ARTICLES

Biological, clinical and population relevance of 95 loci for blood lipids

A list of authors and their affiliations appears at the end of the paper.

Plasma concentrations of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides are among the most important risk factors for coronary artery disease (CAD) and are targets for therapeutic intervention. We screened the genome for common variants associated with plasma lipids in >100,000 individuals of European ancestry. Here we report 95 significantly associated loci ($P < 5 \times 10^{-8}$), with 59 showing genome-wide significant association with lipid traits for the first time. The newly reported associations include single nucleotide polymorphisms (SNPs) near known lipid regulators (for example, *CYP7A1*, *NPC1L1* and *SCARB1*) as well as in scores of loci not previously implicated in lipoprotein metabolism. The 95 loci contribute not only to normal variation in lipid traits but also to extreme lipid phenotypes and have an impact on lipid traits in three non-European populations (East Asians, South Asians and African Americans). Our results identify several novel loci associated with plasma lipids that are also associated with CAD. Finally, we validated three of the novel genes—*GALNT2*, *PPP1R3B* and *TTC39B*—with experiments in mouse models. Taken together, our findings provide the foundation to develop a broader biological understanding of lipoprotein metabolism and to identify new therapeutic opportunities for the prevention of CAD.

Plasma concentrations of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) are heritable risk factors for cardiovascular disease and targets for therapeutic intervention[1]. Genome-wide association studies (GWASs) involving up to 20,000 individuals of European ancestry have identified >30 genetic loci contributing to inter-individual variation in plasma lipid concentrations[2–10]. Half of these loci harboured genes previously known to influence plasma lipid concentrations, establishing the technical validity of the lipid GWAS. Nevertheless, the practical value of the GWAS approach remains a subject of debate[11–14].

Here we focus on three key questions motivated by recent progress in genetic mapping: (1) are loci identified in populations of European descent important in non-European groups, suggesting relevance in different global populations; (2) are these loci of clinical relevance, providing the framework to identify potential novel drug targets for the treatment of extreme lipid phenotypes and prevention of CAD; and (3) do these loci harbour genes with biological relevance, that is, which are directly involved in lipid regulation and metabolism?

We address these questions using several approaches: a genome-wide association screen for plasma lipids in >100,000 individuals of European ancestry; evaluation of mapped variants in East Asians, South Asians and African Americans; association testing in individuals with and without CAD; evaluation of genetic variants in patients with extreme plasma lipid concentrations; and genetic manipulation in mouse models.

GWAS in >100,000 individuals

To identify additional common variants associated with plasma TC, LDL-C, HDL-C and TG concentrations, we performed a meta-analysis of 46 lipid GWASs (Supplementary Tables 1–4). These studies together comprise >100,000 individuals of European descent (maximum sample size 100,184 for TC, 95,454 for LDL-C, 99,900 for HDL-C and 96,598 for TG), ascertained in the United States, Europe or Australia. In each study, we used genotyped single nucleotide

polymorphisms (SNPs) and phased chromosomes from the HapMap CEU (Utah residents with ancestry from northern and western Europe) sample to impute autosomal SNPs catalogued in the HapMap; SNPs with minor allele frequency (MAF) >1% and good imputation quality (see Methods in Supplementary Information) were analysed. A total of ~ 2.6 million directly genotyped or imputed SNPs were tested for association with each of the four lipid traits in each study. For each SNP, evidence of association was combined across studies using a fixed-effects meta-analysis.

We identified 95 loci that showed genome-wide significant association ($P < 5 \times 10^{-8}$) with at least one of the four traits tested (Table 1; Supplementary Fig. 1 and Supplementary Table 2). These include all of the 36 loci previously reported by GWAS at genome-wide significance[2–10] and 59 loci reported here in a GWAS for the first time. Among these 59 novel loci, 39 demonstrated genome-wide significant association with TC, 22 with LDL-C, 31 with HDL-C, and 16 with TG. Among the 36 known loci, 21 demonstrated genome-wide significant association with another lipid phenotype in addition to that previously described. To rule out spurious associations arising as a result of imputation artefact, at nearly all loci we were able to identify proxy SNPs that had been directly genotyped on Illumina and/or Affymetrix arrays and confirm each of the associations (Supplementary Table 5). The full association results for each of the four traits are available at http://www.broadinstitute.org/mpg/pubs/lipids2010/ or http://www.sph.umich.edu/csg/abecasis/public/lipids2010.

To evaluate whether additional independent association signals existed at each locus, we performed conditional association analyses for each of the four lipid traits including genotypes at the lead SNPs for each of the 95 loci as covariates in the association analyses (see Supplementary Methods). These analyses identified secondary signals in 26 loci (Supplementary Table 6); when these additional SNPs are combined with the lead SNPs, the total set of mapped variants explains 12.4% (TC), 12.2% (LDL-C), 12.1% (HDL-C), and 9.6% (TG) of the total variance in each lipid trait in the Framingham Heart Study, corresponding to ~25–30% of the genetic variance for each trait.

Table 1 | Meta-analysis of plasma lipid concentrations in >100,000 individuals of European descent.

Locus	Chr	Lead SNP	Lead trait	Other traits	Alleles/MAF	Effect size	P	eQTL	CAD	Ethnic
LDLRAP1	1	rs12027135	TC	LDL	T/A/0.45	−1.22	4×10^{-11}	Y		+++?
PABPC4	1	rs4660293	HDL		A/G/0.23	−0.48	4×10^{-10}	Y		++++
PCSK9	1	rs2479409	LDL	TC	A/G/0.30	+2.01	2×10^{-28}			++++
ANGPTL3	1	rs2131925	TG	TC, LDL	T/G/0.32	−4.94	9×10^{-43}	Y		++++
EVI5	1	rs7515577	TC		A/C/0.21	−1.18	3×10^{-8}			+++?
SORT1	1	rs629301	LDL	TC	T/G/0.22	−5.65	1×10^{-170}	Y	Y	++++
ZNF648	1	rs1689800	HDL		A/G/0.35	−0.47	3×10^{-10}			+++−
MOSC1	1	rs2642442	TC	LDL	T/C/0.32	−1.39	6×10^{-13}			+++?
GALNT2	1	rs4846914	HDL	TG	A/G/0.40	−0.61	4×10^{-21}			++++
IRF2BP2	1	rs514230	TC	LDL	T/A/0.48	−1.36	5×10^{-14}			+++?
APOB	2	rs1367117	LDL	TC	G/A/0.30	+4.05	4×10^{-114}			++++
		rs1042034	TG	HDL	T/C/0.22	−5.99	1×10^{-45}			+−++
GCKR	2	rs1260326	TG	TC	C/T/0.41	+8.76	6×10^{-133}	Y		++++
ABCG5/8	2	rs4299376	LDL	TC	T/G/0.30	+2.75	2×10^{-47}			++++
RAB3GAP1	2	rs7570971	TC		C/A/0.34	+1.25	2×10^{-8}			+−??
COBLL1	2	rs10195252	TG		T/C/0.40	−2.01	2×10^{-10}	Y		++++
		rs12328675	HDL		T/C/0.13	+0.68	3×10^{-10}			++?+
IRS1	2	rs2972146	HDL	TG	T/G/0.37	+0.46	3×10^{-9}	Y	Y	++++
RAF1	3	rs2290159	TC		G/C/0.22	−1.42	4×10^{-9}			+++?
MSL2L1	3	rs645040	TG		T/G/0.22	−2.22	3×10^{-8}			++−+
KLHL8	4	rs442177	TG		T/G/0.41	−2.25	9×10^{-12}			++++
SLC39A8	4	rs13107325	HDL		C/T/0.07	−0.84	7×10^{-11}	Y		+−?−
ARL15	5	rs6450176	HDL		G/A/0.26	−0.49	5×10^{-8}			−??+
MAP3K1	5	rs9686661	TG		C/T/0.20	+2.57	1×10^{-10}			++++
HMGCR	5	rs12916	TC	LDL	T/C/0.39	+2.84	9×10^{-47}			+++?
TIMD4	5	rs6882076	TC	LDL, TG	C/T/0.35	−1.98	7×10^{-28}			+++?
MYLIP	6	rs3757354	LDL	TC	C/T/0.22	−1.43	1×10^{-11}			+−−+
HFE	6	rs1800562	LDL	TC	G/A/0.06	−2.22	6×10^{-10}			++?+
HLA	6	rs3177928	TC	LDL	G/A/0.16	+2.31	4×10^{-19}	Y		+++?
		rs2247056	TG		C/T/0.25	−2.99	2×10^{-15}			+++−
C6orf106	6	rs2814944	HDL		G/A/0.16	−0.49	4×10^{-9}	Y		+++−
		rs2814982	TC		C/T/0.11	−1.86	5×10^{-11}		Y	−−+?
FRK	6	rs9488822	TC	LDL	A/T/0.35	−1.18	2×10^{-10}	Y		+++?
CITED2	6	rs605066	HDL		T/C/0.42	−0.39	3×10^{-8}			++−+
LPA	6	rs1564348	LDL	TC	T/C/0.17	−0.56	2×10^{-17}		Y	++?+
		rs1084651	HDL		G/A/0.16	+1.95	3×10^{-8}			++?+
DNAH11	7	rs12670798	TC	LDL	T/C/0.23	+1.43	9×10^{-10}			+++?
NPC1L1	7	rs2072183	TC	LDL	G/C/0.25	+2.01	3×10^{-11}			+−+?
TYW1B	7	rs13238203	TG		C/T/0.04	−7.91	1×10^{-9}			+???
MLXIPL	7	rs17145738	TG	HDL	C/T/0.12	−9.32	6×10^{-58}	Y		++++
KLF14	7	rs4731702	HDL		C/T/0.48	+0.59	1×10^{-15}		Y	++++
PPP1R3B	8	rs9987289	HDL	TC, LDL	G/A/0.09	−1.21	6×10^{-25}	Y		++++
PINX1	8	rs11776767	TG		G/C/0.37	+2.01	1×10^{-8}			−+++
NAT2	8	rs1495741	TG	TC	A/G/0.22	+2.85	5×10^{-14}		Y	−+++
LPL	8	rs12678919	TG	HDL	A/G/0.12	−13.64	2×10^{-115}		Y	++++
CYP7A1	8	rs2081687	TC	LDL	C/T/0.35	+1.23	2×10^{-12}			+++?
TRPS1	8	rs2293889	HDL		G/T/0.41	−0.44	6×10^{-11}			++++
		rs2737229	TC		A/C/0.30	−1.11	2×10^{-8}			++−?
TRIB1	8	rs2954029	TG	TC, LDL, HDL	A/T/0.47	−5.64	3×10^{-55}		Y	++++
PLEC1	8	rs11136341	LDL	TC	A/G/0.40	+1.40	4×10^{-13}			++++
TTC39B	9	rs581080	HDL	TC	C/G/0.18	−0.65	3×10^{-12}			+−++

Previous studies have suggested sex-specific heritability of lipid traits[15]. A key challenge in addressing this issue is evaluating enough men and women to achieve adequate statistical power for each sex. We re-analysed the GWAS for the four lipid traits separately in women ($n = 63,274$) and in men ($n = 38,514$). Four of the 95 loci identified in the primary analysis showed significant heterogeneity of effect size ($P < 0.0005$) between men and women (Supplementary Table 7). Moreover, an additional five loci had significant association in only one sex and not in the sex-combined analysis. Two loci associated with HDL-C in the sex-combined analysis (*KLF14* and *ABCA8*) showed female-specific association with TG and LDL-C, respectively. The *KLF14* locus is a striking example, with rs1562398 significantly associated with TG in women (effect size = –0.046 for the C allele, $P = 2 \times 10^{-12}$), but not in men (effect size = –0.012, $P = 0.05$) (Supplementary Fig. 2 and Supplementary Table 7).

To gain insight into how DNA variants in associated loci might influence plasma lipid concentrations, we tested whether the mapped DNA sequence variants regulate the expression levels of nearby genes (expression quantitative trait loci, or eQTLs) in human tissues relevant to lipoprotein metabolism (liver and fat)[16]. We carried out genotyping and RNA expression profiling of >39,000 transcripts in three types of human tissue samples from liver (960 samples), omental fat (741 samples) and subcutaneous fat (609 samples). We examined the correlations between each of the lead SNPs at the 95 loci and the expression levels of transcripts located within 500 kilobases of the SNP. We pre-specified a conservative threshold of statistical significance at $P < 5 \times 10^{-8}$. At this threshold, we identified 38 SNP-to-gene eQTLs in liver, 28 in omental fat, and 19 in subcutaneous fat (Table 1; Supplementary Tables 8–10). Some lead SNPs are quite remote from the associated gene transcripts. For example, rs9987289 (associated with both LDL-C and HDL-C) correlates with a twofold change in liver expression of *PPP1R3B*, yet is 174 kb away from the gene, which as demonstrated below is likely to be a causal gene. Similarly, rs2972146 (associated with both HDL-C and TG in this study, as well as with insulin resistance and type 2 diabetes mellitus in a previous study[17]) correlates with *IRS1* expression in omental fat, despite being located 495 kb away from the gene.

Relevance of GWAS loci in non-Europeans

As all of the individuals studied in our primary GWAS were of European ancestry, it remained unclear if the loci we identified in Europeans are relevant in non-European individuals. To address this

Table 1 | Continued.

Locus	Chr	Lead SNP	Lead trait	Other traits	Alleles/MAF	Effect size	P	eQTL	CAD	Ethnic
ABCA1	9	rs1883025	HDL	TC	C/T/0.25	−0.94	2×10^{-33}			++++
ABO	9	rs9411489	LDL	TC	C/T/0.20	+2.24	6×10^{-13}		Y	????
JMJD1C	10	rs10761731	TG		A/T/0.43	−2.38	3×10^{-12}			++++
CYP26A1	10	rs2068888	TG		G/A/0.46	−2.28	2×10^{-8}			++++
GPAM	10	rs2255141	TC	LDL	G/A/0.30	+1.14	2×10^{-10}			+++?
AMPD3	11	rs2923084	HDL		A/G/0.17	−0.41	5×10^{-8}			++−+
SPTY2D1	11	rs10128711	TC		C/T/0.28	−1.04	3×10^{-8}	Y		+−+?
LRP4	11	rs3136441	HDL		T/C/0.15	+0.78	3×10^{-18}	Y		+++?
FADS1-2-3	11	rs174546	TG	HDL, TC, LDL	C/T/0.34	+3.82	5×10^{-24}	Y		++++
APOA1	11	rs964184	TG	TC, HDL, LDL	C/G/0.13	+16.95	7×10^{-240}		Y	++++
UBASH3B	11	rs7941030	TC	HDL	T/C/0.38	+0.97	2×10^{-10}			+++?
ST3GAL4	11	rs11220462	LDL	TC	G/A/0.14	+1.95	1×10^{-15}	Y		++++
PDE3A	12	rs7134375	HDL		C/A/0.42	+0.40	4×10^{-8}			++++
LRP1	12	rs11613352	TG	HDL	C/T/0.23	−2.70	4×10^{-10}			++?+
MVK	12	rs7134594	HDL		T/C/0.47	−0.44	7×10^{-15}	Y		++?+
BRAP	12	rs11065987	TC	LDL	A/G/0.42	−0.96	7×10^{-12}			++??
HNF1A	12	rs1169288	TC	LDL	A/C/0.33	+1.42	1×10^{-14}		Y	+++?
SBNO1	12	rs4759375	HDL		C/T/0.06	+0.86	7×10^{-9}			+??+
ZNF664	12	rs4765127	HDL	TG	G/T/0.34	+0.44	3×10^{-10}			−+−+
SCARB1	12	rs838880	HDL		T/C/0.31	+0.61	3×10^{-14}			++−?
NYNRIN	14	rs8017377	LDL		G/A/0.47	+1.14	5×10^{-11}			+−++
CAPN3	15	rs2412710	TG		G/A/0.02	+7.00	2×10^{-8}			+??−
FRMD5	15	rs2929282	TG		A/T/0.05	+5.13	2×10^{-11}	Y		+−−−
LIPC	15	rs1532085	HDL	TC, TG	G/A/0.39	+1.45	3×10^{-96}	Y		++++
LACTB	15	rs2652834	HDL		G/A/0.20	−0.39	9×10^{-9}	Y		+???
CTF1	16	rs11649653	TG		C/G/0.40	−2.13	3×10^{-8}	Y		+??−
CETP	16	rs3764261	HDL	TC, LDL, TG	C/A/0.32	+3.39	7×10^{-380}			++++
LCAT	16	rs16942887	HDL		G/A/0.12	+1.27	8×10^{-33}	Y		++++
HPR	16	rs2000999	TC	LDL	G/A/0.20	+2.34	3×10^{-24}			+++?
CMIP	16	rs2925979	HDL		C/T/0.30	−0.45	2×10^{-11}			++++
STARD3	17	rs11869286	HDL		C/G/0.34	−0.48	1×10^{-13}	Y		++++
OSBPL7	17	rs7206971	LDL	TC	G/A/0.49	+0.78	2×10^{-8}	Y		++−+
ABCA8	17	rs4148008	HDL		C/G/0.32	−0.42	2×10^{-10}			++++
PGS1	17	rs4129767	HDL		A/G/0.49	−0.39	8×10^{-9}			++++
LIPG	18	rs7241918	HDL	TC	T/G/0.17	−1.31	3×10^{-49}	Y		++++
MC4R	18	rs12967135	HDL		G/A/0.23	−0.42	7×10^{-9}			++++
ANGPTL4	19	rs7255436	HDL		A/C/0.47	−0.45	3×10^{-8}	Y		++++
LDLR	19	rs6511720	LDL	TC	G/T/0.11	−6.99	4×10^{-117}		Y	++?+
LOC55908	19	rs737337	HDL		T/C/0.08	−0.64	3×10^{-9}			++++
CILP2	19	rs10401969	TC	TG, LDL	T/C/0.07	−4.74	3×10^{-38}		Y	+++?
APOE	19	rs4420638	LDL	TC, HDL	A/G/0.17	+7.14	9×10^{-147}		Y	++++
		rs439401	TG		C/T/0.36	−5.50	1×10^{-30}	Y		+++?
FLJ36070	19	rs492602	TC		A/G/0.49	+1.27	2×10^{-10}			+−+?
LILRA3	19	rs386000	HDL		G/C/0.20	+0.83	4×10^{-16}	Y		+−+−
ERGIC3	20	rs2277862	TC		C/T/0.15	−1.19	4×10^{-10}	Y		+++?
MAFB	20	rs2902940	TC	LDL	A/G/0.29	−1.38	6×10^{-11}			−−+?
TOP1	20	rs6029526	LDL	TC	T/A/0.47	+1.39	4×10^{-19}	Y		++++
HNF4A	20	rs1800961	HDL	TC	C/T/0.03	−1.88	1×10^{-15}			+++−
PLTP	20	rs6065906	HDL	TG	T/C/0.18	−0.93	2×10^{-22}			+−++
UBE2L3	22	rs181362	HDL		C/T/0.20	−0.46	1×10^{-8}	Y		++++
PLA2G6	22	rs5756931	TG		T/C/0.40	−1.54	4×10^{-8}			+??+

The gene name listed in 'Locus' column is either a plausible biological candidate gene in the locus or the nearest annotated gene to the lead SNP. Listed in 'Lead trait' column is the lipid trait with best *P*-value among all four traits. Listed in 'Other traits' are additional lipid traits with $P < 5 \times 10^{-8}$. Listed in 'Alleles/MAF' column are: major allele, minor allele and minor allele frequency (MAF) within the combined cohorts included in this meta-analysis (alleles designated with respect to the '+' strand; Supplementary Table 2). Numbers in 'Effect size' column are in mg dl^{-1} for the lead trait, modelled as an additive effect of the minor allele. *P*-values are listed for the lead traits. In the 'eQTL' column, 'Y' indicates that lead SNP has an eQTL with at least one gene within 500 kb with $P < 5 \times 10^{-8}$ in at least one the three tissues tested (liver, omental fat, subcutaneous fat). In the 'CAD' column, 'Y' indicates that the lead SNP meets the pre-specified statistical significance threshold of $P < 0.001$ for association with CAD and being concordant between the direction of lipid effect and the change in CAD risk. In the 'Ethnic' column, '+' indicates concordant effect on lead trait of the variant between the primary meta-analysis cohort and the European or non-European group, '−' indicates discordant effect on lead trait, and '?' indicates data not available for the group; in order, the ethnic groups are European, East Asian, South Asian and African American (Supplementary Table 11). Chr, chromosome.

question, we performed additional analyses in cohorts comprising >15,000 East Asians (Chinese, Koreans and Filipinos), >9,000 South Asians and >8,000 African Americans (Table 1; Supplementary Table 11). As a similarly sized control, we also performed genotyping in a cohort of 7,000 additional Europeans.

In the European group, we found that 35 of 36 lead SNPs tested against LDL-C had the same direction of association as seen in the primary (>100,000 person) analysis (see Supplementary Table 12 for explanation), 44 of 47 SNPs for HDL-C, and 29 of 32 SNPs for TG. Such directional consistency for the three traits is unlikely to be due to chance ($P = 5 \times 10^{-10}$ for LDL-C, $P = 1 \times 10^{-10}$ for HDL-C, and $P = 1 \times 10^{-6}$ for TG). For further replication evidence, we performed direct genotyping of a subset of the lead SNPs in two European cohorts together totalling 12,000 individuals and found

that 24 of 26 tested SNPs had the same direction of association (Supplementary Table 13).

We observed similar proportions in South Asians, with 29 of 32 lead SNPs tested against LDL-C having the same direction of association as in the primary analysis ($P = 1 \times 10^{-6}$), 35 of 39 SNPs for HDL-C ($P = 2 \times 10^{-7}$), and 24 of 27 SNPs for TG ($P = 3 \times 10^{-5}$). We also had consistent results with East Asians (LDL-C: 29 of 36, $P = 2 \times 10^{-4}$; HDL-C: 38 of 44, $P = 5 \times 10^{-7}$; TG: 26 of 28, $P = 2 \times 10^{-6}$), with more modest evidence for replication in African Americans (LDL-C: 33 of 36, $P = 1 \times 10^{-7}$; HDL-C: 37 of 44, $P = 3 \times 10^{-6}$; TG: 24 of 30, $P = 7 \times 10^{-4}$). Furthermore, we found that the proportions of SNPs that had the same direction of association and $P < 0.05$ were similar in the European, South Asian and East Asian replication groups, with smaller proportions in

African Americans (Supplementary Table 12). Of note, for a majority of the loci, there was no evidence of heterogeneity of effects between the primary European groups and each of the non-European groups (Supplementary Table 11).

These observations indicate that most (but probably not all) of the 95 lipid loci identified in this study contribute to the genetic architecture of lipid traits widely across global populations. They also suggest future studies to localize causal DNA variants by leveraging differences in linkage disequilibrium (LD) patterns among populations. We evaluated the potential for fine mapping by comparing the number of SNPs in LD with lead SNPs in three HapMap populations (Supplementary Table 14). At many loci, only a subset of SNPs in high LD ($r^2 \geq 0.8$) with the lead SNP in HapMap CEU are also in high LD with the lead SNP in HapMap YRI (Yoruba in Ibadan, Nigeria) individuals or in the joint JPT+CHB (Japanese in Tokyo, Japan and Han Chinese in Beijing, China) cohort. Such differential LD patterns can prove useful to refine association boundaries and prioritize SNPs for functional evaluation, as demonstrated for the LDL-C-associated locus on chromosome 1p13 (reported in the accompanying paper ref. 18).

Clinical relevance of GWAS loci

To assess whether the GWAS approach yields clinical insights of potential therapeutic relevance, we sought to determine which of the lipid-associated lead SNPs are also associated with CAD in a manner consistent with established epidemiological relationships (that is, SNP alleles which increase TC, LDL-C or TG or that decrease HDL-C should be associated with increased risk of CAD). Whereas LDL-C is an accepted causal risk factor for CAD, it is unclear whether HDL-C and/or TG are also causal risk factors. This uncertainty was reinforced by the failure of a drug that raised HDL-C via cholesteryl ester transfer protein (CETP) inhibition to reduce the risk of cardiovascular disease[19].

Whether other drugs that specifically raise HDL-C or lower TG can reduce CAD risk remains an open question. In contrast, the most widely marketed drugs for lowering of LDL-C, statins, have been demonstrated in numerous clinical trials to reduce risk of CAD. Statins inhibit hydroxy-3-methylglutaryl coenzyme A reductase (the protein product of *HMGCR*) and thereby reduce LDL-C and TC levels. We observed that the variant of our lead SNP in the *HMGCR* locus that is associated with lower LDL-C levels is also associated with lower CAD risk ($P = 0.004$), consistent with the clinical effects of statins. Analogously, common variants in other lipid-associated loci that are also associated with CAD may implicate genes at these loci as possible therapeutic targets.

We performed association testing for each of the lead SNPs from this study in 24,607 individuals of European descent with CAD and 66,197 without CAD, with a pre-specified one-sided significance threshold of $P < 0.001$ requiring directionality consistent with the relevant lipid–CAD epidemiological relationship. A limited number of loci met this criterion (Table 1; Supplementary Table 15), with most of them being associated with LDL-C—consistent with LDL-C being a causal risk factor for CAD.

Four novel CAD-associated loci related specifically to HDL-C or TG, but not LDL-C: *IRS1* (HDL-C, TG), *C6orf106* (HDL-C), *KLF14* (HDL-C) and *NAT2* (TG). That these loci were associated with CAD shows that there may be selective mechanisms by which HDL-C or TG can be altered in ways that also modulate CAD risk. However, it is also possible that causal genes in these loci may have pleiotropic effects on non-lipid parameters that are causal for CAD risk reduction. For example, the major allele of the lead SNP in the *IRS1* locus is associated with increased risk of type 2 diabetes mellitus, insulin resistance and hyperinsulinemia[17], along with decreased HDL-C, increased TG and increased risk of CAD; it remains unclear which of the metabolic risk factors are responsible for the increased CAD risk.

Besides CAD, a second clinically relevant phenotype is hyperlipidaemia. We asked whether the common variants in the 95 associated loci, each with individually small effects on plasma lipids, combine to contribute to extreme lipid phenotypes. We genotyped individuals identified in three independent studies as having high LDL-C ($n = 532$, mean 219 mg dl^{-1}), high HDL-C ($n = 652$, mean 90 mg dl^{-1}) or high TG ($n = 344$, mean 1,079 mg dl^{-1}). For each extreme case group, individuals with low plasma LDL-C ($n = 532$, mean 110 mg dl^{-1}), HDL-C ($n = 784$, mean 36.2 mg dl^{-1}) or TG ($n = 144$, mean 106 mg dl^{-1}) served as control groups. In each case-control sample set, we calculated risk scores summarizing the number of LDL-C-, HDL-C-, or TG-raising alleles weighted by effect size.

For LDL-C, we found that individuals with an LDL-C allelic dosage score in the top quartile were 13 times as likely to have high LDL-C as individuals in the bottom quartile ($P = 1 \times 10^{-14}$) (Supplementary Fig. 3; Supplementary Tables 16 and 17). For HDL-C, individuals in the top quartile of the HDL-C risk score were four times as likely to have high HDL-C as individuals in the bottom quartile ($P = 2 \times 10^{-16}$). For TG, individuals in the top quartile of the TG risk score were 44 times as likely to be hypertriglyceridaemic as individuals in the bottom quartile ($P = 4 \times 10^{-28}$). These results indicate that the additive effects of multiple common variants contribute to determining membership in the extremes of a quantitative trait distribution.

Biological relevance of GWAS loci

Whether the GWAS approach can yield biological insights that improve our understanding of the mechanisms underlying phenotypes such as plasma lipid concentrations remains an open question. Loci identified through GWAS may explain a very small proportion of the variance in a phenotype through naturally occurring common variants in humans, but they may have a greater impact through rare variants or when targeted by pharmacological or genetic intervention.

We surveyed our 95 GWAS loci and asked whether any nearby genes are linked to known Mendelian lipid disorders. There is remarkable overlap between the loci identified here and 18 genes previously implicated in Mendelian lipid disorders (Supplementary Table 18). Fifteen of the genes underlying these Mendelian disorders lie within 100 kb of one of our lead SNPs, including eight that lie within 10 kb of the nearest lead SNP. In 1,000,000 simulations of 95 randomly drawn SNPs, selected to match our lead SNPs with respect to MAF and the number of nearby genes, the average simulation showed no overlapping loci and none showed more than eight overlapping loci.

An additional two loci represent well-established drug targets for the treatment of hyperlipidaemia: *HMGCR* (statins) and *NPC1L1* (ezetimibe). Several other loci harbour genes that were already known to influence lipid metabolism before this study: *LPA*, which encodes lipoprotein(a); *PLTP*, which encodes phospholipid transfer protein; *ANGPTL3* and *ANGPTL4*, lipoprotein lipase inhibitors; *SCARB1*, a HDL receptor that mediates selective uptake of cholesteryl ester; *CYP7A1*, which encodes cholesterol 7-alpha-hydroxylase; *STARD3*, a cholesterol transport gene; and *LRP1* and *LRP4*, members of the LDL receptor-related protein family. Notably, the protein product of one of the genes implicated by our study—*MYLIP*—is a ubiquitin ligase that had no recognized role in lipid metabolism before our study's inception, but has since been independently demonstrated to be a regulator of cellular LDL receptor levels and is now termed Idol (inducible degrader of the LDL receptor)[20].

GALNT2 (encoding UDP-*N*-acetyl-alpha-D-galactosamine:polypeptide *N*-acetylgalactosaminyl transferase 2) is a member of a family of GalNAc-transferases, which transfer an *N*-acetyl galactosamine to the hydroxyl group of a serine/threonine residue in the first step of *O*-linked oligosaccharide biosynthesis. It is the only gene in the mapped locus on chromosome 1q42 within 150 kb of the lead SNP (rs4846914), which is located in an intron of the gene. We therefore reasoned that *GALNT2* would be an ideal candidate for functional validation in a mouse model. We introduced the mouse orthologue *Galnt2* into mouse liver via a viral vector. Liver-specific overexpression of *Galnt2* resulted in significantly lower plasma HDL-C (24%
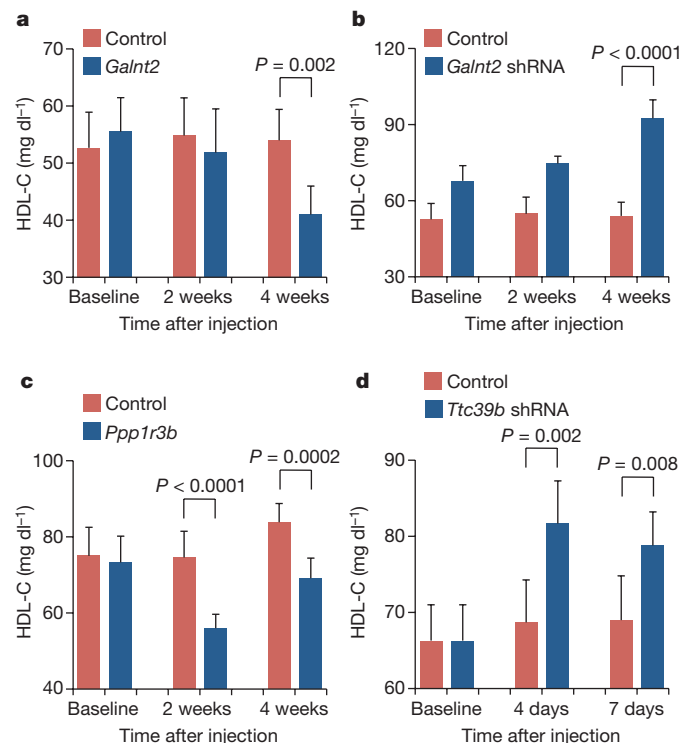
Figure 1 | Effects of altered *Galnt2*, *Ppp1r3b* or *Ttc39b* expression in mouse liver on plasma lipid levels. a, b, Overexpression and knockdown of *Galnt2*. Plasma HDL-C levels at baseline, 2 weeks or 4 weeks after injection of viral vectors are shown. *n* = 6 mice per group. **c**, Overexpression of *Ppp1r3b*. Plasma HDL-C levels at baseline, 2 weeks or 4 weeks after injection of viral vectors are shown. *n* = 7 mice per group. **d**, Knockdown of *Ttc39b*. Plasma HDL-C levels at baseline, 4 days or 7 days after injection of viral vectors are shown. *n* = 6 mice per group. Error bars show s.d. Because independent experiments were performed at different times and/or sites, there is variability in baseline HDL-C levels.

compared to control mice) by 4 weeks (Fig. 1a). We also performed knockdown of endogenous liver *Galnt2* through delivery of a short hairpin RNA via a viral vector. Reduction of the transcript level (~95% knockdown as determined by qRT–PCR) resulted in higher HDL-C levels by 4 weeks (71% compared to control mice) (Fig. 1b). These observations validate *GALNT2* as a biological mediator of HDL-C levels.

We further asked whether eQTL studies could facilitate the identification of causal genes in loci with multiple genes. Out of several genes surrounding a locus on chromosome 8p23 found to be associated with HDL-C, LDL-C and TC (Table 1), only *PPP1R3B* (encoding protein phosphatase 1, regulatory (inhibitor) subunit 3B) was found to have an eQTL in liver (Supplementary Table 7). The allele associated with increased expression correlated with lower levels of each of the lipid traits. This eQTL relationship indicates that higher expression of *PPP1R3B* will lower plasma lipids. Consistent with this prediction, overexpression of the mouse orthologue *Ppp1r3b* in mouse liver via a viral vector resulted in significantly lower plasma HDL-C levels at 2 weeks (25%) and 4 weeks (18%) (Fig. 1c), as well as lower TC levels at 2 weeks (21%) and 4 weeks (14%) (data not shown).

Similarly, on a locus on chromosome 9p22 found to be associated with HDL-C, *TTC39B* (encoding tetratricopeptide repeat domain 39B) was the only one of several genes in the locus to have an eQTL in liver (Supplementary Table 7), with the allele associated with decreased expression correlating with increased HDL-C. Consistent with this eQTL, knockdown of the mouse orthologue *Ttc39b* via a viral vector, with 50% knockdown of transcript as determined by qRT–PCR, resulted in significantly higher plasma HDL-C levels at 4 days (19%) and 7 days (14%) (Fig. 1d). These data indicate *PPP1R3B* and *TTC39B* as causal genes for lipid regulation. These findings, combined

with the demonstration that *SORT1* is a causal gene for LDL-C and is regulated in its expression by a GWAS SNP (reported in the accompanying paper ref. 18), support the use of eQTL studies to prioritize functional validation of GWAS-nominated genes.

Together, these observations establish that some of the identified 95 loci harbour novel bona fide lipid regulatory genes and show that with additional functional studies many, if not all, of the loci will yield insights into the biological underpinnings of lipid metabolism.

New biological, clinical and genetic insights

Through a series of studies, we demonstrate that (1) at least 95 loci across the human genome harbour common variants associated with plasma lipid traits in Europeans, (2) the loci contribute to lipid traits in multiple non-European populations, (3) some of these loci are associated not only with lipids but also with risk for CAD, (4) common variants in the loci combine to contribute to extreme lipid phenotypes and (5) many of the identified loci harbour genes that contribute to lipid metabolism, including the novel lipid genes *GALNT2*, *PPP1R3B* and *TTC39B* that we validated in mouse models.

It has recently been suggested that conducting genetic studies with increasingly larger cohorts will be relatively uninformative for the biology of complex human disease, particularly if initial studies have failed to explain a sizable fraction of the heritability of the disease in question[11]. As the reasoning goes, analysis of a few thousand individuals will uncover the common variants with the strongest effect on phenotype. Larger studies will suffer from a plateau phenomenon in which either no additional common variants will be found or any common variants that are identified will have too small an effect to be of biological interest.

Our study provides strong empirical evidence against this assertion. We extended a GWAS for plasma lipids from ~20,000 to ~100,000 individuals and identified 95 loci (of which 59 are novel) that, in aggregate, explain 10–12% of the total variance (representing ~25–30% of the genetic variance). Even though the lipid-associated SNPs we identified have relatively small effect sizes, some of the 59 new loci contain genes of clear biological and clinical importance—among them *LDLRAP1* (responsible for autosomal recessive hypercholesterolemia), *SCARB1* (receptor for selective uptake of HDL-C), *NPC1L1* (established drug target), *MYLIP* (recently characterized regulator of LDL-C), and *PPP1R3B* (newly characterized regulator of HDL-C). We expect that future investigations of the new loci (for example, resequencing efforts to identify low-frequency and rare variants, or functional experiments in cells and animal models, as demonstrated for *SORT1* in a separate study reported in the accompanying paper ref. 18) will uncover additional important new genes. Thus, the data presented in this study provide a foundation from which to develop a broader biological understanding of lipoprotein metabolism and to identify potential new therapeutic opportunities.

METHODS SUMMARY

The full Methods are in Supplementary Information and provide information about (1) study samples and phenotypes; (2) genotyping and imputation; (3) genome-wide association analyses; (4) meta-analyses of directly typed and imputed SNPs; (5) estimation of effect sizes; (6) conditional analyses of top signals; (7) sex-specific analyses; (8) *cis*-expression quantitative trait locus analyses; (9) analyses of lipid-associated SNPs in European and non-European samples; (10) analyses of lipid-associated SNPs in individuals with and without CAD; (11) analyses of associated SNPs in patients with extreme LDL-C, HDL-C or TG levels; (12) simulation studies to assess overlap between GWAS signals and Mendelian disease loci; and (13) details of mouse studies.

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Tanya M. Teslovich[1]*, Kiran Musunuru[2,3,4,5,6]*, Albert V. Smith[7,8], Andrew C. Edmondson[9,10], Ioannis M. Stylianou[10], Masahiro Koseki[11], James P. Pirruccello[2,5,6], Samuli Ripatti[12,13], Daniel I. Chasman[4,14], Cristen J. Willer[1], Christopher T. Johansen[15], Sigrid W. Fouchier[16], Aaron Isaacs[17], Gina M. Peloso[18,19], Maja Barbalic[20], Sally L. Ricketts[21], Joshua C. Bis[22], Yurii S. Aulchenko[17], Gudmar Thorleifsson[23], Mary F. Feitosa[24], John Chambers[25], Marju Orho-Melander[26], Olle Melander[26], Toby Johnson[27], Xiaohui Li[28], Xiuqing Guo[28], Mingyao Li[9,10], Yoon Shin Cho[29], Min Jin Go[29], Young Jin Kim[29], Jong-Young Lee[29], Taesung Park[30,31], Kyunga Kim[32], Xueling Sim[33], Rick Twee-Hee Ong[34], Damien C. Croteau-Chonka[35], Leslie A. Lange[35], Joshua D. Smith[36], Kijoung Song[37], Jing Hua Zhao[38], Xin Yuan[37], Jian'an Luan[38], Claudia Lamina[39], Andreas Ziegler[40], Weihua Zhang[25], Robert Y. L. Zee[4,14], Alan F. Wright[41], Jacqueline C. M. Witteman[17,42], James F. Wilson[43], Gonneke Willemsen[44], H.-Erich Wichmann[45], John B. Whitfield[46], Dawn M. Waterworth[37], Nicholas J. Wareham[38], Gérard Waeber[47], Peter Vollenweider[47], Benjamin F. Voight[2,5], Veronique Vitart[41], Andre G. Uitterlinden[17,42,48], Manuela Uda[49], Jaakko Tuomilehto[50], John R. Thompson[51], Toshiko Tanaka[52,53], Ida Surakka[12,13], Heather M. Stringham[1], Tim D. Spector[54], Nicole Soranzo[54,55], Johannes H. Smit[56], Juha Sinisalo[57], Kaisa Silander[12,13], Eric J. G. Sijbrands[17,48], Angelo Scuteri[58], James Scott[59], David Schlessinger[60], Serena Sanna[49], Veikko Salomaa[50], Juha Saharinen[12], Chiara Sabatti[61], Aimo Ruokonen[62], Igor Rudan[43], Lynda M. Rose[14], Robert Roberts[63], Mark Rieder[36], Bruce M. Psaty[64], Peter P. Pramstaller[65], Irene Pichler[65], Markus Perola[12,13], Brenda W. J. H. Penninx[56], Nancy L. Pedersen[66], Cristian Pattaro[65], Alex N. Parker[67], Guillaume Pare[68], Ben A. Oostra[69], Christopher J. O'Donnell[4,19], Markku S. Nieminen[57], Deborah A. Nickerson[36], Grant W. Montgomery[46], Thomas Meitinger[70,71], Ruth McPherson[63], Mark I. McCarthy[72,73,74], Wendy McArdle[75], David Masson[11], Nicholas G. Martin[46], Fabio Marroni[76], Massimo Mangino[54], Patrik K. E. Magnusson[66], Gavin Lucas[77], Robert Luben[21], Ruth J. F. Loos[38], Marja-Liisa Lokki[78], Guillaume Lettre[79], Claudia Langenberg[38], Lenore J. Launer[80], Edward G. Lakatta[60], Reijo Laaksonen[81], Kirsten O. Kyvik[82], Florian Kronenberg[39], Inke R. König[40], Kay-Tee Khaw[21], Jaakko Kaprio[12,13,83], Lee M. Kaplan[84], Åsa Johansson[85], Marjo-Riitta Jarvelin[86,87], A. Cecile J. W. Janssens[17], Erik Ingelsson[66], Wilmar Igl[85], G. Kees Hovingh[16], Jouke-Jan Hottenga[44], Albert Hofman[17,42], Andrew A. Hicks[65], Christian Hengstenberg[88], Iris M. Heid[45,89], Caroline Hayward[41], Aki S. Havulinna[50,90], Nicholas D. Hastie[41], Tamara B. Harris[80], Talin Haritunians[28], Alistair S. Hall[91], Ulf Gyllensten[85], Candace Guiducci[5], Leif C. Groop[26,92], Elena Gonzalez[5], Christian Gieger[45], Nelson B. Freimer[93], Luigi Ferrucci[94], Jeanette Erdmann[95], Paul Elliott[86,96], Kenechi G. Ejebe[5], Angela Döring[45], Anna F. Dominiczak[97], Serkalem Demissie[18,19], Panagiotis Deloukas[55], Eco J. C. de Geus[44], Ulf de Faire[98], Gabriel Crawford[5], Francis S. Collins[99], Yii-der I. Chen[28], Mark J. Caulfield[114], Harry Campbell[43], Noel P. Burtt[5], Lori L. Bonnycastle[99], Dorret I. Boomsma[44], S. Matthijs Boekholdt[100], Richard N. Bergman[101], Inês Barroso[55], Stefania Bandinelli[102], Christie M. Ballantyne[103], Themistocles L. Assimes[104], Thomas Quertermous[104], David Altshuler[2,4,5], Mark Seielstad[34], Tien Y. Wong[105], E-Shyong Tai[106], Alan B. Feranil[107], Christopher W. Kuzawa[108], Linda S. Adair[109], Herman A. Taylor Jr[110], Ingrid B. Borecki[24], Stacey B. Gabriel[5], James G. Wilson[110], Hilma Holm[23], Unnur Thorsteinsdottir[8,23], Vilmundur Gudnason[7,8], Ronald M. Krauss[111], Karen L. Mohlke[35], Jose M. Ordovas[112,113], Patricia B. Munroe[114], Jaspal S. Kooner[59], Alan R. Tall[11], Robert A. Hegele[15], John J.P. Kastelein[16], Eric E. Schadt[115], Jerome I. Rotter[28], Eric Boerwinkle[20], David P. Strachan[116], Vincent Mooser[37], Kari Stefansson[8,23], Muredach P. Reilly[9,10], Nilesh J Samani[117], Heribert Schunkert[95], L. Adrienne Cupples[18,19]*, Manjinder S. Sandhu[21,38,55]*, Paul M Ridker[4,14]*, Daniel J. Rader[9,10]*, Cornelia M. van Duijn[17,42]*, Leena Peltonen‡, Gonçalo R. Abecasis[1]*, Michael Boehnke[1]* & Sekar Kathiresan[2,3,4,5]*

[1]Center for Statistical Genetics, Department of Biostatistics, University of Michigan, Ann Arbor, Michigan 48109, USA. [2]Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts 02114, USA. [3]Cardiovascular Research Center, Massachusetts General Hospital, Boston, Massachusetts 02114, USA. [4]Department of Medicine, Harvard Medical School, Boston, Massachusetts 02115, USA. [5]Broad Institute, Cambridge, Massachusetts 02142, USA. [6]Johns Hopkins University School of Medicine, Baltimore, Maryland 21287, USA. [7]Icelandic Heart Association, Heart Preventive Clinic and Research Institute, 201 Kopavogur, Iceland. [8]University of Iceland, 101 Reykjavik, Iceland. [9]Cardiovascular Institute, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104, USA. [10]Institute for Translational Medicine and Therapeutics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104, USA. [11]Division of Molecular Medicine, Department of Medicine, Columbia University, New York, New York 10032, USA. [12]Institute for Molecular Medicine Finland FIMM, University of Helsinki, FI-00014 Helsinki, Finland. [13]National Institute for Health and Welfare, P.O. Box 104, FI-00251 Helsinki, Finland. [14]Division of Preventive Medicine, Brigham and Women's Hospital, Boston Massachusetts 02215, USA. [15]Robarts Research Institute, University of Western Ontario, London, Ontario N6A 5K8, Canada. [16]Department of Vascular Medicine, Academic Medical Centre at the University of Amsterdam, 1105 AZ Amsterdam, The Netherlands. [17]Department of Epidemiology, Erasmus University Medical Center, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands. [18]Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts 02118, USA. [19]National Heart, Lung and Blood Institute's Framingham Heart Study, Framingham, Massachusetts 01702, USA. [20]Human Genetics Center, University of Texas Health Science Center at Houston, Houston, Texas 77030, USA. [21]Department of Public Health and Primary Care, Strangeways Research Laboratory, University of Cambridge, Cambridge CB1 8RN, UK. [22]Cardiovascular Health Research Unit and Department of Medicine, University of Washington, Seattle, Washington 98101, USA. [23]deCODE Genetics, 101 Reykjavik, Iceland. [24]Division of Statistical Genomics in the Center for Genome Sciences, Washington University School of Medicine, St Louis, Missouri 63108, USA. [25]Department of Epidemiology and Public Health, Imperial College London, London W2 1PG, UK. [26]Department of Clinical Sciences, Lund University, SE-20502, Malmö, Sweden. [27]Clinical Pharmacology and Barts and the London Genome Centre, William Harvey Research Institute, Barts and the London School of Medicine, Queen Mary University of London, London EC1M 6BQ, UK. [28]Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California 90048, USA. [29]Center for Genome Science, National Institute of Health, Seoul 122-701, Republic of Korea. [30]Interdisciplinary Program in Bioinformatics, College of Natural Sciences, Seoul National University, Seoul 151-742, Republic of Korea. [31]Department of Statistics, College of Natural Sciences, Seoul National University, Seoul 151-742, Republic of Korea. [32]Department of Statistics, Sookmyung Women's University, Seoul 140-742, Republic of Korea. [33]Centre for Molecular Epidemiology, National University of Singapore, Singapore 117597, Republic of Singapore. [34]Genome Institute of Singapore, Singapore 138672, Republic of Singapore. [35]Department of Genetics, University of North Carolina, Chapel Hill, North Carolina 27599, USA. [36]Department of Genome Sciences, University of Washington, Seattle, Washington 98195, USA. [37]Genetics Division, GlaxoSmithKline R&D, King of Prussia, Pennsylvania 19406, USA. [38]MRC Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK. [39]Division of Genetic Epidemiology, Department of Medical Genetics, Molecular and Clinical Pharmacology, Innsbruck Medical University, Schoepfstrasse 41, A-6020 Innsbruck, Austria. [40]Institut für Medizinische Biometrie und Statistik, Universität zu Lübeck, 23562 Lübeck, Germany. [41]MRC Human Genetics Unit, Institute of Genetics and Molecular

Medicine, Edinburgh EH4 2XU, UK. [42]Netherlands Genomics Initiative (NGI)-sponsored Netherlands Consortium for Healthy Aging (NCHA) and Center of Medical Systems Biology (CMSB), 2300 RC Leiden, The Netherlands. [43]Centre for Population Health Sciences, University of Edinburgh, Edinburgh EH8 9AG, UK. [44]Department of Biological Psychology, VU University Amsterdam, Van der Boechorststraat 1, 1081 BT Amsterdam, The Netherlands. [45]Institute of Epidemiology, Helmholtz Zentrum Munchen – German Research Center for Environmental Health, 85764 Neuherberg, Germany. [46]Genetic Epidemiology Unit, Queensland Institute of Medical Research, PO Royal Brisbane Hospital, Queensland 4029, Australia. [47]Department of Internal Medicine, Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland. [48]Department of Internal Medicine, Erasmus University Medical Center, PO Box 2040, 3000 CA Rotterdam, The Netherlands. [49]Istituto di Neurogenetica e Neurofarmacologia (INN), Consiglio Nazionale delle Ricerche, c/o Cittadella Universitaria di Monserrato, Monserrato, Cagliari 09042, Italy. [50]Department of Chronic Disease Prevention, National Institute for Health and Welfare, FI-00271 Helsinki, Finland. [51]Department of Health Sciences, University of Leicester, Leicester LE1 6TP, UK. [52]Clinical Research Branch, National Institute on Aging, National Institutes of Health, Baltimore, Maryland 21225, USA. [53]Medstar Research Institute, Baltimore, Maryland 21218, USA. [54]Department of Twin Research and Genetic Epidemiology, King's College London, London SE1 7EH, UK. [55]Wellcome Trust Sanger Institute, Hinxton, Cambridge CB10 1SA, UK. [56]Department of Psychiatry, EMGO Institute, Neuroscience Campus Amsterdam, VU University Medical Center, 1007 MB Amsterdam, The Netherlands. [57]Division of Cardiology, Department of Medicine, Helsinki University Central Hospital (HUCH), FI-00029 Helsinki, Finland. [58]Unita Operativa Geriatria, Istituto Nazionale Ricovero e Cura Anziani (INRCA), Istituto Ricovero e Cura a Carattere Scientifico (IRCCS), Via Cassia 1167, 00189 Rome, Italy. [59]Hammersmith Hospital, National Heart and Lung Institute, Imperial College London, London W12 0NN, UK. [60]Gerontology Research Center, National Institute on Aging, 5600 Nathan Shock Drive, Baltimore, Maryland 21224, USA. [61]Department of Health Research and Policy, Stanford University, Stanford, California 94305, USA. [62]Department of Clinical Chemistry, University of Oulu, FI-90220 Oulu, Finland. [63]The John & Jennifer Ruddy Canadian Cardiovascular Genetics Centre, University of Ottawa, Ottawa K1Y 4W7, Canada. [64]Departments of Medicine, Epidemiology, and Health Services, University of Washington, Group Health Research Institute, Group Health Cooperative, Seattle, Washington 98101, USA. [65]Institute of Genetic Medicine, European Academy Bozen/Bolzano (EURAC), Viale Druso 1, 39100 Bolzano, Italy – affiliated institute of the University of Lübeck, Germany. [66]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, SE-17177 Stockholm, Sweden. [67]Amgen, Thousand Oaks, California 91320, USA. [68]Genetic and Molecular Epidemiology Laboratory, McMaster University, Hamilton, Ontario L8N3Z5, Canada. [69]Department of Clinical Genetics, Erasmus University Medical Center, 3000 CA Rotterdam, The Netherlands. [70]Institut fur Humangenetik, Helmholtz Zentrum Munchen, Deutsches Forschungszentrum fur Umwelt und Gesundheit, 85764 Neuherberg, Germany. [71]Institute of Human Genetics, Klinikum rechts der Isar, Technische Universität München, 81675 Muenchen, Germany. [72]Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, UK. [73]Oxford Centre for Diabetes, Endocrinology and Medicine, University of Oxford, Churchill Hospital, Oxford OX3 7LJ, UK. [74]Oxford NIHR Biomedical Research Centre, Churchill Hospital, Oxford OX3 7LJ, UK. [75]Avon Longitudinal Study of Parents and Children, University of Bristol, Bristol BS8 2BN, UK. [76]Institute of Applied Genomics, via Linussio 51, 33100 Udine, Italy. [77]Cardiovascular Epidemiology and Genetics, Institut Municipal d'Investigacio Medica, 08003 Barcelona, Spain. [78]Transplantation Laboratory, Haartman Institute, University of Helsinki, FI-00014 Helsinki, Finland. [79]Montreal Heart Institute (Research Center), Université de Montréal, Montréal, Québec H1T 1C8, Canada. [80]Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, National Institutes of Health, Bethesda, Maryland 20892, USA. [81]Science Center, Tampere University Hospital, FI-33521 Tampere, Finland. [82]Institute of Regional Health Research and the Danish Twin Registry, Institute of Public Health, University of Southern Denmark, JBWinsløws Vej 9B, DK-5000, Odense, Denmark. [83]Faculty of Medicine, Department of Public Health, University of Helsinki, FI-00014 Helsinki, Finland. [84]Massachusetts General Hospital Weight Center, Boston, Massachusetts 02114, USA. [85]Department of Genetics and Pathology, Rudbeck Laboratory, University of Uppsala, SE-75185 Uppsala, Sweden. [86]Department of Epidemiology & Biostatistics, Imperial College London, St Mary's Campus, Norfolk Place, London W2 1PG, UK. [87]Department of Public Health Science and General Practice, University of Oulu, FI-90220 Oulu, Finland. [88]Klinik und Poliklinik für Innere Medizin II, Universität Regensburg, 93053 Regensburg, Germany. [89]Department of Epidemiology and Preventive Medicine Regensburg University Medical Center Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany. [90]Department of Biomedical Engineering and Computational Science, Aalto University School of Science and Technology, FI-00076 Aalto, Finland. [91]LIGHT Research Institute, Faculty of Medicine and Health, University of Leeds, Leeds LS2 9JT, UK. [92]Department of Medicine, Helsinki University Hospital, FI-00029 Helsinki, Finland. [93]Department of Psychiatry, Center for Neurobehavioral Genetics, The Jane and Terry Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine, University of California, Los Angeles, California 90095, USA. [94]Clinical Research Branch, National Institute on Aging, National Institutes of Health, Baltimore, Maryland 21225, USA. [95]Medizinische Klinik II, Universität zu Lübeck, 23538 Lübeck, Germany. [96]MRC-HPA Centre for Environment and Health, Imperial College London, London W2 1PG, UK. [97]BHF Glasgow Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow G12 8TA, UK. [98]Division of Cardiovascular Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, SE-17177 Stockholm, Sweden. [99]National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland 20892, USA. [100]Departments of Vascular Medicine & Cardiology, Academic Medical Centre, 1105 AZ Amsterdam, The Netherlands. [101]Department of Physiology and Biophysics, University of Southern California, Los Angeles, California 90033, USA. [102]Geriatric Unit, Azienda Sanitaria Firenze (ASF), 50125 Florence, Italy. [103]Department of Medicine, Baylor College of Medicine, Houston, Texas 77030, USA. [104]Department of Medicine, Stanford University School of Medicine, Stanford, California 94305, USA. [105]Singapore Eye Research Institute, National University of Singapore, Singapore 168751, Republic of Singapore. [106]Departments of Medicine/Epidemiology and Public Health, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 117597, Republic of Singapore. [107]Office of Population Studies Foundation, University of San Carlos, Cebu City 6000, Philippines. [108]Department of Anthropology, Northwestern University, Evanston, Illinois 60208, USA. [109]Department of Nutrition, Carolina Population Center, University of North Carolina, Chapel Hill, North Carolina 27516, USA. [110]Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi 39126, USA. [111]Children's Hospital Oakland Research Institute, Oakland, California 94609, USA. [112]Department of Cardiovascular Epidemiology and Population Genetics, Centro Nacional de Investigaciones Cardiovasculares, 28029 Madrid, Spain. [113]Nutrition and Genomics Laboratory, Jean Mayer United States Department of Agriculture Human Nutrition Research Center on Aging at Tufts University, Boston, Massachusetts 02111, USA. [114]Clinical Pharmacology and Barts and The London Genome Centre, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, UK. [115]Sage Bionetworks, Seattle, Washington 98109, USA. [116]Division of Community Health Sciences, St George's University of London, London SW17 0RE, UK. [117]Department of Cardiovascular Sciences, University of Leicester, NIHR Biomedical Research Unit in Cardiovascular Disease, Glenfield Hospital, Leicester LE3 9QP, UK.
*These authors contributed equally to this work.
‡Deceased.