



Original Contribution

Multiancestry Genome-Wide Association Study of Lipid Levels Incorporating Gene-Alcohol Interactions

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A person's lipid profile is influenced by genetic variants and alcohol consumption, but the contribution of interactions between these exposures has not been studied. We therefore incorporated gene-alcohol interactions into a multiancestry genome-wide association study of levels of high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides. We included 45 studies in stage 1 (genome-wide discovery) and 66 studies in stage 2 (focused follow-up), for a total of 394,584 individuals from 5 ancestry groups. Analyses covered the period July 2014–November 2017. Genetic main effects and interaction effects were jointly assessed by means of a 2–degrees-of-freedom (df) test, and a 1-df test was used to assess the interaction effects alone. Variants at 495 loci were at least suggestively associated ($P < 1 \times 10^{-6}$) with lipid levels in stage 1 and were evaluated in stage 2, followed by combined analyses of stage 1 and stage 2. In the combined analysis of stages 1 and 2, a total of 147 independent loci were associated with lipid levels at $P < 5 \times 10^{-8}$ using 2-df tests, of which 18 were novel. No genome-wide-significant associations were found testing the interaction effect alone. The novel loci included several genes (proprotein convertase subtilisin/kexin type 5 (*PCSK5*), vascular endothelial growth factor B (*VEGFB*), and apolipoprotein B mRNA editing enzyme, catalytic polypeptide 1 (*APOBEC1*) complementation factor (*A1CF*)) that have a putative role in lipid metabolism on the basis of existing evidence from cellular and experimental models.

alcohol consumption; cholesterol; gene-environment interactions; gene-lifestyle interactions; genome-wide association studies; lipids; triglycerides

Abbreviations: *A1CF*, *APOBEC1* complementation factor gene; *APOBEC1*, apolipoprotein B mRNA editing enzyme, catalytic polypeptide 1; *APOBEC1*, apolipoprotein B mRNA editing enzyme, catalytic polypeptide 1 gene; CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; DEPICT, Data-driven Expression Prioritized Integration for Complex Traits; df, degrees of freedom; FDR, false discovery rate; GWAS, genome-wide association study(ies); HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; *PCSK5*, proprotein convertase subtilisin/kexin type 5; *PCSK5*, proprotein convertase subtilisin/kexin type 5 gene; *PCSK9*, proprotein convertase subtilisin/kexin type 9 gene; TG, triglycerides; VEGF-B, vascular endothelial growth factor B; *VEGFB*, vascular endothelial growth factor B gene.

Serum concentrations of high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) are modifiable risk factors for cardiovascular disease, the leading cause of death globally (1). Lipid levels are influenced by multiple exposures, including genetic and lifestyle factors. The genetic factors influencing lipid levels have been widely studied (2–8), and large-scale genome-wide association studies (GWAS) have identified 236 loci associated with HDL-C, LDL-C, and TG, which account for up to approximately 12% of the total trait variance in the studied populations (5, 7).

Lifestyle factors, such as alcohol consumption, are also considerably associated with lipid levels: In epidemiologic studies, greater alcohol consumption is associated with an improved lipid profile, including associations with HDL-C levels, high-density lipoprotein particle concentrations, and HDL-C subfractions (9, 10). The relationship between alcohol use and LDL-C or TG is less clear, with some studies reporting positive associations while others have reported negative associations (11–20). A causal role of low-to-moderate alcohol consumption in improving overall lipid profile is supported by intervention studies (19), and more recently by Mendelian randomization studies (21, 22).

Potential modification of genetic effects on lipid levels by lifestyle exposures, including alcohol consumption, is relatively unexplored (23). Genetic association studies accounting for potential gene-alcohol interactions may lead to the identification of novel lipid loci and may reveal new biological insights that can potentially be explored for treatment or prevention of dyslipidemia. In order to investigate the potential modulating role of alcohol consumption in the genetic architecture of lipid levels and to identify novel HDL-C, LDL-C, and TG loci, we performed genome-wide gene-alcohol interaction meta-analyses of LDL-C, HDL-C, and TG.

METHODS

Overall design

Table 1 shows the overall design of this study, which was conducted within the setting of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium Gene-Lifestyle Interactions Working Group (24, 25). In order to decrease the computational burden, we carried out genome-wide

analyses in stage 1 and followed up suggestively associated variants in stage 2, with the combined results of analyses carried out in stage 1 and stage 2 serving as the primary analysis (26). We used 2 complementary approaches to model interactions: 1) a 2-degrees-of-freedom (df) test was used to jointly assess both the genetic main effect and the interaction effect on lipid levels, and 2) a 1-df test was used to assess the effect of interactions alone. The 2-df test is more powerful when there is both a genetic main effect and an interaction effect, and it may thus help identify interaction effects for which the 1-df test lacks sufficient power (27).

Overview of participating studies

This analysis covered the period July 2014–November 2017 and included men and women aged 18–80 years from 5 ancestry groups: European, African, Asian, Hispanic, and Brazilian. Investigators in each study obtained informed consent from participants and approval from the appropriate institutional review boards. Although the participating studies are based on different study designs and populations, all of them have data on lipid levels, alcohol consumption, and genotypes across the genome. In total, the analysis comprised 394,584 individuals.

Stage 1 studies. Stage 1 included 89,893 European-ancestry participants, 20,989 African-ancestry participants, 12,450 Asian-ancestry participants, and 3,994 Hispanic-ancestry participants, for an overall total of 127,326 individuals from 45 studies (see Web Table 1, available at <https://academic.oup.com/aje>), namely: the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study (1967—Reykjavik, Iceland), the Atherosclerosis Risk in Communities (ARIC) Study (1987–1989—Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi; and Minneapolis, Minnesota), the Coronary Artery Risk Development in Young Adults (CARDIA) Study (1985–1986—Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California), the Cardiovascular Health Study (CHS) (1989–1990 and 1992–1993—Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania), the CROATIA-Korcula Study (2007—Korcula, Croatia), the CROATIA-Vis Study (2003–2004—Vis, Croatia), the Erasmus

Table 1. Distribution (Number) of Participants by Ancestry in a Genome-Wide Meta-Analysis of Gene-Alcohol Interaction and Lipid Levels, 2017^a

Analysis Stage	Ancestry Group					Meta-Analysis
	European	African	Asian	Hispanic	Brazilian	
1	89,893	20,989	12,450	3,994	0	127,326
2 ^b	136,986	4,475	108,431	13,714	3,652	267,258
Total ^c	226,879	25,464	120,881	17,708	3,652	394,584

Abbreviation: df, degrees of freedom.

^a For each lipid trait, association analyses were performed accounting for 2 alcohol consumption status variables: “current drinker” and “regular drinker.” For each ancestry group, study-specific results were combined to perform the 1-df test for an interaction effect and the 2-df joint test of the genetic main effect and interaction with drinking exposure. Persons from 5 ancestry groups were included: European, African, Asian, Hispanic, and Brazilian.

^b Variants selected for follow-up at $P \leq 1 \times 10^{-6}$ using a 1-df interaction test and a joint 2-df interaction test.

^c Variants found to be significant at $P \leq 5 \times 10^{-8}$ using a joint 2-df interaction test or a 1-df interaction test.

Rucphen Family (ERF) Study (2002–2005—Rotterdam, the Netherlands), the Family Heart Study (FamHS) (1992–1995—Salt Lake City, Utah; Forsyth County, North Carolina; Minneapolis, Minnesota; and Framingham, Massachusetts), the Framingham Heart Study (1948—Framingham, Massachusetts), the Genetic Epidemiology Network of Arteriopathy (GENOA) Study (1995–2000—Rochester, Minnesota and Jackson, Mississippi), the Genetic Epidemiology Network of Salt Sensitivity (GenSalt) Study (2003–2005—provinces of Hebei, Henan, Shandong, Shaanxi, and Jiangsu, China), the Generation Scotland: Scottish Family Health Study (GS_SFHS) (2006–2011—Scotland, United Kingdom), the Health, Aging and Body Composition (HABC) Study (1997–1998—Pittsburgh, Pennsylvania and Memphis, Tennessee), the Healthy Aging in Neighborhoods of Diversity Across the Life Span (HANDLS) Study (2004–2009—Baltimore, Maryland), the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Study (1995–2000—Arizona; Indiana; Minnesota; Texas; and Quebec, Canada), the Howard University Family Study (HUFs) (2001–2008—Washington, DC), the Hypertension Genetic Epidemiology Network (HyperGEN) Study (1996–1999—Birmingham, Alabama; Salt Lake City, Utah; Forsyth County, North Carolina; Minneapolis, Minnesota; and Framingham, Massachusetts), the Jackson Heart Study (JHS) (2000–2004—Jackson, Mississippi), the Multi-Ethnic Study of Atherosclerosis (MESA) (2000–2002—Los Angeles, California; St. Paul, Minnesota; Chicago, Illinois; Winston-Salem, North Carolina; Baltimore, Maryland; and New York, New York), the Netherlands Epidemiology of Obesity (NEO) Study (2008–2012—Leiden, the Netherlands), Rotterdam Study 1 (RS1) (1990—Rotterdam, the Netherlands), Rotterdam Study 2 (RS2) (2000–2001—Rotterdam, the Netherlands), Rotterdam Study 3 (RS3) (2006–2008—Rotterdam, the Netherlands), the Singapore Chinese Eye Study (SCES) (2009–2011—Singapore), the Singapore Chinese Health Study—Coronary Heart Disease Study (SCHS-CHD) (1993–1998—Singapore), the Singapore Malay Eye Study (SiMES) (2004–2006—Singapore), the Singapore Indian Eye Study (SINDI) (2007–2009—Singapore), the Singapore 2 (SP2) Study (SP2-1M and SP2-610) (1982–1998—Singapore), the Women's Genome Health Study (WGHS) (1992–1995—United States), and the Women's Health Initiative (WHI) (WHI Genomics and Randomized Trials Network (WHI_GARNET) and WHI Memory Study (WHI_WHIMS); 1993–1998—United States).

Stage 2 studies. Stage 2 included 136,986 European-ancestry, 4,475 African-ancestry, 108,431 Asian-ancestry, 13,714 Hispanic-ancestry, and 3,652 Brazilian-ancestry participants, for an overall total of 267,258 individuals from the following 66 studies (Web Table 2): the 1982 Pelotas Birth Cohort Study (1982—Pelotas, Brazil), the African American Diabetes Heart Study (AA-DHS) (1998–2005—Winston-Salem, North Carolina), the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) (1998–2000—Denmark, Finland, Ireland, Norway, Sweden, and the United Kingdom), the Baependi Heart Study (2010—Baependi, Brazil), the BioBank Japan (BBJ) Project (2003–2008—Japan), the Beijing Eye Study (BES-Omnixpress) (2001—Beijing, China), the British Genetics of Hypertension (BRIGHT) Study (1995—United Kingdom), the Cardio-metabolic Genome Epidemiology Network Amagasaki Study (CAGE-Amagasaki) (2002–2003—Amagasaki, Japan), the Data From the

Epidemiological Study on the Insulin Resistance Syndrome (DESIR) Study (1994–1996—France), the Dongfeng-Tongji (DFTJ) Cohort Study (2008—Shiyang City, China), the Diabetes Heart Study (DHS) (1998–2005—Winston-Salem, North Carolina), the Dose Responses to Exercise Training (DR's EXTRA) Study (2005–2006—Kuopio, Finland), the Estonian Genome Center of the University of Tartu (EGCUT) Study (2002–2010—Estonia), the European Prospective Investigation Into Cancer and Nutrition (EPIC) (1992–1997—France, Italy, Spain, the United Kingdom, the Netherlands, Germany, Sweden, Denmark, Norway, and Greece), the Fenland Study (Fenland-GWAS and Fenland-Omics) (1950–1975—Cambridgeshire, England, United Kingdom), the Finland-United States Investigation of NIDDM Genetics (FUSION) Study (1994—Finland), the Genetic Studies of Atherosclerosis Risk (GeneSTAR) Study (1983–2006—Baltimore, Maryland), the Gene \times Lifestyle Interactions and Complex Traits Involved in Elevated Disease Risk (GLACIER) Study (1985–2004—Sweden), the Genetic Regulation of Arterial Pressure of Humans in the Community (GRAPHIC) Study (2003–2005—Leicestershire, England, United Kingdom), the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) (2008–2011—Chicago, Illinois; Miami, Florida; New York, New York; and San Diego, California), the Health and Retirement Study (HRS) (2006–2010—United States), the Hypertension Genetic Epidemiology Network (HyperGEN)-Axiom Study (which used the Axiom Genome-Wide ASI 1 Array Plate; Thermo Fisher Scientific, Waltham, Massachusetts) (1996–1999—Birmingham, Alabama; Salt Lake City, Utah; Forsyth County, North Carolina; Minneapolis, Minnesota; and Framingham, Massachusetts), the Italian Network Genetic Isolates—Carlantino (INGI-CARL) Study (2005–2006—Carlantino, Italy), the Italian Network Genetic Isolates—Friuli-Venezia Giulia (INGI-FVG) Study (2013—Friuli-Venezia Giulia, Italy), the EPIC-InterAct Case-Cohort Study (InterAct) (1991–2007—France, Italy, Spain, the United Kingdom, the Netherlands, Germany, Sweden, and Denmark), the Insulin Resistance Atherosclerosis Study (IRAS; IRAS Cohort Study and IRAS Family Study) (1999–2005—San Antonio, Texas and San Luis Valley, Colorado), the Cooperative Health Research in the Augsburg Region S3 (KORA_S3) Study (1994–1995—Augsburg, Germany), the Cooperative Health Research in the Augsburg Region S4 (KORA_S4) Study (1991–2001—Augsburg, Germany), the Lothian Birth Cohort 1936 (LBC1936) Study (2004–2007—Lothian, Scotland, United Kingdom), the LifeLines Cohort Study (2006–2013—the Netherlands), the London Life Sciences Prospective Population (LOLIPOP) Study (2003–2007—London, England, United Kingdom), the Long Life Family Study (LLFS) (2006–2009—Boston, Massachusetts; New York, New York; Pittsburgh, Pennsylvania; and Denmark), the Kingston Gene-by-Environment (Loyola GxE) Study (1994–1995—Kingston, Jamaica), the Spanish Town (Loyola SPT) Study (1994–1995—Kingston, Jamaica), the Metabolic Syndrome in Men (METSIM) Study (2005–2010—Kuopio, Finland), the Netherlands Study of Depression and Anxiety (NESDA) (2004–2007—the Netherlands), the Obesity in Adults (OBA) Study (2005—France), the Prevention of Renal and Vascular End Stage Disease (PREVEND) Study (1997–1998—Groningen, the Netherlands), the Precocious Coronary Artery Disease (PROCARDIS) Study (2004–2008—

United Kingdom, Italy, Sweden, and Germany), the Ragama Health Study (RHS) (2007—Ragama, Sri Lanka), the Stockholm Heart Epidemiology Program (SHEEP) (1992–1994—Stockholm County, Sweden), the Study of Health in Pomerania (SHIP) (participants from the baseline examination (SHIP-0) (1997–2001—Greifswald, Stralsund, and Anklam, Germany) and participants from a new sample for a new cohort drawn from the same area (SHIP-Trend) (2008–2012—Greifswald, Stralsund, and Anklam, Germany)), the Shanghai Women's Health Study/Shanghai Men's Health Study (SWHS/SMHS) (1997–2000—Shanghai, China), the TwinGene Project (data from the Swedish Twin Registry; 2004–2008—Sweden), and the Cardiovascular Risk in Young Finns Study (YFS) (1980—Finland).

Calculation of variance. An additional study not included in stage 1 or stage 2 was used to determine the variance explained by variants at known and new loci: the Airwave Health Monitoring Study (2004–2015—England, Scotland, and Wales, United Kingdom).

Phenotype and lifestyle variables

Three lipid traits were analyzed separately: HDL-C (mg/dL), LDL-C (mg/dL), and TG (mg/dL). HDL-C and TG were directly assayed, while LDL-C was either directly assayed or estimated using the Friedewald equation: $LDL-C = TC - HDL-C - (TG/5)$ (28). Only fasting samples (≥ 8 hours) were used to assay TG, and the Friedewald equation was only used in samples with fasting TG concentrations less than or equal to 400 mg/dL. LDL-C values were adjusted for use of statins (Web Appendix). HDL-C and TG values were natural log-transformed prior to analyses.

Alcohol consumption was assessed using 2 dichotomized alcohol consumption variables: “current drinking” status, defined as any recurrent drinking behavior, and “regular drinking” status, defined as the subset of current drinkers who consumed at least 2 drinks per week. Because the standard pure ethanol content in 1 alcoholic drink may vary among countries, for this study a standard drink was defined to contain approximately 13 g of pure ethanol, and this measure was used to standardize the definitions across studies.

Genotyping and imputation

Information on genotyping and imputation for each of the stage 1 and stage 2 studies is presented in Web Table 3 and Web Table 4, respectively. For imputation, most studies used the 1000 Genomes Project Phase I Integrated Release Version 3 Haplotypes (2010–2011 data freeze; March 14, 2012, haplotypes), which contain haplotypes for 1,092 individuals from multiple ancestry groups (29).

Study-specific analysis

Study-specific regression analyses were performed for each variant, using models containing the genetic variant, the alcohol consumption variable (current drinking status or regular drinking status), and their interaction. Variants were coded according to the additive model, so that the β coefficient represents the effect size per copy of the coded allele. These regressions were adjusted for age, sex, ancestry-informative principal components, and

study-specific variables where appropriate (such as center for multicenter studies). Information on the principal components and study-specific variables adjusted for in each study-specific analysis is provided in Web Tables 3 and 4.

In stage 1, investigators in each study performed genome-wide association analyses within each ancestry group and provided the CHARGE Consortium with information on the estimated genetic main effect, the estimated interaction effect, and a robust estimate of the corresponding covariance matrix. In stage 2, investigators in each study performed analyses only for the selected variants identified in stage 1. Study-specific association analyses were performed using various software programs (Web Appendix and Web Tables 3 and 4). Extensive quality control using the R (R Foundation for Statistical Computing, Vienna, Austria) package “EasyQC” was performed for all study-specific GWAS results, as described in the Web Appendix (30).

Meta-analysis

We implemented METAL software to meta-analyze the genetic main and interaction effects jointly using the 2-df approach of Manning et al. (27) and Willer et al. (31) and to meta-analyze the interaction coefficients alone using inverse-variance-weighted meta-analysis (1-df test). For each meta-analysis, results were obtained from Wald tests, performed using genetic main-effect estimates, interaction effect estimates, and robust estimates of the corresponding covariance matrix.

In stage 1, ancestry-specific meta-analyses were performed for each of the 12 analyses (3 lipids \times 2 alcohol consumption exposures \times 2 tests). Genomic control correction was applied twice (32), first to the study-specific GWAS results (Web Table 5) and then to the ancestry-specific meta-analysis results. The results from each ancestry group were then combined in a transancestry meta-analysis.

The variants that were at least suggestively associated with lipid levels ($P < 1 \times 10^{-6}$) in any of the stage 1 interaction analyses were pursued for stage 2 analysis. In stage 2, we used the same approaches as in stage 1 to perform ancestry-specific and transancestry meta-analyses. Finally, ancestry-specific and transancestry meta-analyses were performed to combine stage 1 results with stage 2 results. Variants with P values less than 5×10^{-8} for either the 2-df joint test of genetic main and interaction effects or the 1-df test of interaction effects were considered genome-wide-significant. False discovery rate (FDR) q values were calculated using the Benjamini and Hochberg method (33) implemented with the “p.adjust” function in R, correcting for the number of tests performed in stage 1. FDR q values less than 0.05 thus indicate a $<5\%$ FDR even after considering the multiple testing introduced by performing genome-wide analyses on multiple outcomes using multiple models. An independent locus was defined as the ± 1 mega-base-pair region surrounding an index variant. For each locus, the closest genes were determined on the basis of proximity to the index variant. For loci with intergenic index variants, we included the closest gene in each direction.

Additional analyses

The percentages of variance in HDL-C, LDL-C, and TG levels explained by all previously known and novel variants

were evaluated in 10 studies on multiple ancestry groups (Web Appendix). The HaploReg (34), RegulomeDB (35), and Genotype-Tissue Expression (GTEx) (36) software packages were used to annotate variants at significant loci. We also used Data-driven Expression Prioritized Integration for Complex Traits (DEPICT) software (37) to prioritize genes at the loci associated with lipid levels in the combined analysis of stages 1 and 2. More details on gene prioritization using DEPICT can be found in the Web Appendix.

Lastly, we examined the associations of index variants at the 147 significant loci with coronary artery disease and myocardial infarction using publicly available summary association results from a large GWAS of these phenotypes performed by the Coronary Artery Disease Genome-Wide Replication and Meta-Analysis (CARDIoGRAM) plus Coronary Artery Disease (C4D) Genetics Consortium (CARDIoGRAMplusC4D Consortium) (38).

RESULTS

Descriptive statistics for the studies participating in stage 1 of the analysis are shown in Web Table 1: 56.1% of stage 1 participants were current drinkers, and 39.9% were regular drinkers. The stage 1 genome-wide analyses identified 25,115 variants in 495 independent loci that were at least suggestively associated ($P < 1 \times 10^{-6}$) with HDL-C, LDL-C, or TG using either the 1-df test of the interaction or the 2-df test that jointly assessed genetic main and interaction effects. The 1-df interaction test identified 356 suggestively associated variants, while the 2-df joint test identified an additional 24,759 variants. Manhattan and quantile-quantile plots are shown in Web Figure 1 and Web Figure 2, respectively.

The 25,115 variants were then evaluated in stage 2. Descriptive statistics for the studies participating in stage 2 are shown in Web Table 2: 58.5% of stage 2 participants were current drinkers, and 41.0% were regular drinkers. The combined analysis of stage 1 and stage 2 findings identified 22,590 variants at 147 independent loci with genome-wide significance ($P < 5 \times 10^{-8}$; Web Table 6). All genome-wide-significant associations were identified through the 2-df joint tests of main and interaction effects. There were no genome-wide-significant 1-df interaction associations in the combined analysis of stage 1 and stage 2. At genome-wide significance, 95 of the 147 loci were associated with HDL-C, 66 were associated with LDL-C, and 58 were associated with TG. Of the 147 loci, 60 loci were associated with more than 1 lipid trait, as shown in a Venn diagram in Figure 1.

Novel loci

Of the 147 identified genome-wide-significant loci, 18 are novel lipid loci that have not been previously identified by other association studies for HDL-C, LDL-C, TG, or total cholesterol (Table 2 and Web Figure 3) (2–8). A concurrent genetic association study of exonic variants also identified 4 of these 18 novel loci (39), as indicated in Table 2. Eight of the novel loci involved HDL-C, 8 involved LDL-C, and 7 involved TG, as shown in the heat map in Figure 2. The most significant associations at each of the 18 novel loci all had FDR q values less than 0.05 (Table 2), indicating that they were unlikely to be false-positive findings introduced by multiple testing. As shown

in forest plots (Web Figure 4), the 2-df associations at the novel loci were predominantly driven by genetic main effects, with a smaller contribution from interaction effects. Furthermore, of the 18 index variants, 15 had at least suggestively significant ($P < 1 \times 10^{-6}$) genetic main effects in stage 1 (Web Appendix and Web Table 7). None of the associations at the 18 novel loci displayed heterogeneity across ancestry groups (Table 2).

Known loci

The remaining 129 of the 147 significant loci had been identified in previous GWAS of lipid traits (Web Table 6) (2–8). This is a subset of all known lipid loci: Web Table 8 shows the significance of 314 reported index variants in all 236 known lipid loci among all 2-df joint tests and 1-df interaction tests of the combined analysis of stage 1 and stage 2, or stage 1 alone for variants not meeting the stage 2 inclusion criteria (2–8). Considering only the 314 known variants, no 1-df interactions were significant in the European, African, or transancestry meta-analyses ($P < 8.8 \times 10^{-6}$, corresponding to $0.05/(314 \text{ variants} \times 3 \text{ lipid traits} \times 2 \text{ alcohol consumption variables} \times 3 \text{ ancestry groups})$).

Additional analyses

The percentages of variance in LDL-C, HDL-C, and TG concentrations explained by various loci were calculated in individual studies of multiple ancestry groups. Across ancestry groups, the mean variance explained by known lipid loci was 9.1% for HDL-C, 10.4% for LDL-C, and 7.5% for TG. The total percentage of additional variance explained by the 18 novel loci, including both genetic main effects and interaction effects, was 0.2 for HDL-C, 0.3 for LDL-C, and 0.4 for TG. Ancestry-specific and study-specific estimates are shown in Web Table 9.

Functional annotations using HaploReg (34) and RegulomeDB (35) for variants at the 147 loci that were associated in the combined analysis of stages 1 and 2 are presented in Web Table 10, and associations of these variants with gene expression levels from the GTEx database (36) in a variety of

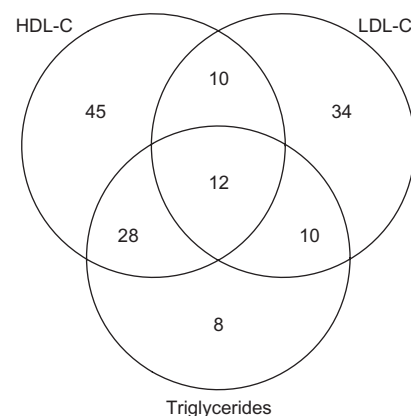


Figure 1. Distribution of genome-wide-significant associations at 147 genetic loci identified as being associated with 3 lipid traits (high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides) in a genome-wide meta-analysis of gene-alcohol interaction and lipid levels, 2017.

Table 2. Novel Loci Discovered in a Genome-Wide Meta-Analysis of Gene-Alcohol Interaction and Lipid Levels (Combined Analysis of Stages 1 and 2) Using a 2-Degrees-of-Freedom Model That Jointly Tested Main and Interaction Effects, 2017

rsID	Chromosome No.:Position	Alleles ^a	Frequency ^b	Closest Gene(s)	Main Effect ^c	Interaction Effect ^c	Joint P Value ^c	Joint FDR q Value ^c	Interaction P Value ^d	Heterogeneity P Value ^e	Most Significant 2-df Model
rs190528931 ^f	11:63911273	A/C	0.04	<i>MACROD1</i>	0.0109	-0.0023	1.9×10^{-16}	3.6×10^{-11}	0.32	0.96	META ^g —HDL-C—CURDRINK ^h
rs7904973 ^f	10:124693587	T/G	0.55	<i>C10orf88</i>	0.9200	-0.1500	1.9×10^{-15}	3.5×10^{-10}	0.38	0.89	META—LDL-C—CURDRINK
rs73729083	7:137559799	C/T	0.91	<i>CREB3L2</i>	4.0100	0.6500	8.2×10^{-15}	1.4×10^{-9}	0.57	0.22	META—LDL-C—CURDRINK
rs80080062	3:185812169	G/C	0.87	<i>ETV5</i>	0.0061	0.0031	1.1×10^{-12}	1.7×10^{-7}	0.38	0.85	META—HDL-C—REGDRINK ⁱ
rs7140110	13:114544024	C/T	0.73	<i>GAS6-AS1</i>	-0.0100	-0.0040	3.4×10^{-12}	5.1×10^{-7}	0.19	0.42	META—TG—CURDRINK
rs34311866	4:951947	C/T	0.83	<i>TMEM175</i>	-0.0200	0.0040	1.5×10^{-11}	2.1×10^{-6}	0.42	0.90	EUR—TG—CURDRINK
rs2911971	8:6607634	G/C	0.34	<i>AGPAT5</i>	-0.7500	0.0100	7.5×10^{-11}	1.1×10^{-5}	0.53	0.49	META—LDL-C—CURDRINK
rs56076449	5:132442190	G/T	0.79	<i>HSPA4/FSTL4</i>	0.0130	-0.0020	9.3×10^{-11}	1.3×10^{-5}	0.80	0.80	META—TG—REGDRINK
rs41274050 ^f	10:52573772	T/C	0.01	<i>A1CF</i>	0.1080	-0.0310	9.6×10^{-10}	1.3×10^{-4}	0.62	1.00	EUR—TG—REGDRINK
rs7035578	9:78745177	A/G	0.15	<i>PCSK5</i>	-1.2700	0.0800	1.2×10^{-9}	1.6×10^{-4}	0.70	0.82	EUR—LDL-C—CURDRINK
rs201445483	2:17890087	I/D	0.83	<i>SMC6</i>	1.4300	0.6800	4.7×10^{-9}	6.0×10^{-4}	0.17	0.46	META—LDL-C—CURDRINK
rs72729610	4:154190965	G/A	0.86	<i>TRIM2</i>	0.0075	-0.0036	5.6×10^{-9}	7.2×10^{-4}	0.08	0.26	META—HDL-C—REGDRINK
rs143528679	4:124558378	G/A	0.10	<i>SPRY1/LINC01091</i>	-1.2000	-5.6300	6.3×10^{-9}	8.0×10^{-4}	6.4×10^{-4}	0.10	AFR—LDL-C—CURDRINK
rs2111622 ^f	2:53984823	G/A	0.77	<i>ASB3/GPR75-ASB3</i>	0.0008	-0.0072	7.9×10^{-9}	9.9×10^{-4}	0.01	0.12	EUR—HDL-C—CURDRINK
rs13284665	9:131513370	G/A	0.88	<i>ZER1</i>	1.9900	-0.8900	1.1×10^{-8}	1.3×10^{-3}	0.35	0.89	EUR—LDL-C—CURDRINK
rs4898521	12:49755162	A/T	0.95	<i>DNAJC22/SPATS2</i>	0.0179	-0.0107	1.3×10^{-8}	1.7×10^{-3}	0.06	1.00	EUR—HDL-C—REGDRINK
rs6063050	20:45604240	C/T	0.75	<i>EYA2</i>	0.0110	0.0000	2.9×10^{-8}	3.6×10^{-3}	0.30	0.39	META—TG—CURDRINK
rs2963472	5:157999022	A/G	0.21	<i>LOC101927697/EBF1</i>	0.0140	-0.0020	3.5×10^{-8}	4.2×10^{-3}	0.96	0.23	EUR—TG—REGDRINK

Abbreviations: *A1CF*, APOBEC1 complementation factor gene; ADP, adenosine diphosphate; AFR, African ancestry; *AGPAT5*, 1-acylglycerol-3-phosphate *O*-acyltransferase 5 gene; APOBEC1, apolipoprotein B mRNA editing enzyme, catalytic polypeptide 1; *AS1*, antisense RNA 1 gene; *ASB3*, ankyrin repeat and SOCS box containing 3 gene; cAMP, cyclic adenosine 3',5'-monophosphate; *C10orf88*, chromosome 10 open reading frame 88 gene; *CREB3L2*, cAMP responsive element binding protein 3 like 2 gene; CURDRINK, current drinkers; df, degrees of freedom; *DNAJC22*, DnaJ heat shock protein family (Hsp40) member C22 gene; EBF, early B cell factor; *EBF1*, EBF transcription factor 1 gene; ETS, E26 transformation-specific; *ETV5*, ETS variant 5 gene; EUR, European ancestry; EYA, eyes absent; *EYA2*, EYA transcriptional coactivator and phosphatase 2 gene; FDR, false discovery rate; *FSTL4*, follistatin like 4 gene; *GAS6*, growth arrest specific 6 gene; *GPR75*, G protein-coupled receptor 75 gene; HDL-C, high-density lipoprotein cholesterol; Hsp, heat shock protein; *HSPA4*, heat shock protein family a (Hsp70) member 4 gene; LDL-C, low-density lipoprotein cholesterol; *LINC01091*, long intergenic non-protein coding RNA 1091 gene; *LOC101927697*, uncharacterized locus 101927697; *MACROD1*, macro domain-containing protein 1 gene; META, meta-analysis; *PCSK5*, proprotein convertase subtilisin/kexin type 5 gene; REGDRINK, regular drinkers; rsID, reference SNP identifier; RTK, receptor tyrosine kinase; *SMC6*, structural maintenance of chromosomes 6 gene; SNP, single nucleotide polymorphism; SOCS, suppressor of cytokine signaling; *SPATS2*, spermatogenesis associated serine rich 2 gene; *SPRY1*, sprouty RTK signaling antagonist 1 gene; TG, triglycerides; *TMEM175*, transmembrane protein 175 gene; *TRIM2*, tripartite motif containing 2 gene; *ZER1*, Zyg-11 related cell cycle regulator gene.

^a Coded allele/noncoded allele.

^b Frequency of the coded allele.

^c These estimates pertain to the 2-df joint test of main and interaction effects.

^d These *P* values pertain to 1-df tests of interaction effects.

^e Significance of the stage 1 heterogeneity across ancestry groups in the most significant 2-df model.

^f These loci were also discovered by Liu et al. (39) in a concurrent association study focused on exonic variants.

^g Trans-ancestry meta-analysis.

^h Alcohol consumption categorized into drinkers and nondrinkers.

ⁱ Alcohol consumption categorized into regular drinkers and non-regular drinkers.

tissues are shown in Web Table 11. A total of 443 variants were associated with gene expression levels, of which 27 variants were indicated by RegulomeDB as having strong evidence for an association with enhancer function.

Our gene prioritization analyses with DEPICT highlighted (FDR q values $<5\%$) 165 genes at HDL-C-associated loci, 110 genes at LDL-C-associated loci, and 87 genes at TG-associated loci (Web Tables 11–14). Thus, at some loci, multiple potential causal genes were prioritized. DEPICT identified 656, 877, and 497 reconstituted gene sets that were significantly enriched (FDR q values $<5\%$) for genes at HDL-C, LDL-C, and TG loci, respectively (Web Table 15). This large number of processes and enriched gene sets underscores the complex genetic, biological, and physiological mechanisms underlying lipid traits. Among the most significantly enriched gene sets were processes related to “total amount of body fat” and “abnormal liver morphology.” Finally, DEPICT revealed that genes at associated HDL-C, LDL-C, or TG loci were significantly enriched (FDR q values $<5\%$) for association with gene expression in 23 tissues, 14 cell types, and 12 physiological systems (Web Table 16). We found a compelling enrichment of genes acting in hepatocytes and liver processes at associated loci for each of the 3 traits and of genes acting in adipose tissues for HDL-C and TG loci (Web Table 16, Web Figure 5).

Fourteen index variants at known lipid loci were associated with coronary artery disease with P values less than 1.7×10^{-4} (0.05/(147 variants \times 2 disease outcomes)), and 11 of these were also associated with myocardial infarction (Web Table 17) (38). None of the index variants at novel loci were significantly associated with these clinical endpoints.

DISCUSSION

We performed a GWAS of lipid levels incorporating interactions with alcohol consumption and identified 147 genome-wide-significant lipid loci, of which 18 are novel.

Despite the large sample of 394,584 individuals, which is comparable to sample sizes in other successful genetic interaction studies (40, 41), genome-wide-significant interactions were not found in the present study. Gene-alcohol interactions also do not appear to have contributed substantially to the discovery of the 18 novel loci, given that the genetic main effect of index variants at 15 of the 18 novel loci passed the stage 1 suggestive significance threshold. Below, we highlight 3 of the novel loci that harbor especially promising candidate genes with putative roles in lipid metabolism based on existing evidence from cellular and experimental models.

One of the newly identified associations for LDL-C maps to the proprotein convertase subtilisin/kexin type 5 gene (*PCSK5*), a member of the same gene family as proprotein convertase subtilisin/kexin type 9 (*PCSK9*), which is targeted by new drugs that successfully lower LDL-C levels (42, 43). Several independent lines of evidence support the involvement of *PCSK5* in the regulation of lipid levels. First, in a candidate gene study, Iatan et al. (44) found that variants in *PCSK5* were associated with levels of HDL-C. Additionally, *in vitro* studies of cell lines show that proprotein convertase subtilisin/kexin type 5 (*PCSK5*) inactivates endothelial lipase directly through cleavage and that

it may also inactivate endothelial lipase and lipoprotein lipase indirectly through activation of angiopoietin-like protein 3 (45). Endothelial lipase, lipoprotein lipase, and angiopoietin-like protein 3 have all been robustly implicated in the regulation of lipid levels, probably with primary roles in the metabolism of HDL-C and TG (3, 46–48). In our study, the *PCSK5* locus was associated at genome-wide significance only with LDL-C levels; it was associated at nominal significance ($P < 0.05$) with TG levels.

One novel locus for TG mapped to the apolipoprotein B mRNA editing enzyme, catalytic polypeptide 1 (*APOBEC1*) complementation factor gene (*AICF*), which encodes *APOBEC1* complementation factor. Liu et al. (39) also identified the same index variant (rs41274050) in association with TG in a concurrent study. They showed that introducing the minor allele of rs41274050 in mice led to increased TG levels, confirming the functional role of this missense variant in the regulation of TG levels (39). *APOBEC1* complementation factor forms an enzymatic complex with *APOBEC1* and deaminates apolipoprotein B mRNA (49). This site-specific deamination of cytidine to uridine results in the production of the apolipoprotein B 48 isoform as opposed to the apolipoprotein B 100 isoform (49). The apolipoprotein B 48 isoform is critical in the assembly and secretion of chylomicrons, which mainly carry dietary-derived TG (50). Interestingly, a recent GWAS carried out among persons of East Asian ancestry identified the apolipoprotein B mRNA editing enzyme, catalytic polypeptide 1 (*APOBEC1*) locus as being associated with HDL-C levels (5)—an association that we confirmed in our analysis (index variant: 12:7725904:ID). At nominal significance, both of the index variants near *AICF* and *APOBEC1* were associated with all 3 lipid traits ($P < 0.05$). Given the role of apolipoprotein B 100 in atherosclerosis, promoting the synthesis of apolipoprotein B 48 instead of apolipoprotein B 100 may represent a possible therapeutic strategy for the prevention of cardiovascular disease (51). Neither the index variant at *AICF* nor *APOBEC1* was significantly associated with coronary artery disease or myocardial infarction in the largest GWAS of these outcomes. However, further studies are needed to characterize their role in cardiovascular disease, given our multiethnic design and the European-driven design of the available GWAS data on cardiovascular disease outcomes (Web Table 17).

Variants closest to the mono-ADP ribosylhydrolase 1 (macro domain-containing protein 1) gene (*MACROD1*) were associated with HDL-C levels and TG levels. This locus was also reported in the concurrent study by Liu et al. (39), although the index variant in their study was located in the phospholipase C beta 3 (*PLCB3*) gene, around 120 kilo-base pairs away from the index variant in the present study. We found that variants at this locus were associated with expression levels of another nearby gene, the vascular endothelial growth factor B gene (*VEGFB*), in adipose and heart tissue (Web Table 11). Vascular endothelial growth factor B (VEGF-B) is reportedly involved in endothelial fatty acid transport, with *Vegfb*^{-/-} mice showing less accumulation of lipids in muscle, heart, and brown adipose tissue but a greater uptake of fatty acids in white adipose tissue and higher body weight (52). Additionally, inhibition of the vascular endothelial growth factor B (Vegfb) protein in a mouse model of type 2 diabetes resulted in an improved glycemic profile, as well as a reduction of dyslipidemia (53). Mice lacking

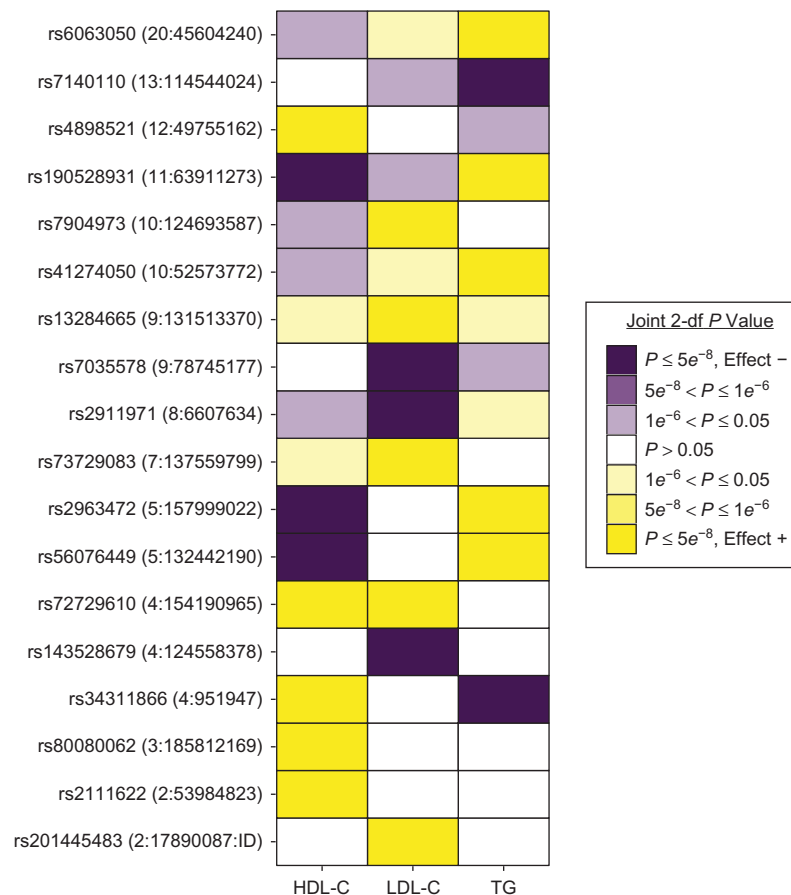


Figure 2. Significance and direction of effects of index genetic variants identified at 18 novel loci for 3 lipid traits (high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG)) in a genome-wide meta-analysis of gene-alcohol interaction and lipid levels, 2017. For each combination of index variant and lipid trait, the effect direction and P value for the most significant association is shown. For example, the rs11:63911273 variant was most significantly associated with HDL-C in the transancestry meta-analysis, using the “current drinker” alcohol consumption variable. Shades of purple and yellow represent negative and positive directions of effect, respectively, while associations of either direction with a P value greater than 0.05 are white. Effect +: the direction of effect is greater than or equal to zero; Effect -: the direction of effect is less than zero. df, degrees of freedom; ID, identification; rs, reference SNP; SNP, single nucleotide polymorphism.

the *Vegfb* protein had lower levels of TG and LDL-C accompanied by higher levels of HDL-C. Subsequent studies in other mouse models did not corroborate these findings: Dijkstra et al. (54) found in an independent strain of mice that knocking out the mouse vascular endothelial growth factor B gene (*Vegfb*) had no effect on TG and total cholesterol levels, while Rubciuc et al. (55) and Rafii and Carmeliet (56) reported that transduction of the human *VEGFB* gene into mice led to increased vascularity in adipose tissue and an improved lipid profile. Our results provide insight into the effects of VEGF-B in humans to complement the divergent reports from rodent studies. The A allele of index variant rs190528931 is associated with decreased expression of *VEGFB* in adipose and heart tissue, decreased levels of HDL-C, and increased levels of TG. Additionally, rs190528931 was also associated with nominally significant increased levels of LDL-C ($P < 0.05$). Hence, evidence from our study suggests that inhibition of VEGF-B does not improve lipid profile but instead promotes dyslipidemia.

The strengths of this study include the large sample size, the diverse ancestral composition of the sample, and the use of a dense reference panel for genotype imputation (57). A limitation of this study is the imbalance in ancestry groups between stage 1 and stage 2. Persons of African ancestry were well-represented in stage 1 but underrepresented in stage 2. In contrast, persons of Asian and Hispanic ancestry were relatively underrepresented in stage 1 as compared with stage 2. A more balanced division of participants across stages 1 and 2 may have led to the identification of additional loci. Additionally, alcohol consumption may be underreported in both self-administered questionnaires and interviews, leading to a loss of statistical power due to misclassification (58). Similarly, the classification of alcohol consumption into categories such as “regular drinkers” and “current drinkers” may have reduced power relative to treating it as a fully quantitative variable (59). Nevertheless, the use of such categories was necessary for harmonizing data from 111 studies with heterogeneous measurement of alcohol consumption. It is plausible that more

comprehensive characterization of alcohol consumption could reveal interactions that were missed in our study.

In conclusion, we identified 18 novel loci that were significantly associated with lipid traits, and these include several loci with genes (*PCSK5*, *VEGFB*, and *AICF*) that have a putative role in lipid metabolism based on existing evidence from cellular and experimental models. The associations identified in this study appear to be driven by genetic main effects, and it remains uncertain whether alcohol consumption modifies the association of genetic variants with lipid levels.

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