Supplementary Note

1. Supplementary Results

Competitive Gene-Set (Pathway) and Tissue Expression Analyses

We used Multi-marker Analysis of GenoMic Annotation (MAGMA)[1] as implemented in the FUMA[2] pipeline to perform a competitive gene-set analysis of curated gene-sets and GO terms (pathways) obtained from the Molecular Signature Database[3], as well as a gene-property analysis for gene expression of GTEx[4] tissues for LDL-C, triglycerides, and HDL-C. As expected, our pathway analysis revealed a significant enrichment for several biological processes related to lipoprotein metabolism including sterol homeostasis, acylglycerol homeostasis, chylomicron mediated transport, acyl reverse cholesterol transport, and regulation of lipoprotein lipase activity (P Bonferroni < 0.05, **Supplementary Table 24-29**). MAGMA gene-property analysis revealed a significant enrichment of GWAS signal overlapping genes expressed in the liver, adrenal gland, and the ovary for LDL-C, subcutaneous and visceral adipose tissue, liver, adrenal gland, and pancreas for triglycerides, and liver for HDL-C (**Supplementary Fig. 12-17**).

Novel Lipid Loci and Association with Coronary Disease

To further evaluate whether novel lipid variants identified in our analysis also influence the risk of CAD, we examined the association of lead variants within the 118 novel lipid loci identified in our study with coronary artery disease (CAD). 115/118 of the lead variants were present in the CARDIoGRAMplusC4D 1000 Genomes GWAS[5]; the remaining 3 (MAF < 0.0035 for each) were present in the MIGen and CARDIoGRAM exome chip GWAS analysis[6]. In total, 25 of the 118 loci showed at least nominal (P < 0.05) association with CAD in the CARDIoGRAM studies (**Supplementary Table 30**). Notably, the previously identified lead locus for CAD at 9p21 (rs1333048, CAD P = 5.7×10^{-94}) is also associated with LDL-C and TC at genome-wide significance in our study. However, the LDL-C raising allele is in the opposite direction of the expected effect on CAD, suggesting that the causal variant(s) at 9p21 may confer CAD risk outside of a lipid pathway as implied by preliminary functional work at the locus[7]. We then examined the direction of effect for LDL-C, TG, and HDL-C raising alleles on CAD for the 118 novel loci in our analysis. Consistent with prior observations, the 32 LDL-C and 63 TG raising alleles (lipid P < 10^{-4}) were more likely to be associated with an increased risk of CAD (two-tailed binomial P = 0.05 and 3.8×10^{-5} for LDL and TG, respectively). The same was not true for 9 alleles associated with a higher HDL-C (P < 10^{-4}) but not also associated with LDL-C or TG (two-tailed binomial P = 0.5).

2. Supplementary Methods

Quality Control Analysis

We excluded: duplicate samples, samples with more heterozygosity than expected, an excess (>2.5%) of missing genotype calls, or discordance between genetically inferred sex and phenotypic gender. In addition, one individual from each pair of related individuals (as measured by the KING[8] software) were removed. Veterans were then divided into three mutually exclusive ethnic groups based on self-identified race/ethnicity and admixture analysis using the ADMIXTURE v1.3 software[9]: 1) non-Hispanic whites (self identified as "non-Hispanic," "white," and > 80% genetic European ancestry), 2) non-Hispanic blacks (self identified as "non-Hispanic," "black," and > 50% genetic African ancestry), and 3) Hispanics (self-identified only). ADMIXTURE plots for black and Hispanic veterans are provided in **Supplementary Figures 1 and 2**. Prior to imputation,

variants that were poorly called (genotype missingness > 5%) or that deviated from their expected allele frequency based on reference data from the 1000 Genomes Project[10] were excluded. In addition, samples with individual missingness > 2.5% were also excluded. After pre-phasing using EAGLE[11] v2, genotypes from the 1000 Genomes Project[10] phase 3, version 5 reference panel were imputed into Million Veteran Program (MVP) participants via Minimac3 software[12]. Ethnicity-specific principal component analysis was performed using the EIGENSOFT software[13].

Following imputation, variant level quality control was performed using the EasyQC R package[14] (see URLs), and exclusion metrics included: ancestry specific Hardy-Weinberg equilibrium[15] $P < 1x10^{-20}$, posterior call probability < 0.9, imputation quality/INFO <0.3, minor allele frequency (MAF) < 0.0003, call rate < 97.5% for common variants (MAF > 1%), and call rate < 99% for rare variants (MAF < 1%). Variants were also excluded if they deviated > 10% from their expected allele frequency based on reference data from the 1000 Genomes Project[10].

Lipid Phenotypes Quality Control and Transformation

Following extraction of prevalent laboratory measurements from the electronic health record, lipid data were evaluated for spurious values (< 0 mg/dL), histograms for each lipid trait were inspected for normality, and extreme outliers (>400 mg/dL, > 1000 mg/dL, > 500 mg/dL, and > 150 mg/dL for low-density lipoprotein cholesterol (LDL-C), triglycerides, total cholesterol, and high-density lipoprotein cholesterol (HDL-C), respectively) were excluded (triglycerides were evaluated based on raw values and then following natural log transformation). For each phenotype: maximum LDL-C, natural log transformed maximum triglycerides, maximum total cholesterol, and minimum HDL-C, residuals were obtained after regressing on age, age^2, sex, and 10 principal components within each ethnic group. Residuals were subsequently inverse normal transformed for association analysis. To minimize confounding from statins and variable adherence, maximum/minimum values were used[16].

Discovery and Replication Association Analysis

We tested DNA sequence variants for association with the transformed lipid values through linear regression assuming an additive model using the SNPTEST (see URLs) statistical software program. In our discovery analysis, we performed association analyses separately for each ethnic group (whites, blacks, and Hispanics) and then meta-analyzed using an inverse variance-weighted fixed effects method implemented in the METAL software program[17]. We excluded variants with a high amount of heterogeneity (I^2 statistic > 75%) across the three ancestries. In addition, we required that variants be observed in at least two ethnic groups. For variants with suggestive associations (association $P < 10^{-4}$), we sought replication of our findings in one of two independent studies.

Replication was first performed using summary statistics from the 2017 Global Lipids Genetics Consortium (GLGC) exome array meta-analysis[18]. In this analysis, 73 studies encompassing up to 319,677 participants contributed association results for plasma lipid levels using genotypes from the HumanExome BeadChip (or exome array). For each phenotype (LDL-C, natural log transformed triglycerides, total cholesterol, and HDL-C), residuals were obtained after regressing on age, age^2, sex, and 4 principal components of ancestry. For studies with data collected after 1994, adjustments to LDL-C and total cholesterol measurements were made (LDL-C/0.7, total cholesterol/0.8) for individuals on lipid lowering medication. No adjustment was made for HDL-C or triglycerides. For studies ascertained on CAD case/control status, the two groups were modeled as separate studies. A total of 242,289 variants were analyzed after quality control and were available for replication.

If a DNA sequence variant was not available for replication in the above exome array-focused study, we sought replication from publicly available summary statistics from the 2013 GLGC "joint meta-analysis[19]." In this analysis, 37 studies of primarily European ancestry genotyped on various arrays and imputed to the HapMap[20] reference panel contributed association results and were meta-analyzed. An additional 2,044,165 variants were available for replication in this study. Association results for variants present in both the 2017 exome array-focused study and the 2013 "joint meta-analysis" were tested for replication only in the exome chip dataset.

We combined results across discovery and replication cohorts using inverse-variance weighted fixed effects meta-analysis. A P <0.05 with a consistent direction of effect was required for replication, and we set an overall (discovery and replication combined) statistical threshold of $P < 5 \times 10^{-8}$ for genome-wide significance. Novel loci were defined as being greater than 1 million base-pairs away from a known lipid genome-wide associated lead variant. Additionally, linkage disequilibrium information from the 1000 Genomes Project[10] was used to determine independent variants where a locus extended beyond 1 million base-pairs. All association P values were two-sided.

Competitive Gene-Set (Pathway) and Tissue Expression Analysis

We used MAGMA[1] as implemented in the FUMA[2] (see URLs) pipeline to perform a competitive gene set analysis for 10,655 gene sets (curated gene sets: 4,738, GO terms: 5,917) present in the Molecular Signature Database[3] (MsigDB 6.1) and a gene-property analysis for gene expression in GTEx v7 with 53 tissue types. The input for these analyses was our 1000 Genomes[10] imputed summary statistics from Stage 1 for LDL-C, triglycerides, and HDL-C. We first ran the combined trans-ethnic summary statistics and then the summary statistics in the European subgroup of participants alone. For the gene-set analyses, a P adjusted for the number of total gene sets tested was calculated and output for gene-sets with two-sided P Bonferroni < 0.05. We note that MAGMA gene-set and gene-property analyses uses the full distribution of SNP p values and differs from pathway enrichment tests that only tests for enrichment of prioritized genes.

Cohort Descriptions and Coronary Artery Disease Definitions for PDE3B Analysis

We sought replication of our *PDE3B* pLoF lipid findings in the DiscovEHR cohort. In this study, median values for serially measured laboratory traits were calculated for all individuals with two or more measurements in the EHR following removal of likely spurious values that were greater than three standard deviations from the intra-individual median value. All measurements were taken after fasting and were adjusted for known lipid-lowering medication use (total cholesterol divided by 0.8; LDL-C divided by 0.7; triglycerides divided by 0.83; and HDL-C divided by 1.04 for individuals on lipid lowering medications). HDL-C and triglycerides measurements were log10-transformed to achieve normality. Residuals were generated for each trait, adjusting for age, age^2, sex, and the first four principal components of ancestry and then rank-based inverse normalized residuals were tested for association with variants using linear regression, under an additive model. MVP and DiscovEHR lipid results were combined using an inverse variance-weighted fixed effects method.

We then examined the effect of damaging and pLoF mutations in Phosphodiesterase 3B on the risk of coronary artery disease across five cohorts. We performed logistic regression of rs150090666 or associated damaging mutations with coronary artery disease adjusted for age, sex, and the first 5 principal components of ancestry across white participants.

In MVP, coronary disease cases and controls were defined after collapsing ICD-9 diagnosis codes to the "Ischemic Heart Disease" phenotype based on the algorithm proposed by Denny et al[21]. Phenotype quality

control was performed as described in the PheWAS methods below. We identified 50,950 coronary artery disease cases and 111,584 controls available for analysis.

In UK Biobank, analysis was performed separately in individuals of European and non-European ancestry. Phasing and imputation were performed centrally, by UK Biobank, using a reference panel combining UK10K and 1000 Genomes samples. 39,235,157 variants included in the Haplotype Reference Consortium[22] were imputed. As recommended by UK Biobank, we excluded any samples with an imputation quality < 0.3 as well as pLoF variants which were not included in the Haplotype Reference Consortium reference panel. Mitochondrial genetic data and sex chromosomes were excluded from this analysis. Individual level genetic data was available from individuals in UK Biobank, after excluding one related individual of each related pair of individuals, individuals whose genetic sex did not match self-reported sex, and individuals with an excess of missing genotype calls or more heterozygosity than expected.

Estimates of the association of rs150090666 with coronary artery disease in UK Biobank were derived using logistic regression with adjustment for age, sex, ten principal components of ancestry and a dummy variable for array type. Coronary artery disease diagnosis was defined as previously described[23].

In the Myocardial Genetics Consortium, whole-exome sequencing of the Myocardial Infarction Genetics Consortium participants was performed between 2010 and 2015 at the Broad Institute as previously described[24]. In brief, sequence data of all participants were aligned to a human reference genome build GRCh37.p13 using the Burrows-Wheeler Aligner algorithm. Aligned non-duplicate reads were locally realigned and base qualities were recalibrated using Genome Analysis Toolkit (GATK) software[25]. Variants were jointly called using GATK HaplotypeCaller software. The sensitivity of the selected variant quality score recalibration threshold was 99.6% for single-nucleotide polymorphisms and 95% for insertion or deletion variants as empirically assessed using HapMap controls with known genotypes included in the genotyping call set.

pLoF and damaging variants in *PDE3B* were identified in the Myocardial Infarction Genetics Consortium using whole-exome sequencing as previously described[24,26,27]. Studies included in the consortium were: 1) the Italian Atherosclerosis Thrombosis and Vascular Biology (ATVB) study (dbGaP Study Accession phs000814.v1.p1); 2) the Exome Sequencing Project Early-Onset Myocardial Infarction (ESP-EOMI) study; 3) a nested case-control cohort from the Jackson Heart Study (JHS); 4) the South German Myocardial Infarction study (dbGaP Study Accession phs000916.v1.p1); 5) the Ottawa Heart Study (OHS) (dbGaP Study Accession phs000806.v1.p1); 6) the Precocious Coronary Artery Disease (PROCARDIS) study (dbGaP Study Accession phs000883.v1.p1) ; 7) the Pakistan Risk of Myocardial Infarction Study (PROMIS) (dbGaP Study Accession phs000917.v1.p1); 8) the Registre Gironi del COR (Gerona Heart Registry or REGICOR) study (dbGaP Study Accession phs000902.v1.p1); 9) the Leicester Myocardial Infarction study (dbGaP Study Accession phs001000.v1.p1); 10) the BioImage study (dbGaP Study Accession phs001058.v1.p1); 11) the North German Myocardial Infarction study (dbGaP Study Accession phs000990.v1.p1); 12) the Bangladesh Risk of Acute Vascular Events (BRAVE) study. A total of 47 putative loss of function variants and nonsynonymous variants predicted to be damaging or possibly damaging by each of 5 computer prediction algorithms (LRT score, MutationTaster, PolyPhen-2, HumDiv, PolyPhen-2 HumVar, and SIFT) with a minor allele frequency < 0.01 were aggregated together for phenotypic analysis.

In Penn Medicine Biobank, genomic DNA samples were transferred to the Regeneron Genetics Center for whole exome sequencing. Sequence reads were aligned to the human reference build GRCh37.p13. Single-nucleotide variants and insertion– deletion (indel) sequence variants were identified with the use of GATK. GATK was used to conduct local realignment of the aligned, duplicate-marked reads of each sample around putative indels. GATK's HaplotypeCaller was then used to process the indel-realigned, duplicate-marked reads to identify all exonic positions at which a sample varied from the genome reference in the genomic VCF

format. Variant Quality Score Recalibration, from GATK, was employed to evaluate the overall quality score of a sample's variants using training datasets (e.g., 1000 Genomes) to assess and recalculate each variant's score.

Following completion of cohort sequencing, samples showing disagreement between genetically-determined and reported sex, high rates of heterozygosity, low sequence coverage, unusually high degrees of cryptic relatedness, or genetically-identified sample duplicates, were excluded. For the purposes of downstream analyses, biallelic variants with missingness rates < 1%, Hardy-Weinberg equilibrium P values > $1.0x10^{-6}$ were retained. Coronary artery disease cases were defined as previously described[28]. Following these exclusions, 7,606 exome sequences of European ancestry were available for downstream analysis. A total of 34 putative loss of function variants and nonsynonymous variants predicted to be damaging or possibly damaging by each of 5 computer prediction algorithms were aggregated together for phenotypic analysis.

In DiscovEHR, samples, DNA sequence variants, and coronary disease cases were defined as previously described[28]. A total of 44 putative loss of function variants and nonsynonymous variants predicted to be damaging or possibly damaging by each of 5 computer prediction algorithms with a minor allele frequency < 0.01 were aggregated together for phenotypic analysis. Variants were tested for association with coronary disease status using Firth's penalized logistic regression, under an additive model, including age, age^2, sex, and the first four principal components of ancestry as covariates.

Novel Lipid Loci and Association with Coronary Disease

To assess whether novel lipid loci in our study modulate the risk of coronary disease, we extracted association results for the lead variant at each locus from either the CARDIoGRAMplusC4D 1000 Genomes imputed GWAS[5] (115/118 variants) or from the MIGen and CARDIoGRAM exome chip GWAS analysis[6] for 3 variants not available in the former. A two-tailed exact binomial test for goodness of fit was performed examining the expected and observed distributions of 1) LDL-C and 2) TG raising alleles ($P < 10^{-4}$), and 3) HDL-C raising alleles ($P < 10^{-4}$) not also associated with LDL-C or TG ($P > 0.05$) and their effect on coronary artery disease risk. We tested the null hypothesis that the lipid-associated variants were equally likely to increase or decrease coronary disease risk and set a two-sided $P < 0.05$ threshold for statistical significance.

PheWAS of Quality Control, Disease Definitions, and Association Analysis

Of 353,323 genotyped veterans, participants were included in the PheWAS analysis if the electronic health record reflected 2 or more separate encounters in the VA Healthcare System in each of the two years prior to enrollment in MVP. We identified 277,531 total veterans spanning 21,209,658 prevalent ICD-9 diagnosis codes available for analysis. We focused on the largest subgroup of 176,913 white participants, in which the mean age was 64.9 ± 12.6 years, and 93.1% (164,767) were male.

ICD-9 diagnosis codes were collapsed to clinical disease groups and corresponding controls using the groupings proposed by Denny et al[21]. Diseases were required to have a prevalence of > 0.25% (~400 cases) to be included in the PheWAS analysis. Each of two nonsense (*LPL* p.Ser474Ter, *ANGPTL8* p.Gln121Ter) and three missense (*ANGPTL4* p.Glu40Lys, *APOA5* p.Ser19Trp, *PCSK9* p.Arg46Leu) DNA sequence variants were tested using logistic regression adjusting for age, sex, and five principal components under the assumption of additive effects using the PheWAS R package in R v3.2.0 (see URLs). In total, 1,004 disease phenotypes were available for analysis.

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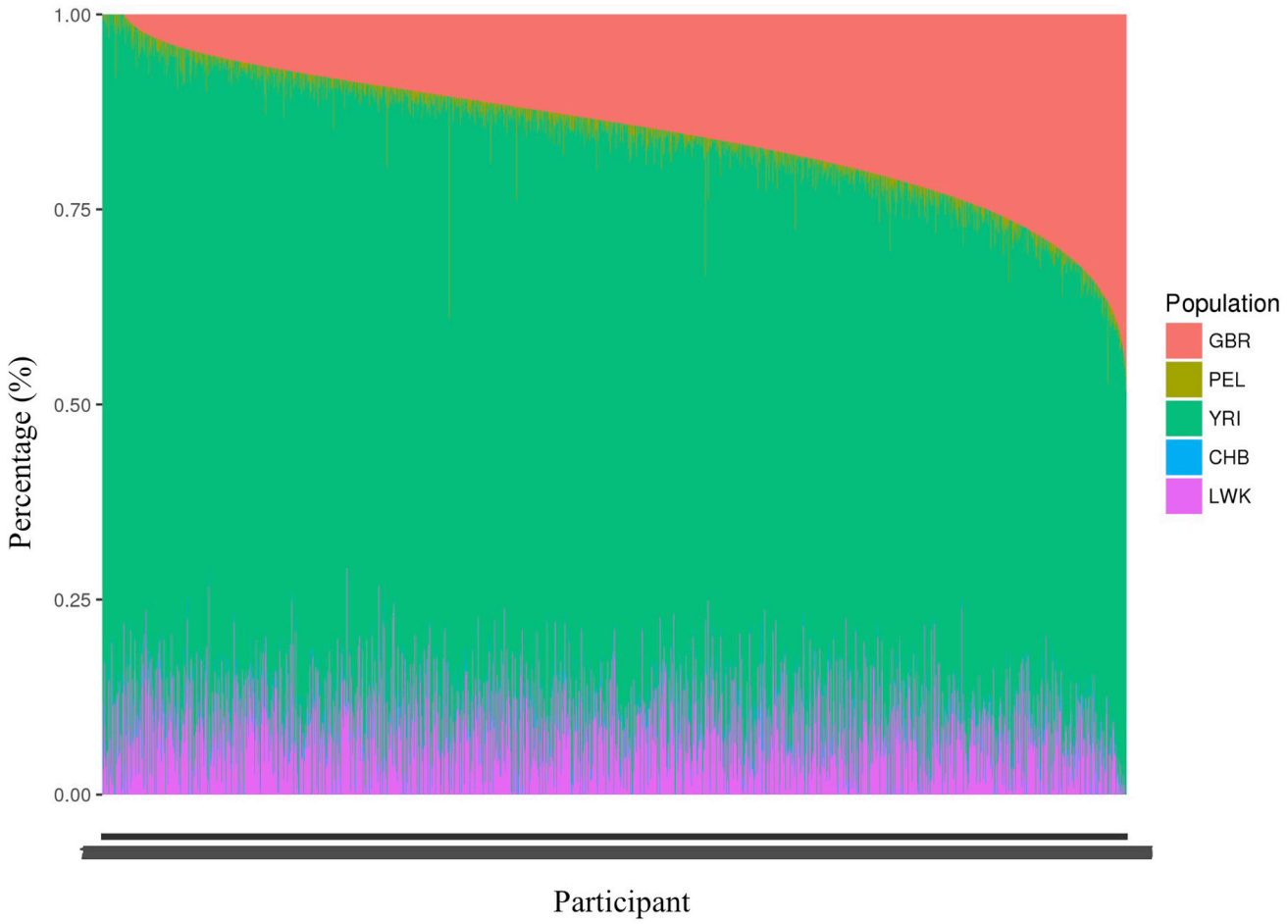
Geisinger-Regeneron DiscovEHR Collaboration

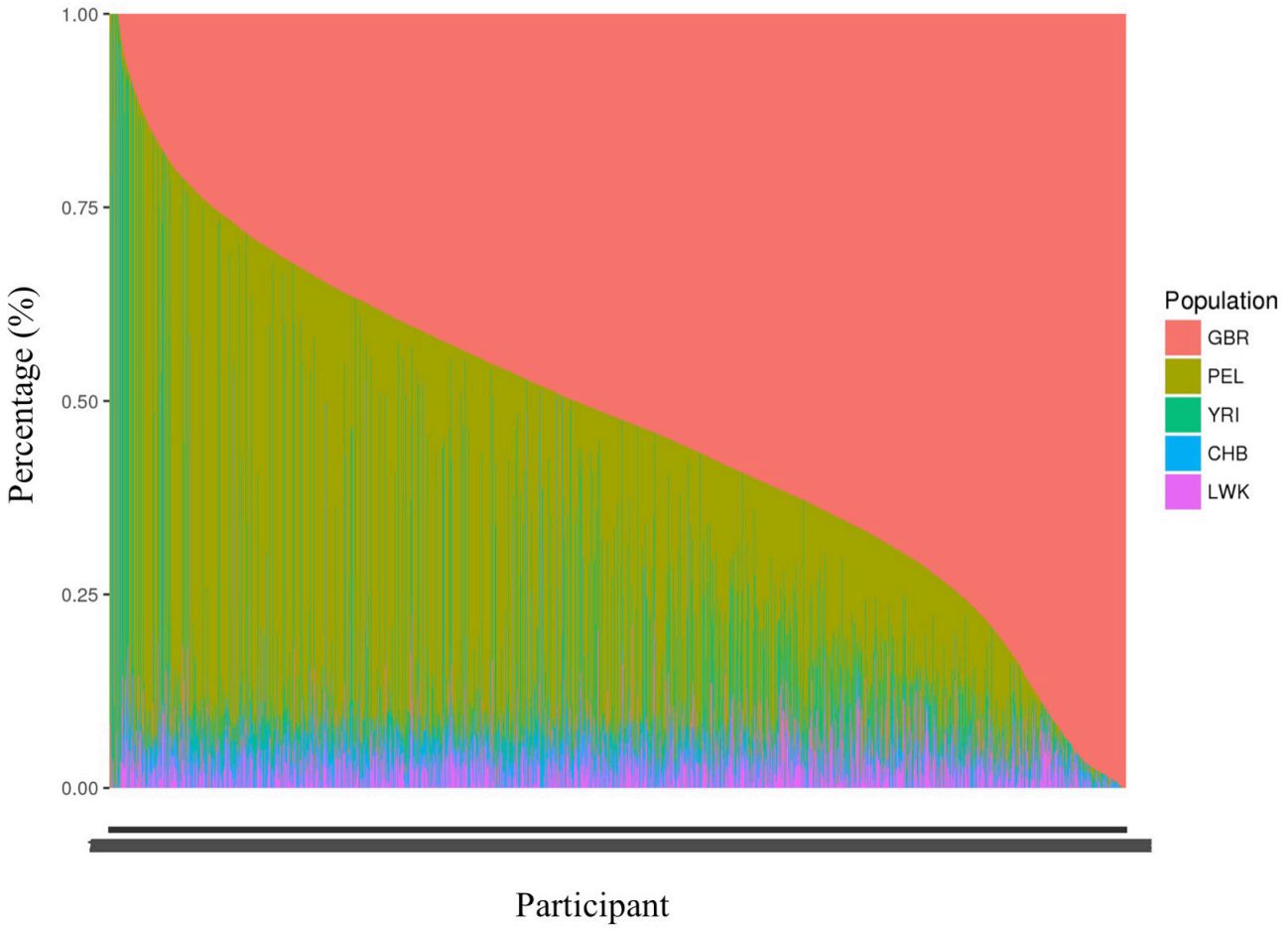
URL: http://www.discovehrshare.com/



Supplementary Figure 1

Admixture plot for non-Hispanic black participants in the Million Veteran Program

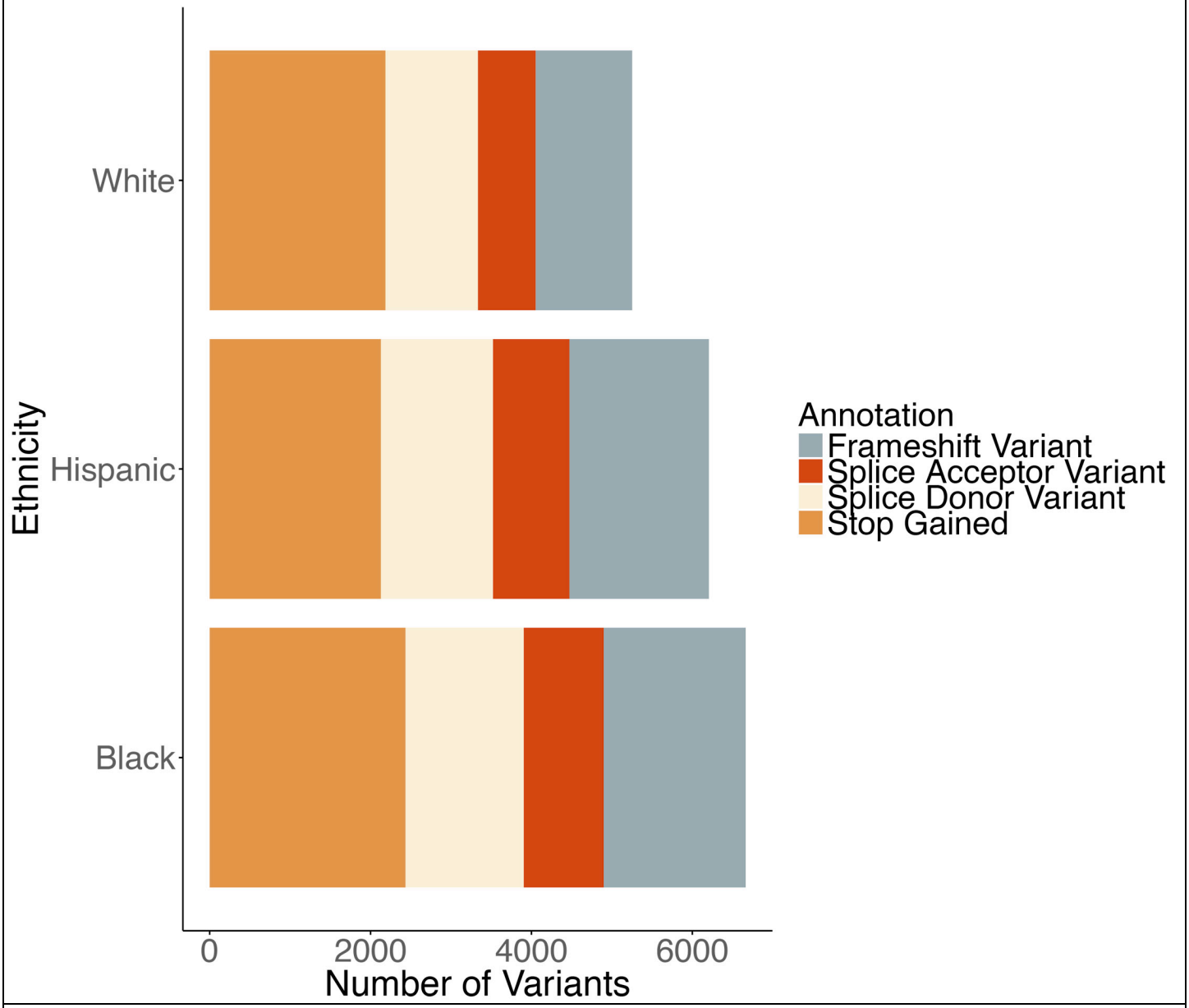
A supervised ADMIXTURE[1] analysis was performed on all MVP samples using 1000 Genomes Project[2] reference samples as the reference panel. Following training of the ADMIXTURE model on 5 populations representing East Asia (CHB), Europe (GBR), East Africa (LWK), South America (PEL), and West Africa (YRI), individuals with at least 50% African (LWK or YRI) ancestry and self-identifying as “non-Hispanic” and “black” were assigned to a separate MVP “black” population. The x-axis depicts each of the 57,332 samples assigned to this group, the Y-axis shows the percentage of each reference population per sample.



Supplementary Figure 2

Admixture plot for Hispanic participants in the Million Veteran Program

A supervised ADMIXTURE[1] analysis was performed on all MVP samples using 1000 Genomes Project[2] reference samples as the reference panel. Following training of the ADMIXTURE model on 5 populations representing East Asia (CHB), Europe (GBR), East Africa (LWK), South America (PEL), and West Africa (YRI), individuals self-identifying as "Hispanic" were assigned to a separate MVP "Hispanic" population. The x-axis depicts each of the 24,743 samples assigned to this group, the Y-axis shows the percentage of each reference population per sample.

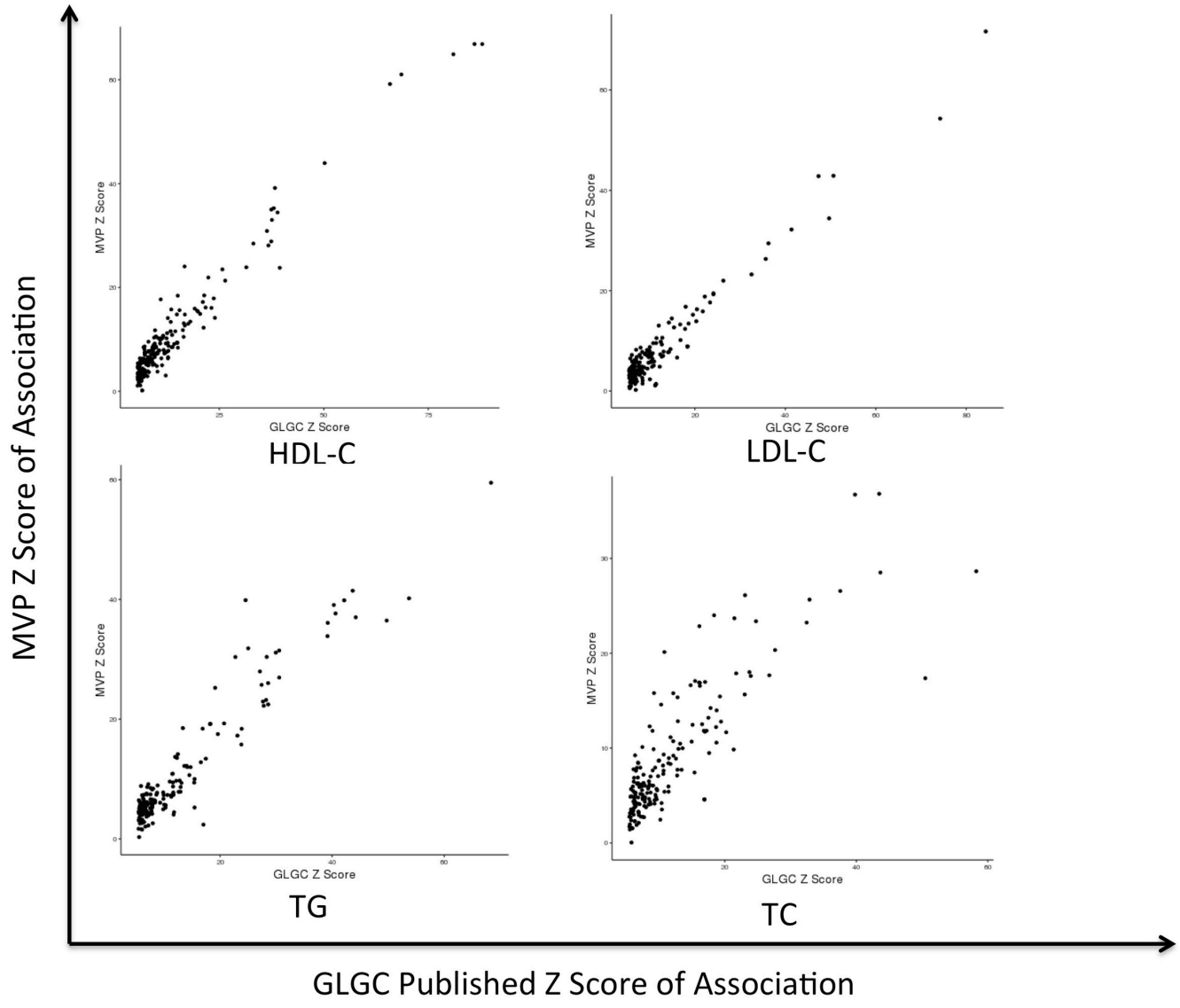


Supplementary Figure 3

Predicted Loss of Function (pLoF) Variation in Million Veteran Program Participants

The number of pLoF variants passing quality control for white, black, and Hispanic participants in MVP. Each pLoF annotation (frameshift, splice donor/acceptor, stop gained) is depicted by a separate color.

Abbreviations: MVP, Million Veteran Program; pLoF, predicted Loss of Function

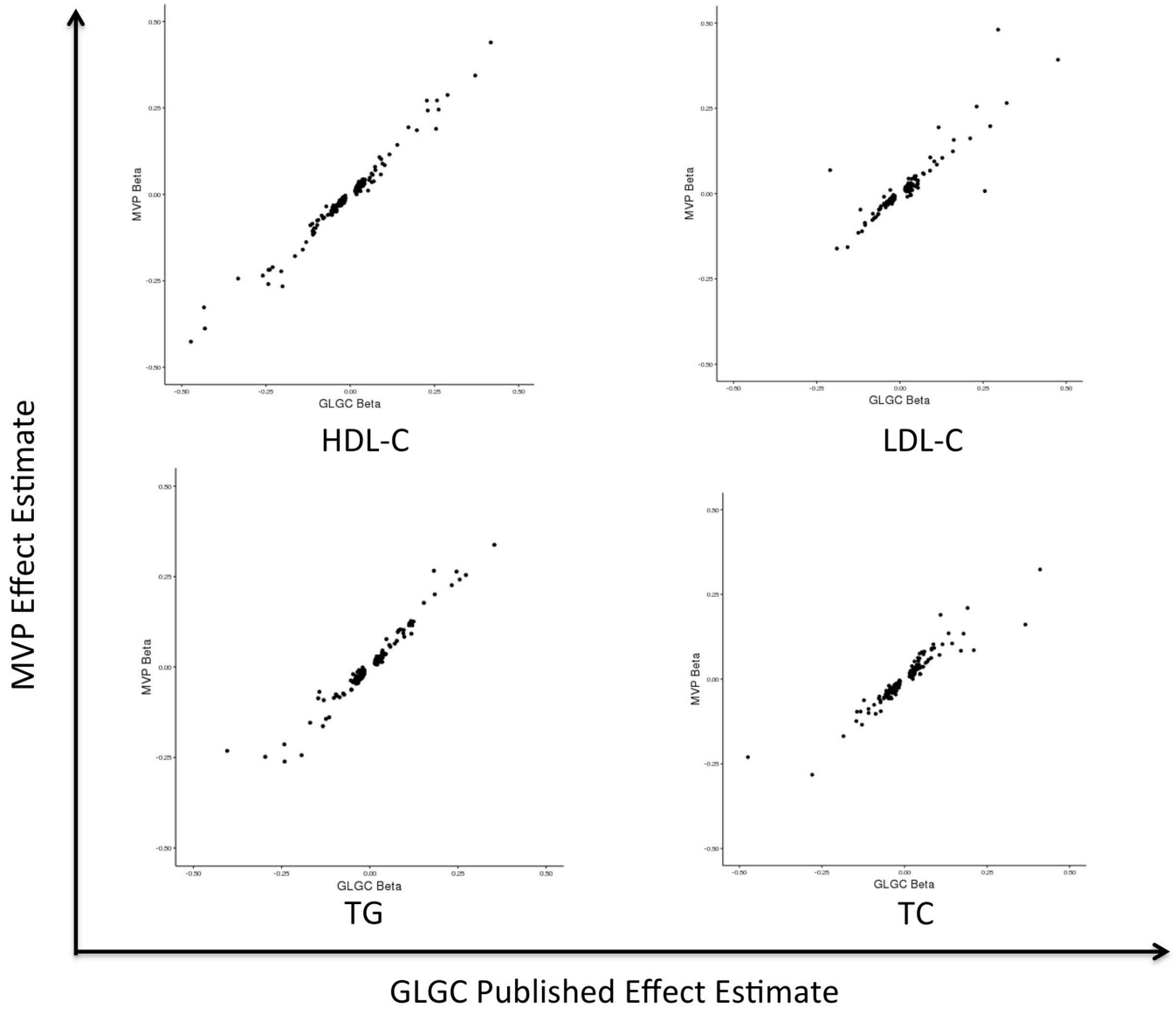


Supplementary Figure 4

Comparison of MVP lipid association Z score to previously published GLGC lipid association Z score

Plot of the linear regression Z score of association (β/SE) for 444 independent lipid exome-wide associated (two-sided $P < 2.2\times10^{-7}$) DNA sequence variants per trait as reported in the published GLGC 2017 exome chip analysis[3] and in our MVP discovery GWAS analysis aligned to the lipid raising allele. A strong association (two-sided linear regression $P < 1.0 \times10^{-100}$) between published (GLGC) and MVP Z scores was observed for each trait.

Abbreviations: SE, standard error; GLGC, Global Lipids Genetics Consortium; MVP, Million Veteran Program; HDL-C, High-Density Lipoprotein Cholesterol; LDL-C, Low-Density Lipoprotein Cholesterol; TG, Triglycerides; TC, Total Cholesterol

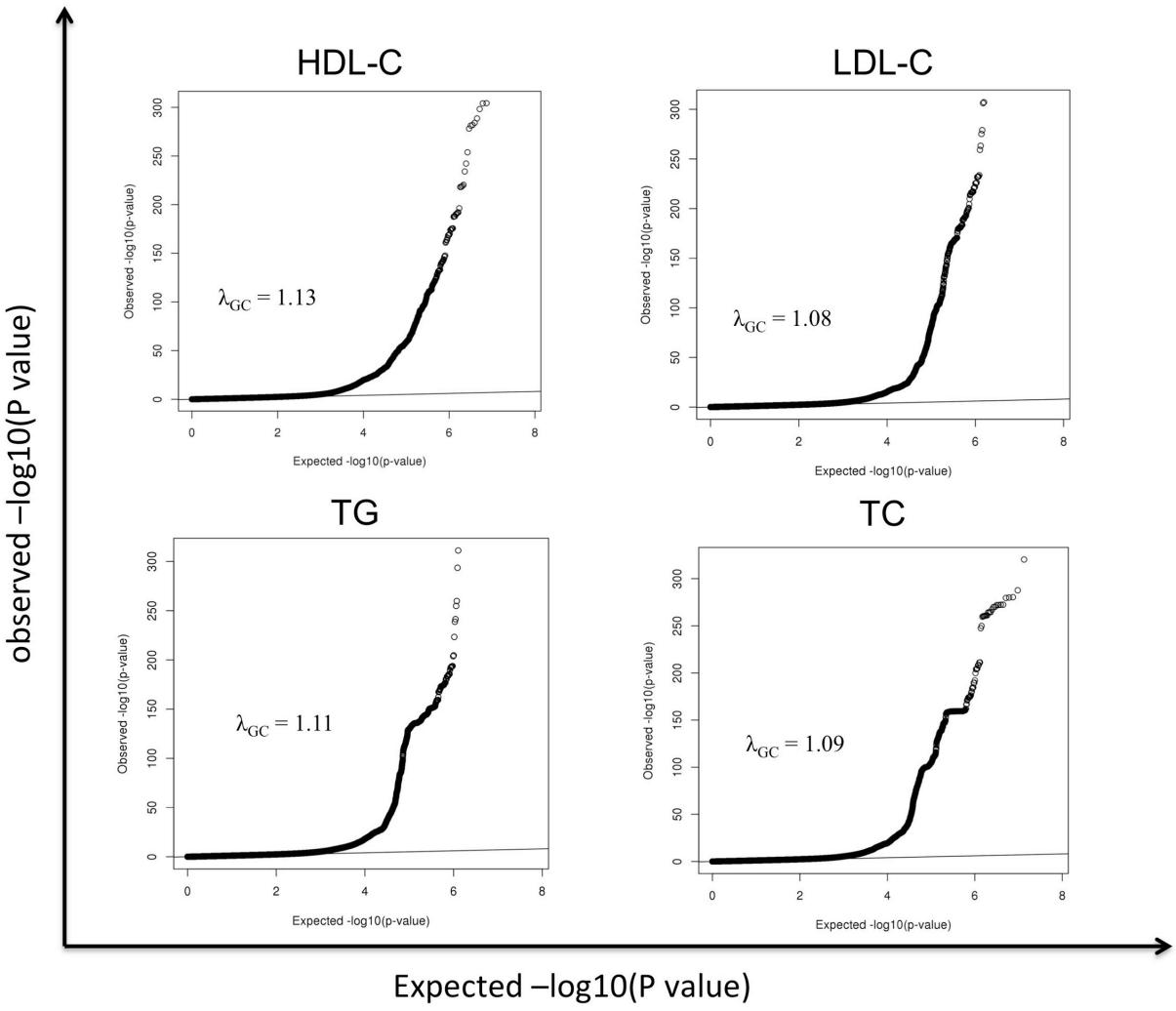


Supplementary Figure 5

Comparison of MVP effect estimates to previously published GLGC effect estimates for lipid traits

Plot of the linear regression effect estimates (β) for 444 independent lipid exome-wide associated (two-sided $P < 2.2\times10^{-7}$) DNA sequence variants per trait as reported in the published GLGC 2017 exome chip analysis[3] and in our MVP discovery GWAS analysis. The linear regression effect estimate between MVP discovery and published (GLGC) β values demonstrated evidence of the winner's curse (β = 0.72, 0.90, 0.85, 0.96 for LDL-C, TG, TC, and HDL-C, respectively after exclusion of extreme outliers).

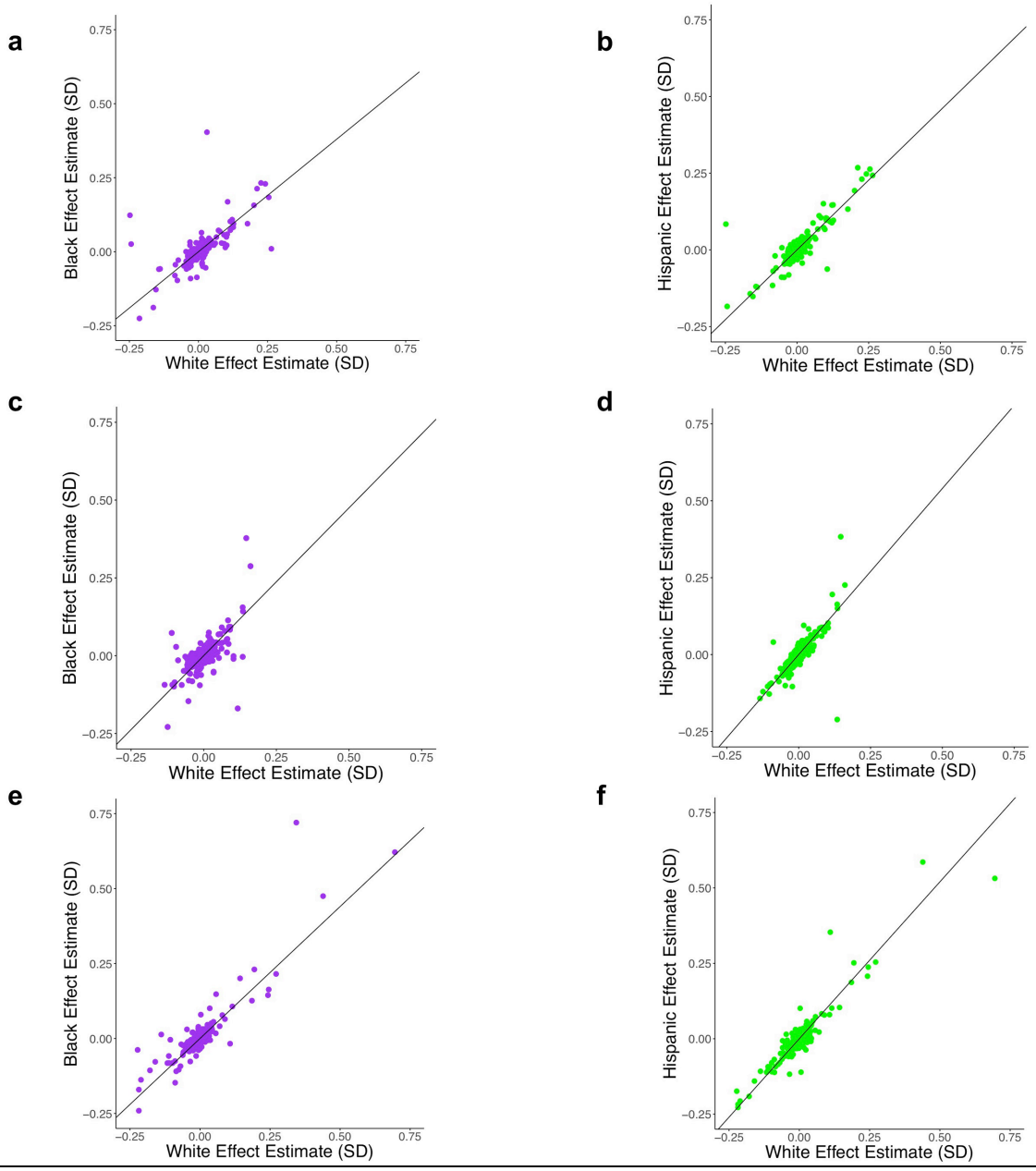
Abbreviations: GLGC, Global Lipids Genetics Consortium; MVP, Million Veteran Program; HDL-C, High-Density Lipoprotein Cholesterol; TG, Triglycerides; LDL-C, Low-Density Lipoprotein Cholesterol; TC, Total Cholesterol



Supplementary Figure 6

Quantile-quantile plots for the discovery lipids GWAS in MVP

The expected linear regression two-sided P values versus the observed distribution of two-sided P values for LDL cholesterol (n=297,218 individuals), triglycerides (n=291,993 individuals), total cholesterol (n=297,626 individuals), and HDL cholesterol (n=291,746 individuals) association are displayed. Quantile-quantile plots were inspected for ancestry specific analyses, and genomic control values were < 1.20 for each racial group (data not shown). The inflation observed (λ_{GC} = 1.08-1.13) is comparable to that observed in other studies of polygenic traits with similar large sample sizes (n > 300,000)[4,5]. Abbreviations: HDL-C, High-Density Lipoprotein Cholesterol; TG, Triglycerides; LDL-C, Low-Density Lipoprotein Cholesterol; TC, Total Cholesterol; MVP, Million Veteran Program

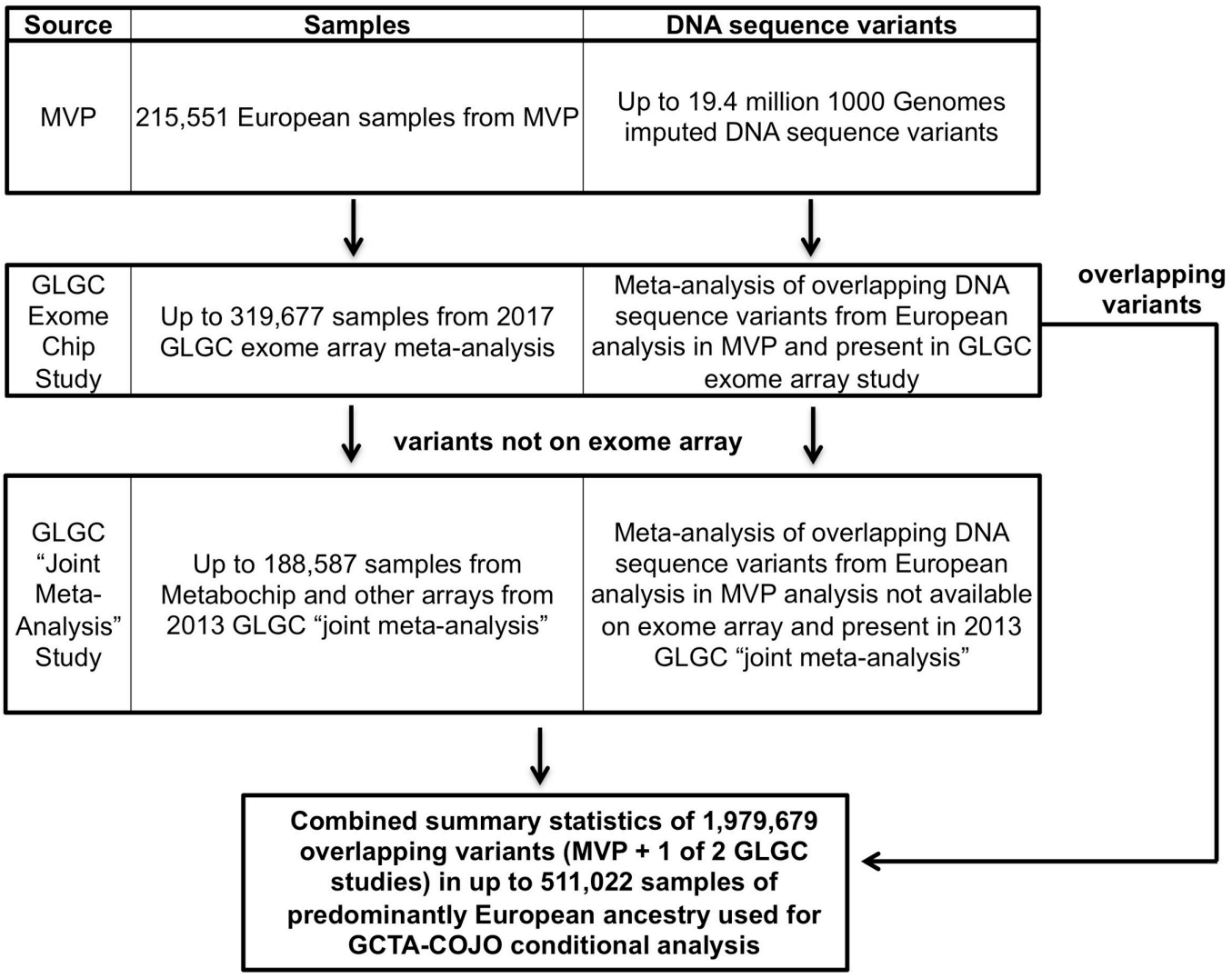


Supplementary Figure 7

Representative comparison of 354 independent lipid variants common to all ethnicities for triglycerides, total cholesterol, and HDL-C

a,b) Effect estimates for association with triglycerides in white individuals (n=211,491; x-axes) compared to black **(a,** n=56,439; β = 0.76**)** or Hispanic **(b,** n=24,063; β =0.91**)** individuals.
c,d) Effect estimates for total cholesterol association in white individuals (n=215,551; x-axes) compared to black **(c,** n=57,332; β = 0.95**)** or Hispanic **(d,** n=24,743; β = 1.08**)** individuals.
e,f) Effect estimates for HDL-C association in white individuals (n=210,967; x-axes) compared to black **(e,** n=56,833; β = 0.88**)** or Hispanic **(f,** n=23,946; β = 1.04**)** individuals.

Abbreviations: SD, Standard Deviations; HDL-C, High-Density Lipoprotein Cholesterol

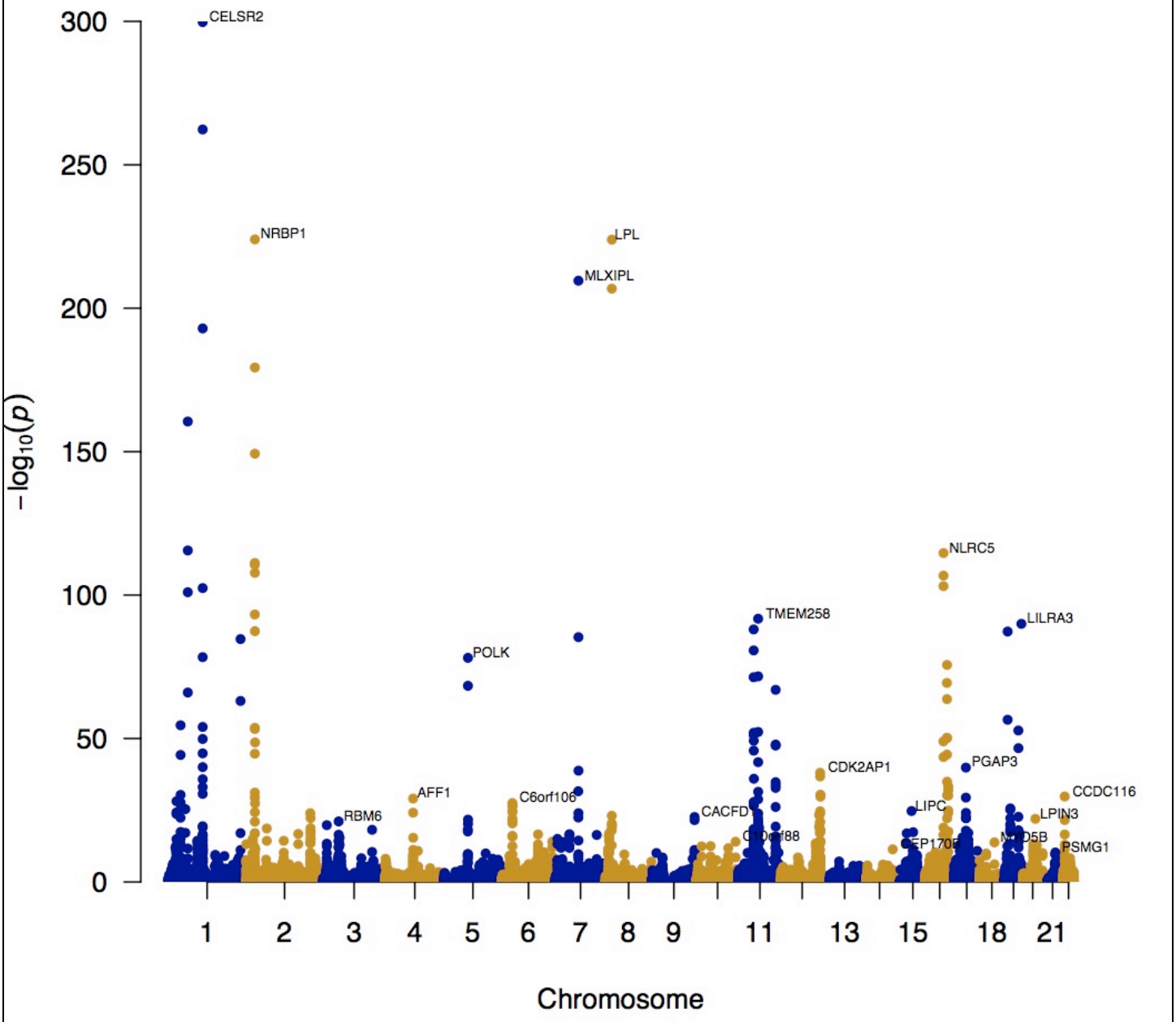


Supplementary Figure 8

Design of lipids stepwise conditional analysis

Flow chart for generation of summary statistics used in GCTA-COJO approximate stepwise conditional analysis. The GCTA-COJO software requires GWAS summary statistics and an LD-matrix of a representative group of samples with similar genetic ancestry to those used for the GWAS. As such, summary statistics were combined from MVP (European ancestry subgroup), the GLGC 2017 exome chip analysis (predominantly European ancestry) and the GLGC 2013 "joint meta-analysis" (predominantly European ancestry) via an inverse-variance weight fixed effects meta-analysis. These combined results were then used with an LD-matrix of 10,000 randomly selected European samples from the UK Biobank interim release[6] for GCTA-COJO stepwise conditional analysis.

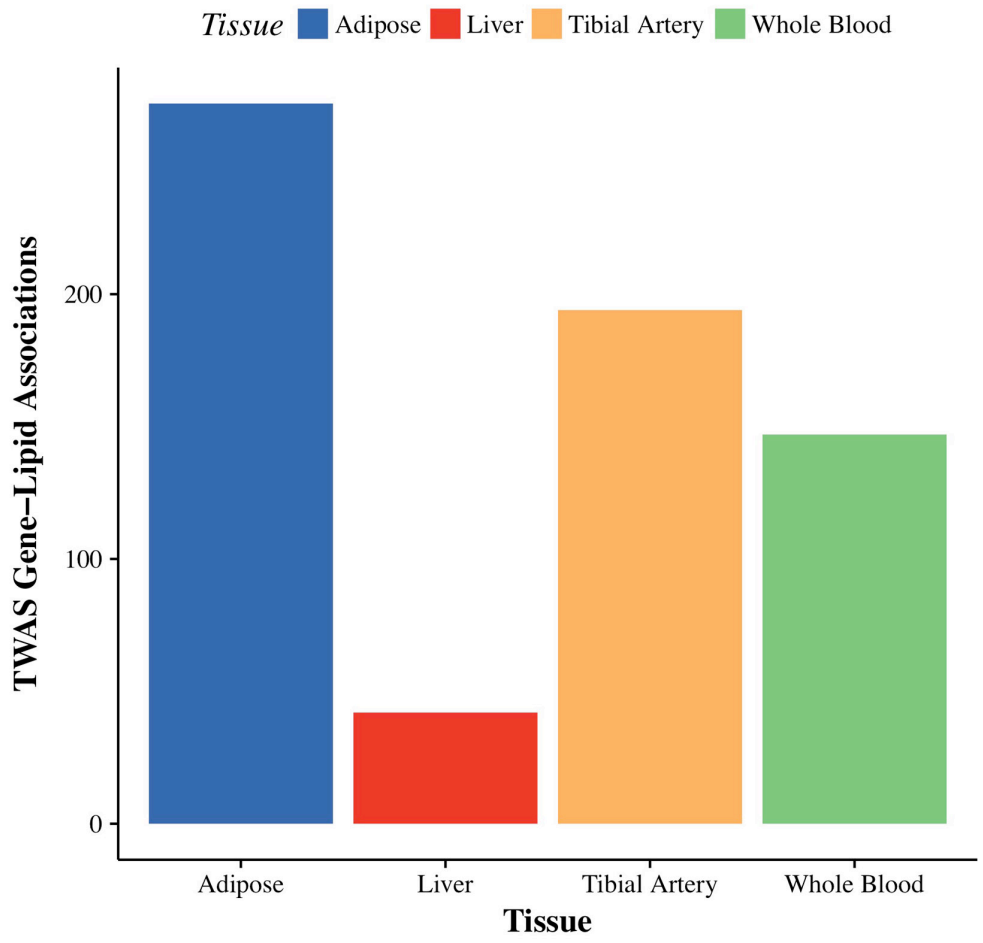
Abbreviations: MVP, Million Veteran Program; GLGC, Global Lipids Genetics Consortium



Supplementary Figure 9

Manhattan plot for the lipids Transcriptome-wide association study (TWAS) using MVP and GLGC combined summary statistics

Plot of -log10(*P*) [two-sided] for lipid-gene associations by chromosomal position for all genes analyzed in the TWAS analysis in up to 511,022 European samples in MVP and GLGC. The genes nearest to the top associated variants are displayed.
Abbreviations: MVP, Million Veteran Program; GLGC, Global Lipids Genetics Consortium

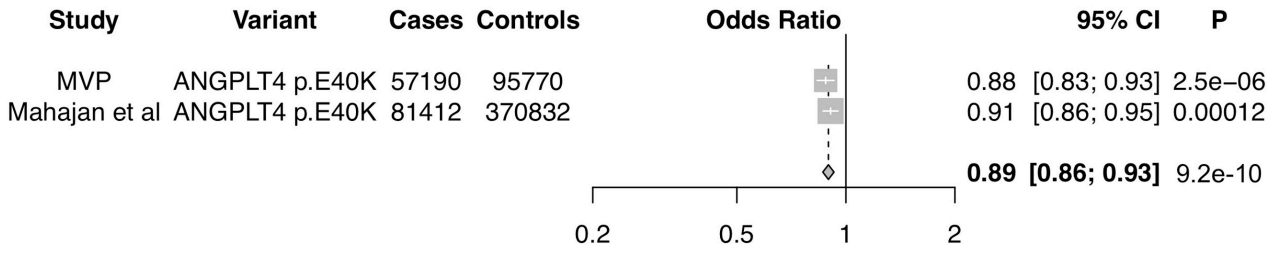


Supplementary Figure 10

Transcriptome-wide association study (TWAS) results for lipids by tissue

Graph of the 655 genome-wide (two-sided TWAS $P < 5x10^{-8}$) gene-lipid associations for each of four tissues (adipose, liver, tibial artery, and whole blood) resulting from the lipids TWAS analysis in up to 511,022 European samples in MVP and GLGC.

Abbreviations: MVP, Million Veteran Program; GLGC, Global Lipids Genetics Consortium

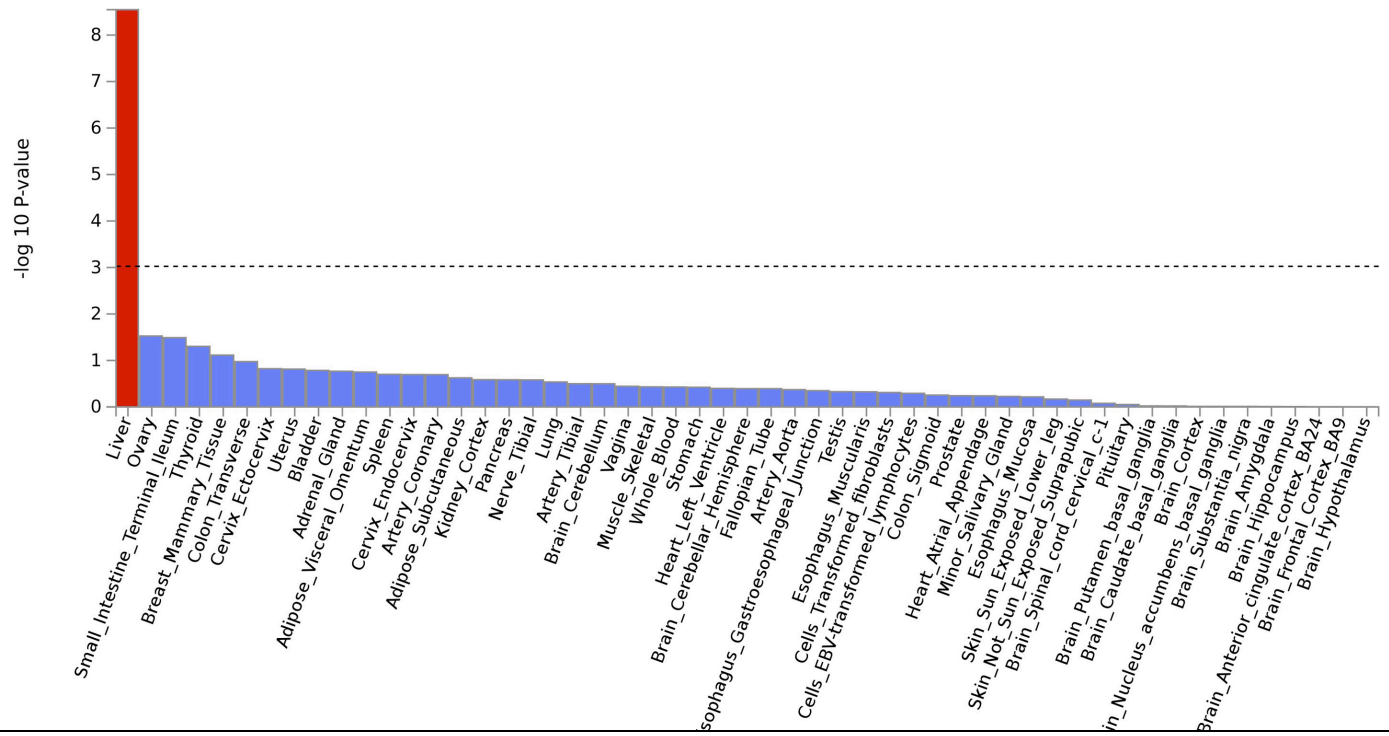


Supplementary Figure 11

***ANGPTL4* 40Lys carrier association with type 2 diabetes**

Independent replication of the *ANGPTL4* p.Glu40Lys association with type 2 diabetes in the recently published meta-analysis by Mahajan et al[7]. Results for the body mass index (BMI) unadjusted logistic regression analysis are displayed with two-sided P values.

Abbreviations: MVP, Million Veteran Program

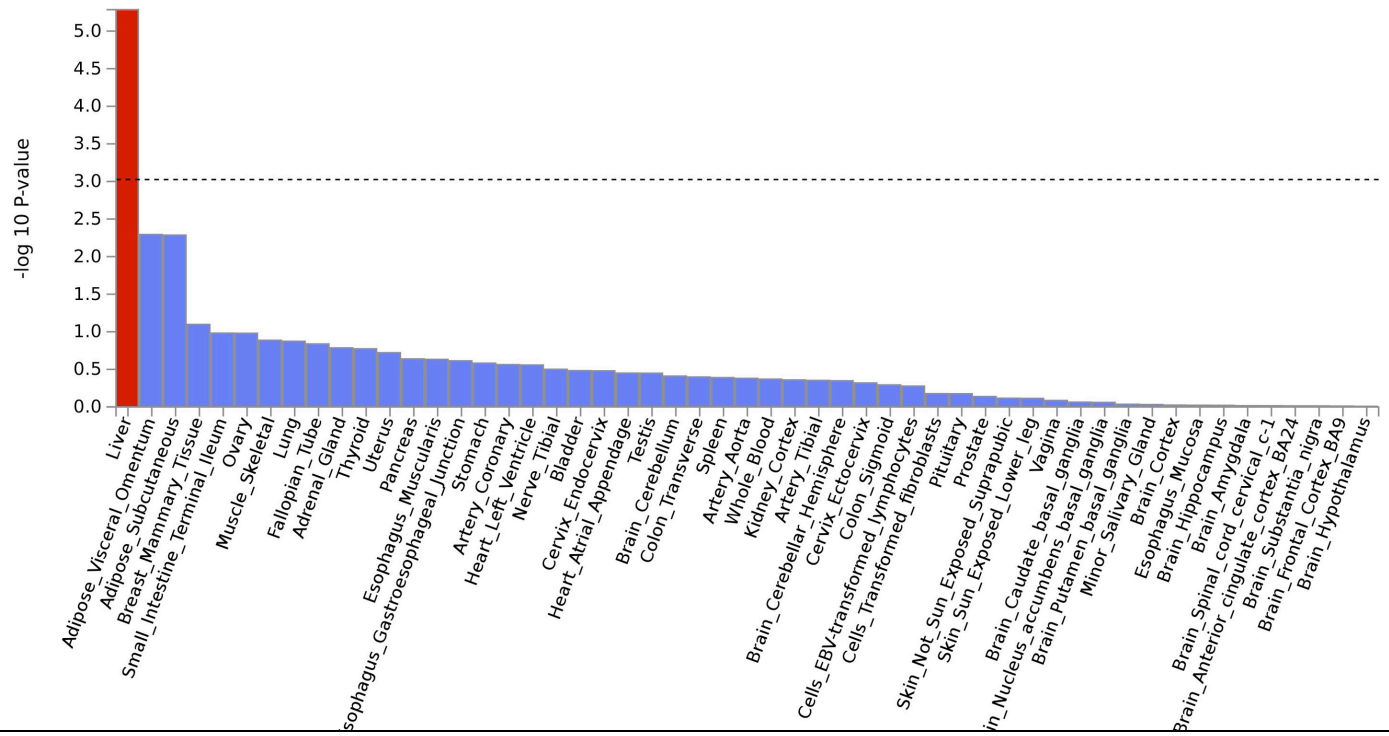


Supplementary Figure 12

Multi-ethnic LDL-C MAGMA gene-property analysis of the expression of genes in 53 tissues included in GTEx

MAGMA[8] tissue expression profile analysis results as performed using the FUMA pipeline[9] for LDL-C in a multi-ethnic Stage 1 meta-analysis of MVP participants (n=297,218). Tissues with a Bonferroni corrected $P < 0.05$ for a two-sided Student's t-test are highlighted in red.

Abbreviations: GTEx, Genotype-Tissue Expression Project; MAGMA, Multi-marker Analysis of GenoMic Annotation; MVP, Million Veteran Program; LDL-C, Low-Density Lipoprotein Cholesterol

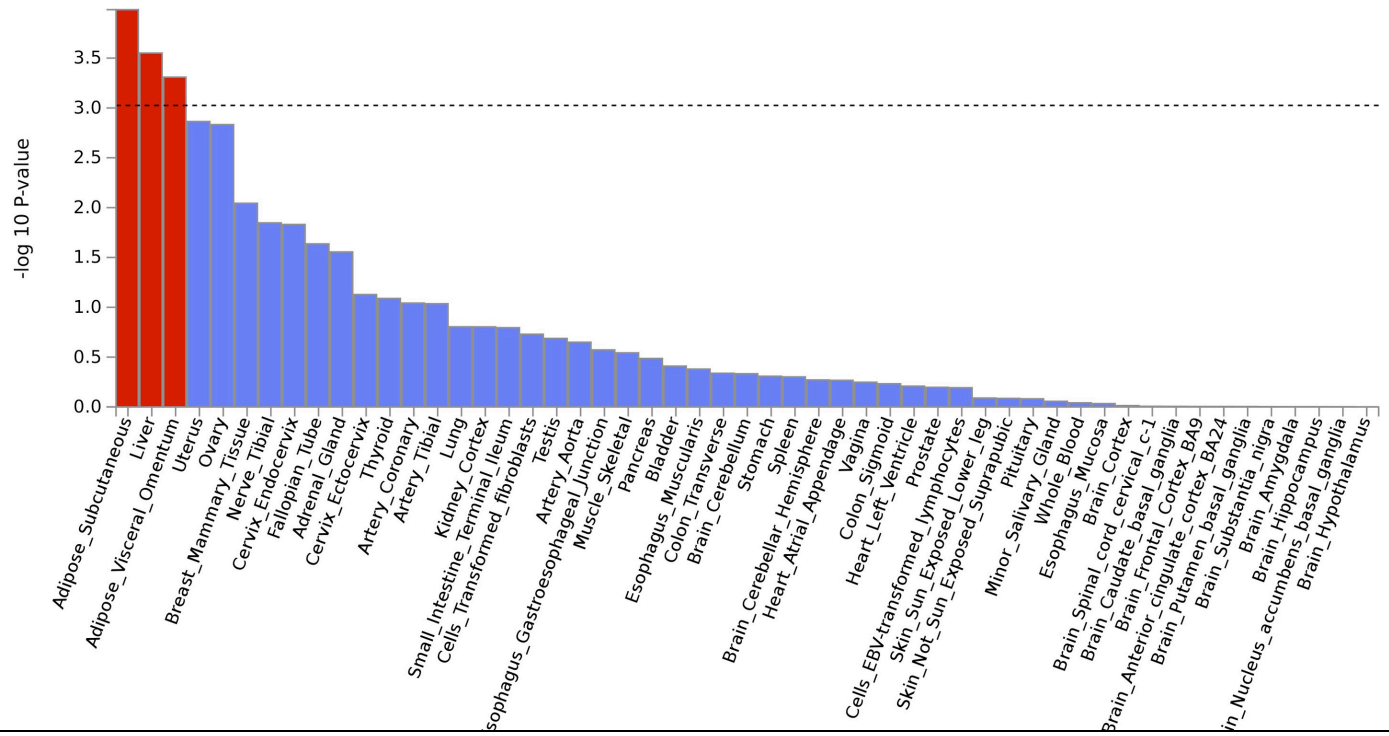


Supplementary Figure 13

Multi-ethnic HDL-C MAGMA gene-property analysis of the expression of genes in 53 tissues included in GTEx

MAGMA[8] tissue expression profile analysis results as performed using the FUMA pipeline[9] for HDL-C in a multi-ethnic Stage 1 meta-analysis of MVP participants (n=291,746). Tissues with a Bonferroni corrected P < 0.05 for a two-sided Student's t-test are highlighted in red.

Abbreviations: GTEx, Genotype-Tissue Expression Project; MAGMA, Multi-marker Analysis of GenoMic Annotation; MVP, Million Veteran Program; HDL-C, High-Density Lipoprotein Cholesterol

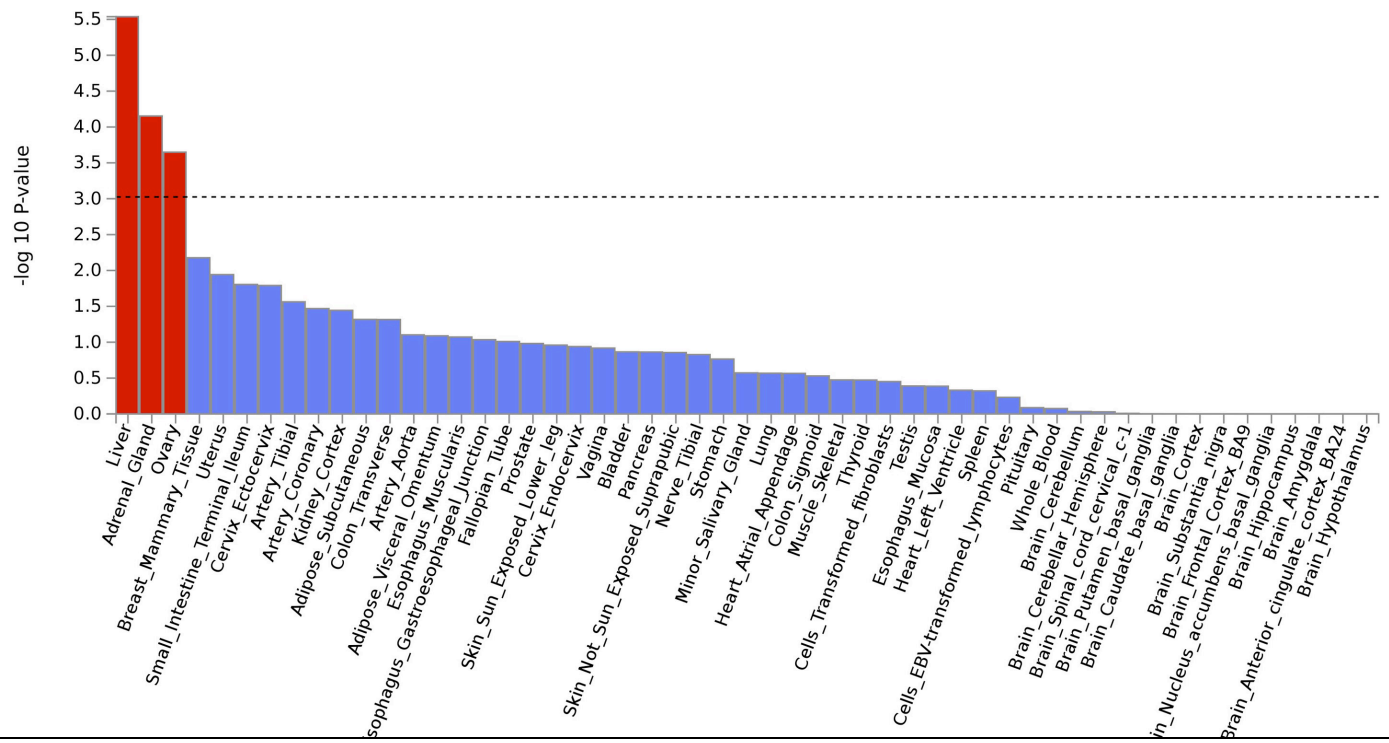


Supplementary Figure 14

Multi-ethnic triglycerides MAGMA gene-property analysis of the expression of genes in 53 tissues included in GTEx

MAGMA[8] tissue expression profile analysis results as performed using the FUMA pipeline[9] for triglycerides in a multi-ethnic Stage 1 meta-analysis of MVP participants (n=291,993). Tissues with a Bonferroni corrected P < 0.05 for a two-sided Student's t-test are highlighted in red.

Abbreviations: GTEx, Genotype-Tissue Expression Project; MAGMA, Multi-marker Analysis of GenoMic Annotation; MVP, Million Veteran Program

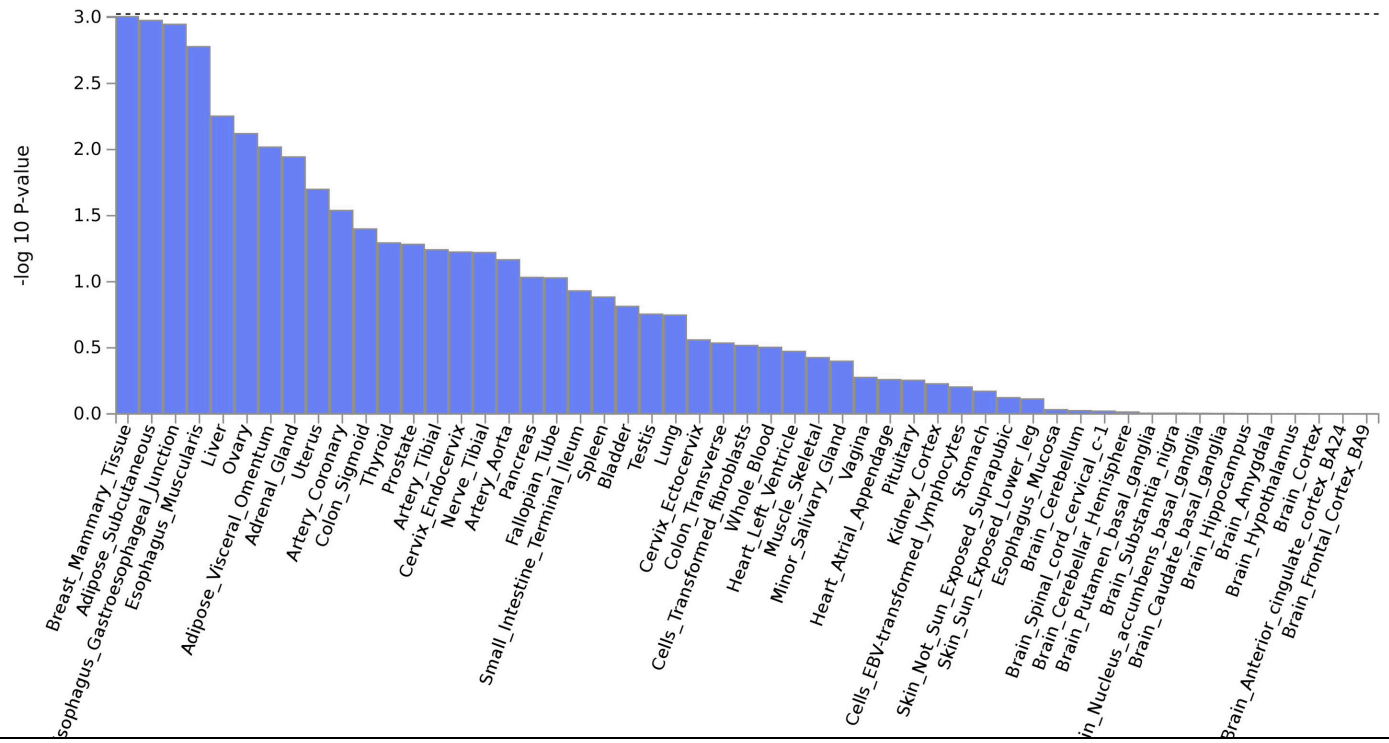


Supplementary Figure 15

European only LDL-C MAGMA gene-property analysis of the expression of genes in 53 tissues included in GTEx

MAGMA[8] tissue expression profile analysis results as performed using the FUMA pipeline[9] for LDL-C in MVP participants of European ancestry alone (n=215,196). Tissues with a Bonferroni corrected $P < 0.05$ for a two-sided Student's t-test are highlighted in red.

Abbreviations: GTEx, Genotype-Tissue Expression Project; MAGMA, Multi-marker Analysis of GenoMic Annotation; MVP, Million Veteran Program; LDL-C, Low-Density Lipoprotein Cholesterol

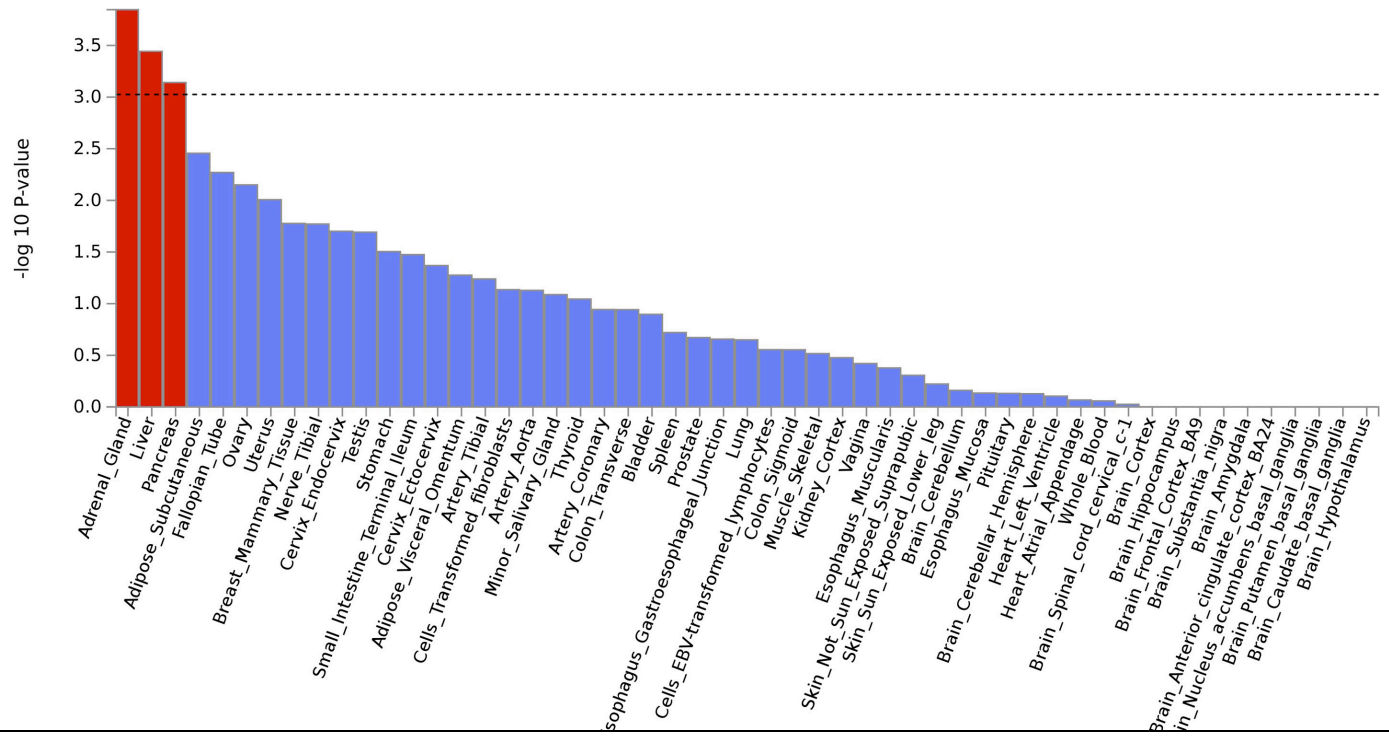


Supplementary Figure 16

European only HDL-C MAGMA gene-property analysis of the expression of genes in 53 tissues included in GTEx

MAGMA[8] tissue expression profile analysis results as performed using the FUMA pipeline[9] for HDL-C in MVP participants of European ancestry alone (n=210,967). Tissues with a Bonferroni corrected $P < 0.05$ for a two-sided Student's t-test are highlighted in red.

Abbreviations: GTEx, Genotype-Tissue Expression Project; MAGMA, Multi-marker Analysis of GenoMic Annotation; MVP, Million Veteran Program; HDL-C, High-Density Lipoprotein Cholesterol



Supplementary Figure 17

European only triglycerides MAGMA gene-property analysis of the expression of genes in 53 tissues included in GTEx

MAGMA[8] tissue expression profile analysis results as performed using the FUMA pipeline[9] for triglycerides in MVP participants of European ancestry alone (n=211,491). Tissues with a Bonferroni corrected $P < 0.05$ for a two-sided Student's t-test are highlighted in red.

Abbreviations: GTEx, Genotype-Tissue Expression Project; MAGMA, Multi-marker Analysis of GenoMic Annotation; MVP, Million Veteran Program

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