Supplementary Online Content

Runhart EH, Khan M, Cornelis SS, et al; *ABCA4* Disease Consortium Study Group. Association of sex with frequent and mild *ABCA4* alleles in Stargardt disease. *JAMA Ophthalmology*. Published online August 20, 2020. doi: 10.1001/jamaophthalmol.2020.2990

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. The Allele Frequencies of Mild and Severe *ABCA4* Variants in the General Non-Finnish European Population

Genomic position	rs ID	cDNA notation	Protein notation	AC gnomAD nFE	AF gnomAD nFE
Selected mild variants[1]					
94473807	rs1800553	c.5882G>A	p.(Gly1961Glu)	488	0.0037783
94476351	rs61751407	c.5714+5G>A	p.[=,Ile1377Hisfs*3]	71	0.0005501
94471055	rs61750641	c.6089G>A	p.(Arg2030Gln)	80	0.0006196
94508969	rs61751374	c.3113C>T	p.(Ala1038Val)	297	0.0023018
94517254	rs76157638	c.2588G>C	p.[Gly863Ala,Gly863del]	1012	0.0078403
Protein truncating variants					
94586601	rs201738997	c.1A>G	p.(Met1?)	0	0.0000000
94586557	rs62645957	c.45G>A	p.(Trp15*)	1	0.0000088
94586541	rs770272033	c.61C>T	p.(Gln21*)	1	0.0000088
94586536	rs775770837	c.65delA	p.(Lys22Argfs*18)	0	0.0000000
94578624	rs398123339	c.67-2A>G	p.?	1	0.0000088
94578623	rs778908435	c.67-1G>A	p.?	0	0.0000000
94578596	rs1191816747	c.93G>A	p.(Trp31*)	0	0.0000000
94578567	rs61751410	c.122G>A	p.(Trp41*)	1	0.0000088
94578566	rs748357067	c.123G>A	p.(Trp41*)	1	0.0000088
94578532	rs764744217	c.157G>T	p.(Glu53*)	0	0.0000000
94577045	rs778817150	c.247_250dupCAAA	p.(Ser84Thrfs*16)	1	0.0000088
94577038		c.256_257delAC	p.(Thr86Profs*12)	1	0.0000088
94576993	rs61751413	c.302+1G>A	p.?	0	0.0000000
94574256	rs765429911	c.319C>T	p.(Arg107*)	8	0.0000619
94574242	rs749252902	c.331_332delGA	p.(Glu111Thrfs*49)	1	0.0000088
94574209	rs1275663715	c.365_366insCA	p.(Gly123Metfs*32)	1	0.0000088
94574203	rs745550261	c.353_371dupAGAGCCAGCACCTTGGCCG	p.(Ile125Glufs*42)	1	0.0000088
94574132	rs754112731	c.442+1G>A	p.?	0	0.0000000
94568699	rs755916591	c.443-2dupA	p.?	0	0.0000000
94568699	rs755916591	c.443-5_443-2delTGTA	p.?	0	0.0000000
94568687	rs62646861	c.454C>T	p.(Arg152*)	4	0.0000352
94568649	rs747950242	c.488_491delTGAC	p.(Leu163Hisfs*18)	1	0.0000088
94564549	rs61748534	c.571-2A>T	p.?	1	0.0000091
94564463	rs757557272	c.655A>T	p.(Arg219*)	0	0.0000000

Genomic position	rs ID	cDNA notation	Protein notation	AC gnomAD nFE	AF gnomAD nFE
94564439	rs63749081	c.666_678delAAAGACGGTGCGC	p.(Lys223Metfs*14)	0	0.0000000
94564428	rs763596438	c.690C>A	p.(Cys230*)	0	0.0000000
94564402	rs755733328	c.716G>A	p.(Trp239*)	1	0.0000088
94548999	rs754536977	c.769-2A>G	p.?	0	0.0000000
94548926	rs757774731	c.838_839delAT	p.(Met280Valfs*41)	0	0.0000000
94548907	rs750954445	c.858+1G>T	p.?	0	0.0000000
94546276	rs769352013	c.859-2A>G	p.?	0	0.0000000
94546247	rs747346334	c.885delC	p.(Leu296Cysfs*4)	4	0.0000354
94546182	rs761093501	c.950delG	p.(Gly317Alafs*57)	1	0.0000088
94546151	rs61751418	c.982G>T	p.(Glu328*)	1	0.0000088
94546094	rs764915204	c.1025_1038delACAATAACTATAAG	p.(Asp342Glyfs*6)	0	0.0000000
94544906	rs150686179	c.1211C>G	p.(Ser404*)	1	0.0000088
94544895	rs61748550	c.1222C>T	p.(Arg408*)	3	0.0000232
94544877	rs765707028	c.1239+1G>C	p.?	1	0.0000077
94544199	rs948132728	c.1302delA	p.(Gln437Argfs*12)	1	0.0000088
94544185	rs61752391	c.1317G>A	p.(Trp439*)	3	0.0000264
94543380	rs780874319	c.1419delT	p.(Thr474Leufs*6)	0	0.0000000
94543244	rs763808930	c.1554+2T>C	p.?	1	0.0000089
94528866	rs1279522242	c.1561delG	p.(Val521Serfs*47)	0	0.0000000
94528787	rs1043103980	c.1640delT	p.(Phe547Serfs*21)	1	0.0000088
94528731	rs943713680	c.1696delC	p.(His566Thrfs*2)	0	0.0000000
94528311	rs754765164	c.1761-2A>G	p.?	1	0.0000089
94528240	rs771051333	c.1830T>A	p.(Tyr610*)	1	0.0000088
94528164	rs145961131	c.1906C>T	p.(Gln636*)	5	0.0000441
94528147	rs1256814849	c.1922dupG	p.(Cys641Trpfs*125)	0	0.0000000
94528132	rs61752401	c.1937+1G>A	p.?	0	0.0000000
94526316	rs61751263	c.1938-1G>A	p.?	0	0.0000000
94526258	rs757302286	c.1995C>A	p.(Tyr665*)	0	0.0000000
94526212	rs61749423	c.2041C>T	p.(Arg681*)	1	0.0000088
94526154	rs61749425	c.2099G>A	p.(Trp700*)	1	0.0000088
94526092	rs61749427	c.2160+1G>C	p.?	1	0.0000088
94522379	rs1401924846	c.2161-1G>A	p.?	0	0.0000000
94564463	rs757557272	c.655A>T	p.(Arg219*)	0	0.0000000
94564439	rs63749081	c.666_678delAAAGACGGTGCGC	p.(Lys223Metfs*14)	0	0.0000000

Genomic position	rs ID	cDNA notation	Protein notation	AC gnomAD nFE	AF gnomAD nFE
94564428	rs763596438	c.690C>A	p.(Cys230*)	0	0.0000000
94564402	rs755733328	c.716G>A	p.(Trp239*)	1	0.0000088
94548999	rs754536977	c.769-2A>G	p.?	0	0.0000000
94548926	rs757774731	c.838_839delAT	p.(Met280Valfs*41)	0	0.0000000
94548907	rs750954445	c.858+1G>T	p.?	0	0.0000000
94546276	rs769352013	c.859-2A>G	p.?	0	0.0000000
94546247	rs747346334	c.885delC	p.(Leu296Cysfs*4)	4	0.0000354
94546182	rs761093501	c.950delG	p.(Gly317Alafs*57)	1	0.0000088
94546151	rs61751418	c.982G>T	p.(Glu328*)	1	0.0000088
94546094	rs764915204	c.1025_1038delACAATAACTATAAG	p.(Asp342Glyfs*6)	0	0.0000000
94544906	rs150686179	c.1211C>G	p.(Ser404*)	1	0.0000088
94544895	rs61748550	c.1222C>T	p.(Arg408*)	3	0.0000232
94544877	rs765707028	c.1239+1G>C	p.?	1	0.0000077
94544199	rs948132728	c.1302delA	p.(Gln437Argfs*12)	1	0.0000088
94544185	rs61752391	c.1317G>A	p.(Trp439*)	3	0.0000264
94543380	rs780874319	c.1419delT	p.(Thr474Leufs*6)	0	0.0000000
94543244	rs763808930	c.1554+2T>C	p.?	1	0.0000089
94528866	rs1279522242	c.1561delG	p.(Val521Serfs*47)	0	0.0000000
94528787	rs1043103980	c.1640delT	p.(Phe547Serfs*21)	1	0.0000088
94528731	rs943713680	c.1696delC	p.(His566Thrfs*2)	0	0.0000000
94528311	rs754765164	c.1761-2A>G	p.?	1	0.0000089
94528240	rs771051333	c.1830T>A	p.(Tyr610*)	1	0.0000088
94528164	rs145961131	c.1906C>T	p.(Gln636*)	5	0.0000441
94528147	rs1256814849	c.1922dupG	p.(Cys641Trpfs*125)	0	0.0000000
94528132	rs61752401	c.1937+1G>A	p.?	0	0.0000000
94526316	rs61751263	c.1938-1G>A	p.?	0	0.0000000
94526258	rs757302286	c.1995C>A	p.(Tyr665*)	0	0.0000000
94526212	rs61749423	c.2041C>T	p.(Arg681*)	1	0.0000088
94526154	rs61749425	c.2099G>A	p.(Trp700*)	1	0.0000088
94526092	rs61749427	c.2160+1G>C	p.?	1	0.0000088
94522379	rs1401924846	c.2161-1G>A	p.?	0	0.0000000
94520873	rs777634165	c.2383-2A>G	p.?	1	0.0000089
94520733	rs143100856	c.2521C>T	p.(Gln841*)	1	0.0000088
94520690	rs61752406	c.2564G>A	p.(Trp855*)	4	0.0000352

Genomic position	rs ID	cDNA notation	Protein notation	AC gnomAD nFE	AF gnomAD nFE
94520666	rs61749439	c.2587+1G>A	p.?	0	0.0000000
94517238	rs751791095	c.2603delC	p.(Pro868Hisfs*33)	0	0.0000000
94517188	rs1212420029	c.2653+1G>T	p.?	2	0.0000176
94517187	rs762823337	c.2653+2T>C	p.?	1	0.0000088
94517186	rs766646086	c.2653+2delT	p.?	0	0.0000000
94512528	rs773330082	c.2864delA	p.(Glu955Glyfs*22)	1	0.0000088
94512504	rs61752410	c.2888delG	p.(Gly963Alafs*14)	0	0.0000000
94512501	rs761689153	c.2891delA	p.(His964Profs*13)	0	0.0000000
94511452	rs1180769486	c.2765delC	p.(His922Leufs*10)	1	0.0000210
94511450		c.2768G>A	p.(Trp923*)	0	0.0000000
94511397	rs1373701354	c.2814_2820delCCCACGT	p.(Glu939Valfs*9)	0	0.0000000
94511391	rs1436534085	c.2825_2826delCA	p.(Gly942Alafs*53)	0	0.0000000
94511353	rs1474617872	c.2864delC	p.(Glu955Glyfs*22)	0	0.0000000
94511313	rs1032359778	c.2905A>T	p.(Lys969*)	0	0.0000000
94508456	rs61752415	c.3191-2A>G	p.?	1	0.0000088
94508455	rs767854160	c.3191-1G>T	p.?	2	0.0000176
94508433	rs61750065	c.3210_3211dupGT	p.(Ser1071Cysfs*14)	4	0.0000352
94506960	rs1324958803	c.3329-2A>T	p.?	2	0.0000176
94506959	rs544428779	c.3329-1G>A	p.?	1	0.0000088
94506884	rs1057517701	c.3403C>T	p.(Gln1135*)	1	0.0000650
94506785	rs1472949364	c.3501delG	p.(Ser1168Alafs*28)	0	0.0000000
94506764	rs1265840106	c.3522+1G>T	p.?	0	0.0000000
94505685	rs1168144507	c.3523-2A>G	p.?	0	0.0000000
94505684	rs766239144	c.3523-1G>A	p.?	4	0.0000331
94502847	rs755283743	c.3665_3666delTG	p.(Val1222Glyfs*14)	0	0.0000000
94502832	rs751987031	c.3681dupA	p.(Glu1228Argfs*9)	0	0.0000000
94502760	rs61752423	c.3754G>T	p.(Glu1252*)	0	0.0000000
94497601	rs769687104	c.3863-2A>G	p.?	0	0.0000000
94497591	rs746541266	c.3871C>T	p.(Gln1291*)	1	0.0000090
94497588	rs61752426	c.3874C>T	p.(Gln1292*)	2	0.0000158
94497564	rs61752427	c.3898C>T	p.(Arg1300*)	0	0.0000000
94497427	rs760519654	c.4033_4034dupAA	p.(Asn1345Lysfs*45)	0	0.0000000
94497417	rs1184956177	c.4044dupA	p.(Gln1349Thrfs*73)	0	0.0000000
94496665	rs139109485	c.4139delC	p.(Pro1380Argfs*9)	0	0.0000000

Genomic position	rs ID	cDNA notation	Protein notation	AC gnomAD nFE	AF gnomAD nFE
94496610	rs62642573	c.4195G>T	p.(Glu1399*)	0	0.0000000
94496571	rs61750137	c.4234C>T	p.(Gln1412*)	2	0.0000155
94496045	rs745544039	c.4290delT	p.(Ala1431Glnfs*5)	0	0.0000000
94496027	rs1283350532	c.4309A>T	p.(Lys1437*)	0	0.0000000
94495983	rs200967229	c.4352+1G>A	p.?	2	0.0000176
94495143	rs1341069538	c.4383_4396delGAAGACTCCTTCTG	p.(Trp1461Cysfs*89)	0	0.0000000
94495097	rs1311903227	c.4442dupA	p.(Val1482Glyfs*73)	0	0.0000000
94495034	rs61750149	c.4506C>A	p.(Cys1502*)	1	0.0000123
94495003	rs281865377	c.4537del	p.(Gln1513Argfs*13)	0	0.0000000
94495001		c.4538_4539insC	p.(Gln1513Hisfs*42)	0	0.0000000
94490606	rs61752435	c.4540-2A>G	p.?	1	0.0000088
94490605	rs754703493	c.4540-1G>C	p.?	0	0.0000000
94490530	rs754897752	c.4614T>A	p.(Tyr1538*)	1	0.0000088
94490509	rs767312869	c.4634+1G>A	p.?	0	0.0000000
94488972	rs1131691612	c.4637T>A	p.(Leu1546*)	1	0.0000089
94488941	rs751319688	c.4667+1G>A	p.?	1	0.0000089
94488940	rs61752436	c.4667+2T>C	p.?	1	0.0000089
94487508	rs1439783011	c.4668-1G>T	p.?	1	0.0000648
94487456	rs1340989734	c.4715_4718dupCGGG	p.(Glu1574Glyfs*24)	0	0.0000000
94487455	rs1282472315	c.4720G>T	p.(Glu1574*)	0	0.0000000
94487454		c.4720delG	p.(Glu1574Lysfs*7)	0	0.0000000
94487442	rs758862120	c.4731_4732delTG	p.(Gly1578Valfs*18)	0	0.0000000
94487401	rs61751376	c.4773+1G>A	p.?	0	0.0000000
94486966	rs61750156	c.4849-1G>A	p.?	4	0.0000353
94486960	rs61752439	c.4854G>A	p.(Trp1618*)	0	0.0000000
94486933	rs763911476	c.4880delT	p.(Leu1627Argfs*35)	1	0.0000088
94486886	rs760706416	c.4924_4927delAGCC	p.(Ser1642Cysfs*19)	0	0.0000000
94486818	rs773880325	c.4996G>T	p.(Glu1666*)	2	0.0000176
94485171	rs144619288	c.5161_5162delAC	p.(Thr1721Hisfs*65)	2	0.0000181
94485164	rs867654589	c.5169delC	p.(Trp1724Glyfs*2)	0	0.0000000
94485158	rs1057518955	c.5175dupG	p.(Thr1726Aspfs*61)	1	0.0000091
94485145	rs886044747	c.5189G>A	p.(Trp1730*)	1	0.0000094
94485137	rs61751377	c.5196+1G>A	p.?	2	0.0000193
94481294	rs886044750	c.5312+1G>A	p.?	1	0.0000649

Genomic position	rs ID	cDNA notation	Protein notation	AC gnomAD nFE	AF gnomAD nFE
94481293	rs1307108997	c.5312+2T>G	p.?	1	0.0000088
94480248	rs759513613	c.5313-2A>G	p.?	1	0.0000088
94480244	rs776757706	c.5315G>A	p.(Trp1772*)	1	0.0000088
94480243	rs61750571	c.5316G>A	p.(Trp1772*)	1	0.0000088
94480222	rs61750573	c.5337C>A	p.(Tyr1779*)	1	0.0000088
94480098	rs61753030	c.5460+1G>C	p.?	1	0.0000088
94480098	rs61753030	c.5460+1G>T	p.?	0	0.0000000
94476817	rs773876335	c.5584+1G>A	p.?	1	0.0000088
94476454	rs748184137	c.5616G>A	p.(Trp1872*)	1	0.0000088
94476355	rs1232476760	c.5714+1G>A	p.?	0	0.0000000
94474362	rs1305924893	c.5778_5779delAA	p.(Arg1927Asnfs*7)	0	0.0000000
94474306	rs1475966997	c.5835+1G>T	p.?	0	0.0000000
94473854	rs61750637	c.5836-2delA	p.?	1	0.0000088
94473286	rs886044756	c.5899-53_5908delATTTTAGACCTTCTTGATCTCTAGGGCCAGGCTAGCTCTGTGTTTTCTCCTAGTGCTTTGGCC	p.?	0	0.0000000
94473277	rs61751389	c.5917delG	p.(Val1973*)	2	0.0000177
94473259	rs61753037	c.5935delA	p.(Thr1979Glnfs*13)	0	0.0000000
94471056	rs61751383	c.6088C>T	p.(Arg2030*)	2	0.0000176
94471036	rs779751119	c.6108T>A	p.(Tyr2036*)	0	0.0000000
94471026	rs61753038	c.6118C>T	p.(Arg2040*)	1	0.0000077
94467550	rs1162214541	c.6148-2A>G	p.?	1	0.0000088
94467413	rs770453727	c.6282+1G>C	p.?	2	0.0000176
94466649	rs1176862742	c.6283-6_6294delCCCCAGGATGAGCCCACC	p.?	1	0.0000088
94466630	rs779353744	c.6313delG	p.(Ala2105Hisfs*10)	1	0.0000088
94466557	rs745654673	c.6386+1G>A	p.?	0	0.0000000
94466556	rs61753043	c.6386+2C>G	p.?	1	0.0000088
94466426	rs61750654	c.6445C>T	p.(Arg2149*)	3	0.0000264
94463532	rs1193437578	c.6606_6613delCTACAACA	p.(Tyr2203Alafs*45)	0	0.0000000
94463488	rs61753046	c.6658C>T	p.(Gln2220*)	0	0.0000000
94463476	rs1425217062	c.6639_6669dupCTCCCTGGCGAGGATCTTCCAGCTCCTCCTC	p.(Ser2224Leufs*37)	1	0.0000088
94461694	rs998363634	c.6787C>T	p.(Arg2263*)	2	0.0001296
94461676	rs372234578	c.6805C>T	p.(Arg2269*)	2	0.0000176

Genomic position	rs ID	cDNA notation	Protein notation	AC gnomAD nFE	AF gnomAD nFE
94461664	rs773599043	c.6816+1G>A	p.?	0	0.0000000
94461664	rs773599043	c.6816+1G>T	p.?	0	0.0000000
94458799	rs775865861	c.6817-1G>A	p.?	1	0.0000088
Total truncating variants				*135*	*0.0014685*
Non-canonical splice site variants with <25% normal RNA[2-6]					
94577135	rs150774447	c.161G>T	p.[Cys54Serfs*14,Cys54Tyr]	0	0.0000000
94576990		c.302+4A>C	p.(Cys54Serfs*14)	0	0.0000000
94574275		c.303-3C>G	p.[Cys54*,Leu102Alafs*14]	0	0.0000000
94564350	rs62645944	c.768G>T	p.(Leu257Valfs*17)	24	0.0001858
94545023	rs780127258	c.1100-6T>A	p.(Thr367Serfs*6)	1	0.0000088
94528128		c.1937+5G>A	p.(Tyr603_Ser646del)	0	0.0000000
94528120		c.1937+13T>G	p.[Phe647*,=]	0	0.0000000
94522386		c.2161-8G>A	p.(His721_Val794del)	0	0.0000000
94514521	rs765263670	c.2654-8T>G	p.[Gly863Valfs*47,=]	0	0.0000080
94510164	rs61751262	c.3050+5G>A	p.(Leu973_His1017delinsPhe)	0	0.0000000
94508465		c.3191-11T>A	p.(Gly1064delinsValProProGly)	0	0.0000000
94505599	rs1064793011	c.3607G>A	p.(Thr1176Metfs*2)	0	0.0000000
94505596		c.3607+3A>T	p.(Thr1176Metfs*2)	0	0.0000000
94502702		c.3812A>G	p.(Gly1203Aspfs*10)	0	0.0000000
94502701		c.3813G>C	p.(Gly1203Aspfs*10)	0	0.0000000
94497334	rs1064797113	c.4128G>A	p.(Gln1376_Ile1377ins4)	0	0.0000000
94497334	rs1064797113	c.4128G>C	p.(Gln1376_Ile1377insValLeuLeuSer)	0	0.0000000
94496679		c.4129-3C>T	p.[=,Ile1377Hisfs*3,Gly1288Aspfs*45]	0	0.0000000
94496548	rs61754044	c.4253+4C>T	p.(Ile1377Hisfs*3)	2	0.0000176
94496547	rs61750138	c.4253+5G>A	p.(Ile1377Hisfs*3)	1	0.0000088
94496547		c.4253+5G>T	p.[Ile1377Hisfs*3,=]	0	0.0000000
94495002		c.4538A>C	p.[Pro1513_Arg1514ins10,Cys1490Glufs*12, Gln1513Pro]	0	0.0000000
94495002	rs281865402	c.4538A>G	p.[Arg1513_Arg1514ins10,Cys1490Glufs*12]	0	0.0000000
94495001		c.4539G>A	p.[Cys1490Glufs*12,=]	0	0.0000000
94490612		c.4540-8T>A	p.(Gln1513insProGln)	0	0.0000000
94488942	rs1385119665	c.4667G>C	p.(Ser1545_Gln1555del)	0	0.0000000
94488942		c.4667G>A	p.(Ser1545_Gln1555del)	0	0.0000000

Genomic position	rs ID	cDNA notation	Protein notation	AC gnomAD nFE	AF gnomAD nFE
94487402		c.4773G>C	p.[Tyr1557_Val1673del,Tyr1557Alafs*18]	0	0.0000000
94487399	rs759672616	c.4773+3A>G	p.[Tyr1557Alafs*18,=]	18	0.0001394
94487397		c.4773+5G>A	p.[Tyr1557Alafs*18,=,Tyr1557_Val1673del]	0	0.0000000
94487193		c.4848+3A>G	p. [Gly1592_Lys1616del,=]	0	0.0000000
94486791		c.5018+5G>A	p.(Val1617Alafs*113)	0	0.0000000
94485131	rs61753023	c.5196+3_5196+6delAAGT	p.(Val1617_Ile1732del)	1	0.0000099
94481292		c.5312+3A>T	p.(Asn1734Glyfs*14)	0	0.0000000
94480249		c.5313-3C>G	p.(Trp1772Aspfs*7)	0	0.0000000
94480094		c.5460+5G>A	p.(Trp1772Argfs*9)	0	0.0000000
94476951	rs1800728	c.5461-10T>C	p.[Thr1821Aspfs*6,Thr1821Valfs*13]	58	0.0004509
94476949		c.5461-8T>G	p.(Thr1821Aspfs*6)	0	0.0000000
94476947		c.5461-6T>G	p.(Thr1821Aspfs*6)	0	0.0000000
94476813	rs61750576	c.5584+5G>A	p.[Thr1821Aspfs*6,Thr1821Valfs*13]	0	0.0000000
94476812	rs61750633	c.5584+6T>C	p.[Thr1821Aspfs*6,Thr1821Valfs*13,Glu1863Leufs*33]	0	0.0000000
94476818		c.5584G>C	p.(Thr1821Aspfs*6)	0	0.0000000
94474432		c.5715-5T>G	p.[Thr1821Serfs*34,=]	0	0.0000000
94473856	rs1064793013	c.5836-3C>A	p.(Lys1945_Ile1946Pheins10)	0	0.0000000
94473786	rs922818626	c.5898+5del	p.(Cys1967Valfs*24)	0	0.0000000
94470997		c.6147G>A	p.(Ser2002Argfs*11)	0	0.0000000
94466388		c.6479+4A>G	p.(Ser2129_Lys2160delinsArg)	0	0.0000000
94463397	rs749526785	c.6729+5_6729+19delGTTGGCCCTGGGGCA	p.(Phe2161Cysfs*3)	0	0.0000000
Total severe non-canonical splice site variants				*105*	*0.0008211*
Deep-intronic variants with <25% normal RNA[3-11]					
94566773	rs888731641	c.570+1798A>G	p.(Phe191Leufs*6)	0	0.0000000
94549785		c.769-788A>T	p.[Leu257Aspfs*3,=]	0	0.0000000
94546914		c.859-640A>G	p.(Phe287Tyrfs*69)	0	0.0000000
94546814		c.859-540C>G	p.(Phe287Tyrfs*33)	0	0.0000000
94546780		c.859-506G>C	p.[Phe287Thrfs*32,=]	0	0.0000000
94528096		c.1937+37C>G	p.(Phe647*)	0	0.0000000
94526934		c.1938-619A>G	p.[Phe647Alafs*22,Phe647Serfs*22,=]	0	0.0000000
94526829		c.1938-514A>G	p.[Phe647Serfs*155,Phe647Serfs*22,=]	0	0.0000000
94517960		c.2588-706C>T	p.[Gly863Alafs*3,=]	0	0.0000000
94511126		c.2919-826T>A	p.[Leu973Phefs*1,=]	0	0.0000000

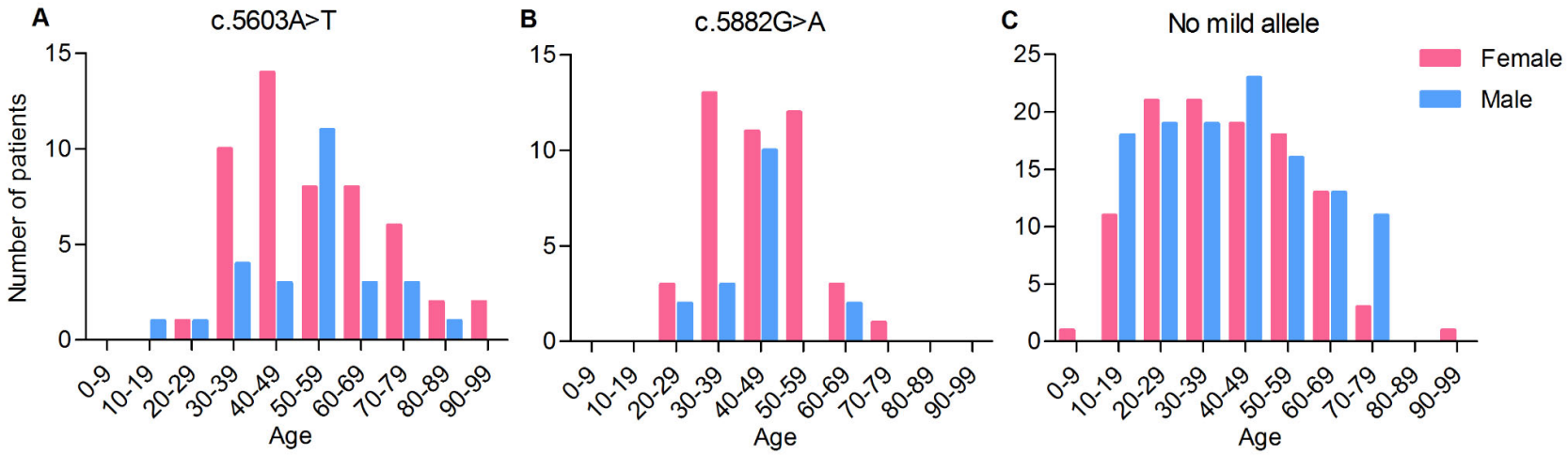
Genomic position	rs ID	cDNA notation	Protein notation	AC gnomAD nFE	AF gnomAD nFE
94509799		c.3050+370C>T	p.(Leu1018Glufs*4)	0	0.0000000
94495923		c.4352+61G>A	p.[Glu1452*,=]	0	0.0000000
94493901		c.4539+1100A>G	p.[Arg1514Valfs*31,Arg1514Glyfs*3,=]	0	0.0000000
94493895		c.4539+1106C>T	p.[Arg1514Glyfs*3,Arg1514Valfs*31,=]	0	0.0000000
94492937		c.4539+2064C>T	p.[Arg1514Leufs*36,=]	0	0.0000000
94489769		c.4634+741A>G	p.[Ser1545Serfs*51,=]	0	0.0000000
94484125	rs886044748	c.5196+1013A>G	p.(Met1733Valfs*2)	0	0.0000000
94484082	rs886044749	c.5196+1056A>G	p.[Met1733Valfs*2,=]	0	0.0000000
94481967		c.5197-557G>T	p.(Met1733*)	0	0.0000000
Total severe deep-intronic variants				*0*	*0.0000000*
Total loss-of-function variants				**240**	**0.0022896**

AC: allele count, AF: allele frequency, gnomAD: genome Aggregation Database, nFE: non-Finnish European

eTable 2. Origin of Participants

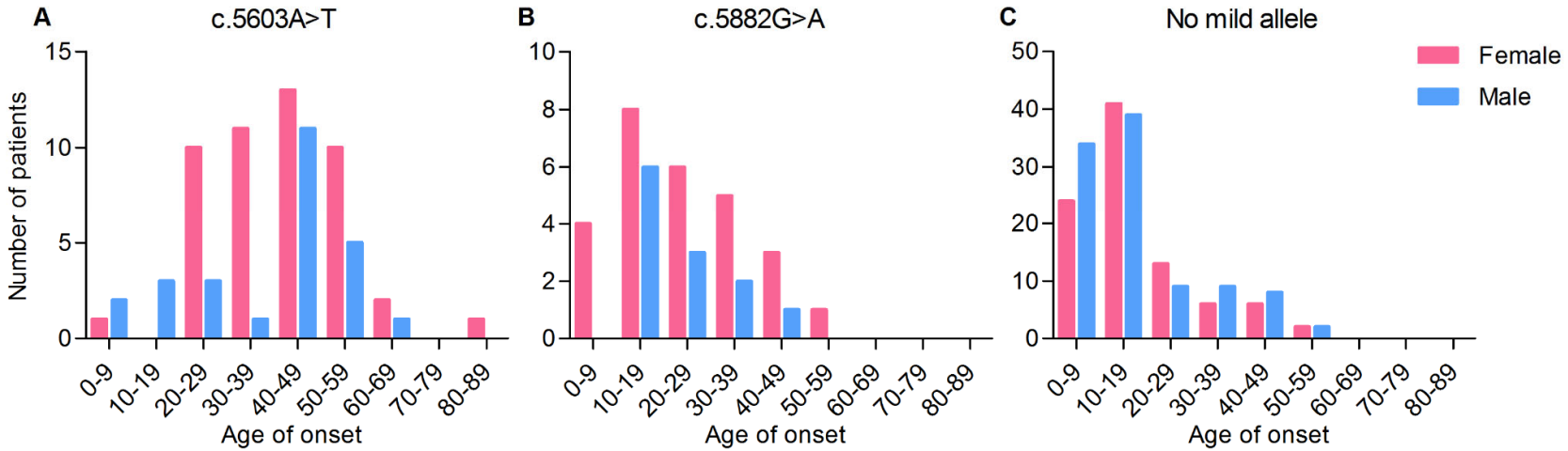
Country of residence	Number of cases	Predominant ethnicity	Non-Finnish European cases count
Argentina	8	non-Finnish European 90%	7
Australia	33	non-Finnish European 85%	28
Brazil	6	non-Finnish European 90%	5
Canada	2	non-Finnish European 100%	2
Czech Republic	42	non-Finnish European 100%	42
France	110	non-Finnish European 95%	104
Germany	62	non-Finnish European 90%	55
Greece	3	non-Finnish European 100%	3
Ireland	17	non-Finnish European 90%	15
Israel	17	Ashkenazi Jewish 100%	0
Italy	20	non-Finnish European 90%	18
Japan	5	East Asian 100%	0
Netherlands	34	non-Finnish European 100%	34
New Zealand	12	non-Finnish European 75%	9
Palestine	10	Arab 100%	0
Poland	14	non-Finnish European 100%	14
Slovenia	11	non-Finnish European 100%	11
South-Africa	94	non-Finnish European 70%	65
Spain	36	non-Finnish European 90%	32
United States	14	non-Finnish European 90%	12
	550		**456 (83%)**

eFigure 1. Age Distribution by Sex



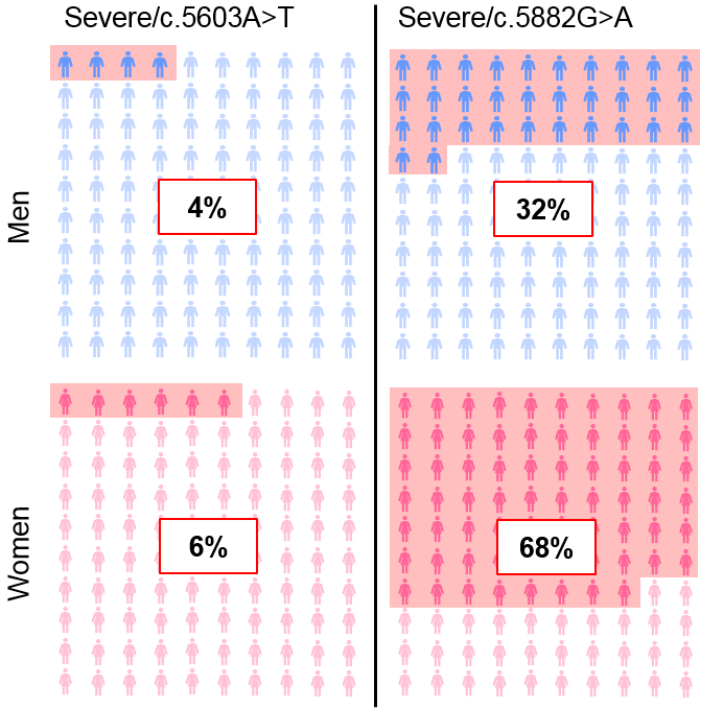
A. Among c.5603A>T cases, median age was 51 years and 53 years for women and men, respectively (Mann-Whitney U, p=.971). B. Female patients carrying c.5882G>A had a median age of 44 years and male patients of 45 years (Mann-Whitney U, p=.664). C. Women and men who did not carry a mild allele had a median age of 40 and 42 years, respectively (Mann-Whitney U, p=.633).

eFigure 2. Age of Onset Distribution by Sex



A. The distribution of age of onset among female patients carrying c.5603A>T was primarily bell-shaped, whereas its distribution among men appeared bimodal, although patient numbers were low. B. In the c.5882G>A subgroup, age at onset was slightly right-skewed. C. Among patients carrying none of the mild alleles, the distribution of age of onset was clearly right-skewed, likely due to the fact that the vast majority of these individuals carried two (moderately) severe alleles and only a minority of variants could have a mild effect.

eFigure 3. Sex-Specific Penetrance Estimates for *ABCA4* Alleles c.5603A>T and c.5882G>A



In a hypothetical population with the genotype 'severe allele and c.5603A>T' in which 10/200 (~5%) individuals have Stargardt disease (STGD1),[12,13] with a STGD1 female:male ratio of 63:37 (Table 1), ~6/100 (~6%) women and ~4/100 (~4%) men would be affected. In a population with the genotype 'severe allele and c.5882G>A', in which ~100/200 (~50%) individuals have STGD1 (Table 2), with a STGD1 female:male ratio of 68:32 (Table 1), ~68/100 (~68%) women and ~32/100 (~32%) men would be affected.

eReferences

1. Cornelis SS, Bax NM, Zernant J, et al. In silico functional meta-analysis of 5,962 ABCA4 variants in 3,928 retinal dystrophy cases. *Hum Mutat.* 2017;38(4):400-408.
2. Sangermano R, Khan M, Cornelis SS, et al. ABCA4 midigenes reveal the full splice spectrum of all reported noncanonical splice site variants in Stargardt disease. *Genome Res.* 2018;28(1):100-110.
3. Bauwens M, Garanto A, Sangermano R, et al. ABCA4-associated disease as a model for missing heritability in autosomal recessive disorders: novel noncoding splice, cis-regulatory, structural, and recurrent hypomorphic variants. *Genet Med.* 2019;21(8):1761-1771.
4. Fadaie Z, Khan M, Del Pozo-Valero M, et al. Identification of splice defects due to noncanonical splice site or deep-intronic variants in ABCA4. *Hum Mutat.* 2019;40(12):2365-2376.
5. Khan M, Cornelis SS, Pozo-Valero MD, et al. Resolving the dark matter of ABCA4 for 1054 Stargardt disease probands through integrated genomics and transcriptomics. *Genet Med.* 2020.
6. Khan M, Cornelis SS, Khan MI, et al. Cost-effective molecular inversion probe-based ABCA4 sequencing reveals deep-intronic variants in Stargardt disease. *Hum Mutat.* 2019;40(10):1749-1759.
7. Braun TA, Mullins RF, Wagner AH, et al. Non-exomic and synonymous variants in ABCA4 are an important cause of Stargardt disease. *Hum Mol Genet.* 2013;22(25):5136-5145.
8. Zernant J, Xie YA, Ayuso C, et al. Analysis of the ABCA4 genomic locus in Stargardt disease. *Hum Mol Genet.* 2014;23(25):6797-6806.
9. Schulz HL, Grassmann F, Kellner U, et al. Mutation Spectrum of the ABCA4 Gene in 335 Stargardt Disease Patients From a Multicenter German Cohort-Impact of Selected Deep Intronic Variants and Common SNPs. *Invest Ophthalmol Vis Sci.* 2017;58(1):394-403.
10. Zernant J, Lee W, Nagasaki T, et al. Extremely hypomorphic and severe deep intronic variants in the ABCA4 locus result in varying Stargardt disease phenotypes. *Cold Spring Harb Mol Case Stud.* 2018;4(4).
11. Sangermano R, Garanto A, Khan M, et al. Deep-intronic ABCA4 variants explain missing heritability in Stargardt disease and allow correction of splice defects by antisense oligonucleotides. *Genet Med.* 2019.
12. Runhart EH, Sangermano R, Cornelis SS, et al. The common ABCA4 Variant p.Asn1868Ile shows nonpenetrance and variable expression of Stargardt disease when present in trans with severe variants. *Invest Ophthalmol Vis Sci.* 2018;59(8):3220-3231.
13. Cremers FPM, Cornelis SS, Runhart EH, Astuti GDN. Author Response: Penetrance of the ABCA4 p.Asn1868Ile allele in Stargardt disease. *Invest Ophthalmol Vis Sci.* 2018;59(13):5566-5568.