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Supplemental Data

Whole-Exome Sequencing Identifies

Rare and Low-Frequency Coding Variants

Associated with LDL Cholesterol

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[21]Acute Lung Injury (ALI), [22]Atherosclerosis Risk in Communities (ARIC), [23]Cardiovascular Health Study (CHS), [24]Chronic Obstructive Pulmonary Disease (COPDGene), [25]Coronary Artery Risk Development in Young Adults (CARDIA), [26]Cystic Fibrosis (CF), [27]Early Pseudomonas Infection Control (EPIC), [28]Framingham Heart Study (FHS), [29]Jackson Heart Study (JHS), [30]Lung Health Study (LHS), [31]Multi-Ethnic Study of Atherosclerosis (MESA), [32]Pulmonary Arterial Hypertension (PAH), [33]Severe Asthma Research Program (SARP), [34]Women's Health Initiative (WHI)

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HeartGO:

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Adults (CARDIA): NHLBI (N01-HC95095 & N01-HC48047, N01-HC48048, N01-HC48049, and N01-HC48050); **Framingham Heart Study (FHS)**: NHLBI (N01-HC-25195 and grant R01 NS17950) with additional support from NIA (AG08122 and AG033193); **Jackson Heart Study (JHS)**: NHLBI and the National Institute on Minority Health and Health Disparities (N01 HC-95170, N01 HC-95171 and N01 HC-95172); **Multi-Ethnic Study of Atherosclerosis (MESA**)**:** NHLBI (N01-HC-95159 through N01-HC-95169 and RR-024156).

Lung GO:

Cystic Fibrosis (CF): Cystic Fibrosis Foundation (GIBSON07K0, KNOWLE00A0, OBSERV04K0, RDP R026), the NHLBI (R01 HL-068890, R02 HL-095396), NIH National Center for Research Resources (UL1 RR-025014), and the National Human Genome Research Institute (NHGRI) (5R00 HG-004316). **Chronic Obstructive Pulmonary Disease (COPDGene):** NHLBI (U01 HL-089897, U01 HL-089856), and the COPD Foundation through contributions made to an Industry Advisory Board comprised of AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, and Sunovian. The COPDGene clinical centers and investigators are available at www.copdgene.org. **Acute Lung Injury (ALI)**: NHLBI (RC2 HL-101779). **Lung Health Study (LHS)**: NHLBI (RC2 HL-066583), the NHGRI (HG-004738), and the NHLBI Division of Lung Diseases (HR-46002). **Pulmonary Arterial Hypertension (PAH):** NIH (P50 HL-084946, K23 AR-52742), and the NHLBI (F32 HL-083714). **Asthma:** NHLBI (RC2 HL-101651), and the NIH (HL-077916, HL-69197, HL-76285, M01 RR-07122).

SWISS and ISGS:

Siblings with Ischemic Stroke Study (SWISS): National Institute of Neurological Disorders and Stroke (NINDS) (R01 NS039987); Ischemic Stroke Genetics Study (ISGS): NINDS (R01 NS042733)

WHISP:

Women's Health Initiative (WHI): The WHI Sequencing Project is funded by the NHLBI (HL-102924) as well as the National Institutes of Health (NIH), U.S. Department of Health and Human Services through contracts N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118-32119, 32122, 42107-26, 42129-32, and 44221. The authors thank the WHI investigators and staff for their dedication, and the study participants for making the program possible. A full listing of WHI investigators can be found at: http://www.whiscience.org/publications/WHI_investigators_shortlist.pdf

Mt Sinai:

The Mount Sinai IPM Biobank Program is supported by The Andrea and Charles Bronfman Philanthropies.

Figure S1. GWAS findings at *PNPLA5*

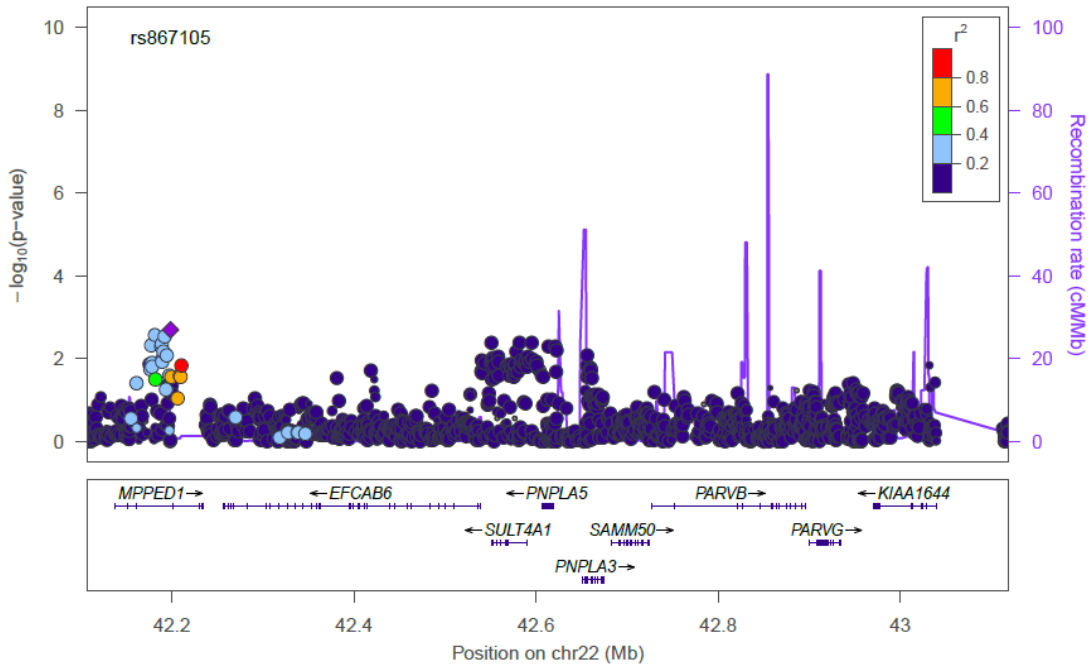
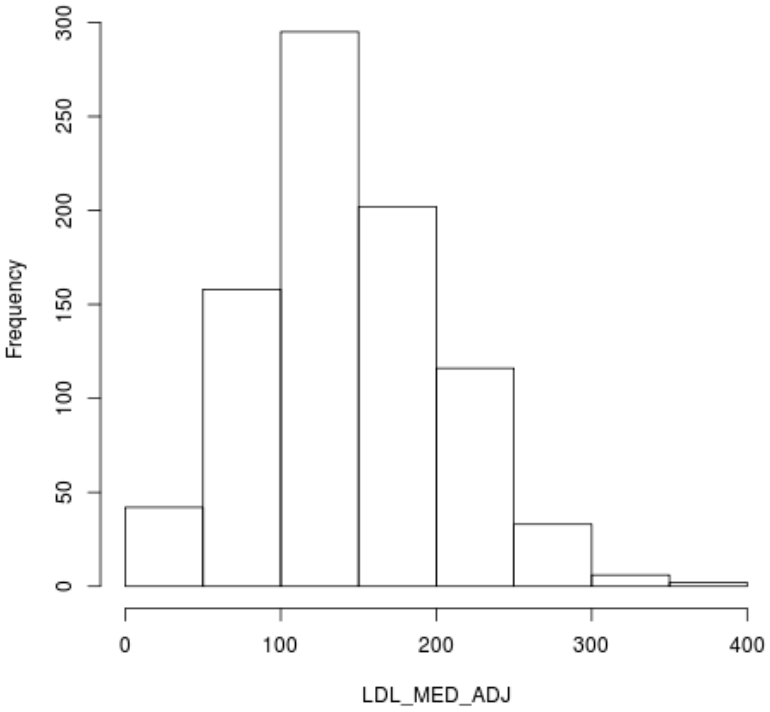


Figure S2. Histogram showing distribution of LDL cholesterol values (after adjustment for lipid lowering medication)

A. African-American individuals (stage 1)



B. European-American individuals (stage 1)

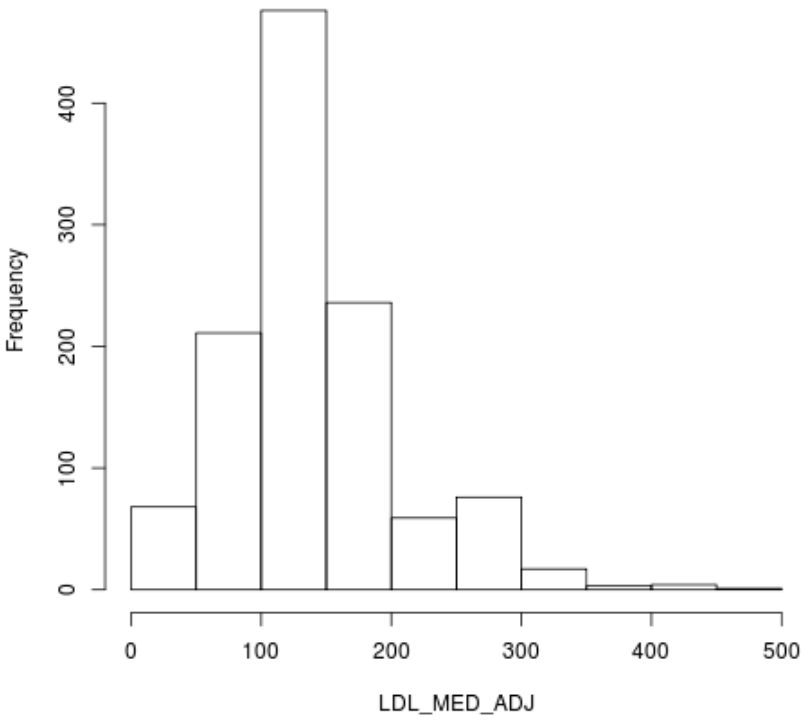
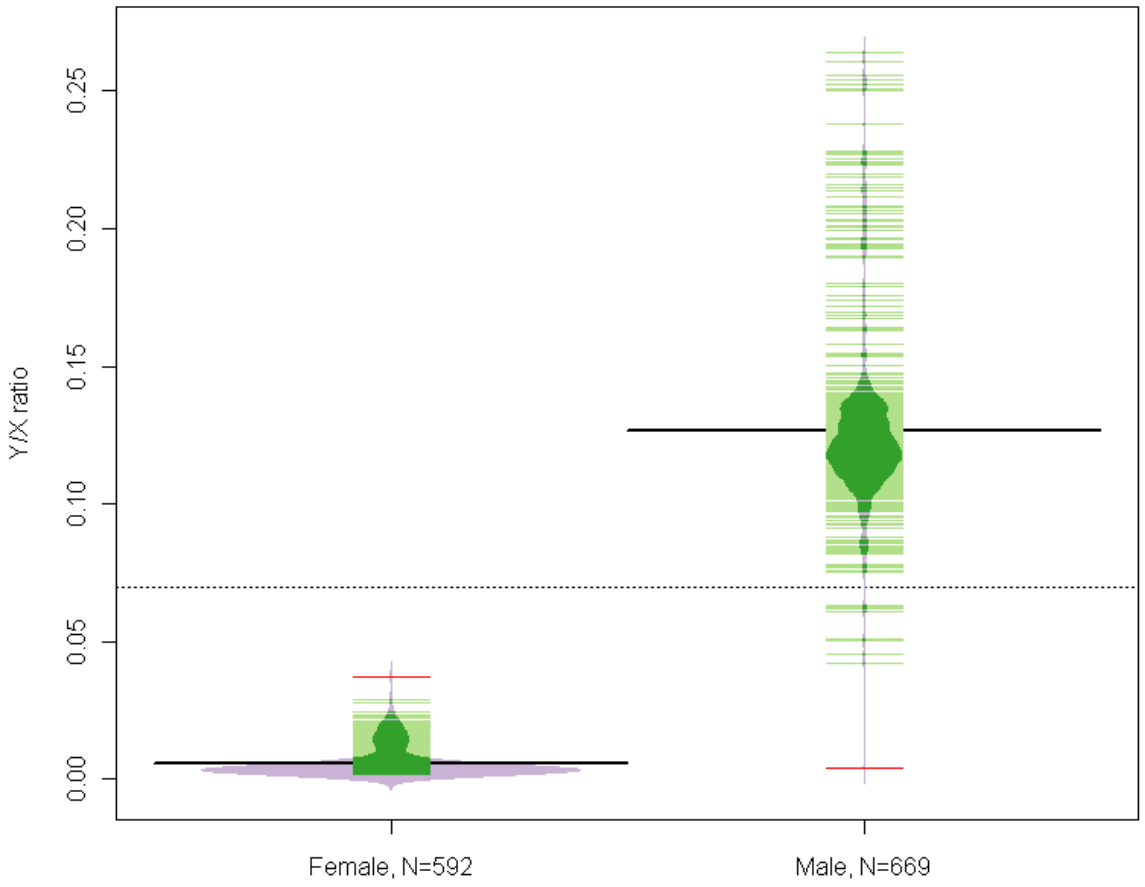


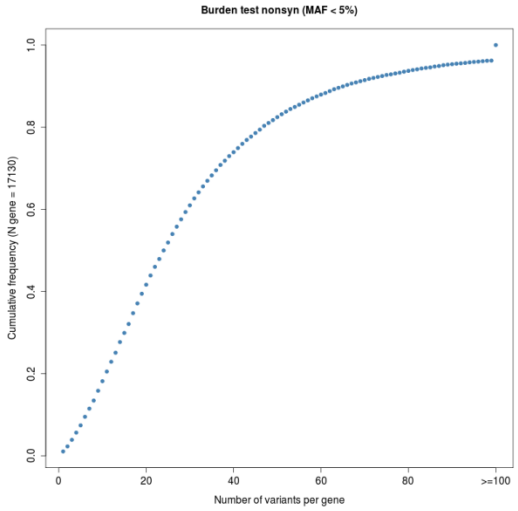
Figure S3. Comparing self-reported sex to the ratio of sequencing data reads that map to Y vs X chromosomes



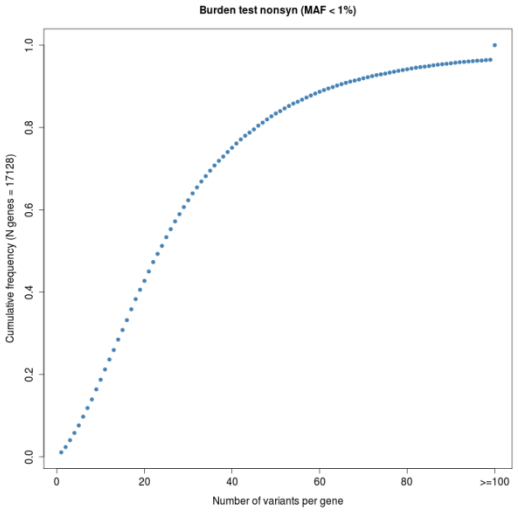
Legend for Figure S4: For each individual, we determined the number of reads that mapped to the Y chromosome to the number of reads that mapped to the X chromosome. The bean plot shows that ratio for individuals based on self-reported sex. Each green line represents one individual, the green or purple outline shows the probability distribution and the black line shows the self-reported sex-specific mean. We identified any samples that fell within 3 standard-deviations of the opposite to the reported sex and excluded those individuals (N=2 from Broad Institute were excluded – shown in red, N = 1 from University of Washington samples were excluded – data not shown).

Figure S4. Number of variant sites observed per gene in each burden test

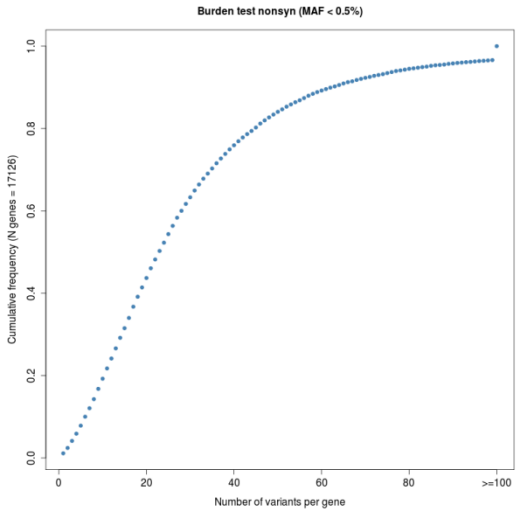
Genes with nonsynonymous+splice variants (MAF < 5%)



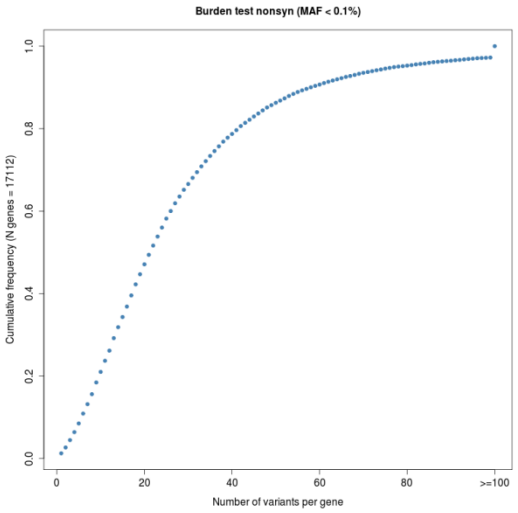
Genes with nonsynonymous+splice variants (MAF < 1%)



Genes with nonsynonymous+splice variants (MAF < 0.5%)



Genes with nonsynonymous+splice variants (MAF < 0.1%)



Genes with loss-of-function variants (MAF < 5%)

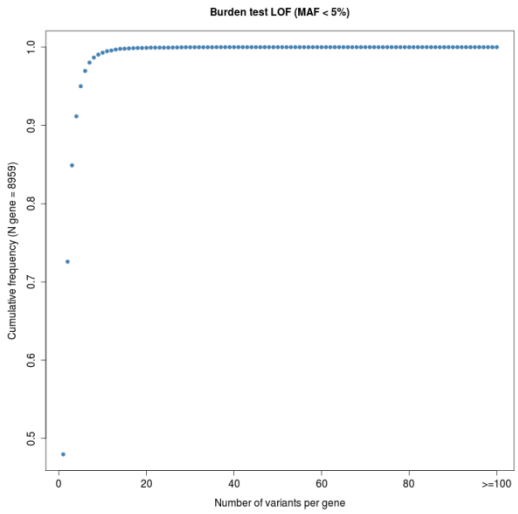
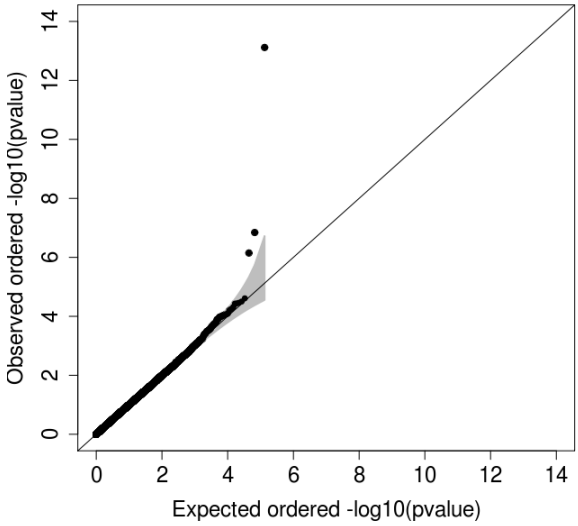
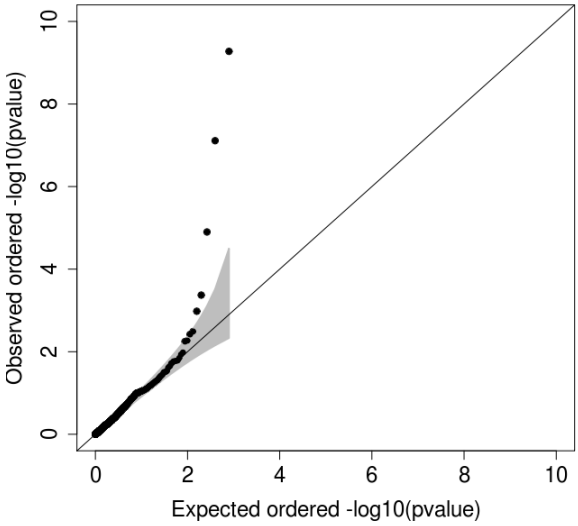


Figure S5. Quantile-quantile plots showing the observed and expected $-\log_{10}$ p-value for single variant tests and 8 different burden tests for all genes tested with a cumulative minor allele count ≥6. We observed no deviation from expectation (no inflated type 1 error). The 95% confidence interval is shown in grey.

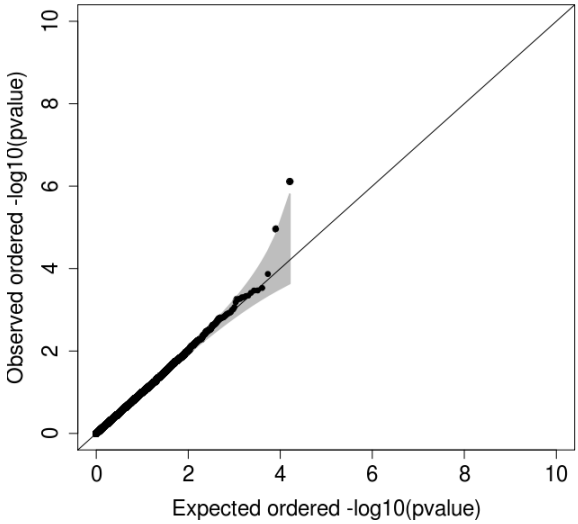
Single variant tests



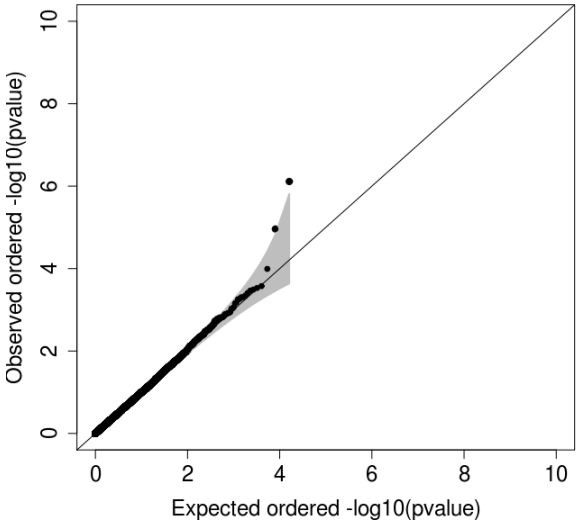
Burden tests (CMC nonsynonymous MAF < 5%)



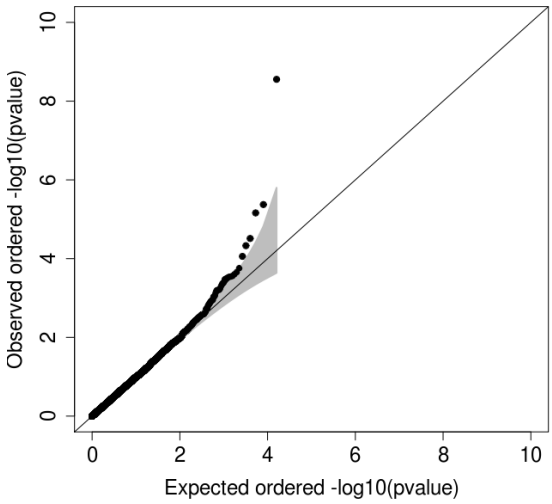
Burden tests (CMC nonsynonymous MAF < 1%)



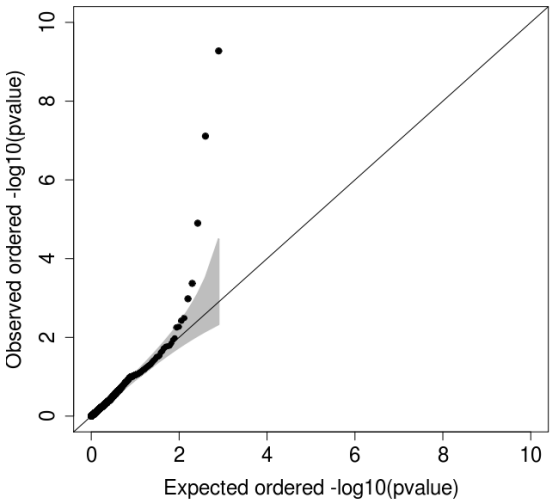
Burden tests (CMC nonsynonymous MAF < 0.5%)



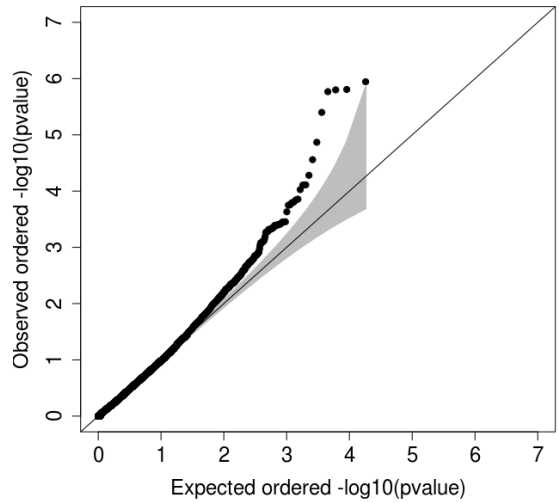
Burden tests (CMC nonsynonymous MAF < 0.1%)



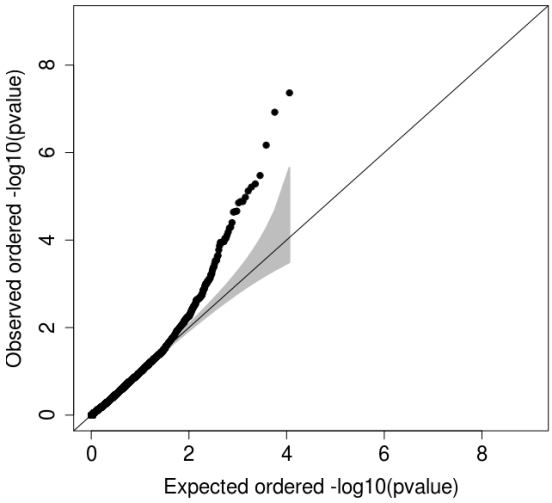
Burden tests (CMC loss of function MAF < 5%)



Burden tests (SKAT-O nonsynonymous MAF < 5%)



Burden tests (SKAT-O MAF < 5% nonsynonymous + “probably damaging” missense)



Burden tests (SKAT-O loss-of-function MAF < 5%)

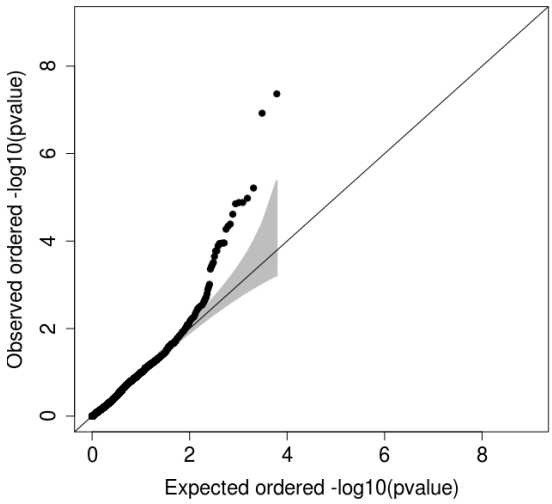


Table S1. Cohort source for samples in stages 1 and 2

	ARIC[1]	CARDIA[2]	CHS[3]	FHS[4]	JHS[5]	MESA[6]	WHI[7]
Baseline Exam	1987-1989	1985-1986	1989-1990	1948, 1971, 2002	2000-2004	2000-2002	1993-1998
N with lipids	15,792	5,115	5,888	14,482	3,443	6,526	28,061
Mean Age, y	54	25	72	40	55	62	63
Women, %	55	54	58	50	63	53	100
				Race/Ethnicity, %			
European	73	48	84	100	0	39	50
African American	27	52	16	0	100	27	32
Other	0	0	0	0	0	34	18
Family Study	No	No	No	Yes	Subset	Subset	No
Event Follow-up	Ongoing	Ongoing	June 2006	Ongoing	Ongoing	Ongoing	Ongoing
DNA available	15,608	3,700	5,455	8,482	3,443	6,467	26,926
Mean adjusted LDL-C of DNA-available individuals (SD)	137.6(39.1)	109.9(30.5)	129.8(35.6)	103.5(33.5)	125.8(36.6)	117.3(31.6)	145.7(42.1)
				Stage 1			
LDL-C extremes (European High/Low)	107/92	4/2	14/20	28/18	0/0	2/4	1/1
LDL-C extremes (African American High/Low)	88/61	0/0	3/7	0/0	49/33	0/2	11/7
Non-extremes (European)	123	94	111	337	0	74	121
Non-extremes (African American)	113	73	24	0	154	65	162
Total # samples exome sequenced	584	173	179	383	236	147	303
				Stage 2			
LDL-C extremes (European High/Low)	10/11	7/7	0/0	1/3	0/0	31/33	12/9
LDL-C extremes (African American High/Low)	5/5	9/8	3/2	0/0	3/6	32/28	44/32
Non-extremes (European)	155	0	1	48	0	102	10
Non-extremes (African American)	46	0	26	0	128	23	462
Total # samples exome sequenced	232	31	32	52	137	249	569

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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