SUPPLEMENTARY MATERIAL

Prevalence of familial hypercholesterolaemia (FH)-causing variants and impact on LDL-C concentration in European, South Asian, and African ancestry groups of the UK Biobank

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Expanded Methods:

Disease definition

CHD was defined using ICD-10 codes I21, I22, I23, I24, I25.0, I25.1, I25.2, I25.3, I25.5, 125.6, I25.8, 125.9, I48, I50, I11.0, I13.0, I13.2, I32.2, I61, I63 and the OPCS-4 codes K40, K41, K42, K43, K44.1, K44.8, K44.9, K45.1, K45.2, K45.3, K45.4, K45.5, K45.8, K45.9, K46.1, K46.2, K46.3, K46.4, K46.8, K46.9, K47.1, K49, K50, K75, K52.1, K57.1, K57.5, K62.1, K62.2, K62.3, K62.4, K62.5, X50.1, X50.2. Type 2 diabetes was defined using the ICD10 code E11. Hypertension was defined as a composite of self-reported antihypertensive medication use, self-reported hypertension, and the ICD-10 code I10.

Supplementary Table S1. Genetic coordinates of the *LDLR, APOE, APOB* and *PCSK9* genes. The genetic coordinates used to extract the FH-causing genes from the whole exome sequencing data are mapped to GRCh38.

Gene name	Chromosome number	Start coordinate	End coordinate
LDLR	19	11,089,262	11,133,820
APOB	2	21,001,429	21,044,073
APOE	19	44,905,791	44,909,393
PCSK9	1	55,039,347	55,064,852

Supplementary Table S2. Pathogenic and likely pathogenic FH-variants identified. A. in European ancestry, **B.** in South Asian ancestry, **C.** in African ancestry. Genetic coordinates are mapped to GRCh38. The asterisk symbol (*) next to a variant in tables B and C indicates variants that are unique to the ancestry group.

A. European ancestry

Gene	Chromosome	Position	Reference allele	Alternate allele	Nucleotide change	Protein	Number of carriers	UKB frequency (1/n)
APOB	2	21006289	G	A	c.10579C>T	p.Arg3527Trp	2	70,220
		21006288	C	T	c.10580G>A	p.Arg3527Gln	99	1,419
APOE	19	44908791	GCTC	G	c.499_501del	p.Leu167del	13	10,803
LDLR	19	11100236	C	G	c.81C>G	p.Cys27Trp	1	140,439
		11100291	T	G	c.136T>G	p.Cys46Gly	1	140,439
		11100294	G	A	c.139G>A	p.Asp47Asn	5	28,088
		11102705	C	T	c.232C>T	p.Arg78Cys	13	10,803
		11102714	C	T	c.241C>T	p.Arg81Cys	2	70,220
		11102732	T	G	c.259T>G	p.Trp87Gly	6	23,407
		11102741	G	A	c.268G>A	p.Asp90Asn	5	28,088
		11102765	G	A	c.292G>A	p.Gly98Ser	10	14,044
		11102774	G	A	c.301G>A	p.Glu101Lys	12	11,703
		11102787	G	A	c.313+1G>A	.	5	28,088
		11102787	G	C	c.313+1G>C	.	1	140,439
		11102787	G	GT	c.313+2dup	.	2	70,220
		11105249	C	T	c.343C>T	p.Arg115Cys	2	70,220
		11105268	G	T	c.362G>T	p.Cys121Phe	2	70,220

11105324	G	A	c.418G>A	p.Glu140Lys	1	140,439
11105339	GTGCTCACCTGTGGTCCCGCCAGC	G	c.435_457del	p.Leu146ProfsTer26	1	140,439
11105407	C	A	c.501C>A	p.Cys167Ter	2	70,220
11105408	G	A	c.502G>A	p.Asp168Asn	14	10,031
11105415	AC	A	c.513del	p.Asp172ThrfsTer34	1	140,439
11105448	C	G	c.542C>G	p.Pro181Arg	2	70,220
11105549	C	T	c.643C>T	p.Arg215Cys	4	35,110
11105567	G	A	c.661G>A	p.Asp221Asn	2	70,220
11105568	A	G	c.662A>G	p.Asp221Gly	5	28,088
11105585	GAC	G	c.680_681del	p.Asp227GlyfsTer12	4	35,110
11105585	GAC	GAG	c.681delinsG	p.Asp227Glu	2	70,220
11105588	G	T	c.682G>T	p.Glu228Ter	2	70,220
11105589	AG	A	c.685del	p.Glu229LysfsTer36	1	140,439
11106579	C	T	c.709C>T	p.Arg237Cys	1	140,439
11106588	G	A	c.718G>A	p.Glu240Lys	20	7,022
11106592	T	C	c.722T>C	p.Phe241Ser	1	140,439
11106631	A	C	c.761A>C	p.Gln254Pro	1	140,439
11107432	C	A	c.858C>A	p.Ser286Arg	1	140,439
11107433	G	A	c.859G>A	p.Gly287Ser	4	35,110
11107436	G	A	c.862G>A	p.Glu288Lys	1	140,439
11107461	G	A	c.887G>A	p.Cys296Tyr	1	140,439
11107481	C	T	c.907C>T	p.Arg303Trp	2	70,220
11107486	C	G	c.912C>G	p.Asp304Glu	4	35,110

11107512	G	A	c.938G>A	p.Cys313Tyr	2	70,220
11110660	G	A	c.949G>A	p.Glu317Lys	35	4,013
11110678	G	A	c.967G>A	p.Gly323Ser	1	140,439
11110714	G	A	c.1003G>A	p.Gly335Ser	3	46,813
11110738	G	A	c.1027G>A	p.Gly343Ser	8	17,555
11110759	C	T	c.1048C>T	p.Arg350Ter	4	35,110
11110760	G	C	c.1049G>C	p.Arg350Pro	4	35,110
11111571	G	A	c.1118G>A	p.Gly373Asp	1	140,439
11111619	C	T	c.1166C>T	p.Thr389Met	8	17,555
11113286	G	A	c.1195G>A	p.Ala399Thr	1	140,439
11113287	C	A	c.1196C>A	p.Ala399Asp	1	140,439
11113292	CTCTTC	CTCT	c.1205_1206del	p.Phe403HisfsTer37	1	140,439
11113307	C	T	c.1216C>T	p.Arg406Trp	5	28,088
11113308	G	A	c.1217G>A	p.Arg406Gln	4	35,110
11113313	G	A	c.1222G>A	p.Glu408Lys	1	140,439
11113322	A	G	c.1231A>G	p.Lys411Glu	1	140,439
11113329	C	T	c.1238C>T	p.Thr413Met	14	10,031
11113337	C	T	c.1246C>T	p.Arg416Trp	2	70,220
11113419	G	C	c.1328G>C	p.Trp443Ser	1	140,439
11113426	C	G	c.1335C>G	p.Asp445Glu	5	28,088
11113554	CA	C	c.1379del	p.His460ProfsTer47	1	140,439
11113590	G	T	c.1414G>T	p.Asp472Tyr	6	23,407
11113608	G	A	c.1432G>A	p.Gly478Arg	2	70,220
11113612	T	C	c.1436T>C	p.Leu479Pro	2	70,220

11113620	G	A	c.1444G>A	p.Asp482Asn	29	4,843
11113650	G	A	c.1474G>A	p.Asp492Asn	1	140,439
11113678	C	T	c.1502C>T	p.Ala501Val	5	28,088
11113705	C	T	c.1529C>T	p.Thr510Met	3	46,813
11113743	G	A	c.1567G>A	p.Val523Met	1	140,439
11116095	T	G	c.1588T>G	p.Phe530Val	10	14,044
11116125	G	A	c.1618G>A	p.Ala540Thr	2	70,220
11116141	G	A	c.1634G>A	p.Gly545Glu	1	140,439
11116198	A	G	c.1691A>G	p.Asn564Ser	2	70,220
11116873	C	T	c.1720C>T	p.Arg574Cys	2	70,220
11116898	T	C	c.1745T>C	p.Leu582Pro	1	140,439
11116918	G	A	c.1765G>A	p.Asp589Asn	1	140,439
11116928	G	A	c.1775G>A	p.Gly592Glu	1	140,439
11116936	C	T	c.1783C>T	p.Arg595Trp	6	23,407
11116937	G	A	c.1784G>A	p.Arg595Gln	2	70,220
11116976	C	G	c.1823C>G	p.Pro608Arg	1	140,439
11120091	G	A	c.1846-1G>A	.	1	140,439
11120106	G	T	c.1860G>T	p.Trp620Cys	1	140,439
11120110	GAT	G	c.1867_1868del	p.Ile623HisfsTer21	1	140,439
11120143	C	T	c.1897C>T	p.Arg633Cys	9	15,604
11120144	G	A	c.1898G>A	p.Arg633His	1	140,439
11120152	G	A	c.1906G>A	p.Gly636Ser	3	46,813
11120212	C	A	c.1966C>A	p.His656Asn	8	17,555
11120370	G	A	c.1988G>A	p.Gly663Glu	1	140,439
11120408	G	A	c.2026G>A	p.Gly676Ser	5	28,088

		11120436	C	T	c.2054C>T	p.Pro685Leu	12	11,703
		11120441	A	T	c.2059A>T	p.Ile687Phe	5	28,088
		11120442	T	TC	c.2061dup	p.Asn688GlnfsTer29	1	140,439
		11123200	G	T	c.2167G>T	p.Glu723Ter	1	140,439
		11128027	C	CA	c.2332dup	p.Arg778LysfsTer4	1	140,439

B. South Asian ancestry

Gene	Chromosome	Position	Reference allele	Alternate allele	Nucleotide change	Protein	Number of carriers	UKB frequency (1/n)
APOB	2	21006289	G	A	c.10579C>T	p.Arg3527Trp	1	4067
LDLR	19	11105579	A	T	c.673A>T	p.Lys225Ter*	1	4067
		11110690	C	T	c.979C>T	p.His327Tyr*	6	2034
		11110714	G	A	c.1003G>A	p.Gly335Ser	1	4067
		11111514	A	G	c.1061A>G	p.Asp354Gly*	1	4067
		11113343	G	A	c.1252G>A	p.Glu418Lys*	1	4067
		11113348	C	G	c.1257C>G	p.Tyr419Ter*	1	4067
		11116141	G	A	c.1634G>A	p.Gly545Glu	2	2034
		11116900	C	T	c.1747C>T	p.His583Tyr*	1	4067
		11116901	A	G	c.1748A>G	p.His583Arg*	1	4067
		11120101	T	C	c.1855T>C	p.Phe619Leu*	1	4067
		11120478	C	T	c.2096C>T	p.Pro699Leu*	1	4067

C. African ancestry

Gene	Chromosome	Position	Reference allele	Alternate allele	Nucleotide change	Protein	Number of carriers	UKB frequency (1/n)
APOB	2	21006288	C	T	c.10580G>A	p.Arg3527Gln	3	1302
LDLR	19	11107436	G	A	c.862G>A	p.Glu288Lys	1	3906
		11107481	C	T	c.907C>T	p.Arg303Trp	2	1953
		11107484	G	A	c.910G>A	p.Asp304Asn*	1	3906
		11110678	G	A	c.967G>A	p.Gly323Ser	3	1302

11111571	G	A	c.1118G>A	p.Gly373Asp	1	3906
11111619	C	T	c.1166C>T	p.Thr389Met	1	3906
11113678	C	T	c.1502C>T	p.Ala501Val	1	3906
11116114	G	A	c.1607G>A	p.Trp536Ter*	1	3906
11120144	G	A	c.1898G>A	p.Arg633His	1	3906

Supplementary Table S3. Variants of uncertain significance (VUS) excluded from the main analysis. A. in European ancestry, **B.** in South Asian ancestry, **C.** in African ancestry. Genetic coordinates are mapped to GRCh38.

A. European ancestry

Gene	Chromosome	Position	Reference allele	Alternate allele	Nucleotide change	Protein	Number of carriers	UKB frequency (1/n)
		21001939	ACTG	A	c.13480_13482delCAG	p.Gln4494del	132	1064
		21006196	C	T	c.10672C>T	p.Arg3558Cys	299	470
APOB	2	21006239	C	G	c.10629C>G	p.Asn3543Lys	3	46813
		21006349	C	T	c.10519C>T	p.Arg3507Trp	1	140438
		21015387	G	C	c.3491G>C	p.Arg1164Thr	1	140438
		55044021	A	G	c.386A>G	p.Asp129Gly	2	70219
PCSK9	1	55052698	G	A	c.706G>A	p.Gly236Ser	4	35110
		55058543	C	G	c.1399C>G	p.Pro467Ala	3	46813
		11100261	G	C	c.106G>C	p.Asp36His	1	140438
		11100322	C	T	c.167C>T	p.Ser56Phe	1	140438
		11100328	A	T	c.173A>T	p.Glu58Val	2	70219
		11100340	C	T	c.185C>T	p.Thr62Met	10	14044
		11102720	A	T	c.247A>T	p.Ile83Phe	1	140438
		11105262	G	C	c.356G>C	p.Gly119Ala	1	140438
		11105337	C	T	c.431C>T	p.Pro144Leu	1	140438
		11105379	C	T	c.473C>T	p.Ser158Phe	1	140438
		11105414	G	A	c.508G>A	p.Asp170Asn	22	6384
		11105415	AC	GC	c.509delinsG	p.Asp170Gly	1	140438
		11106580	G	A	c.710G>A	p.Arg237His	10	14044
LDLR	19	11106593	C	A	c.723C>A	p.Phe241Leu	3	46813
		11106601	C	G	c.731C>G	p.Ser244Cys	1	140438
		11106639	C	T	c.769C>T	p.Arg257Trp	2	70219
		11107472	A	G	c.898A>G	p.Arg300Gly	1	140438
		11111538	A	C	c.1085A>C	p.Asp362Ala	60	2341
		11111558	G	A	c.1105G>A	p.Val369Met	3	46813
		11111609	G	T	c.1156G>T	p.Asp386Tyr	5	28088
		11113278	G	T	c.1187G>T	p.Gly396Val	1	140438
		11113287	C	T	c.1196C>T	p.Ala399Val	1	140438
		11113292	CTCTTC	CTCTTG	c.1206delinsG	p.Phe402Leu	1	140438
		11113362	C	T	c.1271C>T	p.Pro424Leu	3	46813
		11113374	A	C	c.1283A>C	p.Asn428Thr	1	140438

11113409	A	G	c.1318A>G	p.Arg440Gly	4	35110
11113561	TCTCTTCCTA	TCTCTTACTA	c.1391delinsA	p.Ser464Tyr	2	70219
11113625	G	T	c.1449G>T	p.Trp483Cys	1	140438
11113751	T	G	c.1575T>G	p.Asp525Glu	6	23406
11113762	G	T	c.1586G>T	p.Gly529Val	1	140438
11116101	T	C	c.1594T>C	p.Tyr532His	1	140438
11116132	T	A	c.1625T>A	p.Ile542Asn	1	140438
11116205	C	G	c.1698C>G	p.Ile566Met	1	140438
11116885	G	A	c.1732G>A	p.Val578Ile	2	70219
11116914	C	G	c.1761C>G	p.Ser587Arg	4	35110
11116949	T	C	c.1796T>C	p.Leu599Ser	4	35110
11116970	C	A	c.1817C>A	p.Ala606Asp	14	10031
11120454	C	T	c.2072C>T	p.Ser691Leu	4	35110
11120484	G	T	c.2102G>T	p.Gly701Val	1	140438
11120507	A	G	c.2125A>G	p.Arg709Gly	1	140438
11123315	C	T	c.2282C>T	p.Thr761Met	11	12767
11128062	C	A	c.2366C>A	p.Ala789Asp	1	140438
11129553	G	C	c.2430G>C	p.Trp810Cys	1	140438
11129573	A	T	c.2450A>T	p.Asn817Ile	1	140438
11129582	G	A	c.2459G>A	p.Ser820Asn	1	140438
11129633	A	G	c.2510A>G	p.His837Arg	18	7802
11129653	G	A	c.2530G>A	p.Gly844Ser	1	140438
11131299	G	C	c.2566G>C	p.Glu856Gln	1	140438

B. South Asian ancestry

Gene	Chromosome	Position	Reference allele	Alternate allele	Nucleotide change	Protein	Number of carriers	UKB frequency (1/n)
APOB	2	21006289	G	A	c.11477C>T	Thr3826Met	4	1017
LDLR	19	11110710	G	C	c.999G>C	p.Lys333Asn	1	4067
		11113542	C	T	c.1366C>T	p.Leu456Phe	1	4067
		11129527	C	T	c.2404C>T	p.Leu802Phe	1	4067
		11129635	A	G	c.2512A>G	p.Ile838Val	1	4067
PCSK9	1	55052698	G	A	c.706G>A	p.Gly236Ser	5	813

C. African ancestry

Gene	Chromosome	Position	Reference allele	Alternate allele	Nucleotide change	Protein	Number of carriers	UKB frequency (1/n)
APOB	2	21005391	C	T	c.11477C>T	p.Thr3826Met	3	1302
		21006196	C	T	c.10672C>T	p.Arg3558Cys	4	977
LDLR	19	11106630	C	G	c.760C>G	p.Gln254Glu	1	3906
		11116095	T	G	c.1588T>G	p.Phe530Val	1	3906
		11128037	G	GAGA	c.2347_2349dup	p.Lys783dup	1	3906

Supplementary Table S4. Baseline characteristics of European, South Asian, and African ancestry groups. P-value of group differences was calculated using the Kruskal-Wallis Rank Sum Test. Variants of uncertain significance (VUS) were not excluded from this table.

	European	South Asian	African	p-value of group differences	Missing (%)
n	140439	4067	3906		
Age (median [IQR])	58.00 [51.00, 63.00]	53.00 [46.00, 60.00]	50.00 [45.00, 58.00]	<0.001	0.0
Sex (male) (%)	63878 (45.5)	2139 (52.6)	1568 (40.1)	<0.001	0.0
Statin use (%)	18405 (13.1)	826 (20.3)	488 (12.5)	<0.001	0.0
Body mass index, kg/m2 (median [IQR])	26.67 [24.10, 29.78]	26.57 [24.20, 29.44]	28.72 [25.75, 32.41]	<0.001	0.4
Biomarkers					
Total cholesterol, mmol/L (median [IQR])	5.68 [4.94, 6.45]	5.32 [4.56, 6.03]	5.24 [4.52, 5.94]	<0.001	4.9
Imputed LDL-C (unadjusted), mmol/L (median [IQR])	3.53 [2.96, 4.13]	3.36 [2.78, 3.91]	3.24 [2.72, 3.81]	<0.001	0.0
Imputed LDL-C (adjusted for statin users), mmol/L (median [IQR])	3.67 [3.14, 4.25]	3.54 [3.02, 4.08]	3.36 [2.84, 3.95]	<0.001	0.0
HDL-C, mmol/L (median [IQR])	1.41 [1.18, 1.69]	1.21 [1.03, 1.45]	1.39 [1.18, 1.66]	<0.001	12.5
Triglycerides, mmol/L (median [IQR])	1.49 [1.05, 2.14]	1.67 [1.18, 2.40]	1.04 [0.78, 1.46]	<0.001	5.0
Lipoprotein (a), nmol/L (median [IQR])	20.00 [9.31, 59.80]	32.08 [13.60, 64.13]	67.12 [38.22, 106.97]	<0.001	24.0
Disease status					
Prevalent T2D (%)	3623 (2.6)	380 (9.3)	181 (4.6)	<0.001	0.0
Incident T2D (%)	4989 (3.6)	470 (11.6)	297 (7.6)	<0.001	0.0
Incident CHD (%)	5429 (3.9)	248 (6.1)	95 (2.4)	<0.001	0.0
Prevalent CHD (%)	3953 (2.8)	223 (5.5)	56 (1.4)	<0.001	0.0
Prevalent hypertension (%)	10840 (7.7)	465 (11.4)	465 (11.9)	<0.001	0.0
Incident hypertension (%)	20012 (14.2)	686 (16.9)	683 (17.5)	<0.001	0.0

Supplementary Table S5. Assessment of detection rate and false positive rate for screening for FH variant carriers using LDL-C cut-off of 4.9mmol/L in European, South Asian and African ancestry groups. FH+ refers to FH variant carriers.

Ancestry	**Detection rate using Simon Broome LDL-C >=4.9 mmol/L**	**False positive rate using Simon Broome LDL-C >=4.9 mmol/L**
European	37.7% (95% CI: 33.5%; 42.1%)	8.6% (95% CI: 8.4%; 8.7%)
South Asian	33.3% (95% CI: 16.3%; 56.3%)	6.3% (95% CI: 5.6%; 7.1%)
African	46.7% (95% CI: 24.8%; 70.0%)	5.7% (95% CI: 5.0%; 6.4%)

Supplementary Table S6. Self-reported statin use in European, South Asian, and African ancestry individuals. FH+ refers to FH variant carriers.

Ancestry	Total number of individuals taking statins	Proportion of statin intake per ancestry	Number of FH+ taking statins	Proportion of FH+ taking statins
European	18,405	13.1%	165	33.8%
South Asian	826	20.3%	10	55.6%
African	488	12.5%	6	40.0%

MAJOR RESOURCE TABLE

All data can be accessed via UK Biobank approval system

Data & Code Availability

Description	Source / Repository	Persistent ID / URL
Genetic data can be access following the UK Biobank approval procedures	UK Biobank Access Management System	https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access