

SUPPLEMENTAL MATERIAL

An increased burden of common and rare lipid-associated risk alleles contributes to the phenotypic spectrum of hypertriglyceridemia

Running title: Complexity of hypertriglyceridemia

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Supplemental Table I. The Fredrickson or World Health Organization HLP phenotype classification system.

Familial hyperlipidemia	WHO classification	MIM	Inheritance	Diagnostic components		
				TG (mmol/L)	Lipoproteins	Other components
Chylomicronemia	HLP type 1	238600	Monogenic	>10	↑CM	Homozygous mutations in <i>LPL</i> , <i>APOC2</i> , <i>APOA5</i> , <i>LMF1</i> and <i>GPIHBP1</i>
Hypercholesterolemia	HLP type 2A	143890	Monogenic	<3.4	↑LDL	Heterozygous form: mutations in <i>LDLR</i> , <i>APOB</i> or <i>PCSK9</i> ; homozygous form: mutations in <i>LDLR</i> or <i>ARH</i>
Combined hyperlipoproteinemia	HLP type 2B	144250	Polygenic	3.4-10	↑VLDL ↑LDL	LDL cholesterol >95 th percentile
Dysbetalipoproteinemia	HLP type 3	107741	Polygenic	3.4-10	↑VLDL-remnants ↑IDL	Predominantly <i>APOE</i> ε2/ε2 genotype
Primary hypertriglyceridemia	HLP type 4	144600	Polygenic	3.4-10	↑VLDL	
Mixed hyperlipidemia	HLP type 5	144650	Polygenic	>10	↑CM ↑VLDL	

APOB, apolipoprotein B; *APOC2*, apolipoprotein C-II; *APOE*, apolipoprotein E; CM, chylomicron; HLP, hyperlipoproteinemia; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; *LDLR*, low-density lipoprotein receptor; *LPL*, lipoprotein lipase; MIM, Mendelian Inheritance in Man; *PCSK9*, proprotein convertase subtilisin/kexin type 9; TG, triglyceride; VLDL, very low-density lipoprotein; WHO, World Health Organization

Supplemental Table II. Replication of HDL-C-associated loci in patients with polygenic HTG and HLP-HTG phenotypes.

CHR	Gene	SNP	Minor allele/ modeled allele	All HTG (n=504)		HLP type 5 (n=180)		HLP type 4 (n=128)		HLP type 3 (n=37)		HLP type 2B (n=159)	
				OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
7	MLXIPL	rs17145738	T/C	2.28 (1.63-3.19)	1.5X10 ⁻⁶	1.93 (1.16-3.19)	0.011	3.63 (1.75-7.54)	5.4X10 ⁻⁴	1.38 (0.55-3.49)	0.49	2.17 (1.32-3.57)	2.3X10 ⁻³
8	TRIB1	rs10808546	T/C	1.46 (1.21-1.77)	1.0X10 ⁻⁴	1.32 (0.98-1.77)	0.07	1.43 (1.03-1.98)	0.032	1.56 (0.87-2.79)	0.14	1.57 (1.18-2.09)	1.9X10 ⁻³
2	IRS1	rs1515100	C/A	1.28 (1.05-1.55)	0.015	1.22 (0.90-1.65)	0.20	1.53 (1.07-2.18)	0.018	0.98 (0.54-1.79)	0.95	1.26 (0.95-1.68)	0.11
11	FADS1	rs174601	T/T	1.25 (1.04-1.50)	0.019	1.21 (0.91-1.62)	0.20	1.46 (1.05-2.01)	0.023	1.16 (0.64-2.12)	0.63	1.17 (0.89-1.54)	0.27
19	APOE	rs4420638	G/G	0.62 (0.4-0.95)	0.029	0.73 (0.38-1.38)	0.33	0.50 (0.22-1.14)	0.10	0.58 (0.13-2.52)	0.47	0.65 (0.34-1.23)	0.19
16	CETP	rs3764261	A/C	1.23 (1.00-1.50)	0.051	1.26 (0.91-1.73)	0.16	1.26 (0.89-1.80)	0.20	0.82 (0.44-1.52)	0.52	1.36 (1.00-1.85)	0.050
6	CITED2	rs605066	C/C	1.20 (1.00-1.45)	0.052	1.13 (0.85-1.50)	0.41	1.21 (0.87-1.66)	0.25	1.50 (0.84-2.67)	0.17	1.25 (0.95-1.64)	0.11
1	GALNT2	rs4846914	G/G	1.21 (1.00-1.45)	0.052	1.29 (0.97-1.73)	0.084	1.14 (0.82-1.58)	0.45	1.16 (0.64-2.09)	0.63	1.09 (0.83-1.45)	0.53
9	TTC39B	rs643531	C/C	0.77 (0.59-1.01)	0.059	1.05 (0.70-1.56)	0.82	0.68 (0.41-1.12)	0.13	0.49 (0.17-1.41)	0.19	0.78 (0.52-1.18)	0.25
6	LPA	rs1084651	A/A	0.83 (0.64-1.07)	0.16	0.82 (0.54-1.23)	0.33	1.03 (0.67-1.58)	0.91	0.57 (0.23-1.40)	0.22	0.81 (0.55-1.19)	0.28
19	ANGPTL4	rs7255436	C/C	1.15 (0.94-1.40)	0.18	0.93 (0.68-1.26)	0.63	1.20 (0.85-1.69)	0.31	1.32 (0.71-2.49)	0.38	1.25 (0.93-1.69)	0.14
20	PLTP	rs6065906	C/C	1.17 (0.92-1.48)	0.20	1.38 (0.96-1.97)	0.082	1.10 (0.72-1.67)	0.66	0.62 (0.25-1.56)	0.31	1.14 (0.80-1.64)	0.47
1	ZNF648	rs1689800	G/G	1.13 (0.93-1.37)	0.21	1.05 (0.77-1.43)	0.76	0.96 (0.68-1.36)	0.81	1.30 (0.71-2.39)	0.39	1.42 (1.07-1.90)	0.017
12	MVK	rs7134594	C/C	0.90 (0.75-1.08)	0.24	0.87 (0.66-1.16)	0.35	1.08 (0.79-1.48)	0.64	1.10 (0.63-1.91)	0.75	0.83 (0.63-1.09)	0.19
12	LRP1	rs3741414	T/C	1.14 (0.91-1.43)	0.25	1.44 (1.00-2.07)	0.051	0.99 (0.68-1.44)	0.97	1.12 (0.56-2.26)	0.75	1.15 (0.82-1.60)	0.42
11	UBASH3B	rs7115089	G/C	1.12 (0.93-1.34)	0.25	1.24 (0.92-1.67)	0.16	1.26 (0.90-1.76)	0.17	1.23 (0.70-2.17)	0.48	0.88 (0.67-1.15)	0.35
20	HNF4A	rs1800961	T/T	0.75 (0.44-1.28)	0.29	0.42 (0.14-1.21)	0.11	1.52 (0.70-3.29)	0.28	0.56 (0.07-4.33)	0.58	0.83 (0.38-1.78)	0.62
7	KLF14	rs4731702	T/C	0.91 (0.76-1.09)	0.31	1.00 (0.75-1.33)	0.99	0.80 (0.59-1.10)	0.17	0.76 (0.43-1.33)	0.34	0.98 (0.75-1.28)	0.83
8	PPP1R3B	rs9987289	A/A	1.17 (0.84-1.64)	0.35	1.09 (0.65-1.83)	0.76	1.03 (0.58-1.83)	0.92	2.59 (1.18-5.68)	0.018	0.86 (0.50-1.48)	0.57
22	UBE2L3	rs181362	T/T	0.90 (0.71-1.14)	0.39	0.85 (0.59-1.23)	0.38	1.15 (0.77-1.69)	0.50	0.57 (0.25-1.29)	0.18	0.80 (0.55-1.15)	0.23
18	LIPG	rs7241918	G/G	0.90 (0.71-1.15)	0.40	1.02 (0.70-1.48)	0.91	0.90 (0.58-1.37)	0.61	0.68 (0.29-1.57)	0.36	0.90 (0.63-1.29)	0.58
12	SBNO1	rs4759375	T/C	1.16 (0.78-1.72)	0.47	1.50 (0.75-3.01)	0.25	1.71 (0.78-3.77)	0.18	0.48 (0.18-1.27)	0.14	0.71 (0.42-1.19)	0.19
17	PGS1	rs4082919	G/G	1.07 (0.89-1.28)	0.47	1.17 (0.89-1.55)	0.26	1.22 (0.90-1.67)	0.20	0.82 (0.46-1.45)	0.49	1.00 (0.76-1.31)	1.00
15	LIPC	rs1532085	A/G	1.07 (0.89-1.29)	0.49	0.99 (0.74-1.32)	0.95	1.51 (1.08-2.11)	0.016	0.78 (0.45-1.35)	0.37	1.05 (0.80-1.38)	0.74
4	SLC39A8	rs13107325	T/T	0.89 (0.64-1.25)	0.49	0.60 (0.33-1.09)	0.093	1.15 (0.67-1.99)	0.61	0.75 (0.25-2.24)	0.60	1.00 (0.62-1.64)	0.99
15	LACTB	rs2652834	A/A	0.93 (0.73-1.19)	0.56	0.90 (0.60-1.33)	0.59	1.18 (0.79-1.76)	0.43	0.77 (0.35-1.68)	0.51	0.78 (0.53-1.14)	0.20
18	MC4R	rs12967135	A/A	0.94 (0.76-1.18)	0.61	0.91 (0.64-1.28)	0.58	1.11 (0.76-1.62)	0.59	1.85 (0.99-3.48)	0.054	0.86 (0.61-1.21)	0.38

5	ARL15	rs6450176	A/A	0.95 (0.77-1.17)	0.61	0.86 (0.61-1.21)	0.38	1.00 (0.70-1.42)	0.99	0.73 (0.36-1.49)	0.38	0.93 (0.68-1.26)	0.64
2	COBLL1	rs12328675	C/T	1.07 (0.81-1.40)	0.64	1.47 (0.93-2.34)	0.10	0.93 (0.60-1.45)	0.76	1.13 (0.47-2.68)	0.79	0.96 (0.65-1.41)	0.82
11	LRP4	rs3136441	C/T	0.94 (0.73-1.23)	0.67	1.26 (0.81-1.95)	0.30	0.58 (0.38-0.87)	8.0X10 ⁻³	1.08 (0.45-2.57)	0.87	1.02 (0.69-1.49)	0.94
19	LOC55908	rs737337	C/C	1.06 (0.77-1.45)	0.72	0.93 (0.55-1.56)	0.78	0.64 (0.34-1.22)	0.17	1.87 (0.86-4.07)	0.12	1.21 (0.78-1.87)	0.40
16	LCAT	rs16942887	A/G	1.05 (0.80-1.38)	0.73	1.10 (0.71-1.72)	0.66	1.15 (0.71-1.88)	0.57	0.67 (0.31-1.44)	0.30	1.06 (0.71-1.59)	0.76
6	C6orf106	rs2814944	A/A	1.05 (0.80-1.38)	0.73	1.11 (0.73-1.69)	0.63	0.95 (0.57-1.56)	0.83	0.83 (0.34-2.03)	0.68	1.06 (0.71-1.60)	0.76
1	PABPC4	rs4660293	G/G	1.04 (0.84-1.28)	0.74	1.18 (0.85-1.63)	0.32	0.96 (0.67-1.39)	0.83	0.56 (0.27-1.18)	0.13	0.96 (0.70-1.33)	0.82
12	SCARB1	rs838880	C/T	1.02 (0.84-1.24)	0.82	0.92 (0.68-1.23)	0.56	1.01 (0.72-1.41)	0.97	1.11 (0.62-1.99)	0.73	1.15 (0.86-1.55)	0.34
11	AMPD3	rs2923084	G/G	1.02 (0.81-1.28)	0.86	1.04 (0.72-1.49)	0.85	1.05 (0.71-1.57)	0.81	2.20 (1.17-4.12)	0.014	0.95 (0.67-1.35)	0.77
17	STARD3	rs881844	C/C	1.02 (0.84-1.23)	0.86	0.84 (0.61-1.14)	0.26	1.26 (0.91-1.74)	0.17	1.02 (0.55-1.89)	0.96	1.12 (0.84-1.48)	0.44
16	CMIP	rs2925979	T/T	0.99 (0.81-1.21)	0.91	1.12 (0.83-1.51)	0.47	1.13 (0.80-1.59)	0.50	0.62 (0.31-1.24)	0.17	1.02 (0.76-1.38)	0.89
8	TRPS1	rs2293889	T/T	0.99 (0.83-1.19)	0.92	0.99 (0.75-1.31)	0.94	0.97 (0.71-1.32)	0.85	1.21 (0.68-2.15)	0.51	1.10 (0.84-1.44)	0.50
12	PDE3A	rs7134375	A/C	0.99 (0.83-1.19)	0.95	0.88 (0.66-1.18)	0.40	1.26 (0.91-1.76)	0.17	0.98 (0.55-1.76)	0.95	0.87 (0.66-1.14)	0.31
12	ZNF664	rs4765127	T/G	1.00 (0.82-1.20)	0.96	1.16 (0.86-1.58)	0.34	0.91 (0.66-1.26)	0.57	1.44 (0.79-2.63)	0.24	0.88 (0.67-1.17)	0.38
17	ABCA8	rs4148008	G/G	1.00 (0.82-1.21)	0.97	0.92 (0.68-1.26)	0.61	0.99 (0.70-1.39)	0.96	1.58 (0.90-2.78)	0.11	0.96 (0.71-1.28)	0.77
9	ABCA1	rs1883025	T/T	1.00 (0.81-1.22)	0.98	0.86 (0.62-1.21)	0.39	1.20 (0.85-1.69)	0.30	0.61 (0.29-1.27)	0.18	1.15 (0.85-1.55)	0.36
19	LILRA3	rs386000	C/G	1.00 (0.80-1.25)	1.00	1.02 (0.72-1.44)	0.90	1.11 (0.74-1.65)	0.62	0.92 (0.47-1.79)	0.80	0.98 (0.71-1.35)	0.90

CHR, chromosome; CI, confidence interval; HLP, hyperlipoproteinemia; HTG, hypertriglyceridemia; Mb, megabases; NC, not calculated; OR, odds ratio; SNP, single nucleotide polymorphism; T2D, type 2 diabetes mellitus; TG, plasma triglyceride. The modeled allele is the TG-raising allele in the combined HTG cohort.

¹Variant is monomorphic in HTG cases.

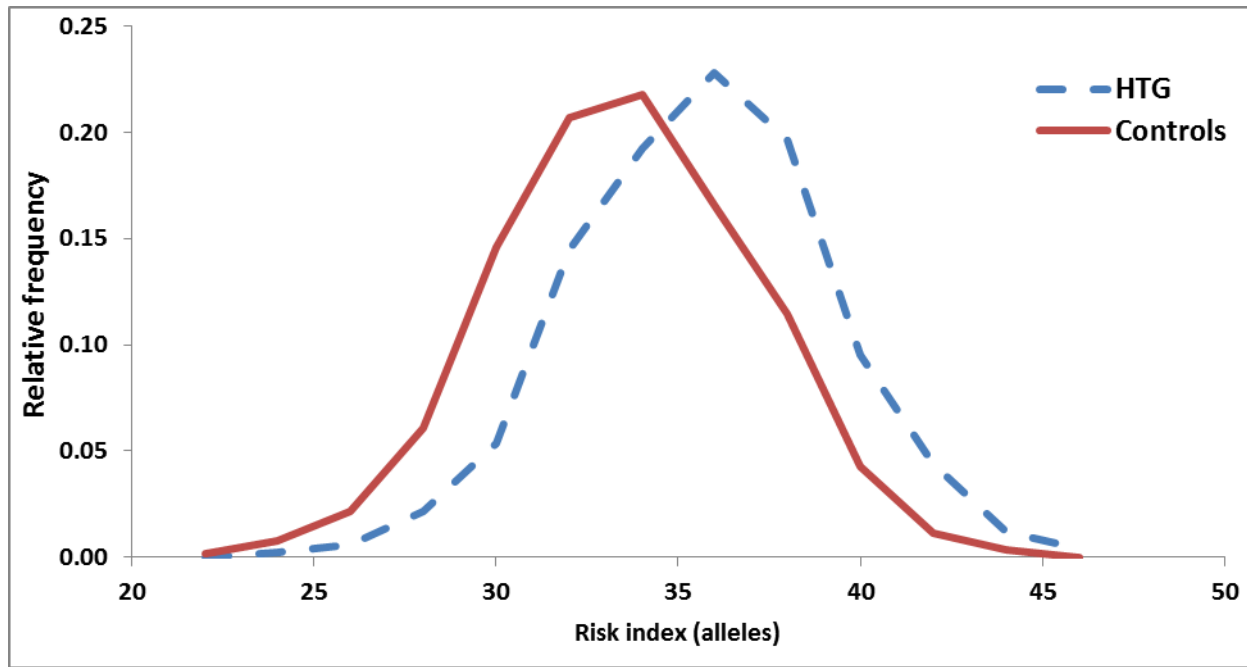
Supplemental Table III. Replication of LDL-associated loci in patients with polygenic HTG and HLP-HTG phenotypes.

CHR	Gene	SNP	Minor allele/ modeled allele	All HTG (n=504)		HLP type 5 (n=180)		HLP type 4 (n=128)		HLP type 3 (n=37)		HLP type 2B (n=159)	
				OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
8	TRIB1	rs2954022	A/C	1.48 (1.23-1.8)	5.3X10 ⁻⁵	1.41 (1.05-1.89)	0.024	1.36 (0.98-1.88)	0.064	1.59 (0.89-2.84)	0.12	1.58 (1.19-2.10)	1.5X10 ⁻³
1	ANGPTL3	rs3850634	G/T	1.49 (1.21-1.83)	1.7X10 ⁻⁴	1.77 (1.26-2.49)	1.1X10 ⁻³	0.97 (0.69-1.37)	0.87	1.24 (0.66-2.32)	0.50	1.61 (1.17-2.20)	3. X10 ⁻³
7	DNAH11	rs12670798	C/C	1.39 (1.13-1.70)	1.7X10 ⁻³	1.26 (0.92-1.74)	0.15	1.41 (0.98-2.02)	0.062	1.30 (0.70-2.43)	0.41	1.32 (0.97-1.78)	0.076
2	ABCG5/8	rs4299376	G/G	1.33 (1.07-1.65)	0.011	1.18 (0.84-1.67)	0.34	1.50 (1.04-2.17)	0.032	1.14 (0.59-2.21)	0.69	1.47 (1.07-2.02)	0.019
19	LDLR	rs6511720	T/G	1.84 (1.12-3.03)	0.017	1.56 (0.75-3.24)	0.23	4.35 (1.30-14.6)	0.017	NC ¹	NC ¹	1.46 (0.74-2.88)	0.27
9	ABO	rs649129	T/T	1.27 (1.04-1.56)	0.021	1.34 (0.96-1.85)	0.082	1.14 (0.79-1.65)	0.49	1.26 (0.66-2.40)	0.49	1.53 (1.13-2.07)	5.7X10 ⁻³
5	HMGCR	rs12916	C/C	1.23 (1.02-1.48)	0.028	1.12 (0.84-1.50)	0.44	1.27 (0.93-1.74)	0.14	1.35 (0.78-2.34)	0.29	1.16 (0.88-1.52)	0.29
11	FADS1	rs174583	T/C	0.81 (0.68-0.98)	0.029	0.84 (0.62-1.12)	0.23	0.72 (0.52-0.99)	0.046	0.78 (0.43-1.41)	0.41	0.87 (0.66-1.15)	0.33
19	APOE	rs4420638	G/G	0.62 (0.4-0.95)	0.029	0.73 (0.38-1.38)	0.33	0.50 (0.22-1.14)	0.10	0.58 (0.13-2.52)	0.47	0.65 (0.34-1.23)	0.19
16	CETP	rs247616	T/C	1.24 (1.01-1.51)	0.041	1.23 (0.89-1.68)	0.21	1.28 (0.90-1.83)	0.17	0.79 (0.42-1.47)	0.46	1.36 (1.00-1.85)	0.049
1	PCSK9	rs2479409	G/G	1.21 (1.00-1.45)	0.045	1.14 (0.85-1.53)	0.38	1.38 (1.00-1.90)	0.052	1.32 (0.74-2.37)	0.35	1.22 (0.92-1.60)	0.17
5	TIMD4	rs6882076	T/C	1.21 (1.00-1.46)	0.051	1.17 (0.87-1.58)	0.30	1.15 (0.83-1.59)	0.40	0.88 (0.50-1.55)	0.66	1.59 (1.18-2.14)	2.4X10 ⁻³
1	SORT1	rs629301	G/T	1.18 (0.94-1.49)	0.16	0.93 (0.65-1.31)	0.66	1.05 (0.71-1.55)	0.80	1.33 (0.63-2.82)	0.45	1.43 (0.99-2.06)	0.059
7	NPC1L1	rs217386	A/G	1.13 (0.94-1.35)	0.19	1.02 (0.77-1.34)	0.91	1.12 (0.83-1.53)	0.46	0.62 (0.35-1.07)	0.087	1.39 (1.06-1.82)	0.017
1	IRF2BP2	rs514230	A/T	1.13 (0.94-1.35)	0.20	1.26 (0.94-1.67)	0.12	1.08 (0.80-1.46)	0.63	1.32 (0.74-2.35)	0.34	1.03 (0.79-1.35)	0.81
6	LPA	rs1564348	C/C	1.15 (0.90-1.47)	0.27	1.11 (0.76-1.63)	0.59	1.15 (0.75-1.75)	0.53	1.36 (0.67-2.76)	0.40	1.16 (0.80-1.67)	0.43
6	HLA	rs3177928	A/A	0.87 (0.68-1.13)	0.30	1.02 (0.69-1.50)	0.93	0.79 (0.50-1.23)	0.30	1.49 (0.72-3.07)	0.28	0.79 (0.54-1.17)	0.24
6	MYLIP	rs3757354	T/C	0.90 (0.72-1.13)	0.36	0.89 (0.64-1.26)	0.52	0.65 (0.45-0.93)	0.017	0.96 (0.48-1.91)	0.90	1.30 (0.92-1.85)	0.14
14	NYNRIN	rs2332328	T/T	0.92 (0.76-1.11)	0.36	0.9 (0.67-1.21)	0.48	1.00 (0.73-1.38)	0.99	1.50 (0.80-2.82)	0.21	0.98 (0.74-1.30)	0.91
8	CYP7A1	rs1030431	A/A	1.09 (0.90-1.32)	0.38	1.11 (0.82-1.50)	0.51	1.46 (1.06-2.02)	0.02	1.22 (0.68-2.18)	0.51	0.92 (0.69-1.23)	0.57
6	HFE	rs1800562	A/G	1.19 (0.81-1.75)	0.38	1.21 (0.66-2.23)	0.54	1.54 (0.73-3.24)	0.25	0.36 (0.15-0.85)	0.019	1.46 (0.79-2.68)	0.22
2	APOB	rs1367117	A/A	1.09 (0.90-1.32)	0.39	1.08 (0.80-1.47)	0.60	0.88 (0.62-1.24)	0.45	0.77 (0.41-1.46)	0.42	1.38 (1.04-1.84)	0.026
8	PLEC1	rs11136341	G/G	1.09 (0.90-1.31)	0.40	0.94 (0.70-1.27)	0.71	1.19 (0.86-1.64)	0.29	1.20 (0.66-2.17)	0.55	1.18 (0.89-1.56)	0.26
6	FRK	rs11153594	T/C	1.08 (0.90-1.29)	0.42	0.89 (0.67-1.18)	0.41	1.27 (0.93-1.74)	0.14	0.74 (0.43-1.29)	0.29	1.21 (0.92-1.59)	0.18
10	GPAM	rs1129555	A/A	1.08 (0.88-1.32)	0.45	0.92 (0.67-1.27)	0.62	0.94 (0.66-1.34)	0.74	1.50 (0.84-2.67)	0.17	1.17 (0.87-1.58)	0.30
12	HNF1A	rs1169288	C/C	1.07 (0.88-1.31)	0.50	0.99 (0.72-1.35)	0.94	1.06 (0.76-1.50)	0.72	1.30 (0.71-2.38)	0.39	1.07 (0.79-1.45)	0.66
17	OSBPL7	rs7225700	T/C	0.94 (0.78-1.14)	0.55	1.25 (0.92-1.69)	0.15	1.01 (0.72-1.42)	0.95	0.61 (0.35-1.07)	0.083	0.71 (0.54-0.93)	0.014

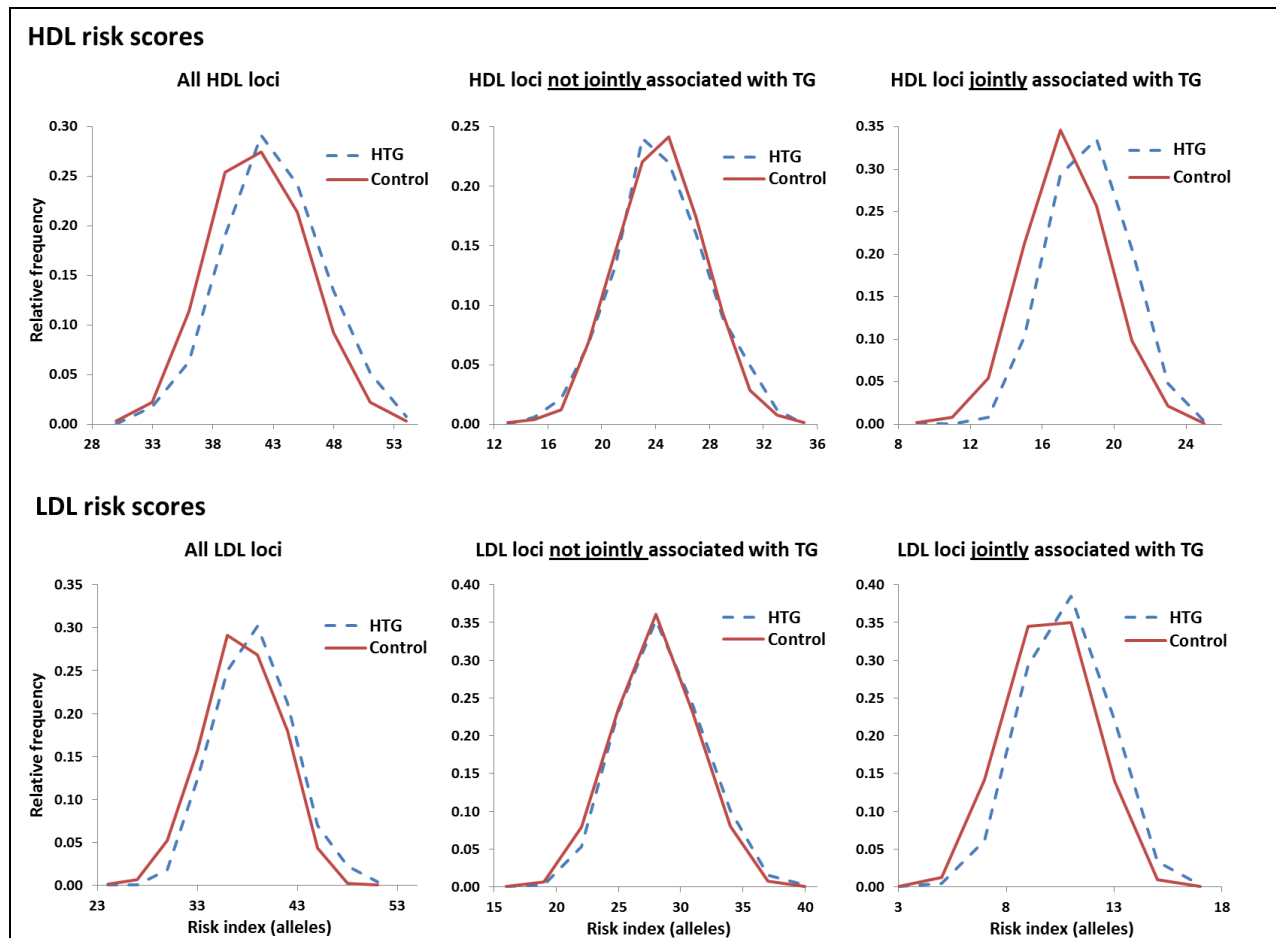
8	PPP1R3B	rs2126259	T/C	0.92 (0.67-1.26)	0.61	1.02 (0.61-1.68)	0.95	1.04 (0.60-1.82)	0.88	0.49 (0.23-1.05)	0.066	1.04 (0.64-1.68)	0.88
1	LDLRAP1	rs12027135	A/T	0.95 (0.79-1.14)	0.61	1.28 (0.95-1.72)	0.10	0.91 (0.66-1.26)	0.57	0.88 (0.50-1.55)	0.65	0.89 (0.68-1.18)	0.42
16	HPR	rs2000999	A/A	1.06 (0.85-1.32)	0.62	1.13 (0.81-1.58)	0.48	0.94 (0.63-1.40)	0.74	1.12 (0.57-2.17)	0.74	1.00 (0.72-1.39)	1.00
12	BRAP	rs11065987	G/A	0.96 (0.80-1.15)	0.65	0.96 (0.72-1.27)	0.76	0.97 (0.71-1.32)	0.84	1.16 (0.65-2.05)	0.62	0.93 (0.71-1.23)	0.61
1	MOSC1	rs2807834	T/G	0.96 (0.79-1.16)	0.66	1.16 (0.84-1.60)	0.38	0.90 (0.64-1.25)	0.52	0.99 (0.53-1.85)	0.98	0.87 (0.65-1.16)	0.35
11	ST3GAL4	rs11220462	A/A	0.97 (0.75-1.27)	0.84	0.85 (0.55-1.30)	0.44	0.82 (0.51-1.34)	0.43	0.77 (0.31-1.90)	0.57	1.28 (0.89-1.85)	0.18
20	MAFB	rs2902941	G/A	0.98 (0.81-1.19)	0.86	0.97 (0.72-1.31)	0.84	0.80 (0.58-1.11)	0.19	1.08 (0.58-2.01)	0.80	1.05 (0.79-1.40)	0.73
20	TOP1	rs909802	T/T	1.00 (0.84-1.20)	0.98	0.99 (0.74-1.32)	0.95	0.91 (0.66-1.25)	0.56	1.00 (0.57-1.76)	0.99	1.05 (0.80-1.38)	0.72

CHR, chromosome; CI, confidence interval; HLP, hyperlipoproteinemia; HTG, hypertriglyceridemia; Mb, megabases; NC, not calculated; OR, odds ratio; SNP, single nucleotide polymorphism; T2D, type 2 diabetes mellitus; TG, plasma triglyceride. The modeled allele is the TG-raising allele in the combined HTG cohort.

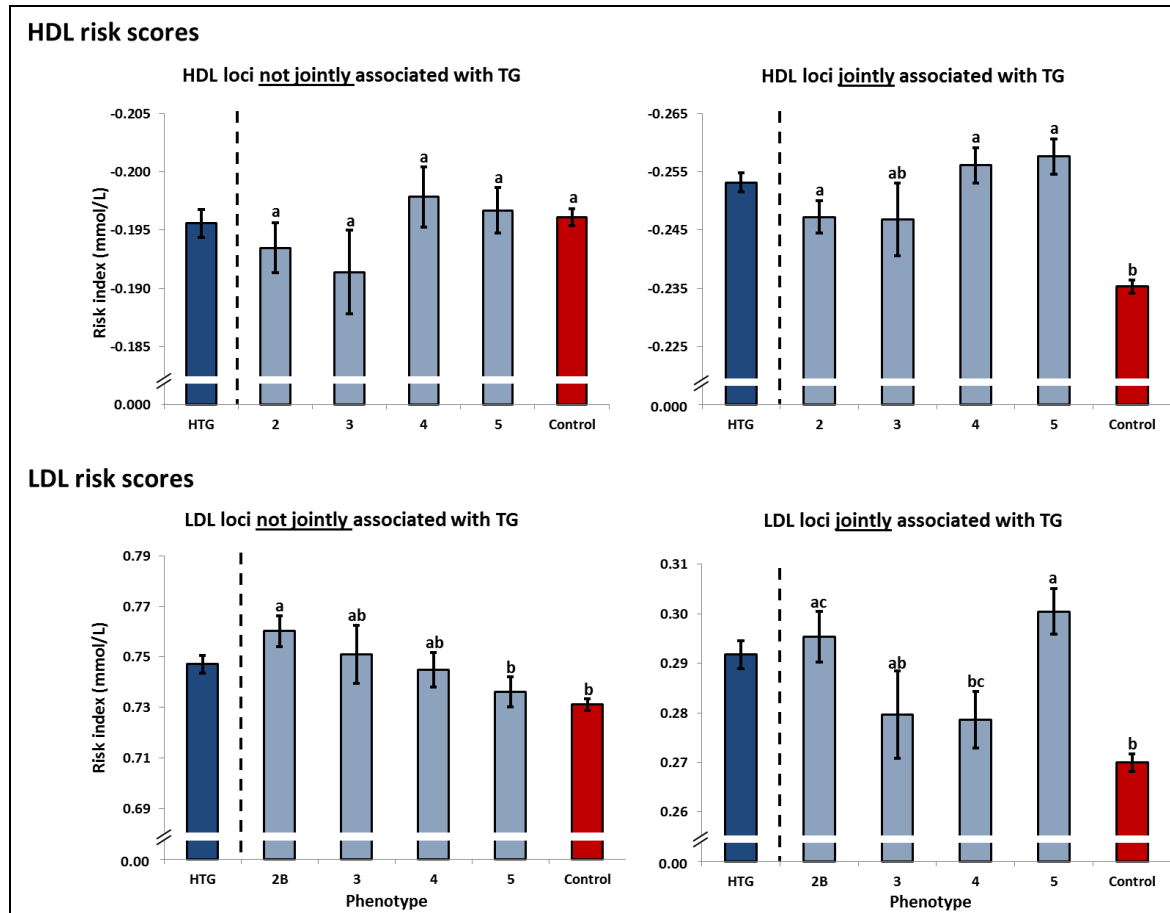
¹Variant is monomorphic in HTG cases.



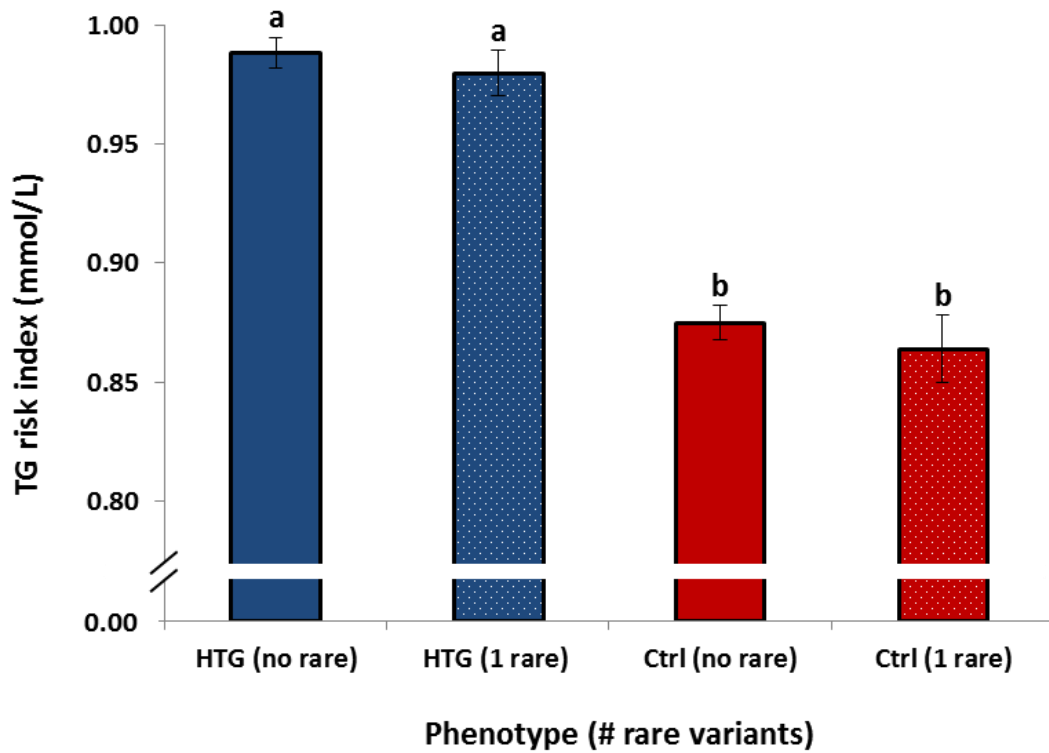
Supplemental Figure I. Unweighted allelic TG scores are increased in polygenic HTG patients versus controls. Allelic risk scores were constructed as the unweighted sum of 32 TG-associated loci.



Supplemental Figure II. Unweighted allelic HDL-C and LDL-C risk scores are increased in polygenic HTG patients versus controls and are driven primarily by loci jointly associated with plasma TG concentration. Allelic risk scores were constructed as the unweighted sum of 47 HDL-C (top; left) or 37 LDL-C (bottom; left) associated loci. Unweighted risk scores were separated by loci associated only with HDL-C (top; middle) or LDL-C (bottom; middle), or loci jointly associated with plasma TG in addition to HDL-C (top; right) or LDL-C (bottom; right).



Supplemental Figure III. Weighted allelic HDL-C and LDL-C risk scores have contributions from loci exclusively associated with HDL-C or LDL-C, and pleiotropic loci jointly associated with plasma TG concentration, causing differences among the polygenic HLP-HTG phenotypes. Differences among weighted risk scores in HLP phenotypes and controls were assessed using ANOVA and *post hoc* pairwise comparisons using Tukey's test ($P < 0.05$). Mean risk score in all HTG patients is provided as a reference only; it was not included in statistical comparisons. Values are mean \pm standard error; means sharing letters are not statistically different.



Supplemental Figure IV. TG risk scores are similar between carriers and non-carriers of rare variants. Differences among TG risk scores were assessed using ANOVA and *post hoc* pairwise comparisons using Tukey's test ($P < 0.05$). Values are mean \pm standard error; means sharing letters are not statistically different. HTG, hypertriglyceridemia.