

Table S2. Most significant results for each burden test in stage 1

Single Variant Test	Nonsyn MAF < 0.1%	Nonsyn MAF < 0.5%	Nonsyn MAF < 1%	Nonsyn MAF < 5%	LOF MAF < 5%	SKAT-O LOF MAF <5%	SKAT-O LOF + Nonsyn Damaging MAF <5%	SKAT-O Nonsyn + splice MAF < 5%
<i>TOMM40</i> 19:45397229 P=8x10 ⁻¹⁴	<i>LDLR*</i> BF = 2.5% p=3x10 ⁻⁹	<i>PCSK9</i> BF=5.7% P=8x10 ⁻⁷	<i>PCSK9</i> BF=5.7% P=8x10 ⁻⁷	<i>PCSK9</i> BF=11.9% P=2x10 ⁻⁸	<i>PCSK9</i> BF=0.89% P=5x10 ⁻¹⁰	<i>LDLR</i> BF=0.20% P=4x10 ⁻⁸	<i>LDLR</i> BF=0.20% P=4x10 ⁻⁸	<i>CHORDC1</i> BF=0.35% P=1x10 ⁻⁶
<i>PVRL2</i> 19:45389174 P=1x10 ⁻⁷	<i>HSPA6</i> BF = 1.1% p=3x10 ⁻⁵	<i>TRIM4</i> BF=1.1% P=1x10 ⁻⁵	<i>TRIM4</i> BF=1.11238% P=1x10 ⁻⁵	<i>SLC35A5</i> BF=7.0% P=2x10 ⁻⁶	<i>LDLR</i> BF=0.11% P=2x10 ⁻⁸	<i>CEP164</i> BF=0.45% P=6x10 ⁻⁶	<i>SPRR2E</i> BF=0.25% P=3x10 ⁻⁶	<i>ANKS1B</i> BF=2.3% P=1x10 ⁻⁶
<i>PTPRZ1</i> 7:121513561 P=3x10 ⁻⁵	<i>PNPLA5</i> BF = 1.1% p=5x10 ⁻⁵	<i>FAM59A</i> BF=3.3% P=1x10 ⁻⁴	<i>SLC35A5</i> BF=2.7% P=1x10 ⁻⁴	<i>ABCG5</i> BF=12.1% P=2x10 ⁻⁴	<i>APOB</i> BF=0.25% P=8x10 ⁻⁸	<i>APOB</i> BF=0.40% P=2x10 ⁻⁵	<i>CEP164</i> BF=0.45 P=4x10 ⁻⁶	<i>PCSK9</i> BF=12.7% P=2x10 ⁻⁶
<i>SSPO</i> 7:149516991 P=6x10 ⁻⁵	<i>YJEFN3</i> BF = 0.68% p=2x10 ⁻⁴	<i>TSHZ3</i> BF=1.5% P=3x10 ⁻⁴	<i>CHORDC1</i> BF=0.33% P=3x10 ⁻⁴	<i>MAN2B2</i> BF=35.6% P=2x10 ⁻⁴	<i>CEP164</i> BF=0.39% P=1x10 ⁻⁵	<i>PCSK9</i> BF=1.25 P=4x10 ⁻⁵	<i>VIM</i> BF=0.40 P=7x10 ⁻⁶	<i>B3GAT1</i> BF=6.7 P=4x10 ⁻⁶
<i>CNTNAP1</i> 17:40836975 P=6x10 ⁻⁵	<i>IPMK</i> BF=0.92% P=2x10 ⁻⁴	<i>CHORDC1</i> BF=0.33% P=3x10 ⁻⁴	<i>SLIT1</i> BF=3.6% P=3x10 ⁻⁴	<i>KLK2</i> BF=6.6% P=3x10 ⁻⁴	<i>OLFM4</i> BF=2.0% P=4x10 ⁻⁴	<i>ART3</i> BF=0.25% P=2x10 ⁻⁴	<i>MGAT1</i> BF=0.25% P=2x10 ⁻⁵	<i>TTC39C</i> BF=0.20% P=1x10 ⁻⁵
<i>RDH8</i> 19:10132290 P=8x10 ⁻⁵	<i>MEIS2</i> BF=0.42 P=3x10 ⁻⁴	<i>NPC1L1</i> BF=10.0% P=3x10 ⁻⁴	<i>APBA3</i> BF=5.1% P=4x10 ⁻⁴	<i>CHORDC1</i> BF=0.33% P=3x10 ⁻⁴	<i>CEP152</i> BF=0.34% P=4x10 ⁻⁴	<i>OLFM4</i> BF=2.0% P=2x10 ⁻⁴	<i>SLC35A5</i> BF=6.3 P=2x10 ⁻⁵	<i>BARHL1</i> BF=0.35 P=3x10 ⁻⁵
<i>PSMC3IP</i> 17:40725656 P=9x10 ⁻⁵	<i>FIGNL1</i> BF=1.8 P=3x10 ⁻⁴	<i>RNLS</i> BF=2.0% P=4x10 ⁻⁴	<i>AZIN1</i> BF=1.8% P=5x10 ⁻⁴	<i>AZIN1</i> BF=1.8% P=5x10 ⁻⁴	<i>ART3</i> BF=0.17% P=4x10 ⁻⁴	<i>MYOM1</i> BF=0.30% P=3x10 ⁻⁴	<i>PCSK9</i> BF=3.8 P=2x10 ⁻⁵	<i>SLC35A5</i> BF=7.1 P=5x10 ⁻⁵
<i>CDH2</i> 18:25543387 P=1x10 ⁻⁴	<i>CHORDC1</i> BF=0.34 P=3x10 ⁻⁴	<i>AZIN1</i> BF=1.8% P=5x10 ⁻⁴	<i>SLC5A6</i> BF=3.1% P=5x10 ⁻⁴	<i>CLNS1A</i> BF=0.39% P=5x10 ⁻⁴	<i>OTOP3</i> BF=0.19 P=9x10 ⁻⁴	<i>SLFN11</i> BF=0.20% P=1x10 ⁻³	<i>TNNI1</i> BF=0.25% P=4x10 ⁻⁵	<i>ABCG5</i> BF=11.8% P=8x10 ⁻⁵
<i>AP1M2</i> 19:10694720 P=1x10 ⁻⁴	<i>FADS6</i> BF=0.95 P=3x10 ⁻⁴	<i>CLNS1A</i> BF=0.39% P=5x10 ⁻⁴	<i>CLNS1A</i> BF=0.39% P=5x10 ⁻⁴	<i>C10orf67</i> BF=0.41% P=5x10 ⁻⁴	<i>PPP6R2</i> BF=0.36% P=1x10 ⁻³	<i>AIPL1</i> BF=0.25% P=2x10 ⁻³	<i>NEUROG1</i> BF=0.35 P=7x10 ⁻⁵	<i>POP5</i> BF=5.9 P=8x10 ⁻⁵
<i>COL5A1</i> 9:137717797 P=1x10 ⁻⁴	<i>PCSK9</i> BF=2.1 P=3x10 ⁻⁴	<i>C10orf67</i> BF=0.41% P=5x10 ⁻⁴	<i>C10orf67</i> BF=0.41% P=5x10 ⁻⁴	<i>SLC12A6</i> BF=2.3% P=5x10 ⁻⁴	<i>P4HA2</i> BF=0.17% P=3x10 ⁻³	<i>CYB561D2</i> BF=0.55% P=2x10 ⁻³	<i>SLC25A48</i> BF=0.20% P=8x10 ⁻⁵	<i>LDLR</i> BF=5.9% P=9x10 ⁻⁵

BF = burden frequency, or percent of individuals who carry at least one copy of the included rare or low frequency alleles; LOF = loss-of-function; Nonsyn = nonsynonymous + splice variants.

Table S3. Genes examined by follow-up sequencing in stage 2 (stage 1 P < 5x10⁻⁵)

Gene	Optimal Test	Ethnicity	Stage 1 (N = 2,005)				Stage 2 (N = 1,302)				Stage 1+ 2 (N = 3,307)			
			P	BF (%)	Effect size (mg/dL)	s.e.	P	BF (%)	Effect size (mg/dL)	s.e.	P	BF (%)	Effect size (mg/dL)	s.e.
			<u>CMC Burden Test</u>											
<i>PCSK9</i>	LOF MAF < 5%	AA	3x10 ⁻¹⁰	2.13	-74.9	11.8	7x10 ⁻¹⁰	2.8	-69.4	11.1	3x10 ⁻¹⁸	3.0	-69.9	8.3
		EA	--	0	--	--	--	0	--	--	--	0	--	--
		Combined	5x10 ⁻¹⁰	0.89	-76.8	12.3	6x10 ⁻¹⁰	1.8	-69.3	11.1	3x10 ⁻¹⁸	1.6	-70.0	8.7
	NS < 5%	AA	1x10 ⁻⁵	25.5	-20.5	4.7	3x10 ⁻⁹	35.0	-23.1	3.8	2x10 ⁻¹²	32.4	-23.3	3.1
		EA	9x10 ⁻⁵	3.2	-40.9	10.4	0.027	5.5	-25.1	11.3	1x10 ⁻⁵	4.4	-31.9	7.9
		Combined	2x10 ⁻⁸	11.9	-24.9	4.4	3x10 ⁻¹⁰	25.0	-23.2	3.6	7x10 ⁻¹⁷	19.1	-24.5	2.9
<i>LDLR</i>	NS MAF<0.1%	AA	4x10 ⁻³	2.8	36.0	12.4	0.013	2.2	31.4	12.7	1x10 ⁻⁴	2.5	39.1	9.2
		EA	4x10 ⁻⁷	2.4	56.3	11.1	2x10 ⁻⁴	2.0	67.8	18.0	4x10 ⁻¹⁰	2.4	64.7	10.5
		Combined	3x10 ⁻⁹	2.5	49.2	8.2	2x10 ⁻⁵	2.1	44.1	10.3	3x10 ⁻¹³	2.4	51.5	6.9
<i>APOB</i>	LOF MAF<5%	AA	0.13	0.07	-89.0	59.3	--	0	--	--	0.13	0.061	-80.4	58.5
		EA	2x10 ⁻⁷	0.39	-123.8	23.6	2x10 ⁻⁴	0.90	-100	26.9	2x10 ⁻¹⁰	0.47	-101.9	23.5
		Combined	8x10 ⁻⁸	0.25	-116.6	21.6	5x10 ⁻⁴	0.31	-94.8	27.2	2x10 ⁻¹⁰	0.26	-98.0	21.3
<i>PNPLA5</i>	NS MAF<0.1%	AA	8x10 ⁻⁵	1.5	65.7	16.5	8x10 ⁻⁴	1.7	47.7	14.1	2x10 ⁻⁷	1.5	53.2	11.7
		EA	0.053	0.96	35.1	18.1	0.55	1.4	13.2	22.2	0.064	1.0	26.7	16.1
		Combined	5x10 ⁻⁵	1.2	50.2	12.3	2x10 ⁻³	1.6	37.1	11.9	3x10 ⁻⁷	1.3	43.5	9.6
<i>SLC35A5</i>	NS MAF<5%	AA	2x10 ⁻⁵	15.5	-23.5	5.5	0.31	15.5	-5.2	5.1	5x10 ⁻⁵	15.9	-12.8	4.0
		EA	3x10 ⁻³	0.92	-61.3	20.8	0.66	0.45	-16.8	38.4	0.012	0.61	-45.2	20.8
		Combined	2x10 ⁻⁶	7.0	-26.2	5.5	0.28	10.4	-5.5	5.1	1x10 ⁻⁵	8.6	-14.8	4.0
<i>HSPA6</i>	NS MAF < 0.1%	AA	0.69	0.86	8.6	21.3	0.35	2.1	12.2	13.0	0.38	1.8	4.1	10.8
		EA	2x10 ⁻⁶	1.3	82.3	17.3	0.15	1.4	32.3	22.3	6x10 ⁻⁶	1.4	70.2	13.6
		Combined	3x10 ⁻⁵	1.1	56.0	13.4	0.12	1.8	17.6	11.2	2x10 ⁻⁵	1.6	31.4	8.5
<i>TRIM4</i>	NS MAF < 1%	AA	6x10 ⁻⁵	1.9	-60.0	14.8	0.56	1.4	-9.3	15.9	3x10 ⁻⁴	1.6	-34.6	11.5
		EA	0.041	0.58	-42.62	20.9	0.23	0.91	32.7	27.1	0.45	0.87	-21.1	17.4
		Combined	1x10 ⁻⁵	1.1	-54.1	12.3	0.96	1.23	0.76	13.7	7x10 ⁻⁴	1.3	-30.4	9.7
<i>CEP164</i>	LOF MAF<5%	AA	.021	0.53	61.3	26.5	0.38	0.58	21.7	24.5	0.016	0.61	46.4	18.5
		EA	1x10 ⁻⁴	0.29	121.3	31.3	0.11	0.44	-61.7	38.3	0.061	0.40	69.7	25.4
		Combined	1x10 ⁻⁵	0.39	89.2	20.3	0.95	0.54	-1.2	20.6	8x10 ⁻⁴	0.51	55.1	15.1
<i>ABCG5</i>	NS MAF < 5%	AA	2x10 ⁻³	23.1	15.2	4.9	0.59	25.6	2.3	4.3	5x10 ⁻³	24.1	8.8	3.4
		EA	0.029	4.1	19.3	8.9	0.85	5.5	2.1	11.4	0.077	5.0	13.5	7.4
		Combined	2x10 ⁻⁴	12.1	16.5	4.4	0.51	18.8	2.6	4.0	8x10 ⁻³	15.0	9.8	3.1
<i>NPC1L1</i>	NS MAF < 0.5%	AA	8x10 ⁻³	16.5	-14.7	5.5	0.83	15.4	1.1	5.2	0.04	15.7	-8.3	4.0

EA	0.018	5.4	-19.5	8.2	0.13	7.7	14.7	9.7	0.42	5.7	-7.6	7.0
Combined	3×10^{-4}	10.0	-16.7	4.6	0.33	12.8	4.4	4.5	0.02	10.9	-8.3	3.5

SKAT-O burden test

<i>MGAT1</i>	SKAT-O LOF +	AA	0.87	0.23	--	--	0.44	0.23	--	--	0.59	0.23	--	--
	Damaging	EA	5×10^{-7}	0.43	--	--	--	0	--	--	5×10^{-8}	0.31	--	--
	Missense MAF<5%	Combined	1×10^{-6}	0.35	--	--	0.46	0.15	--	--	9×10^{-6}	0.27	--	--
<i>BARHL1</i>	SKAT-O NS < 5%	AA	3×10^{-5}	0.83	--	--	0.83	0.58	--	--	0.78	0.58	--	--
		EA	2×10^{-5}	0.17	--	--	--	0	--	--	5×10^{-6}	0.13	--	--
		Combined	3×10^{-5}	0.35	--	--	0.81	0.38	--	--	1×10^{-5}	0.36	--	--
<i>SPRR2E</i>	SKAT-O LOF +	AA	0.74	0.12	--	--	--	0	--	--	0.73	0.06	--	--
	Damaging	EA	1×10^{-5}	0.26	--	--	0.67	0.22	--	--	6×10^{-5}	0.25	--	--
	Missense MAF<5%	Combined	8×10^{-6}	0.20	--	--	0.70	0.08	--	--	3×10^{-5}	0.15	--	--
<i>ABCG5</i>	SKAT-O NS < 5%	AA	5×10^{-3}	21.7	--	--	0.10	25.6	--	--	2×10^{-2}	23.6	--	--
		EA	3×10^{-2}	4.7	--	--	0.59	5.45	--	--	1×10^{-2}	4.90	--	--
		Combined	7×10^{-5}	11.8	--	--	0.10	18.8	--	--	2×10^{-4}	14.6	--	--
<i>TTC39C</i>	SKAT-O NS < 5%	AA	0.19	0.12	--	--	0.29	1.2	--	--	0.03	0.64	--	--
		EA	1×10^{-5}	0.26	--	--	0.62	0.68	--	--	2×10^{-3}	0.38	--	--
		Combined	1×10^{-5}	0.20	--	--	0.41	1.0	--	--	6×10^{-4}	0.51	--	--
<i>VIM</i>	SKAT-O	AA	3×10^{-4}	0.47	--	--	0.47	0.70	--	--	0.05	0.58	--	--
	LOF+Damaging	EA	4×10^{-3}	0.35	--	--	--	0	--	--	0.004	0.25	--	--
	Missense	Combined	7×10^{-6}	0.40	--	--	0.46	0.46	--	--	0.006	0.42	--	--
<i>CEP164</i>	SKAT-O LOF +	AA	4×10^{-2}	0.59	--	--	0.50	5.7	--	--	0.027	5.2	--	--
	Damaging	EA	1×10^{-5}	0.34	--	--	0.29	2.0	--	--	0.052	1.4	--	--
	Missense MAF<5%	Combined	6×10^{-6}	0.45	--	--	0.71	4.5	--	--	0.01	3.4	--	--
<i>ANKS1B</i>	SKAT-O NS < 5%	AA	7×10^{-5}	18.4	--	--	0.87	15.3	--	--	0.25	16.8	--	--
		EA	0.39	13.2	--	--	0.66	13.9	--	--	0.41	13.5	--	--
		Combined	4×10^{-5}	15.5	--	--	0.59	14.8	--	--	0.039	15.2	--	--
<i>CHORDC1</i>	SKAT-O NS < 5%	AA	0.87	0.23	--	--	0.44	0.24	--	--	0.59	0.23	--	--
		EA	5×10^{-7}	0.43	--	--	--	0	--	--	5×10^{-8}	0.32	--	--
		Combined	1×10^{-6}	0.35	--	--	0.46	0.16	--	--	0.63	0.27	--	--

Legend for Table S3: The burden tests performed include the CMC with five categories of variants: nonsynonymous+splice with MAF < 5%, nonsynonymous+splice with MAF < 5%, nonsynonymous+splice with MAF < 5% and presumed loss-of-function variants (nonsense, readthrough and splice) with MAF < 5%, and the SKAT-O test with three categories of variants: nonsynonymous + splice with MAF < 5%, loss-of-function + “probably damaging” missense variants (defined by Polyphen2) with MAF < 5%, and loss-of-function with MAF < 5%. *ABCG5* and *NPC1L1* were selected for follow-up because they are known to cause Mendelian dyslipidemias and were close to the threshold selected for follow-up. BF = burden frequency, or percent of individuals who carry at least one copy of the included rare or low frequency alleles; LOF = loss-of-function; NS = nonsynonymous + splice variants.

Table S4. Genes examined by follow-up genotyping (Illumina HumanExome beadchip array)

Gene	Optimal Burden Test	Stage 1 (N = 2,005)			Stage 1 Using variants on Exome Chip Only (N=2,005)			Genotyping follow-up (Exome Chip)			
		P	BF (%)	Effect size mg/dl (se)	P	BF (%)	Effect size mg/dl (se)	N	P	BF (%)	Effect size mg/dl (se)
<u>Genes selected based on evidence in EA+AA and followed-up in EA+AA</u>											
<i>PCSK9</i>	LOF MAF<5%	5x10 ⁻¹⁰	0.89	-76.8 (12.3)	4x10 ⁻⁹	0.84	-75.7 (12.8)	52,216	2x10 ⁻³⁶	1.5	-27.4 (2.2)
	NS MAF<5%	2x10 ⁻⁸	11.9	-24.9 (4.4)	4x10 ⁻⁷	11.0	-23.4 (4.6)	44,783	5x10 ⁻¹⁷	10.7	-3.9 (0.46)
<i>LDLR</i>	NS MAF<0.1%	3x10 ⁻⁹	2.5	49.2 (8.2)	5x10 ⁻¹⁴	1.1	86.1 (11.4)	52,211	2x10 ⁻¹²	0.26	16.2 (2.3)
<i>SLC35A5</i>	NS MAF<5%	2x10 ⁻⁶	7.0	-26.2 (5.5)	9x10 ⁻⁶	6.6	-25.3 (5.7)	9,196	0.68	3.0	-0.89 (2.1)
<i>ABCG5</i>	NS MAF<5%	2x10 ⁻⁴	12.1	16.5 (4.4)	2x10 ⁻⁴	10.8	17.3 (4.7)	9,204	0.32	9.0	1.0 (1.0)
<i>APOB</i>	LOF MAF<5%	8x10 ⁻⁸	0.25	-116.6 (21.6)	NA	0	NA	46,823	0.47	0.77	-1.9 (2.7)
<i>OR8I2</i>	LOF MAF<5%	2x10 ⁻⁷	5.6	319.8 (60.8)	2x10 ⁻⁷	0.03	319.8 (60.8)	2,034	0.84	0.59	2.8 (14.1)
<i>NPC1L1</i>	NS MAF<0.5%	3x10 ⁻⁴	10.0	-16.7 (4.6)	3x10 ⁻³	7.4	-15.5 (5.2)	9,185	0.95	2.0	0.09 (1.5)
<i>LEFTY2</i>	NS MAF<0.1%	7x10 ⁻⁶	0.25	123.1 (27.3)	2x10 ⁻⁷	0.06	319.8 (60.8)	7,439	0.95	0.11	-0.44 (6.4)
<i>PNPLA5</i>	NS MAF< 0.1%	5x10 ⁻⁵	1.2	50.2 (12.3)	.011	0.75	35.8 (14.1)	52,221	0.81	0.30	-0.5 (2.0)
<i>YJEFN3</i>	NS MAF<0.1%	2x10 ⁻⁴	0.67	59.5 (15.8)	0.06	0.42	37.9 (20.5)	9,200	0.18	0.16	-6.4 (4.8)
<u>Genes selected based on evidence in EA and followed-up in EA only</u>											
<i>FAM69C</i>	NS MAF<5%	5x10 ⁻⁵	0.48	95.9 (23.6)	5x10 ⁻⁶	0.39	117.1 (25.4)	5,399	0.15	0.54	-4.0 (2.7)
<i>PPP1R15A</i>	NS MAF<1%	9x10 ⁻⁵	3.6	36.4 (9.2)	2x10 ⁻⁶	2.8	52.2 (10.9)	5,399	0.26	1.7	-1.8 (1.6)
<i>RNLS</i>	NS MAF<0.1%	2x10 ⁻⁴	0.29	162.4 (43.9)	4x10 ⁻⁷	0.20	315.5 (61.8)	5,399	0.69	0.040	-4.1 (10.2)
<i>RHAG</i>	NS MAF<1%	0.011	0.82	44.5 (17.4)	7x10 ⁻⁷	0.34	126.4 (25.3)	5,399	0.92	0.32	-0.36 (3.5)
<u>Genes selected based on evidence in AA and followed-up in AA only</u>											
<i>TMEM64</i>	NS MAF<5%	0.012	0.33	86.2 (34.3)	3x10 ⁻⁵	0.070	245.4 (58.8)	2,040	0.27	0.050	-53.2 (48.6)

BF = burden frequency, or percent of individuals who carry at least one copy of the included rare or low frequency alleles. LOF = loss-of-function; NS = nonsynonymous + splice variants.

Table S5A. Variants identified in PCSK9 in stage 1 or 2 samples that contributed to the optimal burden test (nonsynonymous or splice with MAF < 5%)

Variant (hg19)	Alleles (major/minor, + strand)	Annotation	AA	EA	N High LDL-C	N Low LDL-C	N High LDL-C	N Low LDL-C
			MAF (%)	MAF (%)	AA with variant (N=298)	AA with variant (N=197)	EA with variant (N=234)	EA with variant (N=208)
1:55505647	G/T	p.Arg46Leu	0.31	1.62	1	0	1	11
1:55505679	G/A	p.Glu57Lys	0.32	0.23	3	1	1	0
1:55509522	T/G	p.Trp72Gly	0	0.04	0	0	0	1
1:55509527	G/T	p.Arg73Ser	0	0.11	0	0	1	0
1:55509585	C/T	p.Arg93Cys	0.06	0	0	0	0	0
1:55509618	C/T	p.Arg104Cys	0.06	0	0	0	0	0
1:55509625	G/T	p.Gly106Val	0.06	0	0	0	0	0
1:55512222	C/G	p.(Tyr142Ter)	0.38	0	0	8	0	0
1:55512266	A/G	p.Asn157Ser	0.06	0	0	1	0	0
1:55512267	C/A	p.Asn157Lys	0	0.09	0	0	0	1
1:55512275	G/A	p.Arg160Gln	0	0.11	0	0	0	1
1:55512295	C/T	p.Arg167Trp	0.06	0	0	0	0	0
1:55517953	G/A	p.Gly176Arg	0.06	0	0	0	0	0
1:55517960	G/A	p.Ser178Asn	0	0.04	0	0	0	0
1:55518321	A/G	c.658-2A>G	0.06	0	0	0	0	0
1:55518362	G/T	p.Val233Leu	0.06	0	0	0	0	0
1:55518371	G/A	p.Gly236Ser	0.18	0	0	3	0	0
1:55518374	C/T	p.Arg237Trp	0	0.13	0	0	0	1
1:55518386	G/A	p.Val241Met	0	0.05	0	0	0	1
1:55518417	G/A	p.Arg251His	0.06	0	0	0	0	0
1:55518419	G/A	p.Val252Met	0.06	0	0	0	0	0
1:55518422	C/T	p.Leu253Phe	0.36	0	1	2	0	0
1:55521701	C/A	p.Pro279Thr	0.39	0	2	2	0	0
1:55521713	C/A	p.Leu283Met	0.09	0	0	0	0	0
1:55523076	C/T	p.Arg357Cys	0.06	0	0	0	0	0
1:55523106	G/T	p.Asp367Tyr	0	0.04	0	0	1	0
1:55523178	C/A	p.His391Asn	0.24	0	0	1	0	0
1:55523187	G/A	p.Gly394Ser	0	0.11	0	0	0	1
1:55523739	C/T	p.Pro404Leu	0.06	0	0	0	0	0
1:55523779	C/A	p.His417Gln	0.18	0	1	1	0	0
1:55523802	A/G	p.Asn425Ser	1.40	0	3	9	0	0
1:55523822	G/A	p.Asp432Asn	0.06	0	0	0	0	0
1:55523838	C/A	p.Thr437Asn	0.06	0	0	1	0	0
1:55523855	G/A	p.Ala443Thr	8.44	0.14	23	37	0	1
1:55524222	C/T	p.Arg469Trp	0.79	0	5	2	0	0
1:55524244	G/A	p.Arg476His	0	0.04	0	0	0	1
1:55524249	G/A	p.Ala478Thr	0	0.04	0	0	0	0
1:55524262	A/G	p.Glu482Gly	0.18	0	1	0	0	0
1:55524304	G/A	p.Arg496Gln	0	0.05	0	0	1	0
1:55524309	G/A	p.Glu498Lys	0	0.10	0	0	0	3

Variant (hg19)	Alleles (major/ minor, + strand)	Annotation			N High LDL-C	N Low LDL-C	N High LDL-C	N Low LDL-C
			AA MAF (%)	EA MAF (%)	AA with variant (N=298)	AA with variant (N=197)	EA with variant (N=234)	EA with variant (N=208)
1:55524313	G/T	p.Arg499Leu	0.06	0.05	0	0	0	1
1:55525276	C/T	p.Pro541Ser	0	0.12	0	0	0	0
1:55525298	C/A	p.Thr548Asn	0.06	0	0	0	0	0
1:55525301	G/A	p.Arg549His	0.06	0	0	0	0	0
1:55525313	A/G	p.His553Arg	1.13	0	6	1	0	0
1:55525315	C/G	p.Gln554Glu	0.24	0	0	2	0	0
1:55527221	C/T	p.(Gln619Ter)	0.08	0	0	1	0	0
1:55527222	A/C	p.Gln619Pro	1.13	0	1	5	0	0
1:55529108	G/A	p.Val644Ile	0.06	0	0	0	0	0
1:55529123	G/A	p.Ala649Thr	0.06	0	0	0	0	0
1:55529153	C/T	p.Arg659Trp	0.06	0	0	0	0	0
1:55529159	G/A	p.Val661Ile	0.06	0	0	0	0	0
1:55529169	C/T	p.Thr664Ile	0	0.04	0	0	0	1
1:55529215	C/A	p.(Cys679Ter)	1.13	0	1	16	0	0

Table S5B. Variants identified in LDLR in stage 1 or 2 samples that contributed to the optimal burden test (nonsynonymous or splice with MAF < 0.1%)

Variant (hg19)	Alleles (major/ minor, + strand)	Annotation			N High LDL-C	N Low LDL-C	N High LDL-C	N Low LDL-C
			AA MAF (%)	EA MAF (%)	AA with variant (N=298)	AA with variant (N=197)	EA with variant (N=234)	EA with variant (N=208)
19:11200282	G/A	p.Gly20Arg	0	0.16	0	0	0	0
19:11210979	G/T	p.Ala50Ser	0.06	0.13	0	0	0	1
19:11211016	C/T	p.Thr62Met	0	0.04	0	0	0	0
19:11213450	G/A	p.Glu101Lys	0	0.09	0	0	2	0
19:11216011	C/A	p.(Cys143Ter)	0	0.04	0	0	0	0
19:11216090	G/A	p.Asp170Asn	0	0.04	0	0	0	0
19:11216172	G/T	p.Cys197Phe	0.06	0	1	0	0	0
19:11216264	G/C	p.Glu228Gln	0.07	0	1	0	0	0
19:11217256	G/A	p.Arg237His	0.06	0.04	1	0	0	0
19:11217303	C/T	p.Arg253Trp	0.09	0	1	0	0	0
19:11217304	G/A	p.Arg253Gln	0.06	0	0	0	0	0
19:11217328	G/T	p.Cys261Phe	0	0.11	0	0	1	0
19:11217334	A/G	p.Asp263Gly	0	0.04	0	0	1	0
19:11217344	T/A	p.Asp266Glu	0	0.06	0	0	2	0
19:11217352	G/A	p.Gly269Asp	0	0.04	0	0	0	0
19:11218068	T/G	p.Val273Gly	0	0.11	0	0	0	0
19:11218079	G/A	p.Glu277Lys	0	0.04	1	1	0	0
19:11218157	C/T	p.Arg303Trp	0.08	0	1	1	0	0
19:11218160	G/A	p.Asp304Asn	0.06	0	1	0	0	0
19:11221354	G/A	p.Gly323Ser	0.06	0	0	0	0	0

Variant (hg19)	Alleles (major/ minor, + strand)	Annotation	AA	EA	N High LDL-C	N Low LDL-C	N High LDL-C	N Low LDL-C
			MAF (%)	MAF (%)	AA with variant (N=298)	AA with variant (N=197)	EA with variant (N=234)	EA with variant (N=208)
19:11222214	A/C	p.Asp362Ala	0	0.06	0	0	0	0
19:11222295	C/T	p.Thr389Met	0.06	0	0	0	0	0
19:11223968	C/G	p.Leu401Val	0.09	0	3	0	0	0
19:11223991	G/C	p.Glu408Asp	0	0.04	0	0	1	0
19:11224037	C/A	p.Pro424Thr	0.06	0	0	0	0	0
19:11224210	G/A	c.1359-1G>A	0	0.04	0	0	1	0
19:11224228	C/G	p.Ala459Gly	0	0.11	0	0	0	0
19:11224284	G/A	p.Gly478Arg	0.06	0	1	0	0	0
19:11224296	G/A	p.Asp482Asn	0	0.04	0	0	1	0
19:11224398	G/A	p.Gly516Ser	0.06	0	0	0	0	0
19:11227559	G/A	p.Trp577Ter	0	0.04	0	0	1	0
19:11227600	A/G	p.Asn591Asp	0.06	0	0	0	0	0
19:11227604	G/A	p.Gly592Glu	0	0.04	0	0	1	0
19:11227645	G/T	p.Ala606Ser	0	0.04	0	0	0	0
19:11230798	G/A	p.Glu626Lys	0	0.09	0	0	0	0
19:11231057	T/C	p.Cys667Arg	0.18	0	2	0	0	0
19:11231112	C/T	p.Pro685Leu	0	0.04	0	0	1	0
19:11231154	C/T	p.Pro699Leu	0.06	0	1	0	0	0
19:11231159	G/A	p.Gly701Ser	0	0.04	0	0	0	0
19:11231164	G/A	p.Met702Ile	0	0.09	0	0	1	0
19:11231199	G/A	c.2140+1G>A	0	0.04	0	0	1	0
19:11233961	G/A	p.Arg751Gln	0.06	0	0	0	0	0
19:11234010	G/A	p.Met767Ile	0.06	0	0	0	0	0
19:11234014	C/T	p.His769Tyr	0.06	0	0	0	0	0
19:11238684	C/T	p.Ala771Val	0.06	0	0	0	0	0
19:11238692	G/A	p.Asp774Asn	0.06	0	1	0	0	0
19:11240240	G/A	p.Arg814Gln	0.29	0	2	0	0	0
19:11240278	G/A	p.Val827Ile	0	0.13	0	0	1	0
19:11240309	A/G	p.His837Arg	0	0.04	0	0	0	0
19:11240345	C/T	p.Ser849Leu	0.06	0.11	0	1	0	0
19:11241984	G/A	p.Val859Met	0.06	0	0	0	0	0

Table S5C. Variants identified in APOB in stage 1 or 2 samples that contributed to the optimal burden test (loss-of-function variants with MAF < 5%)

Variant (hg19)	Alleles (major/ minor, - strand)	Annotation	AA	EA	N High LDL-C	N Low LDL-C	N High LDL-C	N Low LDL-C
			MAF (%)	MAF (%)	AA with variant (N=298)	AA with variant (N=197)	EA with variant (N=234)	EA with variant (N=208)
2:21260985	A/G	c.384-2A>G	0	0.04	0	0	0	0
2:21255263	C/T	p.(Arg439Ter)	0	0.04	0	0	0	1
2:21249731	C/T	p.(Gln725Ter)	0	0.11	0	0	0	1
2:21249659	G/A	c.2244+1G>A	0	0.04	0	0	0	1

Variant (hg19)	Alleles (major/ minor, - strand)	Annotation			N High LDL-C	N Low LDL-C	N High LDL-C	N Low LDL-C
			AA MAF (%)	EA MAF (%)	AA with variant (N=298)	AA with variant (N=197)	EA with variant (N=234)	EA with variant (N=208)
2:21237944	G/C	c.3696+1G>C	0	0.04	0	0	0	1
2:21237384	G/T	p.(Glu1260Ter)	0	0.04	0	0	0	1
2:21235237	T/G	p.(Tyr1501Ter)	0	0.11	0	0	0	1
2:21235089	C/T	p.(Gln1551Ter)	0	0.04	0	0	0	1
2:21233706	C/T	p.(Arg2012Ter)	0.06	0	0	1	0	0
2:21233500	T/A	p.(Tyr2080Ter)	0	0.04	0	0	0	1
2:21228340	T/G	p.(Tyr3800Ter)	0	0.11	0	0	0	1
2:21228099	C/T	p.(Gln3881Ter)	0	0.11	0	0	0	1

Table S5D. Variants identified in PNPLA5 in stage 1 or 2 samples that contributed to the optimal burden test (nonsynonymous or splice with MAF < 0.1%)

Variant (hg19)	Alleles (major/ minor, - strand)	Annotation			N High LDL-C	N Low LDL-C	N High LDL-C	N Low LDL-C
			AA MAF (%)	EA MAF (%)	AA with variant (N=298)	AA with variant (N=197)	EA with variant (N=234)	EA with variant (N=208)
22:44287586	G/A	p.Val59Ile	0.06	0	1	0	0	0
22:44287165	G/T	p.Cys68Phe	0	0.05	0	0	0	0
22:44287133	G/T	p.Glu79Ter	0.06	0	0	0	0	0
22:44287109	C/A	p.His87Asn	0	0.11	0	0	0	0
22:44287083	C/A	p.His95Gln	0	0.05	0	0	0	0
22:44287071	G/C	p.Gln99His	0	0.11	0	0	0	1
22:44287051	C/T	p.Pro106Leu	0.07	0	1	0	0	0
22:44285723	T/C	p.Phe150Leu	0.06	0.22	0	0	1	1
22:44285418	C/T	p.Arg165Cys	0.12	0	3	0	0	0
22:44285417	G/A	p.Arg165His	0.12	0	0	0	0	0
22:44285379	G/A	p.Ala178Thr	0.06	0	1	0	0	0
22:44285315	G/T	p.Ser85Ile	0	0.09	0	0	1	0
22:44285245	C/G	p.Phe108Leu	0	0.11	0	0	0	0
22:44282369	G/A	c. 422-1G>A	0.12	0	0	0	0	0
22:44282368	G/T	p.Gly141Val	0.06	0	0	0	0	0
22:44282243	C/A	p.Pro183Thr	0.06	0	2	0	0	0
22:44280225	C/T	p.Ala203Val	0	0.04	0	0	0	0
22:44280193	C/T	p.Arg214Trp	0	0.04	0	0	1	0
22:44280150	C/T	p.Thr228Met	0	0.09	0	0	1	0
22:44280103	C/T	p.Arg244Cys	0.06	0	1	0	0	0
22:44277512	G/C	p.Trp261Cys	0.21	0	1	0	0	0
22:44277510	T/C	p.Met262Thr	0.06	0	0	0	0	0
22:44277459	C/G	p.Ala279Gly	0.06	0	0	0	0	0
22:44276701	G/A	p.Glu308Lys	0.06	0	0	0	0	0

Table S6. Power estimates for alternative study designs of one ethnic group (stage 1)

Gene	Test	Standardized Effect size (AA)	Burden frequency (AA) %	Power in AA (N=2005, $\alpha = 1 \times 10^{-6}$)	Standardized Effect size (EA)	Burden Frequency (EA) %	Power in EA (N=2005, $\alpha = 1 \times 10^{-6}$)
<i>PCSK9</i>	LOF < 5%	-1.2	2.1	99.9	--	0	NA
	NS < 5%	-0.3	25.5	94.7	-0.6	3.2	56.2
<i>LDLR</i>	NS < 0.1%	0.6	2.8	30.0	0.9	2.4	93.3
<i>APOB</i>	LOF < 5%	-1.5	0.1	0.4	-1.9	0.4	95.9
<i>PNPLA5</i>	NS < 0.1%	1.1	1.5	84.2	0.5	1.0	0.8

Legend for Table S6: Power was estimated assuming the same sample size as stage 1 (N=2,005) but consisting of entirely one ethnic group, either African-American (AA) or European-American (EA). For each gene burden test, standardized effect sizes (SD units) and burden frequencies were estimated from stage 1+2 ethnic-specific samples. NS = nonsynonymous + splice variants. Burden frequency is the percent of individuals who carry at least one copy of the included rare or low frequency alleles.

Table S7. Comparison of burden tests results for LDL-C associated genes

Gene	NS MAF < 0.1%	NS MAF < 0.5%	NS MAF < 1%	NS MAF < 5%	LOF MAF < 5%	SKAT-O LOF MAF <5%	SKAT-O Damaging NS MAF <5%	SKAT-O NS MAF < 5%
N (genes or SNPs)	14,534	15,342	15,477	15,622	2,241	2,045	6,711	16,141
PCSK9	P=3x10 ⁻⁴ BF=2.1 rank=14	P=8x10 ⁻⁷ BF=5.7 rank = 1	P=8x10 ⁻⁷ BF=5.7 rank=1	P=2x10 ⁻⁸ BF=11.9 rank=1	P=5x10 ⁻¹⁰ BF=0.89 rank=1	P=4x10 ⁻⁵ BF=1.2 rank=4	P=2x10 ⁻⁵ BF=3.8 rank = 7	P=2x10 ⁻⁶ BF=12.7 rank=3
LDLR	P=3x10 ⁻⁹ BF=2.5 rank=1	P=2x10 ⁻³ BF=4.3 rank=37	P=2x10 ⁻³ BF=5.3 rank=31	P=2x10 ⁻³ BF=5.3 rank=18	P=2x10 ⁻⁸ BF=0.11 rank=2	P=4x10 ⁻⁸ BF=0.20 rank=1	P=4x10 ⁻⁸ BF=0.20 rank=1	P=1x10 ⁻⁴ BF=5.9 rank=10
PNPLA5	P=5x10 ⁻⁵ BF=1.2 rank=5	P=2x10 ⁻³ BF=2.8 rank=49	P=2x10 ⁻³ BF=2.8 rank=49	P=.25 BF=9.0 rank=4361	P=.47 BF=0.11 rank=5174	NA	NA	P=0.25 BF=9.5 rank=3808
APOB	P=0.19 BF=10.1 rank=3280	P=0.36 BF=21.0 rank=6167	P=0.51 BF=30.6 rank=8803	P =0.35 BF=60.3 rank=5871	P=8x10 ⁻⁸ BF=0.25 rank=3	P=2x10 ⁻⁵ BF=0.40 rank=3	P=2x10 ⁻³ BF=23.4 rank=43	P=0.02 BF=60.3 rank=408
ABCG5	P=0.10 BF=1.7 rank=1629	P=0.08 BF=4.5 rank=1297	P=0.02 BF=5.8 rank=400	P=2x10 ⁻⁴ BF=12.1 rank=3	P=5x10 ⁻³ BF=0.08 rank=85	NA	P=0.21 BF=1.3 rank=1413	P=7x10 ⁻⁵ BF=11.8 rank=8
NPC1L1	P=0.02 BF=4.0 rank=368	P=3x10 ⁻⁴ BF=10.0 rank=6	P=0.04 BF=13.2 rank=730	P=0.81 BF=23.2 rank=13900	P=0.40 BF=0.11 rank=4760	P=0.46 BF=1.2 rank=671	P=0.17 BF=5.7 rank=1156	P=0.45 BF=23.0 rank=6990

Legend for Table S7: The rank indicates the rank of that gene p-value against all other genes examined with that burden test (BF > 0.24% for NS tests and BF > 0.10% required for LOF tests). BF = burden frequency, or percent of individuals who carry at least one copy of the included rare or low frequency alleles. NS = nonsynonymous and splice variants. LOF = loss-of-function. Damaging = “probably damaging” by Polyphen2.

Table S8. Number and type of variants identified by exome sequencing of 1,151 European-Americans and 854 African-Americans (stage 1)

Population	Variant type	Total number of variants called	Number of variants per individual (SD)	Number of unique variants per individual (SD)	% in dbSNP	Ts/Tv ratio
European-Americans (N = 1,151)	Splice	1,778	16.6 (3.4)	1.1 (1.1)	6.9	1.88
	Nonsense	4,037	46.9 (5.6)	2.5 (1.6)	7.6	2.38
	Read-through	226	15.4 (2.8)	0.10 (0.32)	23.9	1.31
	Missense	189,668	5,865 (184)	91.1 (20.1)	17.6	2.42
	Synonymous	124,484	7,088 (226)	47.3 (12.2)	28.5	5.78
	Noncoding	213,695	12,429 (947)	75.6 (20.1)	25.3	2.44
African-Americans (N= 854)	Splice	1,588	24.0 (4.6)	1.14 (1.08)	8.6	1.88
	Nonsense	3,616	53.5 (7.3)	2.46 (1.58)	9.8	2.30
	Read-through	281	17.7 (4.2)	0.13 (0.36)	24.6	1.11
	Missense	214,756	7,284 (535)	110 (17.1)	18.6	2.39
	Synonymous	161,999	9,113 (582)	64.9 (11.4)	26.6	5.61
	Noncoding	278,354	15,849 (1576)	103 (19.4)	21.9	2.44
Combined (N = 2,005)	Splice	3,093	19.8(5.4)	1.14(1.1)	5.0	1.88
	Nonsense	6,958	49.7(7.2)	2.49(1.6)	5.9	2.33
	Read-through	424	16.4(3.7)	0.12(0.34)	16.7	1.16
	Missense	345,569	6,469(796)	99.2(21.1)	12.6	2.37
	Synonymous	232,182	7,951(1085)	54.8(14.7)	19.6	5.63
	Noncoding	392,897	13,886(2106)	87.2(23.9)	16.1	2.42

Ts/Tv ratio: the ratio of transition to transversion variants

Table S9. Metrics used for SVM filtering of variants identified by sequencing (stage 1)

Metric short form	Metric Description	Criteria for defining negative SNP set for SVM training (3 or more required)
QUAL	SNP quality	< 20
DP	overall depth	DP < N, or DP > 1000N
MQ	mapping quality (RMS)	
NS	number of samples with coverage	NS < 1700
	number of alleles with coverage (NS*2 for autosomes)	
AN		
AB	allele balance in heterozygotes	> 0.65
STR	strand bias (corr)	STR < -0.1, STR > 0.1
STZ	strand bias (z-score)	
CBR	cycle bias (corr)	CBR < -0.15, CBR > 0.1
CBZ	cycle bias (z-score)	
QBR	base quality bias (corr)	
QBZ	base quality bias (z-score)	
MBR	mapping quality bias (corr)	
MBZ	mapping quality bias (z-score)	
IOR	inflation of non-ref, non-alt allele (corr)	
IOZ	inflation of non-ref, non-alt allele (z-score)	
AOZ	z-score on the distribution of alt bases	
AOI	AOZ + IOZ	> 3
ABE	allele balance from base quality	
ABZ	allele balance z-score	
BCS	Bayesian SNP call score	
FIC	inbreeding coefficient	
LQR	fraction of low quality (q<13) bases	
MQ0	fraction of bases with MQ=0	
MQ10	fraction of bases with MQ<10	
MQ20	fraction of bases with MQ<20	> 0.1
MQ30	fraction of bases with MQ<30	

Table S10. Sensitivity analyses using different burden test models in stage 1 for known LDL-C associated genes

	Model	Linear Regression	Linear Regression	Linear Regression	Linear Regression	Linear Regression	Linear Regression	Linear Regression	Reverse Regression
	Covariates	age, sex, PC1, PC2, ethnicity, ESP-phenotype	age, sex, PC1, PC2, ethnicity, cohort	age, sex, PC1, PC2, ethnicity, cohort, ESP-phenotype	age, sex, PC1, PC2, cohort, ESP-phenotype, meta EA/AA	age, sex, PC1, PC2, ethnicity, cohort, ESP-phenotype	age, sex, PC1, PC2, ethnicity, cohort, ESP-phenotype	age, sex, PC1, PC2, ethnicity, cohort, ESP-phenotype	age, sex, PC1, PC2, ethnicity, cohort
	Missing Data	Dosage	Dosage	Dosage	Dosage	Dosage	Dosage	Dosage	Multiple imputation
	Phenotype	LDL	LDL	LDL	LDL	LDL	Inverse normal transformed LDL	LDL	LDL
	Genotype completeness	>50%	>50%	>50%	>50%	>90%	>50%	>50%	>50%
	Sample	2005	2005	2005	2005	2005	2005	2005	2005
Gene	P-value	Asymptotic	Asymptotic	Asymptotic	Asymptotic	Asymptotic	Asymptotic	Permutation (10 million)	Asymptotic
<i>PCSK9</i>	NS <5%	1.8x10 ⁻⁸	3.0x10 ⁻⁸	1.3x10 ⁻⁸	5.7x10 ⁻⁹	1.5x10 ⁻⁴	4.6x10 ⁻⁹	< 1x10 ⁻⁷	5.1x10 ⁻⁸
<i>LDLR</i>	NS <0.1%	2.8x10 ⁻⁹	1.1x10 ⁻⁹	1.8x10 ⁻⁹	1.0x10 ⁻⁸	8.8x10 ⁻⁹	4.5x10 ⁻⁷	< 1x10 ⁻⁷	1.7x10 ⁻⁷
<i>APOB</i>	LOF <5%	7.7x10 ⁻⁸	3.9x10 ⁻⁷	8.9x10 ⁻⁸	8.1x10 ⁻⁷	9.6x10 ⁻⁸	5.7x10 ⁻⁹	4.0x10 ⁻⁶	4.5x10 ⁻⁴
	Spearman correlation (ρ^2)	--	0.93	0.97	0.8-0.88	0.85	0.94	NA	0.90
	Spearman correlation for LOF test (ρ^2)	--	0.92	0.97	0.76	0.94	0.94	NA	0.73
	Lambda GC (based on median p)	0.95-1.0	0.96-0.99	0.95-1.0	0.97-1.02	0.95-0.98	0.97-1.0	NA	0.97-1.0
	Lambda GC for LOF (based on median p)	0.95	0.98	0.95	0.91	0.92	0.99	NA	0.99

GC = Genomic control factor. LOF = loss-of-function.

Supplemental References

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