/138	NG_017059.1	Crow et al [2015], Straussberg et al [2015]
SLC1A4	Spastic tetraplegia, thin corpus callosum, & progressive microcephaly (OMIM 616657)	AR	c.766G>A	p.Glu256Lys	~100% [3]	1/108	NM_003038.5 NP_003029.2	Zlotogora et al [2018]
SLC3A1	Cystinuria (OMIM 220100)	AR	c.808C>T	p.Arg270Ter	~100% [3]	1/61	NM_000341.4 NP_000332.2	
SLC26A4	Pendred syndrome	AR	c.349C>T	p.Leu117Phe	~100% [3]	1/98	NM_000441.2 NP_000432.1	
SLC38A8	Foveal hypoplasia (OMIM 609218)	AR	c.848A>C	p.Asp283Ala	~100% [3]	1/81	NM_001080442.3 NP_001073911.1	
SMARCAL1	Schimke immunoosseous dysplasia	AR	c.863-2A>G	--	~100% [3]	1/189	NM_014140.4	

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Gene	Disorder	MOI	DNA Nucleotide Change	Predicted Protein Change	Proportion of Pathogenic Variants in Gene [1]	Carrier Frequency	Reference Sequences	References [2]
SMPD1	Acid sphingomyelinase deficiency	AR	c.1493G>T	p.Arg498Leu	54%-55%	1/95 to 1/116	NM_000543.5 NP_000534.3	Scott et al [2010], Lazarin et al [2013], Zlotogora et al [2018]
			c.996delC	p.Phe333SerfsTer52	29%			
SPATA16	Spermatogenic failure (OMIM 102530)	AR	c.848G>A	p.Arg283Gly	~100% [3]	1/196	NM_031955.6 NP_114161.3	Zlotogora et al [2018]
STRC	Deafness	AR	c.4171C>G	p.Arg1391Gly	~100% [3]	1/200	NM_153700.2 NP_714544.1	
TECPR2	Hereditary sensory & autonomic neuropathy w/intellectual disability	AR	c.1319delT	p.Leu440ArgfsTer19	<100% [4]	1/154	NM_014844.5 NP_055659.2	Zlotogora et al [2018], Neuser et al [2021]
THG1L	Spinocerebellar ataxia type 28 (OMIM 618800)	AR	c.164T>C	p.Val55Ala	~100% [3]	1/110 to 1/130	NM_017872.5 NP_060342.2	Zlotogora et al [2018]
TKT	Short stature, developmental delay, & congenital heart defects (OMIM 606781)	AR	c.769_770insCTACCTCCTTATCTT	p.Trp257delinsSerThrSerLeuSerSerGly	~100% [3]	1/169 to 1/625	NM_001135055.3 NP_001128527.1	
TMEM216	Joubert syndrome	AR	c.218G>T	p.Arg73Leu	~100% [3]	1/92 to 1/143	NM_001173990.3 NP_001167461.1	Edvardson et al [2010], Valente et al [2010], Zlotogora et al [2018]

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Gene	Disorder	MOI	DNA Nucleotide Change	Predicted Protein Change	Proportion of Pathogenic Variants in Gene [1]	Carrier Frequency	Reference Sequences	References [2]
TSPEAR	Ectodermal dysplasia (OMIM 618180)	AR	c.1915G>A	p.Asp639Asn	98%	1/93	NM_144991.3 NP_659428.2	Zlotogora et al [2018]
VPS11	Hypomyelination & developmental delay (OMIM 616683)	AR	c. 2536T>G	p.Cys846Gly	~100% [3]	1/159 to 1/204	NM_021729.6 NP_068375.3	

Included if ≤3 pathogenic variants account for ≥50% of variants identified in a specific ethnic group
AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; NA = not applicable
1. This percentage does not account for the possibility of rare *de novo* pathogenic variants occurring in this population.
2. See also www.jewishgeneticdiseases.org.
3. To date, additional pathogenic variants in this gene have not been reported in individuals of Ashkenazi Jewish descent.
4. At least one additional variant reported in this population in ≥1 family
5. Does not conform to standard HGVS nomenclature
6. RTEL1 variant c.3791G>A affects transcript variant rtel1at, an isoform of *RTEL1*.

Revision History

- 20 October 2022 (sw) Revision: edited based on information in Zlotogora et al [2018]
- 13 December 2018 (sw) Initial posting

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