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%
TOMM40 19:45397229 $P=8\times10^{-14}$	*LDLR** BF = 2.5% $p=3\times10^{-9}$	*PCSK9* BF=5.7% $P=8\times10^{-7}$	*PCSK9* BF=5.7% $P=8\times10^{-7}$	*PCSK9* BF=11.9% $P=2\times10^{-8}$	*PCSK9* BF=0.89% $P=5\times10^{-10}$	*LDLR* BF=0.20% $P=4\times10^{-8}$	*LDLR* BF=0.20% $P=4\times10^{-8}$	*CHORDC1* BF=0.35% $P=1\times10^{-6}$
PVRL2 19:45389174 $P=1\times10^{-7}$	*HSPA6* BF = 1.1% $p=3\times10^{-5}$	*TRIM4* BF=1.1% $P=1\times10^{-5}$	*TRIM4* BF=1.11238% $P=1\times10^{-5}$	*SLC35A5* BF=7.0% $P=2\times10^{-6}$	*LDLR* BF=0.11% $P=2\times10^{-8}$	*CEP164* BF=0.45% $P=6\times10^{-6}$	*SPRR2E* BF=0.25% $P=3\times10^{-6}$	*ANKS1B* BF=2.3% $P=1\times10^{-6}$
PTPRZ1 7:121513561 $P=3\times10^{-5}$	*PNPLA5* BF = 1.1% $p=5\times10^{-5}$	*FAM59A* BF=3.3% $P=1\times10^{-4}$	*SLC35A5* BF=2.7% $P=1\times10^{-4}$	*ABCG5* BF=12.1% $P=2\times10^{-4}$	*APOB* BF=0.25% $P=8\times10^{-8}$	*APOB* BF=0.40% $P=2\times10^{-5}$	*CEP164* BF=0.45 $P=4\times10^{-6}$	*PCSK9* BF=12.7% $P=2\times10^{-6}$
SSPO 7:149516991 $P=6\times10^{-5}$	*YJEFN3* BF = 0.68% $p=2\times10^{-4}$	*TSHZ3* BF=1.5% $P=3\times10^{-4}$	*CHORDC1* BF=0.33% $P=3\times10^{-4}$	*MAN2B2* BF=35.6% $P=2\times10^{-4}$	*CEP164* BF=0.39% $P=1\times10^{-5}$	*PCSK9* BF=1.25 $P=4\times10^{-5}$	*VIM* BF=0.40 $P=7\times10^{-6}$	*B3GAT1* BF=6.7 $P=4\times10^{-6}$
CNTNAP1 17:40836975 $P=6\times10^{-5}$	*IPMK* BF=0.92% $P=2\times10^{-4}$	*CHORDC1* BF=0.33% $P=3\times10^{-4}$	*SLIT1* BF=3.6% $P=3\times10^{-4}$	*KLK2* BF=6.6% $P=3\times10^{-4}$	*OLFM4* BF=2.0% $P=4\times10^{-4}$	*ART3* BF=0.25% $P=2\times10^{-4}$	*MGAT1* BF=0.25% $P=2\times10^{-5}$	*TTC39C* BF=0.20% $P=1\times10^{-5}$
RDH8 19:10132290 $P=8\times10^{-5}$	*MEIS2* BF=0.42 $P=3\times10^{-4}$	*NPC1L1* BF=10.0% $P=3\times10^{-4}$	*APBA3* BF=5.1% $P=4\times10^{-4}$	*CHORDC1* BF=0.33% $P=3\times10^{-4}$	*CEP152* BF=0.34% $P=4\times10^{-4}$	*OLFM4* BF=2.0% $P=2\times10^{-4}$	*SLC35A5* BF=6.3 $P=2\times10^{-5}$	*BARHL1* BF=0.35 $P=3\times10^{-5}$
PSMC3IP 17:40725656 $P=9\times10^{-5}$	*FIGNL1* BF=1.8 $P=3\times10^{-4}$	*RNLS* BF=2.0% $P=4\times10^{-4}$	*AZIN1* BF=1.8% $P=5\times10^{-4}$	*AZIN1* BF=1.8% $P=5\times10^{-4}$	*ART3* BF=0.17% $P=4\times10^{-4}$	*MYOM1* BF=0.30% $P=3\times10^{-4}$	*PCSK9* BF=3.8 $P=2\times10^{-5}$	*SLC35A5* BF=7.1 $P=5\times10^{-5}$
CDH2 18:25543387 $P=1\times10^{-4}$	*CHORDC1* BF=0.34 $P=3\times10^{-4}$	*AZIN1* BF=1.8% $P=5\times10^{-4}$	*SLC5A6* BF=3.1% $P=5\times10^{-4}$	*CLNS1A* BF=0.39% $P=5\times10^{-4}$	*OTOP3* BF=0.19 $P=9\times10^{-4}$	*SLFN11* BF=0.20% $P=1\times10^{-3}$	*TNNI1* BF=0.25% $P=4\times10^{-5}$	*ABCG5* BF=11.8% $P=8\times10^{-5}$
AP1M2 19:10694720 $P=1\times10^{-4}$	*FADS6* BF=0.95 $P=3\times10^{-4}$	*CLNS1A* BF=0.39% $P=5\times10^{-4}$	*CLNS1A* BF=0.39% $P=5\times10^{-4}$	*C10orf67* BF=0.41% $P=5\times10^{-4}$	*PPP6R2* BF=0.36% $P=1\times10^{-3}$	*AIPL1* BF=0.25% $P=2\times10^{-3}$	*NEUROG1* BF=0.35 $P=7\times10^{-5}$	*POP5* BF=5.9 $P=8\times10^{-5}$
COL5A1 9:137717797 $P=1\times10^{-4}$	*PCSK9* BF=2.1 $P=3\times10^{-4}$	*C10orf67* BF=0.41% $P=5\times10^{-4}$	*C10orf67* BF=0.41% $P=5\times10^{-4}$	*SLC12A6* BF=2.3% $P=5\times10^{-4}$	*P4HA2* BF=0.17% $P=3\times10^{-3}$	*CYB561D2* BF=0.55% $P=2\times10^{-3}$	*SLC25A48* BF=0.20% $P=8\times10^{-5}$	*LDLR* BF=5.9% $P=9\times10^{-5}$

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) P	BF (%)	Effect size (mg/dL)	s.e.	Stage 2 (N = 1,302) P	BF (%)	Effect size (mg/dL)	s.e.	Stage 1+ 2 (N = 3,307) P	BF (%)	Effect size (mg/dL)	s.e.
			CMC Burden Test											
PCSK9	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
LDLR	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
APOB	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
PNPLA5	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
SLC35A5	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
HSPA6	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
TRIM4	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
CEP164	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
ABCG5	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
NPC1L1	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	$3x10^{-4}$	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							
MGAT1	SKAT-O LOF +	AA	0.87	0.23	--	--	0.44	0.23	--	--	0.59	0.23	--	--
	Damaging	EA	$5x10^{-7}$	0.43	--	--	--	0	--	--	$5x10^{-8}$	0.31	--	--
	Missense	Combined	$1x10^{-6}$	0.35	--	--	0.46	0.15	--	--	$9x10^{-6}$	0.27	--	--
	MAF<5%													
BARHL1	SKAT-O NS < 5%	AA	$3x10^{-5}$	0.83	--	--	0.83	0.58	--	--	0.78	0.58	--	--
		EA	$2x10^{-5}$	0.17	--	--	--	0	--	--	$5x10^{-6}$	0.13	--	--
		Combined	$3x10^{-5}$	0.35	--	--	0.81	0.38	--	--	$1x10^{-5}$	0.36	--	--
SPRR2E	SKAT-O LOF +	AA	0.74	0.12	--	--	--	0	--	--	0.73	0.06	--	--
	Damaging	EA	$1x10^{-5}$	0.26	--	--	0.67	0.22	--	--	$6x10^{-5}$	0.25	--	--
	Missense	Combined	$8x10^{-6}$	0.20	--	--	0.70	0.08	--	--	$3x10^{-5}$	0.15	--	--
	MAF<5%													
ABCG5	SKAT-O NS < 5%	AA	$5x10^{-3}$	21.7	--	--	0.10	25.6	--	--	$2x10^{-2}$	23.6	--	--
		EA	$3x10^{-2}$	4.7	--	--	0.59	5.45	--	--	$1x10^{-2}$	4.90	--	--
		Combined	$7x10^{-5}$	11.8	--	--	0.10	18.8	--	--	$2x10^{-4}$	14.6	--	--
TTC39C	SKAT-O NS < 5%	AA	0.19	0.12	--	--	0.29	1.2	--	--	0.03	0.64	--	--
		EA	$1x10^{-5}$	0.26	--	--	0.62	0.68	--	--	$2x10^{-3}$	0.38	--	--
		Combined	$1x10^{-5}$	0.20	--	--	0.41	1.0	--	--	$6x10^{-4}$	0.51	--	--
VIM	SKAT-O	AA	$3x10^{-4}$	0.47	--	--	0.47	0.70	--	--	0.05	0.58	--	--
	LOF+Damaging	EA	$4x10^{-3}$	0.35	--	--	--	0	--	--	0.004	0.25	--	--
	Missense	Combined	$7x10^{-6}$	0.40	--	--	0.46	0.46	--	--	0.006	0.42	--	--
CEP164	SKAT-O LOF +	AA	$4x10^{-2}$	0.59	--	--	0.50	5.7	--	--	0.027	5.2	--	--
	Damaging	EA	$1x10^{-5}$	0.34	--	--	0.29	2.0	--	--	0.052	1.4	--	--
	Missense	Combined	$6x10^{-6}$	0.45	--	--	0.71	4.5	--	--	0.01	3.4	--	--
	MAF<5%													
ANKS1B	SKAT-O NS < 5%	AA	$7x10^{-5}$	18.4	--	--	0.87	15.3	--	--	0.25	16.8	--	--
		EA	0.39	13.2	--	--	0.66	13.9	--	--	0.41	13.5	--	--
		Combined	$4x10^{-5}$	15.5	--	--	0.59	14.8	--	--	0.039	15.2	--	--
CHORDC1	SKAT-O NS < 5%	AA	0.87	0.23	--	--	0.44	0.24	--	--	0.59	0.23	--	--
		EA	$5x10^{-7}$	0.43	--	--	--	0	--	--	$5x10^{-8}$	0.32	--	--
		Combined	$1x10^{-6}$	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%, 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) P	Stage 1 (N = 2,005) BF (%)	Stage 1 (N = 2,005) Effect size mg/dl (se)	Stage 1 Using variants on Exome Chip Only (N=2,005) P	Stage 1 Using variants on Exome Chip Only (N=2,005) BF (%)	Stage 1 Using variants on Exome Chip Only (N=2,005) Effect size mg/dl (se)	Genotyping follow-up (Exome Chip) N	Genotyping follow-up (Exome Chip) P	Genotyping follow-up (Exome Chip) BF (%)	Genotyping follow-up (Exome Chip) Effect size mg/dl (se)
		Genes selected based on evidence in EA+AA and followed-up in EA+AA									
PCSK9	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)
LDLR	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)
SLC35A5	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)
ABCG5	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)
APOB	LOF MAF<5%	$8x10^{-8}$	0.25	-116.6 (21.6)	NA	0	NA	46,823	0.47	0.77	-1.9 (2.7)
OR8I2	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)
NPC1L1	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)
LEFTY2	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)
PNPLA5	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)
YJEFN3	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)
		Genes selected based on evidence in EA and followed-up in EA only									
FAM69C	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)
PPP1R15A	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)
RNLS	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)
RHAG	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)
		Genes selected based on evidence in AA and followed-up in AA only									
TMEM64	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 MAF (%)	EA MAF (%)	N High LDL-C AA with variant (N=298)	N Low LDL-C AA with variant (N=197)	N High LDL-C EA with variant (N=234)	N Low LDL-C 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	AA MAF (%)	EA MAF (%)	N High LDL-C AA with variant (N=298)	N Low LDL-C AA with variant (N=197)	N High LDL-C EA with variant (N=234)	N Low LDL-C 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	AA MAF (%)	EA MAF (%)	N High LDL-C AA with variant (N=298)	N Low LDL-C AA with variant (N=197)	N High LDL-C EA with variant (N=234)	N Low LDL-C 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 MAF (%)	EA MAF (%)	N High LDL-C AA with variant (N=298)	N Low LDL-C AA with variant (N=197)	N High LDL-C EA with variant (N=234)	N Low LDL-C 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 MAF (%)	EA MAF (%)	N High LDL-C AA with variant (N=298)	N Low LDL-C AA with variant (N=197)	N High LDL-C EA with variant (N=234)	N Low LDL-C 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	AA MAF (%)	EA MAF (%)	N High LDL-C AA with variant (N=298)	N Low LDL-C AA with variant (N=197)	N High LDL-C EA with variant (N=234)	N Low LDL-C 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	AA MAF (%)	EA MAF (%)	N High LDL-C AA with variant (N=298)	N Low LDL-C AA with variant (N=197)	N High LDL-C EA with variant (N=234)	N Low LDL-C 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, $\alpha = 1x10^{-6}$)	Standardized Effect size (EA)	Burden Frequency (EA) %	Power in EA (N=2005, $\alpha = 1x10^{-6}$)
PCSK9	LOF < 5%	-1.2	2.1	99.9	--	0	NA
	NS < 5%	-0.3	25.5	94.7	-0.6	3.2	56.2
LDLR	NS < 0.1%	0.6	2.8	30.0	0.9	2.4	93.3
APOB	LOF < 5%	-1.5	0.1	0.4	-1.9	0.4	95.9
PNPLA5	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**
	$P=3x10^{-4}$	$P=8x10^{-7}$	$P=8x10^{-7}$	$P=2x10^{-8}$	$P=5x10^{-10}$	$P=4x10^{-5}$	$P=2x10^{-5}$	$P=2x10^{-6}$
PCSK9	BF=2.1	BF=5.7	BF=5.7	BF=11.9	BF=0.89	BF=1.2	BF=3.8	BF=12.7
	rank=14	rank = 1	rank=1	rank=1	rank=1	rank=4	rank = 7	rank=3
	$P=3x10^{-9}$	$P=2x10^{-3}$	$P=2x10^{-3}$	$P=2x10^{-3}$	$P=2x10^{-8}$	$P=4x10^{-8}$	$P=4x10^{-8}$	$P=1x10^{-4}$
LDLR	BF=2.5	BF=4.3	BF=5.3	BF=5.3	BF=0.11	BF=0.20	BF=0.20	BF=5.9
	rank=1	rank=37	rank=31	rank=18	rank=2	rank=1	rank=1	rank=10
	$P=5x10^{-5}$	$P=2x10^{-3}$	$P=2x10^{-3}$	P=.25	P=.47			P=0.25
PNPLA5	BF=1.2	BF=2.8	BF=2.8	BF=9.0	BF=0.11	NA	NA	BF=9.5
	rank=5	rank=49	rank=49	rank=4361	rank=5174			rank=3808
	P=0.19	P=0.36	P=0.51	P =0.35	$P=8x10^{-8}$	$P=2x10^{-5}$	$P=2x10^{-3}$	P=0.02
APOB	BF=10.1	BF=21.0	BF=30.6	BF=60.3	BF=0.25	BF=0.40	BF=23.4	BF=60.3
	rank=3280	rank=6167	rank=8803	rank=5871	rank=3	rank=3	rank=43	rank=408
	P=0.10	P=0.08	P=0.02	$P=2x10^{-4}$	$P=5x10^{-3}$		P=0.21	$P=7x10^{-5}$
ABCG5	BF=1.7	BF=4.5	BF=5.8	BF=12.1	BF=0.08	NA	BF=1.3	BF=11.8
	rank=1629	rank=1297	rank=400	rank=3	rank=85		rank=1413	rank=8
	P=0.02	$P=3x10^{-4}$	P=0.04	P=0.81	P=0.40	P=0.46	P=0.17	P=0.45
NPC1L1	BF=4.0	BF=10.0	BF=13.2	BF=23.2	BF=0.11	BF=1.2	BF=5.7	BF=23.0
	rank=368	rank=6	rank=730	rank=13900	rank=4760	rank=671	rank=1156	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
AN	number of alleles with coverage (NS*2 for autosomes)	
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

Gene	P-value	Model	Covariates	Missing Data	Phenotype	Genotype completeness	Sample	P-value	Model	Covariates	Missing Data	Phenotype	Genotype completeness	Sample	P-value	Model	Covariates	Missing Data	Phenotype	Genotype completeness	Sample	P-value	Model	Covariates	Missing Data	Phenotype	Genotype completeness	Sample	P-value	Model	Covariates	Missing Data	Phenotype	Genotype completeness	Sample	P-value
PCSK9	NS <5%	Linear Regression	age, sex, PC1, PC2, ethnicity, ESP-phenotype	Dosage	LDL	>50%	2005	Asymptotic	Linear Regression	age, sex, PC1, PC2, ethnicity, cohort	Dosage	LDL	>50%	2005	Asymptotic	Linear Regression	age, sex, PC1, PC2, ethnicity, cohort, ESP-phenotype	Dosage	LDL	>50%	2005	Asymptotic	Linear Regression	age, sex, PC1, PC2, cohort, ESP-phenotype, meta EA/AA	Dosage	LDL	>50%	2005	Asymptotic	Linear Regression	age, sex, PC1, PC2, ethnicity, cohort, ESP-phenotype	Dosage	LDL	>90%	2005	Asymptotic	Linear Regression	age, sex, PC1, PC2, ethnicity, cohort, ESP-phenotype	Dosage	Inverse normal transformed LDL	>50%	2005	Asymptotic	Linear Regression	age, sex, PC1, PC2, ethnicity, ESP-phenotype	Dosage	LDL	>50%	2005	Permutation (10 million)	Reverse Regression	age, sex, PC1, PC2, ethnicity, cohort	Multiple imputation	LDL	>50%	2005	Asymptotic
PCSK9	NS <5%							1.8×10^{-8}							3.0×10^{-8}							1.3×10^{-8}							5.7×10^{-9}							1.5×10^{-4}							4.6×10^{-9}							$< 1\times10^{-7}$							5.1×10^{-8}
LDLR	NS <0.1%							2.8×10^{-9}							1.1×10^{-9}							1.8×10^{-9}							1.0×10^{-8}							8.8×10^{-9}							4.5×10^{-7}							$< 1\times10^{-7}$							1.7×10^{-7}
APOB	LOF <5%							7.7×10^{-8}							3.9×10^{-7}							8.9×10^{-8}							8.1×10^{-7}							9.6×10^{-8}							5.7×10^{-9}							4.0×10^{-6}							4.5×10^{-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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