SUPPLEMENTARY MATERIAL

Supplementary Note

Supplementary Tables (Supplementary Tables 3, 11 and 14-16 are separate excel files)

Supplementary Figures

I. Cohort Descriptions

East Asian Exome Chip Cohorts

Chinese Eye Study (CHES)

CHES study is a 5-year, population-based study recruited 4570 non-institutionalized Chinese Americans, aged 50 years and older, in the city of Monterey Park in Los Angeles County, and to determine risk indicators associated with these ocular diseases[1].

China Health and Nutrition Survey (CHNS)

CHNS was designed to understand how the wide-ranging social and economic changes in China affect a wide array of nutrition and health-related outcomes. Since 1989, CHNS has collected longitudinal anthropometry, blood pressure, diet and lifestyle data on ~4,400 households with a total of ~26,000 individuals in nine Chinese provinces that vary substantially in geography, economic development and health indicators. In the 2009 survey, the CHNS collected blood from which major cardiovascular and nutrition biomarkers were measured and DNA was extracted. Genome-wide genotyping were carried out in a subset of 8,405 individuals[2]. All blood samples were processed in a national central lab in Beijing. HDL-C and LDL-C were measured via homogeneous enzymatic methods, TG was measured using GPO-PAP method, and TC were measured by CHOD-PAP method.

Cebu Longitudinal Health and Nutrition Survey(CLHNS)

CLHNS is an ongoing community-based birth cohort study that began in 1983. The baseline survey randomly recruited 3,327 pregnant women from the Metropolitan Cebu area, the Philippines in 1983-84 (3,080 singleton live births), and since followed them and their offspring to the present[3]. Trained field staff conducted in-home interviews and collected anthropometric measurements at each visit. Blood samples for biomarker measurement and DNA extraction were obtained in 2005. For this study of 1,779 CLHNS mothers, weight, height, and the calculated BMI were ascertained in the 2005 survey.

Fangchenggang Area Male Health and Examination Survey(FAMHES)

All samples in this study were collected from the Fangchenggang Area Male Health and Examination Survey (FAMHES)[4], which was mainly focused on environmental and genetic factors, as well as their interrelations. In the comprehensive demographic and health survey, 4303 men participated in routine physical examination at the Medical Centre in Fangchenggang First People's Hospital from September to December 2009. As a population-based study conducted among non-institutionalized Chinese men aged from 18 to 88 years old in Guangxi, FAMHES investigated the development of age-related chronic disease.

Guizhou-Bijie Type 2 Diabetes Study (GBTDS)

GBTDS is a population-based case-control study conducted from September 2009 to January 2010 in Bijie city of Guizhou province[5]. The participants include 1,824 type 2 diabetic cases (955 male and 869 female) and 1,719 nondiabetic controls (828 male and 891 female) aged 30 to 80 years, with at least 10 years residence in Bijie city. All participants are unrelated Chinese Hans and recruited through advertisement. The participants were asked to attend a complete physical examination in the Bijie People's Hospital to collect standard anthropometric measurements and blood samples, and to complete a comprehensive questionnaire to collect information on demographic variables, health status, health behavior, and physical activity. Total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides were enzymatically measured in fasting blood samples by an automatic analyzer (Hitachi 7080, Japan). For the current study, 846 T2D cases and 829 controls were genotyped using exome array. After quality control, 837 T2D cases and 815 controls were included in the analysis.

The University of Hong Kong Theme-based Research Scheme (HKU-TRS)

HKU-TRS is a collaborative study aiming to identify genetic factors contributing to cardiovascular disease[6]. We genotyped 6,048 Southern Chinese subjects recruited from the Chinese CAD Cohort of the Queen Mary Hospital in Hong Kong; Hong Kong Cardiovascular Risk Factor Prevalence Study (CRISPS) and Hong Kong West Diabetes Registry (HKWDR). Fasting blood samples were collected and plasma lipids were measured by standard enzymatic methods. LDL-C level was calculated using the Friedewald equation or by direct enzymatic colorimetric test if TG was >4.5 mmol/L. For the quantitative blood lipids analyses, we included 5,233 subjects (2,372 CAD cases and 3,388 non-CAD controls) who were not taking any lipid-lowering drug or those with their pre-treatment lipid levels available.

Hubei Coronary Artery Disease study (HuCAD)

The HuCAD initially included a total of 5111 CAD patients and 5002 age (±5 years) and gender (matched on frequency) matched controls recruited in Hubei, Wuhan, China. CAD patients were recruited consecutively from 3 hospitals in Wuhan, Hubei, China (Tongji Hospital, Union Hospital and Wugang Hospital) between 2004 and 2012[7]and Dongfeng Central Hospital in Shiyan, Hubei, China between 2008 and 2012 (most of these patients have been registered into Dongfeng–Tongji cohort[8]). The diagnostic criteria for CAD cases included having a documented history ofcoronary artery bypass graft or percutaneous coronary intervention, the presence ofa stenosis ≥50% in at least 1 of the major segments of coronary arteries on coronary angiography, and/or a diagnosis of CAD based on the World Health Organization criteria. Controls were selected from the DFTJ cohort(*Wang F et al., Int J Epidemiol, 2013*), the Wuhan-Zhuhai cohort (*Song Y et al., BMC Public Health, 2014*) and the Wuhan cohort of coke oven workers(*Li X et al., PLoS One, 2012*). All controls were free of ischemic heart disease, stroke, diabetes and cancer by the time when the study was conducted. Of the initially genotyped 10113 individuals, 4664 CAD cases and 4533 controls passed quality control criteria, among which 4327 cases and 4187 controls available for complete lipid traits were eligible for the present analysis. Blood specimens were obtained after participants had fasted overnight (≥8 h). The plasma TC, TG, LDL-C and HDL-C levels were measured by the ARCHITECT Ci8200 automatic analyzer (ABBOTT Laboratories. Abbott Park, Illinois, USA) using the Abbott Diagnostics reagents according to the manufacturer's instructions in each hospital or examination center.

The Nutrition and Health of Aging Population in China (NHAPC)

The NHAPC is a population-based study among non-institutionalized Chinese people aged 50 to 70 years in Beijing and Shanghai, which was designed to investigate the effects of environmental and genetic factors and their interaction on the development of age-related chronic diseases[9]. The study design, methods and measurements of this cohort study have been described in detail elsewhere. Briefly, the participants were recruited using a multistage sampling method from 2 urban districts and 1 rural district of each city. Data on demographic variables, health status, health behavior, and physical activity was collected using a standardized questionnaire, and standard anthropometric measurements and overnight fasting blood samples were collected using a standardized protocol when the participants attended a physical examination. A total of 3,289 eligible participants (1,458 men and 1,831 women) were recruited. For this study, the exome-wide association study was conducted among 3,161 individuals. After stringent quality control, 1,999 subjects were included in the analysis. Peripheral venous ethylenediaminetetraacetic acid blood

samples were collected and centrifuged at 4℃, 3,000 rpm for 15 min. After being frozen, the samples were shipped in dry ice to the Institute for Nutritional Sciences and stored at −80°C until analysis. Total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides were enzymatically measured on an automatic analyzer (Hitachi 7080, Japan) with reagents purchased from Wako Pure Chemical Industries (Osaka, Japan).

Peking University Health Science Center and the University of Michigan Medical School study of Myocardial Infarction (PUUMA.Capital)

Samples from China were collected by the Joint Institute of the Peking University Health Science Center and the University of Michigan Medical School study of Myocardial Infarction (PUUMA-MI)[6]. PUUMA-MI is a large-scale project designed to study cardiovascular disease and related traits including myocardial infarction (MI) and plasma lipid levels. Fasting plasma lipid levels (including serum total cholesterols, LDL cholesterol, HDL cholesterol and triglycerides) were tested using Roche cobas 8000 modular analyzer series (Indianapolis , IN, USA) in Beijing Shijingshan cohort samples (N=836) and Beckman coulter UniCelDxC 800 Synchron (Brea, CA, USA) in Peking University First Hospital-based samples (N=7,339) after overnight fasting, respectively.

Peking University Health Science Center and the University of Michigan Medical School study of Myocardial Infarction (PUUMA.Case, PUUMA.Control)

Samples from China were collected by the Joint Institute of the Peking University Health Science Center and the University of Michigan Medical School study of Myocardial Infarction (PUUMA-MI)[6]. PUUMA-MI is a large-scale project designed to study cardiovascular disease and related traits including myocardial infarction (MI) and plasma lipid levels. Blood samples were taken in the morning after an overnight fast and collected into vacuum tubes containing EDTA for the measurement of plasma lipids. Clinical chemical analyses were conducted at the central chemistry lab of Peking University Third Hospital. Using Beckman Coulter AU 5800 Auto-Analyzer (Tokyo, Japan), total cholesterol was measured by an enzymatic method (Baiding Biological Engineering Ltd., Beijing, China); triglycerides were measured by an enzymatic (with peroxidase) method (Biosino Bio-Technology Co., Ltd., Beijing, China); and high density lipoprotein cholesterol and low density lipoprotein cholesterol were measured by a liquid selective detergent method (Sekisui Medical Co., Ltd., Tokyo, Japan). The day-to-day coefficients of variation were 0.9%-

2.0% for total cholesterol, 1.6% for high density lipoprotein-cholesterol, 1.5% for low density lipoprotein-cholesterol and 0.8% - 2.1% for triglyceride.

Shanghai breast cancer study(SBCS)

The SBCS is a population-based, case-control study conducted in urban Shanghai[10]. Subject recruitment in the initial phase of the SBCS (SBCS-I) was conducted between August 1996 and March 1998. The second phase (SBCS-II) of recruitment occurred between April 2002 and February 2005. Controls were randomly selected using the Shanghai Resident Registry. Only controls were included in this study.

Singapore Chinese Eye Study (SCES)

The SCES is the Chinese equivalent to SiMES, where the sampling was similarly performed in the same 15 residential districts and included 3,353 Singaporean Chinese subjects[11]. Non-fasting venous blood was collected for SiMES subjects and serum blood lipids using enzymatic methods implemented in the Advia 2400 Chemistry System (Siemens Medical Solutions Diagnostics, Deerfield, IL). In total 2,461 Singaporean Chinese adult subjects from SCES were genotyped on the Illumina HumanExomeBeadchip. Sample QC measures excluded 1 subjects with low call-rates (<99%), 66 subjects with low heterozygozity (< Median + 3*IQR), 39 1st degree related individuals and 9 PCA outliers and 2,461 SCES Chinese adult samples were available for subsequent statistical analysis.

Singapore Malay Eye Study (SiMES)

The SiMESis a population-based and cross-sectional study which aimed to investigate the epidemiology of eye diseases in Singapore Malays aged 40-80[12]. Initially, resident adults were selected through an age-stratified random sampling from the 15 residential districts in South-western Singapore to obtain approximately equal numbers in each decade between the ages 40-80. 3280 Malay adults were eligible and participated in the study. Non-fasting venous blood was collected for SiMES subjects and serum blood lipids using enzymatic methods implemented in the Advia 2400 Chemistry System (Siemens Medical Solutions Diagnostics, Deerfield, IL). A total of 2,469 SiMES Singaporean Malay subjects were genotyped on the Illumina HumanExomeBeadchip. Sample QC measures excluded 11 subjects with low call-rates (<99%), 7 subjects with low

heterozygozity(< Median + 3*IQR), 4 1st degree related individuals and 2 PCA outliers and 2,445 SiMES Malay subjects were available for subsequent statistical analysis.

Shanghai Men's Health Study(SMHS)

The SMHS is a population-based cohort study of 61,480 Chinese men between ages 40 and 74 who lived in 8 urban communities in Shanghai at enrollment (2002-2006)[13]. Detailed information on dietary and other lifestyle factors was collected at baseline and is being updated in follow-up surveys. Biological samples (blood, and or urine) were collected from 89% of cohort members. The cohort has been followed up for cancer occurrence and deaths.

Singapore Prospective Study Program (SP2)

The SP2 is a population-based study of diabetes and cardiovascular disease in Singapore that has been described previously[12]. The SP2 has recruited 10,633 Chinese, Malay, and Indian subjects from four cross-sectional studies that were conducted in Singapore between 1984 and 1998. Subjects were aged 18-69 at baseline and represented a random sample of the Singapore population, with over-sampling of the minority Malay and Indian ethnic groups to achieve a ratio of 60:20:20 in the overall sample. From 2003 to 2007, 7,772 subjects were re-contacted and interviewed, 5,094 of whom provided fasting blood samples, after a 10 hour overnight fast, and other clinical data. Serum lipids were measured using kits from Boehringer Mannheim Systems (Mannheim, Germany) and read on a BM/Hitachi 747 analyzer (Roche Diagnostics, Corp. Indianapolis, IN). In total 961 Singaporean Chinese adult subjects were genotyped on the Illumina HumanExomeBeadchip. Sample QC measures excluded 9 subjects with low call-rates (<99%), 11 1st degree related individuals and 4 PCA outliers and 936 SP2 Chinese adult samples were available for subsequent statistical analysis.

Shanghai Women's Health Study(SWHS)

The Shanghai Women's Health Study (SWHS) is a large population-based prospective cohort study initiated in 1996[14]. Approximately 75,000 Chinese women who lived in Shanghai were recruited into the study. In addition to survey data, blood and urine samples were collected from most

study participants at the baseline recruitment. This cohort of women has been followed for cause-specific mortality and site-specific cancer incidence.

Taiwan USA Diabetes Retinopathy(TUDR)

TUDR study is a cohort that enrolled subjects with T2DM receiving care at Taichung Veterans General Hospital, Taichung, Taiwan, and a small number of subjects were included from Tri-Service General Hospital, Taipei, Taiwan. All TUDR subjects underwent a complete fundoscopic examination to carefully document the presence and extent of retinopathy[15].

Chinese GWAS Cohorts

The Beijing Atherosclerosis Study (BAS)

The BAS consisted of 505 cases of MI and 1,021 controls[16-17]. All participants were from Beijing, China. All cases had a validated history of MI and were verified by hospital records and by cardiologists according to standard protocol. Controls were randomly selected from subjects participating in a community based survey of cardiovascular risk factors in Beijing. The control subjects were judged to be free of CAD by history, clinical examination, electrocardiography, and Rose questionnaire. Detailed data were collected through in-person interviews with each case and control. Subjects with congenital heart disease, cardiomyopathy, valvular disease, and renal or hepatic disease were excluded. Overnight fasting blood samples were drawn by venipuncture to measure lipid levels. Blood specimens were processed in the central clinical laboratory at the Department of Population Genetics at Fuwai Hospital of the Chinese Academy of Medical Sciences in Beijing. This laboratory participates in the Lipid Standardization Program of the US Centers for Disease Control and Prevention and National Heart, Lung, and Blood Institute. Study obtained approval from institutional review boards of Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, and other medical institutions, and all participants gave written informed consents.

The China Atherosclerosis Study (CAS)

The CAS consisted of 1,010 cases of CAD and 3,998 controls[16-17]. 1,010 cases from the Northern provinces in China were enrolled from Fuwai Hospital, National Center For Cardiovascular Diseases. 83.8% of cases have a family history of CAD. Controls of CAS study were recruited from

the International Collaborative Study of Cardiovascular Disease in Asia (InterASIA in China). InterASIA used a four-stage stratified sampling method to select a nationally representative sample of the general population aged 35 to 74 years in China. 3,998 controls were individuals who did not develop incident CAD and had no family history of CAD during the 8 yr follow-up period of the study from four northern field centers of InterASIA. Overnight fasting blood samples were drawn by venipuncture to measure lipid levels. Blood specimens were processed in the central clinical laboratory at the Department of Population Genetics at Fuwai Hospital of the Chinese Academy of Medical Sciences in Beijing.Study obtained approval from institutional review boards of Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, and other medical institutions, and all participants gave written informed consents.

GLGC Exome Chip Cohorts:

British 1958 Birth Cohort (1958BC)

The National Child Development Study (NCDS) follows the lives of 17,000 people born in England, Scotland and Wales in a single week of 1958[18]. Also known as the 1958 Birth Cohort Study, it collects information on physical and educational development, economic circumstances, employment, family life, health behaviour, wellbeing, social participation and attitudes. The NCDS is managed by CLS and funded by the Economic and Social Research Council. Since the birth survey in 1958, there have been nine further 'sweeps' of all cohort members at ages 7, 11, 16, 23, 33, 42, 46, 50 and 55. In 2003 (at age 45), 9,000 cohort members also participated in a special bio-medical survey so we could learn more about how development, environments and lifestyles affect people's health.

Anglo–Danish–Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care - Denmark screening cohort (ADDITION)

The Danish ADDITION Study (Anglo–Danish–Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care) is a high-risk screening and intervention study for type 2 diabetes in general practice sampled by Department of General Practice at University of Aarhus, Denmark (ClinicalTrials.gov ID-no: NCT00237548)[19]. The 8,662 participants from the initial screening cohort with available DNA included 1,626 participants with screen-detected and untreated T2D and 7,036 non-diabetic subjects. Patients with T2D were diagnosed by two independent diabetic values at baseline investigation or at one-year follow-up. Phenotypes include anthropometrics, basal fasting biochemistry (e.g.

plasma glucose, serum insulin, HbA1C and lipids) and health and lifestyle questionnaires. Here 2238 participants from the Danish screening cohort with information on lipids and exome chip were analyzed.

Age gene/environment susceptibility Reykjavik study (AGES)

The AGES study has been described previously[20]. The study was initiated in 2002 to examine genetic susceptibility and gene/environment interactions related to disease and disability in old age. The AGES study is comprised of 5764 individuals drawn from the Reykjavik Study, a population-based cohort comprised of individuals born between 1907 and 1935 and followed since 1967 by the Icelandic Heart Association. 3219 individuals chosen randomly among 5307 AGES individuals with 'mid-life' data available from the Reykjavik Study were genotyped on a genome-wide association (GWA) array. 2983 individuals randomly selected from the 3219 individuals with GWA were further genotyped for the ExomeChip.

Academic Medical Center Premature Atherosclerosis Study (AMCPAS)

Cases were recruited as part of a prospective cohort study (Academic Medical Centre Amsterdam Premature Atherosclerosis Study (AMC-PAS) with symptomatic CAD before the age of 51 years, defined as MI, coronary revascularization, or evidence of at least 70% stenosis in a major epicardial artery[21].

Atherosclerosis Risk in Communities Study (ARIC-AA, ARIC-EA)

The ARIC study has been described in detail previously[22]. Men and women aged 45-64 years at baseline were recruited from four communities: Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis, Minnesota; and Washington County, Maryland. A total of 15,792 individuals, predominantly White (EA) and African American (AA), participated in the baseline examination in 1987-1989, with three additional triennial follow-up examinations and a fifth exam in 2011-2013.

Anglo-Scandinavian Cardiac Outcome Trial [Scandinavians] (ASCOT-SC)

ASCOT is a randomised control clinical trial investigating the cardiac outcomes of blood pressure lowering and lipid lowering treatments[23]. Of 19,342 hypertensive patients (40–79 years of age with at least three other cardiovascular risk factors) who were randomized to one of two antihypertensive regimens in ASCOT, 10,305 with non-fasting TC concentrations of 6.5 mmol/l or less (measured at the non-fasting screening visit) had been randomly assigned additional atorvastatin 10 mg or placebo. These patients formed the lipid-lowering arm of the study. Only a proportion of United Kingdom, Irish, Sweden, Norway, Finland and Denmark consented to contribute DNA and participate in genetic studies. Blood lipid levels used in this analysis were measured at the (fasting) randomization visit and LDL- C was estimated using the Friedewald equation. The ASCOT-SC sample analysed here is restricted to the patients from Scandinavia, of which a total of 2,468 were genotyped on the Exome-Chip and passed QC for inclusion into this analysis.

Anglo-Scandinavian Cardiac Outcome Trial [UK/Ireland] (ASCOT-UK)

ASCOT is a randomised control clinical trial investigating the cardiac outcomes of blood pressure lowering and lipid lowering treatments[23]. Of 19,342 hypertensive patients (40–79 years of age with at least three other cardiovascular risk factors) who were randomized to one of two antihypertensive regimens in ASCOT, 10,305 with non-fasting TC concentrations of 6.5 mmol/l or less (measured at the non-fasting screening visit) had been randomly assigned additional atorvastatin 10 mg or placebo. These patients formed the lipid-lowering arm of the study. Only a proportion of United Kingdom, Irish, Sweden, Norway, Finland and Denmark consented to contribute DNA and participate in genetic studies. Blood lipid levels used in this analysis were measured at the (fasting) randomization visit and LDL- C was estimated using the Friedewald equation. The ASCOT-UK sample analysed here is restricted to the patients from UK and Ireland, of which a total of 3,246 were genotyped on the Exome-Chip and passed QC for inclusion into this analysis.

Italian Atherosclerosis, Thrombosis, and Vascular Biology Working Group (ATVB-Cases, ATVB-Controls)

ATVB is a nationwide prospective case control study involving 1,693 patients hospitalised for a first ST segment elevation MI before the age of 45 years, and 1,668 healthy subjects matched for age, gender and geographical origin[24].

The BioImage Study (BioImage-African, BioImage-Asian, BioImage-European, BioImage-Hispanic)

The BioImage Study (BioImage Study: A Clinical Study of Burden of Atherosclerotic Disease in an At-Risk Population, NCT00738725), a prospective, observational study aimed at characterizing subclinical atherosclerosis in U.S. adults (55 to 80 years old) at risk for clinical

atherosclerotic cardiovascular disease[25]. Between January 2008 and June 2009, the BioImage Study enrolled 7,687 asymptomatic men 55 to 80 years of age and women 60 to 80 years of age who were members of the Humana Health System and residents of the Chicago, Illinois, or Fort Lauderdale, Florida, metropolitan areas. A total of 6,397 individuals with exome chip genotypes and plasma lipids were analyzed.

Vanderbilt University electronic medical record-linked DNA repository (BioVU)

Vanderbilt University Medical Center Biorepository, BioVU, links DNA samples extracted from discarded blood samples from routine clinical testing at Vanderbilt University hospital to de-identified electronic medical records where individual level data can be extracted (e.g. cholesterol levels) and analyzed[26,27]. For the present study, we identified a total of 14156 individuals of European American ancestry with available information on LDL, HDL, total cholesterol, or triglyceride levels.

Bangladesh Risk of Acute Vascular Events study (BRAVE_Cases, BRAVE_Controls)

BRAVE is a retrospective case-control study of first-ever confirmed acute myocardial infarction (MI) in Bangladesh[28]. Patients (male or female; age between 30-80 years) admitted to the emergency rooms of the collaborating hospital in Dhaka, Bangladesh were eligible for inclusion as MI cases on the basis of symptoms, ECG and troponin-I. Controls were hospital based and frequency-matched to cases on age (within 5 year age bands) and sex, and without a self-reported history of cardiovascular disease. Commercial assay kits manufactured by Roche Diagnostics (GmbH, D-68298 Mannheim, Germany) were used to determine total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides. All analyses were done on Roche automated clinical chemistry analysers, Hitachi 902, Hitachi Ltd, Tokyo, Japan.

British Genetics of Hypertension Study (BRIGHT)

Participants of the BRIGHT Study are recruited from the Medical Research Council General Practice Framework and other primary care practices in the UK[29]. Each case had a history of hypertension diagnosed prior to 60 years of age with confirmed blood pressure recordings corresponding to seated levels >150/100mmHg (1 reading) or mean of 3 readings >145/95 mmHg. BRIGHT is focused on recruitment of hypertensive individuals with BMI<30. Sample selection for Exome Chip study was based on DNA availability and quantity.

The Coronary Artery Risk Development in Young Adults study (CARDIA-white, CARDIA-black)

The Coronary Artery Risk Development in Young Adults study is a prospective multi-center investigation of the etiology and natural history of cardiovascular disease initiated in 1985-1986. The study's initial enrollment consisted of 5115 European American and African American men and women between 18 and 30 years old (52% African American and 55% women) recruited from 4 field centers (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA). The institutional review board at each of the study sites approved the study protocols, and written informed consent was obtained from all participants. Detailed information about the CARDIA study design and methods of data collection have been previously published[30]. Briefly, participants' age, race, and sex were self-reported during the recruitment phase and verified during the baseline clinic visit. Blood pressure was measured at the baseline examination on the right arm using a random-zero sphygmomanometer with the participant seated and following a 5 minute rest. Systolic and diastolic pressures were recorded as Phase I and Phase V Korotkoff sounds. Three measurements were taken at one minute intervals. The average of the second and third measurements was taken as the blood pressure value. The present analysis included 4,151 individuals (2,175 European Americans and 1,976 African Americans) with baseline BP measures and genotype data.

Copenhagen City Heart Study (CCHS)

CCHS is a population-based prospective study initiated in 1976 with follow-up examinations from 1981 to 1983, 1991 to 1994, and 2001 to 2003[31]. Participants were selected on the basis of the national Danish Civil Registration System to reflect the adult Danish population age 20 to $\geqslant$80 years. Non-fasting plasma levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides and glucose were measured using colorimetric assays.

Copenhagen General Population Study (CGPS)

The CGPS is a population-based prospective study initiated in 2003 with ongoing enrollment[32,33]. Participants were selected on the basis of the national Danish Civil Registration System to reflect the adult Danish population age 20 to $\geqslant$80 years. Data were obtained from a questionnaire, a physical examination, and blood samples including deoxyribonucleic acid extraction. Non-fasting plasma levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides and glucose were measured in fresh samples using colorimetric assays.

Cardiovascular Health Study (CHS-EA, CHS-AA)

The CHS is a population-based cohort study of risk factors for coronary heart disease and stroke in adults ⩾65 years conducted across four field centers[34]. The original predominantly Caucasian cohort of 5,201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists, and an additional 687 African-Americans were enrolled subsequently for a total sample of 5,888. DNA was extracted from blood samples drawn on all participants at their baseline examination in 1989-90. 750 African-American and 4,021 European- American individuals were genotyped using the IlluminaHumanExomeBeadChip array. CHS was approved by institutional review committees at each field center and individuals in the present analysis had available DNA and gave informed consent including consent to use of genetic information for the study of cardiovascular disease.

Copenhagen Ischemic Heart Disease Study (CIHDS)

This study comprised 5185 cases with myocardial infarction and other major acute coronary syndromes recruited from Copenhagen University Hospital during the period from 1991 to 2009[32,33]. In addition to a diagnosis of acute coronary syndrome, these cases also had stenosis or atherosclerosis on coronary angiography and/or positive results on exercise electrocardiography. Cases were classified by World Health Organization International Classification of Diseases-Eighth Revision, codes 410 to 414; International Classification of Diseases-Tenth Revision, codes I20 to I25, and through review of all hospital admissions and diagnoses entered in the national Danish Patient Registry and all causes of death entered in the national Danish Causes of Death Registry. Non-fasting plasma levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides and glucose were measured in fresh samples using colorimetric assays.

CROATIA-Korcula (CROATIA-Korcula)

The CROATIA-Korcula study, Croatia, is a family-based, cross-sectional study in the isolated island of Korcula that included 965 examinees aged 18-95[35]. Blood samples were collected in 2007 along with many clinical and biochemical measures and lifestyle and health questionnaires. In the present study 855 genotyped individuals were included in the analysis.

DIABNORD (Exome Chip) (DIABNORD)

The DIABNORD Study is nested within the Västerbotten Health Survey, which is part of the Northern Sweden Health and Disease Study, a population-based prospective cohort study from northern Sweden[36]. Participants with incident type 2 diabetes were identified from the Diabetes Register in Northern Sweden (DiabNorth). A total of 909 Caucasian, non-diabetic participants from the DIABNORD Study had complete genotype and phenotype data necessary for the current analyses. Capillary blood was drawn following an overnight fast. Fasting serum lipid concentrations were measured with a Reflotron bench-top analyzer (Roche Diagnostics Scandinavia AB). Participants were genotyped with IlluminaHumanExomeBeadchip 12 v1.1. Ethical approval for the DIABNORD Study was obtained from the Regional Ethical Review Board in Umeå, Sweden.

Diabetes register in Vasa (DIREVA)

DIREVA (Diabetes register in Vasa) is a regional project in western Finland. All diabetes patients at all ages in the Vasa region are included. The aim of the registry is to describe the spectrum of diabetes subgroups in western Finland and to link genetic and phenotypic information at diagnosis of diabetes to outcome data and data on response to treatment. The study is coordinated by the Central hospital in Vasa.

The Finnish Diabetes Prevention Study (DPS)

DPS is a prospective randomized controlled trial aimed at preventing the progression from IGT to diabetes[37]. The original DPS was initiated in 1993. A total of 522 middle-aged, overweight subjects with IGT at baseline were randomized into either a lifestyle intervention or a standard-care control group. They were followed for occurrence of diabetes until the year 2000, when the first interim analysis of the data was carried out as originally planned. At this point, the randomized trial was prematurely terminated due to markedly lower diabetes incidence rate in the lifestyle intervention group as compared to the control group. Since the termination of the randomized phase of the DPS, the original cohorts are no longer offered different treatments. However, all participants are monitored with yearly visits for long-term development of type 2 diabetes and complications.

The Dose Responses to Exercise Training Study (DR's EXTRA)

DR's EXTRA is a 4-year randomized controlled trial on the health effects of aerobic and resistance exercise training and a diet with low saturated fat, high unsaturated fat, and high fiber in a population sample of middle-aged and older men and women[38]. The target population was a representative sample of 3,000 individuals (1,500 men, 1,500 women) who lived in the city of Kuopio in Finland and who were 55-74 years of age

in 2002, when they were randomly selected from the national population register. Of these individuals, 2,062 were willing to participate and 1,479 (72%) participated in the baseline examinations in 2005-2006. 1,410 individuals were randomly allocated into one of the six study groups, each of which included about 235 persons.

Duke Catheterization Genetics (Duke-AA-Cases, Duke-AA-Controls, Duke-EA-Cases, Duke-AA-Controls)

The Duke CATHGEN cohort consists of samples collected from individuals undergoing cardiac catheterization at Duke University Medical Center between 2001 and 2010[39]. These samples were matched with the findings of coronary anatomy, fasting chemistry data, as well as development of health habits and cardiovascular disease later in life through follow-up questionnaires. The data on the absence or presence of coronary artery disease were used in this analysis.

The Exeter Family Study of Childhood Health (EFSOCH)

The Exeter Family Study of Childhood Health is a prospective study, set up to test the fetal insulin hypothesis, and to identify genetic polymorphisms that play a role in determining birth weight and early postnatal growth[40]. We recruited 1017 families from a postcode-defined area in central Exeter. Specific inclusion criteria were established to obtain a homogeneous, non-diabetic, UK Caucasian cohort. Detailed anthropometric measurements were taken from both parents at 28 weeksÕ gestation, and from their children at birth, 12 weeks, 1 year and 2 years of age. Insulin and other biochemical analysis were measured in fasting parental samples and an umbilical cord blood sample taken at delivery. Parental and offspring DNA were extracted to allow molecular genetic analysis of candidate genes implicated in fetal growth.

Estonian Genome Center, University of Tartu (EGCUT)

The Estonian cohort is from the population-based biobank of the Estonian Genome Project of University of Tartu (EGCUT)[41]. The whole project is conducted according to the Estonian Gene Research Act and all participants have signed the broad informed consent. The current cohort size is over 51,515, from 18 years of age and up, which reflects closely the age distribution in the adult Estonian population. Subjects are recruited by the general practitioners and physicians in the hospitals were randomly selected from individuals visiting general practitioners offices or hospitals. Each participant filled out a Computer Assisted Personal interview during 1-2 hours at a doctor's office, including personal data (place of birth, place(s) of living, nationality etc.), genealogical data (family history, three generations), educational and occupational history and lifestyle data (physical activity, dietary habits, smoking, alcohol consumption, women's health, quality of life). All diseases are defined according to the ICD10

coding. Lipids for current study where directly measured in clinical setting, both phenotype and genotype where available for 1,405 Estonian Biobank participants.

European Prospective Investigation into Cancer and Nutrition - Cardiovascular Disease Study (EPIC-CVD)

EPIC is a multi-centre prospective cohort study of 519,978 participants (366,521 women and 153,457 men, mostly aged 35–70 years) recruited between 1992 and 2000 in 23 centres located in 10 European countries[42]. Participants were invited mainly from population-based registers (Denmark, Germany, certain Italian centres, the Netherlands, Norway, Sweden, UK). Other sampling frameworks included: blood donors (Spain and Turin and Ragusa in Italy); screening clinic attendees (Florence in Italy and Utrecht in the Netherlands); people in health insurance programmes (France); and health conscious individuals (Oxford, UK). About 97% of the participants were of white European ancestry. EPIC-CVD employs a nested case-cohort design, analogous to the EPIC-InterAct study for type-2 diabetes, which established a common set of referents through selection of a random sample of the entire cohort ("subcohort"). Baseline measurements of all serum biomarkers were performed using a Roche MODULAR ANALYTICS EVO analyser by SHL groep in the Netherlands.

EPIC-InterAct (EPIC-InterAct T2D cases)

The InterAct study is a case-cohort study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohorts, and includes 12,403 incident cases of T2D and a subcohort of 16,154 individuals (including 778 randomly selected incident T2D cases)[43]. Up to 2,192 incident cases of T2D were included in the current analysis.

Family Heart Study (FamHS-EA)

The collection of phenotypes and covariates as well as clinical examination have been previously described (https://dsgweb.wustl.edu/fhscc/)[44]. In brief, the FamHS began in 1992 with the ascertainment of 1,200 families, half randomly sampled and half selected because of an excess of CHD or risk factor abnormalities as compared with age- and sex-specific population rates. The families, with approximately 6,000 European descent subjects, were sampled from four population-based parent studies: the Framingham Heart Study, the Utah Family Tree Study, and two centers for the ARIC study. Informed consent was obtained from all participants, and this project was approved by the Institutional Review Boards of all participating institutions. The participants attended a clinic visit between the years 1994-1996 and a broad range of phenotypes was assessed in the general domains of CHD, atherosclerosis, cardiac and vascular function, inflammation and hemostasis, lipids and lipoproteins, blood pressure,

diabetes and insulin resistance, pulmonary function, diet, habitual physical activity, anthropometry, medical history and medication use. Approximately 8 years later, 2,756 subjects belonging to the 510 of the largest and most informative pedigrees were invited for a second clinical exam (2002-2004). The most important CHD risk factors were measured again. Medical history and medication use were updated. A total of 3,794 subjects from the first clinical visit participated in the current study. The subjects were genotyped using the IlluminaInfiniumHumanExome v1.0 BeadChip.

The Fenland Study (Fenland)

The Fenland Study is an ongoing, population-based cohort study (started in 2005) designed to investigate the association between genetic and lifestyle environmental factors and the risk of obesity, insulin sensitivity, hyperglycemia and related metabolic traits in men and women aged 30 to 55 years[45]. Potential volunteers were recruited from General Practice sampling frames in the Fenland, Ely and Cambridge areas of the Cambridgeshire Primary Care Trust in the UK. Exclusion criteria for the study were: prevalent diabetes, pregnant and lactating women, inability to participate due to terminal illness, psychotic illness, or inability to walk unaided. All participants had measurements done at the MRC Epidemiology Unit Clinical Research Facilities in Ely, Wisbech and Cambridge. Participants attended after an overnight fast for a detailed clinical examination, and blood samples were collected. The Local Research Ethics Committee granted ethical approval for the study and all participants gave written informed consent.

Framingham Heart Study (FHS)

The FHS is a three generational prospective cohort that has been described in detail previously[46]. Individuals were initially recruited in 1948 in Framingham, USA to evaluate cardiovascular disease risk factors. The second generation cohort (5,124 offspring of the original cohort) was recruited between 1971 and 1975. The third generation cohort (4,095 grandchildren of the original cohort) was collected between 2002 and 2005. Fasting lipid levels were measured at exam 1 of the Offspring (1971-1975) and third generation (2002-2005) cohorts, using standard LRC protocols. 8,153 European-American individuals were genotyped using the IlluminaHumanExomeBeadChip array.

FIN-D2D 2007 (FIN-D2D 2007)

The purpose of the study is to gather information about prevalence of diabetes and cardiovascular diseases and of the risk factors associated with these within the Finnish population[47]. The survey assists in the evaluation of the effects of the national type 2 diabetes prevention plan. The study

sample consists of 4,500 people randomly selected from the Finnish population register between the ages of 45 and 74 years and living in one of the three hospital districts chosen for the study: South Ostrobothnia, Central Finland, and Pirkanmaa.

National FINRISK 2007 Study (FINRISK 2007 T2D cases, FINRISK 207 T2D controls)

The Finnish National Public Health Institute performed the FINRISK health study in five areas of Finland during spring 2007 to investigate the people's health behavior and the risk factors of chronic diseases and public health problems[48]. The survey is a continuation of a series of studies begun in Eastern Finland in 1972 and performed once every five years since then. The purpose of the study is to gather information about the protective and risk factors of the major Finnish public health problems, such as cardiovascular diseases, diseases of the brain and the central nervous system, cancers, diabetes, asthma and allergies, and the prevalence of those factors in the population. The survey also monitors the state of health of the Finnish population.

Finland-United States Investigation of NIDDM Genetics Study (FUSION T2D cases, FUSION T2D controls)

FUSION1 cases included FUSION samples each reporting at least one T2D sibling and Finrisk 2002 T2D cases from a Finnish population-based risk factor survey[49,50]. Controls included 219 subjects from Vantaa, Finland who were NGT at ages 65 and 70 years, NGT spouses of FUSION subjects, and Finrisk 2002 NGT subjects. FUSION1 controls were approximately frequency-matched to the cases by five-year age category, sex, and birth province. FUSION2 includes subjects chosen from the following studies: Dehko 2D (D2D) 2004: a population-based study to screen individuals regarding T2D risk and to prevent T2D development; Finrisk 1987: an early round of the 5-yearly Finrisk national population-based health surveys; Finrisk 2002: a population-based survey of non-communicable diseases in >13,000 individuals aged 25-74 years living in 80 communities of Finland; Action LADA: a study of latent autoimmune diabetes in adults (LADA). Action LADA investigators screened individuals aged 30-69 years with recently-diagnosed diabetes and identified 373 T2D cases who agreed to participate in FUSION; Health 2000: a population-based study of people aged ⩾30 years from throughout Finland; Savitaipale Diabetes Study: a study of diabetes in the town of Savitaipale in eastern Finland.

Gene x Lifestyle Interactions and Complex Traits Involved in Elevated Disease Risk (Exome Chip) (GLACIER)

The Gene-Lifestyle interactions And Complex traits Involved in Elevated disease Risk (GLACIER) Study is nested within the Västerbotten Health Survey, which is part of the Northern Sweden Health and Disease Study, a population-based prospective cohort study from northern Sweden[36]. A total of 921 Caucasian, non-diabetic participants from the GLACIER Study had complete genotype and phenotype data necessary for the current analyses. Capillary blood was drawn following an overnight fast. Fasting serum lipid concentrations were measured with a Reflotron bench-top analyzer (Roche Diagnostics Scandinavia AB). Participants were genotyped with IlluminaHumanExomeBeadchip 12 v1.1. Ethical approval for the GLACIER Study was obtained from the Regional Ethical Review Board in Umeå, Sweden.

Genetics of Diabetes Audit and Reasearch in Tayside Scotland study (GoDARTS_CAD)

A high quality resource, initially funded by the Wellcome Trust and supported by Diabetes UK, has been created with successful recruitment of consented patients with type 2 diabetes and matching controls (non diabetics) throughout Tayside, Scotland[51]. This resource is already available to researchers worldwide and is helping to define genetic factors related to diabetes including susceptibility, complications and response to treatment. This analysis used the coronary artery disease subset of the cohort. First-ever CAD event. Defined as fatal and non-fatal myocardial infarction, unstable angina or coronary revascularisation. Controls were free of coronary artery disease, stroke and peripheral vascular disease.

Genetics of Diabetes Audit and Research Tayside (GoDARTS-cases, GoDARTS-controls)

A high quality resource, initially funded by the Wellcome Trust and supported by Diabetes UK, has been created with successful recruitment of consented patients with type 2 diabetes and matching controls (non diabetics) throughout Tayside, Scotland[51].

Genetic regulation of arterial pressure in humans in the community (GRAPHIC)

The Genetic Regulation of Arterial Pressure in Humans in the Community (GRAPHIC) Study is a family based population study comprising of 510 nuclear families (two parents aged 40-60 years at recruitment and two adult offspring aged 18-40 years) recruited through primary care in Leicestershire between 2003 and 2005[52]. All subjects are of white European origin. The primary objective of the GRAPHIC study was to investigate the genetic basis of blood pressure variation and all subjects underwent 24-hour ambulatory BP measurements. In addition, all subjects had extensive phenotyping including a full medical history and recording of risk factors and medication, dietary history, physical activity assessment, clinic BP, 12 lead ECG, measurement of height, weight, WHR and skinfold thickness. Available laboratory data include serum and urine electrolytes, plasma lipids measured by NMR and CRP. A total of 1851 subjects were included in this analysis.

Generation Scotland_Scottish Family Health Study (GS-SFHS)

Generation Scotland-SFHS recruited almost 24,000 participants from throughout Scotland. The study enlisted individuals aged 18-65 and their family members. Volunteers were asked to provide information about their lifestyle and diet, their medical history, and samples of blood and urine. Participation was by invitation through local GPs, or families volunteering directly. As the name suggests, the SFHS is based on families so at least one brother or sister of the initial recruit was required and preferably other family members. In the present study 9946 genotyped individuals were included in analysis.

Health2006/Health2008 (Health)

The Health2006 and Health2008 studies are cohort studies of adults aged 18-69 years who live in the greater Copenhagen area[53]. The aim of the studies was to identify lifestyle related risk factors for chronic diseases such as diabetes, heart disease, asthma, musculoskeletal disorders, chronic lung disease and mental disorders. Potential participants were excluded if they emigrated from the study location. Baseline examinations were conducted between 2006 and 2008. Data is collected through two questionnaires pertaining to lifestyle factors and mental health, and through medical exams assessing lung and cardiopulmonary function, and muscle strength. Blood samples were also collected from each participant for genetic and/or biomarker studies. The studies were approved by the Ethical Committee of Copenhagen County and the Danish Data Protection Agency. Here 3616 participants with information on lipids and exome chip were analysed.

Hellenic Isolated Cohorts - MANOLIS cohort (HELIC MANOLIS)

The HELIC (Hellenic Isolated Cohorts; www.helic.org) MANOLIS (Minoan Isolates) collection focuses on the Mylopotamos villages. Recruitment of this population-based sample was primarily carried out at the village medical centres. All individuals were older than 17 years and had to have at least one parent from the Mylopotamos area. The study includes biological sample collection for DNA extraction and lab-based blood measurements, and interview-based questionnaire filling. The phenotypes collected include anthropometric and biometric measurements, clinical evaluation data, biochemical and haematological profiles, self-reported medical history, demographic, socioeconomic and lifestyle information. The study was approved by the Harokopio University Bioethics Committee and informed consent was obtained from every participant. The total sample size in the collection is approximately 1,500 and 825 individuals genotyped on the exome chip and with lipid data available were included in this analysis.

Hellenic Isolated Cohorts - Pomak cohort (HELIC Pomak)

The HELIC (Hellenic Isolated Cohorts; www.helic.org) Pomak collection focuses on the Pomak villages, a set of isolated mountainous villages in the North of Greece. Recruitment of this population-based sample was primarily carried out at the village medical centres. The study includes biological sample collection for DNA extraction and lab-based blood measurements, and interview-based questionnaire filling. The phenotypes collected include anthropometric and biometric measurements, clinical evaluation data, biochemical and haematological profiles, self-reported medical history, demographic, socioeconomic and lifestyle information. The study was approved by the Harokopio University Bioethics Committee and informed consent was obtained from every participant. The total sample size in the collection is approximately 1,700 and 971 individuals genotyped on the exome chip and with lipid data available were included in this analysis.

The Nord-Trondelag Health Study (HUNT-Case)

We included 5,440 individuals with at least one lipid measurement from the second survey of the Nord-Trondelag Health Study (HUNT): 2,662 cases with hospital diagnosed myocardial infarction (primary phenotype) and 2,778 healthy controls without cardiovascular disease matched on sex, birth year (+/- 1 year), and municipality or geographical region to minimize population stratification[54]. HUNT is a population based health study (www.ntnu.edu/hunt) with personal and family medical histories on approximately 120,000 individuals from Nord-Trondelag County, Norway, collected in three surveys (HUNT 1, 2, and 3). Self-reported questionnaires, clinical examination, and non-fasting venous blood samples were collected on 62,816 individuals (66.9% of invited).

The Nord-Trondelag Health Study (HUNT-Control)

We included 5,440 individuals with at least one lipid measurement from the second survey of the Nord-Trondelag Health Study (HUNT): 2,662 cases with hospital diagnosed myocardial infarction (primary phenotype) and 2,778 healthy controls without cardiovascular disease matched on sex, birth year (+/- 1 year), and municipality or geographical region to minimize population stratification[54]. HUNT is a population based health study with personal and family medical histories on approximately 120,000 individuals from Nord-Trondelag County, Norway, collected in three surveys (HUNT 1, 2, and 3)19,35. HUNT 2 was conducted in 1995-97, inviting all residents ³20 years of age in Nord-Tr¿ndelag County, Norway. Self-reported questionnaires, clinical examination, and non-fasting venous blood samples were collected on 62,816 individuals (66.9% of invited).

Inter99 (Inter99)

The Inter99 study carried out in 1999-2001 included invitation of 12934 persons aged 30-60 years drawn from an age- and sex-stratified random sample of the population[55]. The baseline participation rate was 52.5%, and the study included 6784 persons. The Inter99 study was a population-based randomized controlled trial (CT00289237, ClinicalTrials.gov) and investigated the effects of lifestyle intervention on CVD. Here 5827 participants with information on lipids and exome chip were analysed.

The Mount Sinai BioMeBiobank (IPM BioMe-African, IPM BioMe-European, IPM BioMe-Hispanic)

The BioMeBiobank is an ongoing, prospective, hospital- and outpatient- based population research program operated by The Charles Bronfman Institute for Personalized Medicine (IPM) at Mount Sinai. BioMe has enrolled over 33,000 participants between September 2007 and December 2015. BioMe is an Electronic Medical Record (EMR)-linked biobank that integrates research data and clinical care information for consented patients at The Mount Sinai Medical Center, which serves diverse local communities of upper Manhattan with broad health disparities. IPM BioMe populations include 25% of African American ancestry (AA), 36% of Hispanic Latino ancestry (HL), 30% of white European ancestry (EA), and 9% of other ancestry. The IPM BioMe disease burden is reflective of health disparities in the local communities. BioMe operations are fully integrated in clinical care processes, including direct recruitment from clinical sites waiting areas and phlebotomy stations by dedicated BioMe recruiters independent of clinical care providers, prior to or following a clinician standard of care visit. Recruitment currently occurs at a broad spectrum of over 30 clinical care sites. Information on anthropometrics, demographics, lipid levels and use of lipid-lowering medication was derived from participants' EMR.

Jackson Heart Study (JHS)

The JHS is a large, population-based observational study evaluating the etiology of cardiovascular, renal, and respiratory diseases among African Americans residing in the three counties (Hinds, Madison, and Rankin) that make up the Jackson, Mississippi metropolitan area[56]. Data and biologic materials have been collected from 5301 participants, including a nested family cohort of 1,498 members of 264 families. The age at enrollment for the unrelated cohort was 35-84 years; the family cohort included related individuals >21 years old. Participants provided extensive medical and social history, had an array of physical and biochemical measurements and diagnostic procedures, and provided genomic DNA during a baseline examination (2000-2004) and two follow-up examinations (2005-2008 and 2009-2012). The study population is characterized by a high prevalence of diabetes, hypertension, obesity, and related disorders. Annual follow-up interviews and cohort surveillance are ongoing. 2,154

African-American individuals were genotyped using the IlluminaHumanExomeBeadChip array. Individuals that overlapped with ARIC were randomly split between the two cohorts, except individuals in a known JHS family were kept in JHS.

KooperativeGesundheitsforschung in der Region Augsburg (KORA)

The KORA Study is a series of population-based epidemiological surveys of persons living in or near the city of Augsburg, Germany[57,58]. All survey participants are residents of German nationality identified through the registration office and between 25 and 75 years old at the time of enrollment. Survey S4 was conducted between 1999 and 2001. KORA F4 is a 7-year follow up of S4. IlluminaExome Chip data is available for participants from KORA F4. Cryptically related persons have been removed as well as population outliers and non-fasting samples. The final study sample consists of 2723 persons.

Lothian Birth Cohort 1921 (LBC 1921)

The LBC1921 cohort consists of 550 relatively healthy individuals, 316 females and 234 males, assessed on cognitive and medical traits at about 79 years of age[59,60]. They were all born in 1921 and most took part in the Scottish Mental Survey of 1932. When tested, the sample had a mean age of 79.1 years (SD = 0.6). They were all Caucasian, community-dwelling, and almost all lived in the Lothian region (Edinburgh city and surrounding area) of Scotland. Genotyping was performed at the Wellcome Trust Clinical Research Facility, Edinburgh using the IlluminaHumanExomeBeadChip.

Lothian Birth Cohort 1936 (LBC1936)

The LBC1936 consists of 1091 relatively healthy individuals assessed on cognitive and medical traits at about 70 years of age[60,61]. They were all born in 1936 and most took part in the Scottish Mental Survey of 1947. At baseline the sample of 548 men and 543 women had a mean age 69.6 years (SD = 0.8). They were all Caucasian, community-dwelling, and almost all lived in the Lothian region (Edinburgh city and surrounding area) of Scotland. Genotyping was performed at the Wellcome Trust Clinical Research Facility, Edinburgh using the IlluminaHumanExomeBeadChip.

The London Life Sciences Population Study (LOLIPOP-ExomeChip)

LOLIPOP is an ongoing population based cohort study of 17,606 Indian Asian and 7,766 European men and women aged 35-75 years, recruited from the lists of 58 General Practitioners in West London, United Kingdom[62]. Participants classified as having Indian Asian ancestry reported having all four grandparents born on the Indian subcontinent. Biochemical analysis included total and HDL cholesterol and triglycerides, using standard commercial assays. Aliquots of whole blood, plasma and serum are frozen at –80℃. In the present study, 970 and 1,664 Indian Asian samples were genotyped on the IlluminaExomChip array and the IlluminaOmniExpressExome array, respectively.

The London Life Sciences Population Study (LOLIPOP-OmniExpressExome)

LOLIPOP is an ongoing population based cohort study of 17,606 Indian Asian and 7,766 European men and women aged 35-75 years, recruited from the lists of 58 General Practitioners in West London, United Kingdom[62]. Participants classified as having Indian Asian ancestry reported having all four grandparents born on the Indian subcontinent. Biochemical analysis included total and HDL cholesterol and triglycerides, using standard commercial assays. Aliquots of whole blood, plasma and serum are frozen at –80℃. In the present study, 970 and 1,664 Indian Asian samples were genotyped on the IlluminaExomChip array and the IlluminaOmniExpressExome array, respectively.

Malmo Diet and Cancer Study (MDC)

The Malmö Diet Cancer Study is an ongoing longitudinal prospective cohort study of the middle-aged population of Malmö designed to screen for dietary habits and genetic markers in order to predict incident cancers in the general population and to screen for cardiovascular risk factors and early atherosclerosis in a sub-sample[63]. 28,000 subjects living in Malmö were during 1992-1996 invited by letter to a clinical examination, food-frequency questionnaire and blood sampling. Individuals were between ages 45-70 at first screening. Self-completed questionnaires, clinical examinations, and extracts from registers are available for the years 1992-2009. A subgroup of the patients totaling less than 5,000 individuals with complete phenotype data was analyzed as one cohort in this study of plasma lipid levels.

Multi-Ethnic Study of Atherosclerosis (MESA-EA, MESA-AA, MESA-Chinese, MESA-Hispanic)

The Multi-Ethnic Study of Atherosclerosis (MESA) is a study of the characteristics of subclinical cardiovascular disease (disease detected non-invasively before it has produced clinical signs and symptoms) and the risk factors that predict progression to clinically overt cardiovascular disease or progression of the subclinical disease[64]. MESA researchers study a diverse, population-based sample of 6,814 asymptomatic men and women aged 45-84. Thirty-eight percent of the recruited participants are White, 28 percent African-American, 22 percent Hispanic, and 12 percent

Asian, predominantly of Chinese descent. 2,128 additional individuals from 594 families were recruited through MESA Family by utilizing the existing MESA framework, yielding 3,026 sibpairs divided between African Americans and Hispanic-Americans. Participants were recruited from six field centers across the United States: Wake Forest University, Columbia University, Johns Hopkins University, University of Minnesota, Northwestern University and University of California - Los Angeles. For the present analyses, we included 2490 White, 2496 African American, 2081 Hispanic and 701 Chinese participants.

Metabolic Syndrome in Men Study (METSIM)

The METSIM study aims to investigate the metabolic syndrome, type 2 diabetes, cardiovascular disease, and cardiovascular risk factors[65]. It is an ongoing study of men aged 50 to 70 years, randomly selected from the population registry of the town of Kuopio, in Eastern Finland.

Montreal Heart Institute Biobank (MHI Biobank)

The Montreal Heart Institute (MHI) Biobank is a longitudinal hospital cohort, which was initiated in 2005 with the aim to recruit 30,000 patients of the MHI for clinical and genetic research[66]. Participants are recruited from different departments within the MHI and its affiliated prevention centre. The MHI Biobank collects data by using a detailed questionnaire administered by a research nurse at baseline including demographics, personal and family medical history, diet, tobacco, medication use, as well as depression and hostility questionnaires. Blood, DNA, and plasma are collected at baseline and stored at the Beaulieu-Saucier Pharmacogenomics Centre. The patients health information is confirmed and complemented by the research nurse from the hospital's health record. The cohort's database is updated daily with patient's medical information from the hospital's electronic records including laboratory and lipid measurements and a follow-up study questionnaire is administered every four years. The questionnaire is updated every 4 years. The cohort is comprised of over 20,000 participants as of January 2016 with a median follow up period of 4.2 years. Genotyping was performed on the first 11,556 participants using the IlluminaHumanExome chip v1.1. Lipid measurements for the current project were obtained from the hospital records, by selecting the records with sampling dates that were the closest to that of the baseline questionnaire. Following clinical and genetic data cleanup procedures, 6421 patients with both lipid and genotype data were available for analysis.

MOnica Risk, Genetics, Archiving and Monograph project (MORGAM)

MORGAM is a consortium of prospective cohort studies from around Europe[67]. For this project, participants were included from the ATBC study (Finland), Augsburg-KORA (Germany), Brianza (ltaly) and PRIME cohorts Belfast (UK), Lille, Strasbourg and Tolouse (all France). A case-cohort design was used comparing incident coronary disease cases with participants randomly selected from within each study. Lipids were measured at baseline using standard approaches.

Northern Finland Birth Cohort 1986 (NFBC1986)

The NFBC1986 study includes 9432 live-born individuals with expected dates of birth between July 1st 1985 and June 30th 1986 in the provinces of Oulu and Lapland, in Finland. The University of Oulu Ethics Committee and the Ethical Committee of Northern Ostrobothnia Hospital District have approved the study. Cohort has been followed up since early pregnancy until adolescence. Growth measurements were obtained from communal child health clinics. Samples were stored at -80 ¼ C until analyzed and DNA extracted. Fasting serum total cholesterol and triglycerides were determined using an Hitachi 911 automatic analyser and commercial reagents (Roche, Mannheim, Germany). HDL- and LDL-C were also determined using the same analyzer and methods previously described (Sugiuchi J et al, 1995, ClinChem; Wieland H et al, 1983, J Lipid Res). The intra- and interassay coefficients of variation were 0.7 and 1.5% for total cholesterol, 0.5 and 3.2% for HDL-C, 1.6 and 2.6% for LDL-C, 0.9 and 2.4% for triglycerides.

Oxford BioBank (OBB)

The Oxford Biobank is a collection of 30-50 year old healthy men and women living in Oxfordshire. All participants have undergone a detailed examination at a screening visit, donated DNA and given informed consent to be re-approached. The Oxford Biobank is a resource for medical research to translate early discoveries to the benefit of patients in the future. In the present study, a total of 4442 individuals were inlcuded in the analysis (http://www.oxfordbiobank.org.uk/).

Ottawa Heart Study (Ottawa-Cases, Ottawa-Controls)

The Ottawa Heart Study is an ongoing, hospital-based study of coronary heart disease at the Ottawa Heart Institute in Ottawa, Canada. All patients at the Institute who undergo coronary artery bypass grafting, coronary artery angiography, or care for acute myocardial infarction are invited to participate in the study. Healthy elderly controls (men > 65y, women > 70y) were recruited via an extensive newspaper and television advertising campaign in the Ottawa community. Controls were carefully interviewed by a physician or nurse to ascertain that they were free of symptoms of

possible ischemic arterial disease and had no past history of cardiovascular symptoms, a positive stress test, coronary angiography demonstrating stenosis (>50%) in any artery or clinical cardiovascular events. Individuals with the same ethnic background as the cases (Caucasian) were included in this study (total sample of 1100 cases and 2361 controls). In the present study, a total of 951 cases and 2103 controls were included into analysis.

Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) / Uppsala Longitudinal Study of Adult Men (ULSAM) (PIVUS-ULSAM)

The PIVUS study started in 2001 with the primary aim to investigate the predictive power of different measurements of endothelial function and arterial compliance in a random sample of 1000 subjects aged 70 living in the community of Uppsala[68]. ULSAM is a unique, ongoing, longitudinal, epidemiologic study based on all available men, born between 1920 and 1924, in Uppsala County, Sweden[69]. The men were investigated at the ages of 50, 60, 70, 77, 82 and 88 years. Individuals investigated at age 70 were included in the current analysis. In the present study a total of 2006 samples (944 PIVUS / 1062 ULSAM) were included into analysis.

Prevalence, Prediction and Prevention of Diabetes (PPP)-Botnia study

The Prevalence, Prediction and Prevention of diabetes (PPP)–Botnia Study is a population-based study in Western Finland carried out from 2004 to 2008 to obtain accurate estimates of prevalence and risk factors for type 2 diabetes, impaired glucose tolerance, impaired fasting glucose and the metabolic syndrome in the adult population and to use this information for prediction and prevention of the disease[70]. The participants were randomly recruited from the national Finnish Population Registry to represent 6 to 7% of the population in the 18- to 75-year age range. Altogether 5,208 individuals participated in the study (54.7% of those invited).

PROCARDIS (Procardis Cases, Procardis Controls)

The PROCARDIS Study is a an ongoing study of coronary heart disease at multiple centers in Europe (the universities of Oxford and Münster; the Karolinska Institute; the Mario Negri Institute; DigilabBioVisioN GmbH; Centre National de Genotypage; Institut de Recerca del Hospital de la Santa Creu I Sant Pau; UniversitàdegliStudi di Milano; Clinical Gene Networks AB; CF consulting S.r.l.; Metabometrix Limited) and AstraZeneca[71]. Families with members with patients with myocardial infarction or symptomatic acute coronary syndrome occurring before the age

of 65 as evidenced by typical clinical symptoms, EKG findings, and biomarker elevation were selected. The study aims to identify new susceptibility genes of coronary artery disease through a genome-wide screen.

Pakistan Risk of Myocardial Infarction Study (PROMIS_Cases, PROMIS_Controls)

PROMIS is a retrospective case-control study of first-ever confirmed acute MI in Pakistan[72]. Patients aged 30-80 years who were admitted to the emergency rooms of nine recruitment centres across Pakistan were eligible for inclusion as cases on the basis of symptoms, ECG and troponin levels. Controls were hospital based and frequency-matched to cases on age (within 5 year age bands) and sex, and without a self-reported history of cardiovascular disease. Nonfasting blood samples were drawn from each participant and centrifuged within 45 minutes of venepuncture. Serum samples were stored at -80℃. Total cholesterol, HDL-C, and triglyceride concentrations were measured using enzymatic methods (Roche Diagnostics, USA) at the Center for Non-Communicable Diseases, Pakistan.

Prospective Study of Pravastatin in the Elderly at Risk clinical trial (PROSPER)

PROSPER was a controlled, randomised study involving 2,804 men and 3,000 women aged 70-82, with a history of, or risk factors for cardiovascular disease[73]. Participants were randomised to either 40mg pravastatin per day or matching placebo. A nested case-control design was used for this study, selecting as cases individuals who self-reported a history of coronary disease at baseline or who had a coronary event during follow-up. Controls were participants who were free of cardiovascular disease at baseline and at the end of follow-up, frequency matched to the cases for sex and age (in 5-year bands). Baseline lipid levels were measured using standard assays at the Department of Pathological Biochemistry at the Glasgow Royal Infirmary.

SardiNIA study on aging (SardiNIA)

The SardiNIA study is a longitudinal, population-based study that includes 6,921 individuals, representing >60% of the adult population of 4 villages in the Lanusei valley on Sardinia (Italy)[74]. These individuals are clustered in 1,257 multigenerational families, up to 5 generations deep, and have been characterized for hundreds of quantitative traits. All participants gave informed consent to study protocols, which were approved by the Sardinian local research ethic committees: ComitatoEtico di Azienda Sanitaria Locale 8, Lanusei (2009/0016600) and ComitatoEtico di Azienda Sanitaria Locale 1, Sassari (2171/CE)) and by the NIH Office of Human Subject Research as governed by Italian institutional review board approval.

Steno Diabetes Center (SDC)

Patients with T2D (above 18 years of age) were recruited from the outpatient clinic at Steno Diabetes Center, Gentofte, Denmark[75]. Anthropometrics and basal fasting biochemistry (e.g. plasma glucose, serum insulin, HbA1C and lipids) have been measured. Here 499 T2D cases with information on lipids and exome chip were analysed.

Twins UK (TwinsUK)

The TwinsUK cohort is an adult twin British registry recruited from the general population in the United Kingdom[76]. In the present study, a total of 923 individuals were included into analysis.

VejleBiobank - T2D cases and Controls (VejleCases, VejleControls)

VejleBiobank is a sample of clinical-onset T2D patients, and non-diabetic control individuals with matched age and gender distribution, examined at Vejle Hospital during a three year period[75]. Control individuals were non-diabetic by self-report and according to fasting plasma glucose levels. The main objectives of the study were to investigate the development of late diabetic complications and lack of treatment effect. Anthropometrics, including body fat percentage, basal fasting biochemistry (e.g. plasma glucose, serum insulin, HbA1C and lipids), detailed biochemistry (e.g. measures of kidney function and serum CRP) have been assessed and questionnaires regarding lifestyle, health, diabetic complications and use of anti-diabetic medication filled out. Here 1879 T2D cases and 424 T2D controls with information on lipids and exome chip were analysed.

Women's Genome Health Study (WGHS)

The Women's Genome Health Study (WGHS) is a prospective cohort of initially healthy, female North American health care professionals at least 45 years old at baseline representing participants in the Women's Health Study (WHS) who provided a blood sample at baseline and consent for blood-based analyses[77]. The WHS was a 2x2 trial beginning in 1992-1994 of vitamin E and low dose aspirin in prevention of cancer and cardiovascular disease with about 10 years of follow-up. Since the end of the trial, follow-up has continued in observational mode.

Women's Health Initiative (WHI-EA, WHI-AA)

The WHI is one of the largest (n = 161,808) US studies of women's health. This project was approved by the ethics committee at the Fred Hutchinson Cancer Research Center. The WHI consists of 2 main components: (i) a clinical trial that enrolled 68,132 post-menopausal women aged 50–79 years and randomized them to 1 of 3 placebo-controlled clinical trials of hormone therapy, dietary modification or supplementation with calcium and vitamin D and (ii) an observational study that enrolled 93,676 women of the same age range in a parallel prospective study[78].

West of Scotland Coronary Prevention Study (WOSCOPS)

WOSCOPS was a controlled, randomised study involving 6,595 men aged 45-64, with elevated LDL cholesterol but no history of myocardial infarction[79]. Participants were randomised to either 40mg pravastatin per day or matching placebo. A nested case-control design was used for this study, selecting as cases individuals who had a coronary event during follow-up. Controls were participants who were free of cardiovascular disease at baseline and at the end of follow-up, frequency matched to the cases on age (in 5-year bands). Baseline lipid levels were measured using enzymatic cholesterol and triglyceride assays at the Department of Pathological Biochemistry at the Glasgow Royal Infirmary.

II. Disclosures

Nothing to disclose

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Supplementary Tables

Supplementary Table 1. Coverage of exome array for coding variants present in ExAC

	Polymorphic variants on Asian exome array		Comparison to ExAC sequenced Asian samples			
Variant type	MAF in exome array	Number of variants genotyped by exome array	MAF in ExAC Asian	Number of variants identified by ExAC	Number of variants identified by exome array	Percentage
LoF	< 0.01%	2317	1 copy	11139	468	4.20%
	0.01%~0.1%	863	2 copy~0.1%	3530	520	14.73%
	0.1%~1%	505	0.1%~1%	1161	567	48.84%
	1%~5%	117	1%~5%	232	123	53.02%
	5%~50%	150	5%~50%	280	145	51.79%
Missense	< 0.01%	71212	1 copy	263400	17097	6.49%
	0.01%~0.1%	39693	2 copy~0.1%	116045	23300	20.08%
	0.1%~1%	22988	0.1%~1%	40855	24605	60.23%
	1%~5%	6433	1%~5%	9627	7034	73.07%
	5%~50%	11288	5%~50%	16725	11954	71.47%
LoF+Missense	< 0.01%	73529	1 copy	274539	17565	6.40%
	0.01%~0.1%	40556	2 copy~0.1%	119575	23820	19.92%
	0.1%~1%	23493	0.1%~1%	42016	25172	59.91%
	1%~5%	6550	1%~5%	9859	7157	72.59%
	5%~50%	11438	5%~50%	17005	12099	71.15%

LoF: Loss of function. LoF is defined as stop-gain, stop-loss, or splice site changes.

Supplementary Table 2. Association results at 7 previously known loci reaching suggestive significance ($P < 4.46 \times 10^{-6}$, 0.05/11,215)

Gene	Position	rsID	Alleles	Variant	ALT.FREQ	trait	Effect	*P*	N
GALNT2	1:230294916	rs2144300	T/C		0.19	HDL	0.04(0.008)	2.16E-06	47456
CCHCR1	6:31116210	rs130071	A/G	p.Leu482Leu	0.09	TG	0.068(0.014)	6.10E-07	35389
HLA-DRA	6:32398648	rs3129853	A/G		0.17	TG	0.043(0.009)	3.84E-06	43728
MIR148A	7:25997536	rs4719841	G/A		0.63	LDL	-0.033(0.007)	1.98E-06	44985
ZNF335	20:44601293	rs16990971	G/A		0.06	TG	0.082(0.017)	1.78E-06	28538
UBE2L3	22:21928641	rs181359	A/G		0.51	HDL	-0.033(0.007)	8.10E-07	45989
PNPLA3	22:44324727	rs738409	G/C	p.Ile148Met	0.36	TG	-0.039(0.008)	7.53E-07	35920

ALT.FREQ, alternative allele frequency.
Position is reported in human genome build hg19.
Alleles are listed as alternative / reference allele on the forward strand of the reference genome.
There are 11,215 polymorphic variants within 500k from the known loci where novariants did reach exome-wide significance with lipid traits.

Supplementary Table 4. Association results of multiple independent variants in 12 loci identified by sequential conditional analysis

Gene	Trait	rsID	chrpos.hg19	Allele	Variant	ALT.FREQ	Effect	*P*	N	index	chrpos.hg19.index	r^2
APOB	LDL	rs13306194	2:21252534	A/G	p.Arg532Trp	0.12	-0.098(0.01)	9.53E-22	44985	rs1367117	2:21263900	0.016
		rs376825639	2:21228437	G/A	p.Ile3768Thr	0.0015	-0.579(0.098)	3.35E-09	34108			0.001
	TC	rs13306194	2:21252534	A/G	p.Arg532Trp	0.12	-0.114(0.01)	1.45E-29	46025			0.016
		rs376825639	2:21228437	G/A	p.Ile3768Thr	0.0015	-0.659(0.097)	8.44E-12	36514			0.001
HMGCR	LDL	rs3846663	5:74655726	T/C		0.52	0.07(0.007)	2.60E-25	44985	rs12916	5:74656539	1.000
		rs191835914	5:74646765	C/A	p.Tyr311Ser	0.02	-0.19(0.026)	2.20E-13	43617			0.018
LPL	HDL	rs10096633	8:19830921	T/C		0.09	0.165(0.011)	5.78E-47	47456	rs12678919	8:19844222	0.970
		rs13702	8:19824492	C/T		0.19	0.116(0.009)	4.15E-42	47456			0.427
ABCA1	HDL	rs1883025	9:107664301	T/C		0.23	-0.08(0.008)	1.23E-23	45804	rs1883025	9:107664301	1.000
		rs2066714	9:107586753	C/T	p.Ile883Met	0.71	0.052(0.007)	1.41E-12	47456			0.014
		rs2230808	9:107562804	C/T	p.Lys1587Arg	0.61	0.047(0.007)	2.49E-12	47456			0.003
APOA5	HDL	rs2075291	11:116661392	A/C	p.Gly185Cys	0.06	-0.288(0.014)	3.91E-91	47456	rs964184	11:116648917	0.018
		rs2266788	11:116660686	A/G		0.78	0.106(0.008)	5.07E-40	47456			0.976
		rs180327	11:116623659	T/C		0.66	0.1(0.009)	3.45E-31	30661			0.543
		rs12718465	11:116707736	T/C	p.Ala61Thr	0.03	-0.116(0.019)	5.50E-10	45989			0.007
	TG	rs651821	11:116662579	T/C		0.73	-0.285(0.009)	3.42E-198	28538			0.692
		rs2266788	11:116660686	A/G		0.78	-0.209(0.008)	5.40E-139	43728			0.976
		rs2075291	11:116661392	A/C	p.Gly185Cys	0.06	0.363(0.015)	1.12E-131	43728			0.018
		rs180327	11:116623659	T/C		0.66	-0.178(0.009)	3.10E-88	28538			0.543
		rs7123454	11:116704178	A/C		0.63	-0.107(0.012)	2.73E-19	15933			0.095
ACACB	TG	rs2075260	12:109696838	A/G	p.Val2141Ile	0.74	0.043(0.008)	3.95E-08	43728	rs7134594	12:110000193	0.010
LIPC	HDL	rs2043085	15:58680954	C/T		0.53	-0.1(0.007)	8.98E-52	47456	rs1532085	15:58683366	0.967
		rs1800588	15:58723675	T/C		0.39	0.095(0.007)	1.70E-38	39648			0.004
	TC	rs1532085	15:58683366	G/A		0.54	-0.047(0.007)	1.58E-12	46025			1.000
		rs1800588	15:58723675	T/C		0.39	0.047(0.007)	3.12E-10	38217			0.004
	TG	rs1800588	15:58723675	T/C		0.39	0.066(0.008)	7.62E-18	35920			0.004
		rs1532085	15:58683366	G/A		0.54	-0.051(0.007)	1.39E-13	43728			1.000

CETP	HDL	rs247616	16:56989590	T/C		0.16	0.235(0.009)	1.66E-156	47456	rs3764261	16:56993324	0.992
		rs2303790	16:57017292	G/A	p.Asp459Gly	0.02	0.407(0.025)	7.53E-62	38181			0.044
		rs7499892	16:57006590	T/C		0.16	-0.162(0.01)	7.20E-61	38539			0.034
		rs201790757	16:56997025	G/T	p.Tyr74*	0	1.117(0.182)	8.97E-10	47456			0.000
	TC	rs247616	16:56989590	T/C		0.16	0.065(0.009)	2.65E-13	46025			0.992
		rs7499892	16:57006590	T/C		0.16	-0.066(0.01)	2.24E-11	38574			0.034
PKD1L3	TC	rs7185272	16:72013797	C/G	p.Thr429Ser	0.74	0.054(0.008)	1.65E-12	45494	rs2000999	16:72108093	0.031
		rs17358402	16:71967927	T/C	p.Arg1572His	0.05	0.088(0.015)	1.96E-09	46025			0.002
	LDL	rs7185272	16:72013797	C/G	p.Thr429Ser	0.74	0.059(0.008)	4.87E-14	43086			0.031
		rs17358402	16:71967927	T/C	p.Arg1572His	0.05	0.088(0.015)	2.11E-08	43617			0.002
LIPG	HDL	rs4939883	18:47167214	C/T		0.82	0.064(0.009)	1.23E-13	45989	rs7241918	18:47160953	0.595
		rs2000813	18:47093864	T/C	p.Thr111Ile	0.31	0.043(0.007)	1.04E-09	47456			0.008
APOE	HDL	rs769449	19:45410002	A/G		0.09	-0.108(0.012)	2.48E-19	44817	rs4420638	19:45422946	0.617
		rs7412	19:45412079	T/C	p.Arg176Cys	0.09	0.104(0.016)	3.95E-11	25746			0.008
	LDL	rs445925	19:45415640	A/G		0.09	-0.408(0.012)	1.12E-275	44985			0.006
		rs7412	19:45412079	T/C	p.Arg176Cys	0.09	-0.472(0.016)	4.87E-197	25730			0.008
		rs769449	19:45410002	A/G		0.09	0.14(0.012)	4.36E-30	42445			0.617
		rs4420638	19:45422946	G/A		0.12	0.085(0.015)	3.27E-08	20114			1.000
	TC	rs445925	19:45415640	A/G		0.09	-0.246(0.011)	2.39E-103	46025			0.006
		rs7412	19:45412079	T/C	p.Arg176Cys	0.09	-0.281(0.016)	1.46E-71	25904			0.008
		rs2075650	19:45395619	G/A		0.09	0.116(0.011)	1.82E-24	46025			0.489
	TG	rs439401	19:45414451	C/T		0.43	0.069(0.007)	2.18E-23	43728			0.146
		rs445925	19:45415640	A/G		0.09	0.115(0.012)	9.53E-23	43728			0.006
		rs769449	19:45410002	A/G		0.09	0.103(0.012)	4.32E-17	42556			0.617
		rs4420638	19:45422946	G/A		0.12	0.081(0.015)	1.57E-07	19977			1.000
LDLR	LDL	rs200990725	19:11217315	T/C	p.Arg257Trp	0	0.882(0.109)	6.35E-16	44985	rs6511720	19:11202306	0.000
		rs11557092	19:11257018	C/T		0.75	0.06(0.008)	9.65E-15	44985			0.003
	TC	rs11557092	19:11257018	C/T		0.75	0.051(0.008)	3.18E-11	46025			0.003
		rs200990725	19:11217315	T/C	p.Arg257Trp	0	0.677(0.109)	5.57E-10	46025			0.000

ALT.FREQ, alternative allele frequency. Position is reported in human genome build hg19.
Alleles are listed as alternative / reference allele on the forward strand of the reference genome.

Supplementary Table 5. Genes with a Burden of Rare or Low-Frequency Variants Significantly Associated with lipid levels

Gene	Trait	N	*P*	No. of variants	beta	se	Best tests	Coding variants
PCSK9	LDL	44985	2.60E-83	16	-0.374	0.024	SKAT,0.05	1:55505647/G/T,1:55509585/C/T,1:55517953/G/A,1:55518085/G/T,1:55518371/G/A,1:55518419/G/A,1:55521713/C/A,1:55523178/C/A,1:55523802/A/G,1:55523855/G/A,1:55524222/C/T,1:55524237/G/A,1:55524309/G/A,1:55525301/G/A,1:55527093/C/T,1:55529108/G/A
	TC	46025	2.79E-76	15	-0.345	0.024	SKAT,0.05	1:55505647/G/T,1:55509585/C/T,1:55517953/G/A,1:55518085/G/T,1:55518371/G/A,1:55518419/G/A,1:55521713/C/A,1:55523178/C/A,1:55523855/G/A,1:55524222/C/T,1:55524237/G/A,1:55524309/G/A,1:55525301/G/A,1:55527093/C/T,1:55529108/G/A
EVI5	TC	46025	3.32E-08	21	0.157	0.028	GRANVIL,0.01	1:92979254/G/A,1:92979520/C/T,1:93089742/C/G,1:93089862/C/G,1:93089890/C/T,1:93089891/G/A,1:93101886/C/G,1:93131510/C/T,1:93131543/G/A,1:93142746/G/A,1:93159398/G/T,1:93159438/G/C,1:93159450/G/C,1:93159927/G/A,1:93160880/A/G,1:93160892/C/T,1:93163431/C/T,1:93163436/T/C,1:93163460/G/A,1:93167754/G/A,1:93201961/T/C
	LDL	44985	1.37E-07	22	0.146	0.029	SKAT,0.01	1:92979254/G/A,1:92979520/C/T,1:93070892/C/T,1:93089742/C/G,1:93089862/C/G,1:93089890/C/T,1:93089891/G/A,1:93101886/C/G,1:93131510/C/T,1:93131543/G/A,1:93142746/G/A,1:93159398/G/T,1:93159438/G/C,1:93159450/G/C,1:93159927/G/A,1:93160880/A/G,1:93160892/C/T,1:93163431/C/T,1:93163436/T/C,1:93163460/G/A,1:93167754/G/A,1:93201961/T/C
HMGCR	LDL	44985	3.47E-13	2	-0.184	0.026	SKAT,0.05	5:74646765/A/C,5:74652199/A/G
	TC	46025	2.80E-10	2	-0.156	0.025	SKAT,0.05	5:74646765/A/C,5:74652199/A/G

CD36	HDL	47456	5.17E-12	29	0.162	0.026	SKAT,0.01	7:80276061/G/T,7:80276070/G/T,7:80276111/C/A,7:80285955/C/T,7:80286003/C/T,7:80286010/C/T,7:80290384/G/A,7:80290467/C/A,7:80290477/C/T,7:80290500/T/C,7:80290507/T/C,7:80290509/C/T,7:80292305/G/C,7:80292414/T/C,7:80292423/A/T,7:80292448/C/T,7:80295802/A/G,7:80295807/T/C,7:80299280/T/C,7:80300449/T/G,7:80301244/C/T,7:80301276/G/T,7:80301310/T/G,7:80302093/G/T,7:80302102/T/G,7:80302104/C/T,7:80302116/C/T,7:80302123/A/T,7:80303453/C/T
APOA1	HDL	47456	6.72E-10	2	-0.114	0.018	GRANVIL,0.05	11:116707044/A/T,11:116707736/C/T
PCSK7	TG	43728	3.81E-7	12	0.053	0.012	SKAT,0.05	11:117076939/C/T,11:117076940/G/A,11:117077009/A/C,11:117089205/C/T,11:117090309/G/A,11:117094001/T/G,11:117097932/G/A,11:117098967/C/T,11:117100134/C/A,11:117100257/C/T,11:117100340/G/A,11:117100550/C/T
CETP	HDL	47456	1.60E-75	10	0.205	0.019	SKAT,0.05	16:56997025/T/G,16:57005908/C/A,16:57007387/C/T,16:57012012/G/A,16:57012039/G/A,16:57012094/A/G,16:57015076/G/A,16:57015091/G/C,16:57016086/G/A,16:57017292/A/G
	TC	46025	9.15E-13	10	0.042	0.019	SKAT,0.05	16:56997025/T/G,16:57005908/C/A,16:57007387/C/T,16:57012012/G/A,16:57012039/G/A,16:57012094/A/G,16:57015076/G/A,16:57015091/G/C,16:57016086/G/A,16:57017292/A/G

LDLR	LDL	44985	5.35E-11	16	0.502	0.074	VT,0.05	19:11213441/G/A,19:11213450/G/A,19:11213462/C/T,19:11215926/G/A,19:11216275/C/A,19:11217303/C/T,19:11217315/C/T,19:11218079/G/A,19:11221357/G/A,19:11221411/G/A,19:11222300/G/A,19:11223991/G/C,19:11230789/A/G,19:11231112/C/T,19:11233940/G/A,19:11238731/G/A,19:11240240/G/A,19:11241988/C/T
	TC	46025	1.04E-7	16	0.411	0.073	VT,0.01	19:11213441/G/A,19:11213450/G/A,19:11213462/C/T,19:11215926/G/A,19:11216275/C/A,19:11217303/C/T,19:11217315/C/T,19:11218079/G/A,19:11221357/G/A,19:11221411/G/A,19:11222300/G/A,19:11223991/G/C,19:11230789/A/G,19:11231112/C/T,19:11233940/G/A,19:11238731/G/A,19:11240240/G/A,19:11241988/C/T
PPARA	TG	43728	2.27E-07	6	-0.088	0.018	SKAT,0.05	22:46611114/G/A,22:46615880/T/C,22:46627735/C/T,22:46627780/C/T,22:46631108/A/T,22:46631206/A/C

Supplementary Table 6. Association results for all significant coding variants at previously mapped GWAS loci

GENE	Position	rsID	Allele	Variant	ALT.FREQ	Trait	Effect	*P*	N
PCSK9	1:55509585	rs151193009	T/C	p.Arg93Cys	0.0132	LDL	-0.542(0.029)	7.62E-77	44985
					0.0134	TC	-0.508(0.029)	3.96E-70	46025
EVI5	1:93159927	rs117711462	A/G	p.Arg354Cys	0.0069	TC	0.212(0.04)	1.41E-07	46025
					0.0067	LDL	0.21(0.041)	3.23E-07	44985
APOB	2:21225281	rs1042034	T/C	p.Ser4338Asn	0.2651	TC	-0.053(0.008)	3.40E-12	46025
					0.2659	LDL	-0.041(0.008)	9.75E-08	44985
	2:21228437	rs376825639	G/A	p.Ile3768Thr	0.0015	TC	-0.659(0.097)	8.44E-12	36514
					0.0015	LDL	-0.579(0.098)	3.35E-09	34108
	2:21231524	rs676210	A/G	p.Pro2739Leu	0.7327	TC	0.049(0.008)	2.00E-09	38217
	2:21252534	rs13306194	A/G	p.Arg532Trp	0.1243	TG	-0.073(0.01)	1.38E-12	43728
					0.1239	TC	-0.114(0.01)	1.45E-29	46025
					0.1245	LDL	-0.098(0.01)	9.53E-22	44985
	2:21252807	noRS	T/C	p.Cys478Tyr	9.00E-04	LDL	-0.772(0.141)	4.19E-08	28290
					9.00E-04	TC	-0.876(0.138)	2.08E-10	30697
	2:21263900	rs1367117	A/G	p.Thr98Ile	0.1296	TC	0.064(0.01)	8.96E-11	46025
					0.1301	LDL	0.063(0.01)	4.26E-10	43617
GTF3C2	2:27559188	rs76217877	C/G	p.Ala411Gly	0.0526	TG	-0.083(0.015)	5.68E-08	43728
GCKR	2:27730940	rs1260326	C/T	p.Leu446Pro	0.4957	TG	-0.114(0.007)	1.26E-62	43728
					0.4939	TC	-0.047(0.007)	1.70E-12	46025
C2orf16	2:27801759	rs1919128	G/A	p.Ile774Val	0.4768	TG	0.077(0.007)	1.34E-29	43728
					0.4773	TC	0.034(0.007)	2.97E-07	46025
GPN1	2:27851918	rs3749147	A/G	p.Arg12Lys	0.2935	TG	0.071(0.009)	7.87E-17	33583
ANKRD31	5:74400516	rs56174528	C/G	p.Thr1566Arg	0.1276	TC	0.059(0.01)	3.01E-09	46025
					0.1277	LDL	0.065(0.01)	2.55E-10	43617
	5:74442964	rs6893216	C/T	p.Arg758Gly	0.152	LDL	0.056(0.01)	6.73E-08	35811
	5:74443132	rs1422698	T/C	p.Asp702Asn	0.4505	LDL	0.035(0.007)	2.23E-07	44985
HMGCR	5:74646765	rs191835914	C/A	p.Tyr311Ser	0.0174	TC	-0.16(0.025)	2.00E-10	46025
					0.0173	LDL	-0.19(0.026)	2.20E-13	43617

MLXIPL	7:73012042	rs35332062	A/G	p.Ala358Val	0.1094	TG	-0.109(0.011)	2.03E-23	43728
	7:73020337	rs3812316	G/C	p.Gln241His	0.1001	TG	-0.105(0.013)	2.16E-15	32630
CD36	7:80302116	rs148910227	T/C	p.Arg386Trp	0.0031	HDL	0.342(0.058)	3.17E-09	47456
NAT2	8:18258103	rs1799930	A/G	p.Arg197Gln	0.2535	TG	-0.044(0.008)	1.30E-08	43728
LPL	8:19819724	rs328	G/C	p.Ser474*	0.0912	HDL	0.162(0.012)	7.55E-44	45989
					0.0915	TG	-0.169(0.012)	1.93E-45	43728
ABCA1	9:107562804	rs2230808	C/T	p.Lys1587Arg	0.6097	HDL	0.047(0.007)	2.49E-12	47456
	9:107586753	rs2066714	C/T	p.Ile883Met	0.7124	TC	0.041(0.007)	3.72E-08	46025
					0.7123	HDL	0.052(0.007)	1.41E-12	47456
ABO	9:136131651	rs1053878	A/G	p.Pro156Leu	0.19	TC	0.065(0.009)	4.22E-14	46025
					0.19	LDL	0.066(0.009)	5.07E-14	44985
GPAM	10:113940329	rs2792751	C/T	p.Ile43Val	0.7064	HDL	-0.049(0.007)	7.14E-12	47456
					0.7064	TC	-0.043(0.007)	5.67E-09	46025
BUD13	11:116633947	rs10488698	A/G	p.Arg120Cys	0.082	HDL	0.095(0.012)	2.14E-15	47456
					0.0818	TG	-0.095(0.012)	2.59E-14	43728
APOA5	11:116661392	rs2075291	A/C	p.Gly185Cys	0.0556	TG	0.363(0.015)	1.12E-131	43728
					0.0558	HDL	-0.288(0.014)	3.91E-91	47456
APOA4	11:116692334	rs5104	T/C	p.Ser147Asn	0.6728	HDL	0.044(0.007)	2.79E-10	47456
					0.6727	TG	-0.121(0.007)	8.24E-61	43728
APOA1	11:116707736	rs12718465	T/C	p.Ala61Thr	0.0327	HDL	-0.116(0.019)	5.50E-10	45989
PAFAH1B2	11:117042377	rs4936367	A/G	p.Val151Met	0.5048	TG	-0.056(0.007)	5.60E-16	43728
PCSK7	11:117100257	rs11542139	T/C	p.Ala102Thr	0.045	TG	0.108(0.017)	9.85E-11	42556
ACACB	12:109696838	rs2075260	A/G	p.Val2141Ile	0.7434	TG	0.043(0.008)	3.95E-08	43728
MMAB	12:109994870	rs9593	T/A	p.Met239Lys	0.304	HDL	0.037(0.007)	2.92E-07	45989
ALDH2	12:112241766	rs671	A/G	p.Glu457Lys	0.2043	HDL	-0.048(0.008)	1.16E-08	47456
HNF1A	12:121416650	rs1169288	C/A	p.Ile27Leu	0.4036	TC	0.038(0.007)	4.86E-08	43531
CETP	16:56997025	rs201790757	G/T	p.Tyr74*	3.00E-04	HDL	1.117(0.182)	8.97E-10	47456
	16:57016092	rs5882	A/G	p.Val362Ile	0.5426	HDL	-0.055(0.007)	6.49E-17	47456
	16:57017292	rs2303790	G/A	p.Asp459Gly	0.0223	HDL	0.407(0.025)	7.53E-62	38181
					0.0222	TC	0.145(0.025)	3.34E-09	38217
SLC12A4	16:67997920	rs3785100	C/T	p.Glu4Gly	0.1098	HDL	0.059(0.011)	5.13E-08	44817

PKD1L3	16:71967927	rs17358402	T/C	p.Arg1572His	0.05411	TC	0.088(0.015)	1.96E-09	46025
					0.05405	LDL	0.085(0.015)	2.11E-08	43617
	16:72011181	rs1559401	T/G	p.His571Gln	0.7374	LDL	0.058(0.008)	3.66E-14	44985
					0.7386	TC	0.052(0.008)	4.54E-12	46025
	16:72013797	rs7185272	C/G	p.Thr429Ser	0.7392	LDL	0.059(0.008)	4.87E-14	43086
					0.7398	TC	0.054(0.008)	1.65E-12	45494
PMFBP1	16:72156842	rs16973716	G/T	p.Lys768Asn	0.2896	TC	0.042(0.008)	1.75E-07	38217
LIPG	18:47093864	rs2000813	T/C	p.Thr111Ile	0.3106	HDL	0.043(0.007)	1.04E-09	47456
LDLR	19:11217315	rs200990725	T/C	p.Arg257Trp	9.00E-04	TC	0.677(0.109)	5.57E-10	46025
					9.00E-04	LDL	0.882(0.109)	6.35E-16	44985
SPC24	19:11257018	rs11557092	C/T	p.Lys175Arg	0.7483	LDL	0.06(0.008)	9.65E-15	44985
					0.7478	TC	0.051(0.008)	3.18E-11	46025
TM6SF2	19:19379549	rs58542926	T/C	p.Glu167Lys	0.0695	TG	-0.094(0.013)	2.09E-12	43728
					0.06918	TC	-0.066(0.013)	4.25E-07	46025
BCAM	19:45322744	rs1135062	G/A	p.Thr539Ala	0.1091	LDL	-0.056(0.011)	2.19E-07	44985
APOE	19:45412079	rs7412	T/C	p.Arg176Cys	0.0882	TC	-0.281(0.016)	1.46E-71	25904
					0.0882	TG	0.091(0.016)	7.32E-09	25722
					0.0882	LDL	-0.472(0.016)	4.87E-197	25730
					0.0883	HDL	0.104(0.016)	3.95E-11	25746
PPARA	22:46615880	rs1800234	C/T	p.Val227Ala	0.0421	TG	-0.094(0.018)	3.17E-07	35920

ALT.FREQ, alternative allele frequency.
Position is reported in human genome build hg19.
Alleles are listed as alternative / reference allele on the forward strand of the reference genome.

Supplementary Table 7. Protein-altering variants are either the top signals, explain the signal or are independent of the original association signals

	Index variants						Protein-altering variants							r^2
Trait	Locus	rsID	CHR_POS	MAF	*P*	P.adjcoding	GENE	rsID	CHR_POS	Variants	MAF	*P*	P.adjindex	
Protein-altering variants are the top signals														
LDL	*PCSK9*	rs2479409	1:55504650	32.66%	6.35E-01	3.12E-01	*PCSK9*	rs151193009	1:55509585	p.Arg93Cys	1.32%	7.62E-77	2.59E-75	0.006
TC	*EVI5*	rs7515577	1:93009438	4.31%	2.49E-02	3.23E-02	*EVI5*	rs117711462	1:93159927	p.Arg354Cys	0.69%	1.41E-07	2.35E-07	0.000
HDL	*CD36*	rs3211938	7:80300449	0.00%	8.69E-01	8.69E-01	*CD36*	rs148910227	7:80302116	p.Arg386Trp	0.31%	3.17E-09	3.60E-09	0.000
HDL	*MVK*	rs7134594	12:110000193	30.33%	6.99E-07	7.32E-01	*MMAB*	rs9593	12:109994870	p.Met239Lys	30.42%	2.92E-07	8.00E-01	0.993
HDL	*BRAP*	rs11065987	12:112072424	0.3%	9.00E-01	9.83E-01	*ALDH2*	rs671	12:112241766	p.Glu457Lys	20.43%	1.16E-08	1.80E-08	0.001
HDL	*LCAT*	rs16942887	16:67928042	3.01%	7.02E-02	3.00E-01	*SLC12A4*	rs3785100	16:67997920	p.Glu4Gly	10.98%	5.13E-08	3.01E-07	0.266
LDL	*LDLR*	rs6511720	19:11202306	0.98%	4.19E-05	4.78E-05	*LDLR*	rs200990725	19:11217315	p.Arg257Trp	0.09%	6.35E-16	8.05E-16	0.000
TG	*PPARA*	rs4253772	22:46627603	0.18%	7.24E-01	7.01E-01	*PPARA*	rs1800234	22:46615880	p.Val227Ala	4.21%	3.17E-07	3.16E-07	0.000
TG	*GCKR*	rs1260326	2:27730940	49.57%	1.26E-62	1.00E+00	*GCKR*	rs1260326	2:27730940	p.Leu446Pro	49.57%	1.26E-62	1.00E+00	1.000
TG	*MLXIPL*	rs17145738	7:72982874	10.85%	7.05E-23	9.18E-01	*MLXIPL*	rs35332062	7:73012042	p.Ala358Val	10.94%	2.03E-23	1.23E-01	0.977
TC	*HNF1A*	rs1169288	12:121416650	40.36%	4.86E-08	1.00E+00	*HNF1A*	rs1169288	12:121416650	p.Ile27Leu	40.36%	4.86E-08	1.00E+00	1.000
TG	*TM6SF2*	rs10401969	19:19407718	9.00%	3.15E-10	3.34E-01	*TM6SF2*	rs58542926	19:19379549	p.Glu167Lys	7.00%	2.09E-12	1.87E-03	0.677
Protein-altering variants explain the original signals														
TG	*LPL*	rs12678919	8:19844222	9.07%	2.18E-45	1.94E-01	*LPL*	rs328	8:19819724	p.Ser474*	9.15%	1.93E-45	2.13E-01	0.964
LDL	*ABO*	rs635634	9:136155000	21%	3.11E-15	1.22E-02	*ABO*	rs1053878	9:136131651	p.Pro156Leu	18.56%	5.07E-14	3.94E-01	0.801
TC	*GPAM*	rs2255141	10:113933886	29.49%	5.33E-09	7.15E-01	*GPAM*	rs2792751	10:113940329	p.Ile43Val	29.36%	5.67E-09	8.95E-01	0.990
TC	*HPR*	rs2000999	16:72108093	25.88%	1.12E-08	2.54E-01	*PMFBP1*	rs16973716	16:72156842	p.Lys768Asn	28.96%	1.75E-07	6.59E-02	0.748
Protein-altering variants are independent of original signals														
LDL	*APOB*	rs1367117	2:21263900	13.01%	4.26E-10	3.18E-07	*APOB*	rs13306194	2:21252534	p.Arg532Trp	12.45%	9.53E-22	1.20E-18	0.016
						1.20E-09	*APOB*	rs376825639	2:21228437	p.Ile3768Thr	0.15%	3.35E-09	6.62E-09	0.001
						9.44E-10	*APOB*	noRS	2:21252807	p.Cys478Tyr	0.09%	4.19E-08	6.26E-08	0.000
TC	*HMGCR*	rs3846663	5:74655726	52.48%	1.26E-23	9.79E-20	*HMGCR*	rs191835914	5:74646765	p.Tyr311Ser	1.74%	2.00E-10	5.17E-07	0.018
HDL	*ABCA1*	rs1883025	9:107664301	22.84%	1.23E-23	1.03E-23	*ABCA1*	rs2230808	9:107562804	p.Lys1587Arg	39.03%	2.49E-12	8.09E-12	0.003
						8.85E-21	*ABCA1*	rs2066714	9:107586753	p.Ile883Met	28.77%	1.41E-12	1.84E-09	0.014
HDL	*APOA1*	rs964184	11:116648917	22.00%	7.63E-39	4.63E-55	*APOA5*	rs2075291	11:116661392	p.Gly185Cys	5.56%	3.91E-91	1.97E-106	0.018

						8.61E-41	*APOA1*	rs12718465	11:116707736	p.Ala61Thr	3.27%	5.50E-10	8.95E-13	0.007
TG	*MVK*	rs7134594	12:110000193	30.33%	6.69E-01	9.67E-01	*ACACB*	rs2075260	12:109696838	p.Val2141Ile	25.66%	3.95E-08	7.48E-08	0.010
HDL	*CETP*	rs3764261	16:56993324	16.45%	4.73E-152	1.02E-120	*CETP*	rs2303790	16:57017292	p.Asp459Gly	2.23%	7.53E-62	3.37E-33	0.044
						2.31E-149	*CETP*	rs201790757	16:56997025	p.Tyr74*	0.03%	8.97E-10	1.42E-10	0.000
TC	*HPR*	rs2000999	16:72108093	25.88%	1.12E-08	5.00E-06	*PKD1L3*	rs7185272	16:72013797	p.Thr429Ser	26%	1.65E-12	5.94E-10	0.031
						1.33E-08	*PKD1L3*	rs17358402	16:71967927	p.Arg1572His	5.41%	1.96E-09	2.49E-09	0.002
HDL	*LIPG*	rs7241918	18:47160953	11.73%	2.38E-04	7.95E-05	*LIPG*	rs2000813	18:47093864	p.Thr111Ile	31.06%	1.04E-09	2.52E-10	0.008
LDL	*APOE*	rs4420638	19:45422946	12.25%	3.27E-08	1.64E-04	*APOE*	rs7412	19:45412079	p.Arg176Cys	8.82%	4.87E-197	3.46E-184	0.008

Protein-altering is top: protein-altering variants are the most significant variants in the known loci.
Explaining index: Conditional on the coding variants, the adjusted *P* for index variants (*P*.adj.coding) >0.01.
Independent of index: Conditional on the index variants, the adjusted *P* for coding variants (*P*.adj.index) with significance ($P < 4.5e-7$)
MAF, minor allele frequency

Supplementary Table 8. Genes previously identified to cause Mendelian dyslipidemia

Genes	Mendelian disorders of Lipids
ABCA1	Tangier disease
APOA1	ApoA-I deficiency hyperalphalipoproteinemia
APOA5	ApoA-V deficiency hyperalphalipoproteinemia
APOB	Familial hypercholesterolemia
APOE	Familial hyperlipoproteinemia
CETP	Cholesteryl ester transfer protein deficiency hyperalphalipoproteinemia
LDLR	Familial hypercholesterolemia
LPL	Lipoprotein lipase deficiency hypertriglyceridemia
LIPG	LIPG deficiency hyperalphalipoproteinemia
PCSK9	Autosomal-dominant hypercholesterolemia

Supplementary Table 9. The association of the novel and potential functional lipid-associated variants with coronary artery disease in the CARDIoGRAM datasets and East Asian CAD data

					CARDIOGRAMPlusC4D			East Asian CAD			
Loci	Position	rsID	Allele	Variant	OR 95%CI	ALT.FREQ	*P*	OR 95%CI	ALT.FREQ	*P*	N
					Novel variants						
ACVR1C	2:158437683	rs4377290	C/T		0.98(0.96-1)	0.453	1.84E-02	0.99(0.95-1.03)	0.315	7.14E-01	27373
MCU	10:74637326	rs7901016	C/T		0.94(0.91-0.98)	0.094	**4.55E-04**	0.94(0.90-0.98)	0.274	**2.80E-03**	28899
CD163	12:7649484	rs4883263	C/T	p.Ile342Val	1.01(0.97-1.04)	0.905	5.98E-01	1.02(0.98-1.06)	0.687	3.87E-01	28899
					Known lipid loci						
LDL cholesterol											
PCSK9	1:55509585	rs151193009	T/C	p.Arg93Cys				0.64(0.46-0.81)	0.014	**7.19E-07**	22365
APOB	2:21252534	rs13306194	A/G	p.Arg532Trp				0.9(0.84-0.96)	0.123	**2.86E-04**	28899
APOB	2:21228437	rs376825639	G/A	p.Ile3768Thr				0.19(-0.51-0.88)	0.001	**2.06E-06**	22365
APOB	2:21252807	noRS	T/C	p.Cys478Tyr				0.32(-0.43-1.07)	0.001	**2.92E-03**	22365
HMGCR	5:74646765	rs191835914	C/A	p.Tyr311Ser				0.85(0.7-1)	0.02	**3.76E-02**	22365
ABO	9:136131651	rs1053878	A/G	p.Pro156Leu	1.02(0.98-1.05)	0.082	3.29E-01	1.07(1.02-1.13)	0.202	**8.02E-03**	23176
PKD1L3	16:71967927	rs17358402	T/C	p.Arg1572His	0.99(0.97-1.02)	0.232	6.46 E-01	1.05(0.97-1.13)	0.054	2.43E-01	28899
PKD1L3	16:72013797	rs7185272	C/G	p.Thr429Ser	1.01(0.99-1.03)	0.765	3.68 E-01	1.04(0.99-1.08)	0.75	1.45E-01	23176
LDLR	19:11217315	rs200990725	T/C	p.Arg257Trp				2.99(2.43-3.55)	0.001	**1.41E-04**	22365
APOE	19:45412079	rs7412	T/C	p.Arg176Cys	0.87(0.83-0.91)	0.074	**8.17E-11**	0.83(0.71-0.96)	0.084	**4.77E-03**	10731
Total cholesterol											
EVI5	1:93159927	rs117711462	A/G	p.Arg354Cys				1.15(0.9-1.4)	0.007	2.79E-01	22365
HNF1A	12:121416650	rs1169288	C/A	p.Ile27Leu	1.05(1.03-1.07)	0.347	**1.98E-06**	1.05(1.01-1.09)	0.42	**1.71E-02**	28899
PMFBP1	16:72156842	rs16973716	G/T	p.Lys768Asn	1.02(1-1.04)	0.436	**6.67E-02**	1.05(1.01-1.09)	0.287	**1.47E-02**	28899
Triglycerides											
GCKR	2:27730940	rs1260326	C/T	p.Leu446Pro	1(0.98-1.02)	0.61	7.35E-01	0.95(0.91-0.98)	0.476	**3.42E-03**	28899
MLXIPL	7:73012042	rs35332062	A/G	p.Ala358Val	1.01(0.98-1.04)	0.12	6.26E-01	0.99(0.93-1.05)	0.118	7.16E-01	28899
LPL	8:19819724	rs328	G/C	p.Ser474*	0.95(0.92-0.98)	0.096	**1.81E-03**	0.97(0.91-1.04)	0.087	4.04E-01	28899
APOA5	11:116661392	rs2075291	A/C	p.Gly185Cys				1.15(1.07-1.22)	0.061	**5.95E-04**	28899
ACACB	12:109696838	rs2075260	A/G	p.Val2141Ile	1.01(0.99-1.03)	0.769	4.53E-01	1.04(1-1.08)	0.731	**4.60E-02**	28899

TM6SF2	19:19379549	rs58542926	T/C	p.Glu167Lys	0.95(0.91-0.99)	0.074	**5.20E-03**	0.94(0.86-1.02)	0.065	1.09E-01	28899
PPARA	22:46615880	rs1800234	C/T	p.Val227Ala				0.99(0.89-1.1)	0.054	9.18E-01	21650
HDL cholesterol											
CD36	7:80302116	rs148910227	T/C	p.Arg386Trp				0.71(0.35-1.06)	0.004	5.34E-02	22365
ABCA1	9:107562804	rs2230808	C/T	p.Lys1587Arg	1.02(1-1.04)	0.71	1.12E-01	0.98(0.94-1.02)	0.624	3.76E-01	28899
ABCA1	9:107586753	rs2066714	C/T	p.Ile883Met	1.05(1.02-1.07)	0.166	**3.22 E-04**	1.04(1-1.08)	0.727	6.53E-02	28899
GPAM	10:113940329	rs2792751	C/T	p.Ile43Val	0.99(0.97-1.01)	0.712	3.01E-01	0.98(0.94-1.02)	0.682	4.15E-01	28899
APOA1	11:116707736	rs12718465	T/C	p.Ala61Thr				1.08(0.97-1.19)	0.032	1.83E-01	28899
MMAB	12:109994870	rs9593	T/A	p.Met239Lys	1.01(0.99-1.02)	0.511	5.83E-01	1.01(0.97-1.05)	0.301	5.40E-01	28899
ALDH2	12:112241766	rs671	A/G	p.Glu457Lys				1.08(1.03-1.12)	0.203	**2.07E-03**	28899
CETP	16:56997025	rs201790757	G/T	p.Tyr74*				0.47(-0.65-1.59)	0	1.89E-01	22365
CETP	16:57017292	rs2303790	G/A	p.Asp459Gly				0.99(0.86-1.12)	0.025	9.20E-01	27373
SLC12A4	16:67997920	rs3785100	C/T	p.Glu4Gly	1.01(0.99-1.04)	0.145	3.26E-01	1.03(0.97-1.09)	0.115	3.87E-01	28899
LIPG	18:47093864	rs2000813	T/C	p.Thr111Ile	0.97(0.95-0.99)	0.289	9.11E-03	1.02(0.98-1.06)	0.293	4.43E-01	28899

ALT.FREQ, alternative allele frequency.
Position is reported in human genome build hg19.
Alleles are listed as alternative / reference allele on the forward strand of the reference genome.

Supplementary Table 10. Association results of the novel variants in combined current studies, HUNT, GLGC GWAS, and Chinese GWAS samples

				East Asian and GLGC exome			HUNT		GLGC GWAS		Chinese GWAS		Combined Samples		
Gene	rsID	Allele	Trait	EAF	N	*P*	N	*P*	N	*P*	N	*P*	N	BETA(S.E.)	*P*
ACVR1C	rs4377290	C/T	TC	0.44	358251	6.06E-08	61924	0.005	48567	0.064	13648	0.014	482390	-0.014(0.002)	5.583E-11
MCU	rs7901016	C/T	LDL	0.12	298452	2.21E-09	61898	0.370	44290	0.178	14028	1.28E-03	418668	-0.027(0.004)	3.004E-11
CD163	rs4883263	C/T	HDL	0.9	356397	6.30E-13	61907	0.120	48286	0.756	14137	5.91E-04	480727	-0.031(0.004)	2.134E-14
PDGFC	rs4691380	T/C	HDL	0.35	335481	1.07E-07	61907	0.0004	48426	3.84E-04	13936	0.727	459750	0.016(0.002)	4.919E-12
FAM114A2	rs2578377	T/C	HDL	0.67	335481	1.74E-07	61907	0.520	48428	0.035	14141	0.166	459957	-0.013(0.002)	2.194E-08
MGAT1	rs634501	G/A	HDL	0.72	337027	9.36E-08	61907	0.004	2992	0.084	12365	0.899	414291	-0.015(0.002)	4.451E-09
ASCC3	rs9390698	A/G	TC	0.39	358251	5.22E-09	61924	0.0002	45531	0.015	14150	0.210	479856	0.016(0.002)	1.056E-13
			LDL	0.39	331991	5.84E-08	61898	0.0006	41339	0.008	14063	0.026	449291	0.016(0.002)	1.317E-12
LOC100996634	rs884366	A/G	HDL	0.31	327673	1.45E-08	61907	0.003	88652	8.50E-05	14148	0.083	492380	-0.017(0.002)	8.678E-14
EEPD1	rs4302748	A/G	LDL	0.18	333359	2.10E-08	61898	0.012	44285	0.721	13991	0.577	453533	0.016(0.003)	4.69E-09
PLCE1	rs2274224	C/G	TC	0.44	150798	9.92E-08	61924	0.0006	89016	0.132	9329	0.094	311067	-0.017(0.003)	6.752E-10
EIF4B	rs7306523	G/A	TC	0.71	338266	5.36E-08	61924	0.180	48567	0.671	14150	0.505	462907	-0.015(0.003)	4.309E-08
			LDL	0.71	313750	1.38E-07	61898	0.210	44290	0.454	14063	0.129	434001	-0.016(0.003)	2.654E-08
SLC17A8	rs7965082	T/C	TC	0.52	358251	8.28E-09	61924	0.013	48567	8.58E-04	14151	0.106	482893	-0.015(0.002)	7.577E-13
			LDL	0.52	333359	9.21E-08	61898	0.009	44290	0.025	14064	0.082	453611	-0.014(0.002)	4.939E-11

We performed in silico replication of significant variants in the HUNT-MI study (Health in Nord-Trøndelag and University of Michigan) (max n= 62,168) (Int J Epidemiol. 2013;42:968-77), GLGC GWAS samples (max n=89,016) (being careful to exclude the samples overlapping GLGC exome samples) (Nat Genet. 2013;45:1274-83), and Chinese subjects from Chinese lipids GWAS (max n= 14,151) (Circ Cardiovasc Genet 2016;9:37-44).

Supplementary Table 12. Expression quantitative trait locus (eQTL)of novel variants and proxies (*P* < 4.5e-7)

Gene	rsID	chr.pos	Lead /proxy	r^2 with lead SNP	Gencode Id	Effect Size	*P*	Tissue
FAM114A2	rs34077744	5:153376314	proxy	0.99(rs2578377)	ENSG00000055147.13	0.16	3.64E-07	Whole_Blood
ASCC3	rs9390698	6:101296389	lead		ENSG00000112249.9	-0.23	2.35E-08	Artery_Tibial
LOC100996634	rs884366	6:109574095	lead		ENSG00000203799.6	-0.53	1.38E-16	Whole_Blood
EEPD1	rs11771125	7:36190426	proxy	0.95(rs4302748)	ENSG00000122547.6	-0.26	3.79E-07	Whole_Blood
PLCE1	rs2274224	10:96039597	lead		ENSG00000173145.7	0.53	5.78E-10	Adrenal_Gland

For each of the newly discovered loci, all proxies (r^2 > 0.8) were identified using data from 1000 genome East Asian. *Cis*-eQTL (defined as genes within 1 Mb) of lead variants and their proxies were investigated in public databases including the following tissues and cell lines: liver, artery, LCL, adipose, heart, blood and adrenal gland.

Supplementary Table 13. The association of the potential functional lipid-associated variants identified in East Asian with lipid levels in GLGC

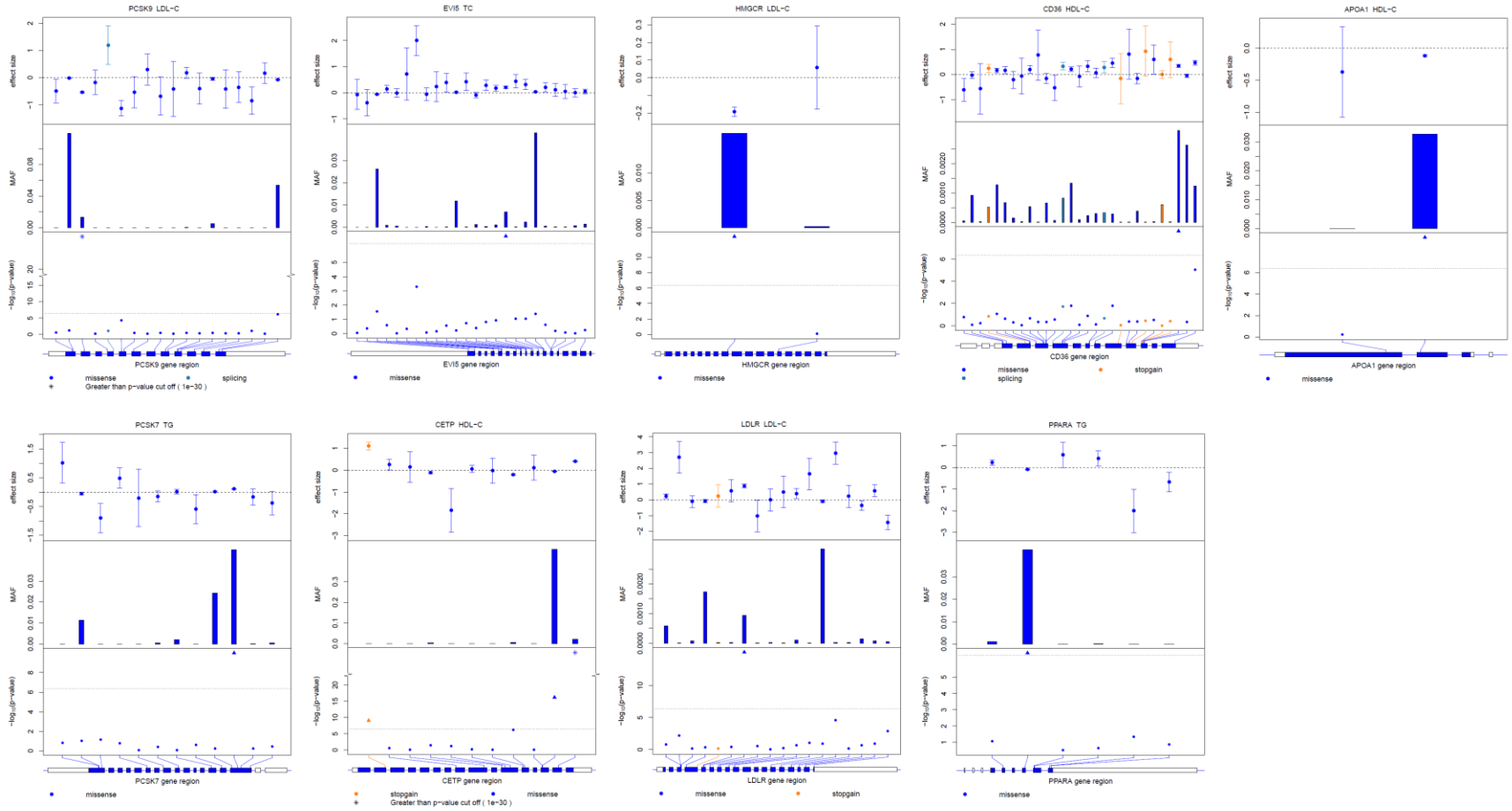
						East Asian			GLGC		
Loci	Position	rsID	Allele	Variant	Trait	ALT.FREQ	Effect	*P*	ALT.FREQ	Effect	*P*
Low-frequency and rare coding variants in East Asian are not significant in GLGC											
EVI5	1:93159927	rs117711462	A/G	p.Arg354Cys	TC	0.69%	0.212(0.04)	1.41E-07	0.03%	0.097(0.083)	0.245
					LDL	0.67%	0.21(0.041)	3.23E-07	0.03%	0.078(0.085)	0.3608
APOB	2:21228437	rs376825639	G/A	p.Ile3768Thr	TC	0.15%	-0.659(0.097)	8.44E-12			
					LDL	0.15%	-0.579(0.098)	3.35E-09			
APOB	2:21252807	noRS	T/C	p.Cys478Tyr	LDL	0.09%	-0.772(0.141)	4.19E-08			
					TC	0.09%	-0.876(0.138)	2.08E-10			
HMGCR	5:74646765	rs191835914	C/A	p.Tyr311Ser	TC	1.74%	-0.16(0.025)	2.00E-10	0.04%	-0.102(0.064)	0.1087
					LDL	1.73%	-0.19(0.026)	2.20E-13	0.04%	-0.117(0.067)	0.07949
CD36	7:80302116	rs148910227	T/C	p.Arg386Trp	HDL	0.31%	0.342(0.058)	3.17E-09	0.02%	0.215(0.084)	0.01045
APOA1	11:116707736	rs12718465	T/C	p.Ala61Thr	HDL	3.27%	-0.116(0.019)	5.50E-10	0.02%	0.075(0.099)	0.4487
CETP	16:56997025	rs201790757	G/T	p.Tyr74*	HDL	0.03%	1.117(0.182)	8.97E-10	0.001%	0.719(0.352)	0.04113
CETP	16:57017292	rs2303790	G/A	p.Asp459Gly	HDL	2.23%	0.407(0.025)	7.53E-62	0.02%	0.384(0.092)	3.16E-05
					TC	2.22%	0.145(0.025)	3.34E-09	0.02%	0.065(0.092)	0.4828
LDLR	19:11217315	rs200990725	T/C	p.Arg257Trp	TC	0.09%	0.677(0.109)	5.57E-10	0.001%	1.897(0.502)	1.57E-04
					LDL	0.09%	0.882(0.109)	6.35E-16	0.001%	1.869(0.502)	1.96E-04
PPARA	22:46615880	rs1800234	C/T	p.Val227Ala	TG	4.21%	-0.094(0.018)	3.17E-07	0.15%	-0.058(0.037)	0.1179
Low-frequency and rare coding variants in East Asian are significant in GLGC											
PCSK9	1:55509585	rs151193009	T/C	p.Arg93Cys	TC	1.34%	-0.508(0.029)	3.96E-70	0.01%	-0.71(0.133)	1.03E-07
					LDL	1.32%	-0.542(0.029)	7.62E-77	0.01%	-0.801(0.139)	7.62E-09
Common coding variants in East Asian are not significant in GLGC											
APOB	2:21252534	rs13306194	A/G	p.Arg532Trp	TC	12.39%	-0.114(0.01)	1.45E-29	0.19%	-0.084(0.031)	0.006743
					LDL	12.45%	-0.098(0.01)	9.53E-22	0.20%	-0.085(0.032)	0.008126
					TG	12.43%	-0.073(0.01)	1.38E-12	0.19%	-0.133(0.032)	2.96E-05
ABO	9:136131651	rs1053878	A/G	p.Pro156Leu	LDL	18.56%	0.066(0.009)	5.07E-14	8.06%	0.016(0.005)	0.001346
ACACB	12:109696838	rs2075260	A/G	p.Val2141Ile	TG	74.34%	0.043(0.008)	3.95E-08	80.23%	0.011(0.003)	5.32E-04

ALDH2	12:112241766	rs671	A/G	p.Glu457Lys	HDL	20.43%	-0.048(0.008)	1.16E-08	0.08%	-0.005(0.052)	0.928
PKD1L3	16:71967927	rs17358402	T/C	p.Arg1572His	TC	5.41%	0.088(0.015)	1.96E-09	24.44%	-0.009(0.003)	0.003724
					LDL	5.41%	0.085(0.015)	2.11E-08	24.44%	-0.013(0.003)	8.47E-05
PMFBP1	16:72156842	rs16973716	G/T	p.Lys768Asn	TC	28.96%	0.042(0.008)	1.75E-07	44.69%	0.014(0.003)	2.66E-07
Common functional coding variants in East Asian are significant in GLGC											
GCKR	2:27730940	rs1260326	C/T	p.Leu446Pro	TC	49.39%	-0.047(0.007)	1.70E-12	63.19%	-0.058(0.003)	5.84E-101
					TG	49.57%	-0.114(0.007)	1.26E-62	63.23%	-0.121(0.003)	0
MLXIPL	7:73012042	rs35332062	A/G	p.Ala358Val	TG	10.94%	-0.109(0.011)	2.03E-23	11.61%	-0.123(0.004)	6.40E-188
LPL	8:19819724	rs328	G/C	p.Ser474NA	HDL	9.12%	0.162(0.012)	7.55E-44	9.83%	0.163(0.004)	1.18E-306
					TG	9.15%	-0.169(0.012)	1.93E-45	9.84%	-0.183(0.004)	0
ABCA1	9:107562804	rs2230808	C/T	p.Lys1587Arg	HDL	60.97%	0.047(0.007)	2.49E-12	72.96%	0.027(0.003)	9.78E-19
ABCA1	9:107586753	rs2066714	C/T	p.Ile883Met	TC	71.24%	0.041(0.007)	3.72E-08	15.11%	0.032(0.004)	6.95E-18
					HDL	71.23%	0.052(0.007)	1.41E-12	15.13%	0.043(0.004)	2.03E-30
GPAM	10:113940329	rs2792751	C/T	p.Ile43Val	TC	70.64%	-0.043(0.007)	5.67E-09	72.98%	-0.028(0.003)	1.62E-21
					HDL	70.64%	-0.049(0.007)	7.14E-12	72.99%	-0.027(0.003)	3.90E-20
APOA5	11:116661392	rs2075291	A/C	p.Gly185Cys	TG	5.56%	0.363(0.015)	1.12E-131	0.16%	0.37(0.033)	1.94E-29
					HDL	5.58%	-0.288(0.014)	3.91E-91	0.16%	-0.262(0.033)	1.20E-15
MMAB	12:109994870	rs9593	T/A	p.Met239Lys	HDL	30.42%	0.037(0.007)	2.92E-07	53.14%	0.03(0.003)	9.15E-29
HNF1A	12:121416650	rs1169288	C/A	p.Ile27Leu	TC	40.36%	0.038(0.007)	4.86E-08	33.01%	0.037(0.003)	5.88E-38
SLC12A4	16:67997920	rs3785100	C/T	p.Glu4Gly	HDL	10.98%	0.059(0.011)	5.13E-08	14.09%	0.072(0.004)	7.57E-67
PKD1L3	16:72013797	rs7185272	C/G	p.Thr429Ser	TC	73.98%	0.054(0.008)	1.65E-12	78.69%	0.021(0.003)	6.11E-11
					LDL	73.92%	0.059(0.008)	4.87E-14	78.68%	0.021(0.003)	7.44E-11
LIPG	18:47093864	rs2000813	T/C	p.Thr111Ile	HDL	31.06%	0.043(0.007)	1.04E-09	28.61%	0.039(0.003)	1.76E-41
TM6SF2	19:19379549	rs58542926	T/C	p.Glu167Lys	TC	6.92%	-0.066(0.013)	4.25E-07	7.44%	-0.131(0.005)	5.71E-156
					TG	6.95%	-0.094(0.013)	2.09E-12	7.46%	-0.119(0.005)	1.20E-123
APOE	19:45412079	rs7412	T/C	p.Arg176Cys	TG	8.82%	0.091(0.016)	7.32E-09	7.42%	0.124(0.007)	2.54E-79
					HDL	8.83%	0.104(0.016)	3.95E-11	7.42%	0.098(0.006)	2.63E-52
					LDL	8.82%	-0.472(0.016)	4.87E-197	7.38%	-0.535(0.007)	0

ALT.FREQ, alternative allele frequency.
Position is reported in human genome build hg19.
Alleles are listed as alternative / reference allele on the forward strand of the reference genome.

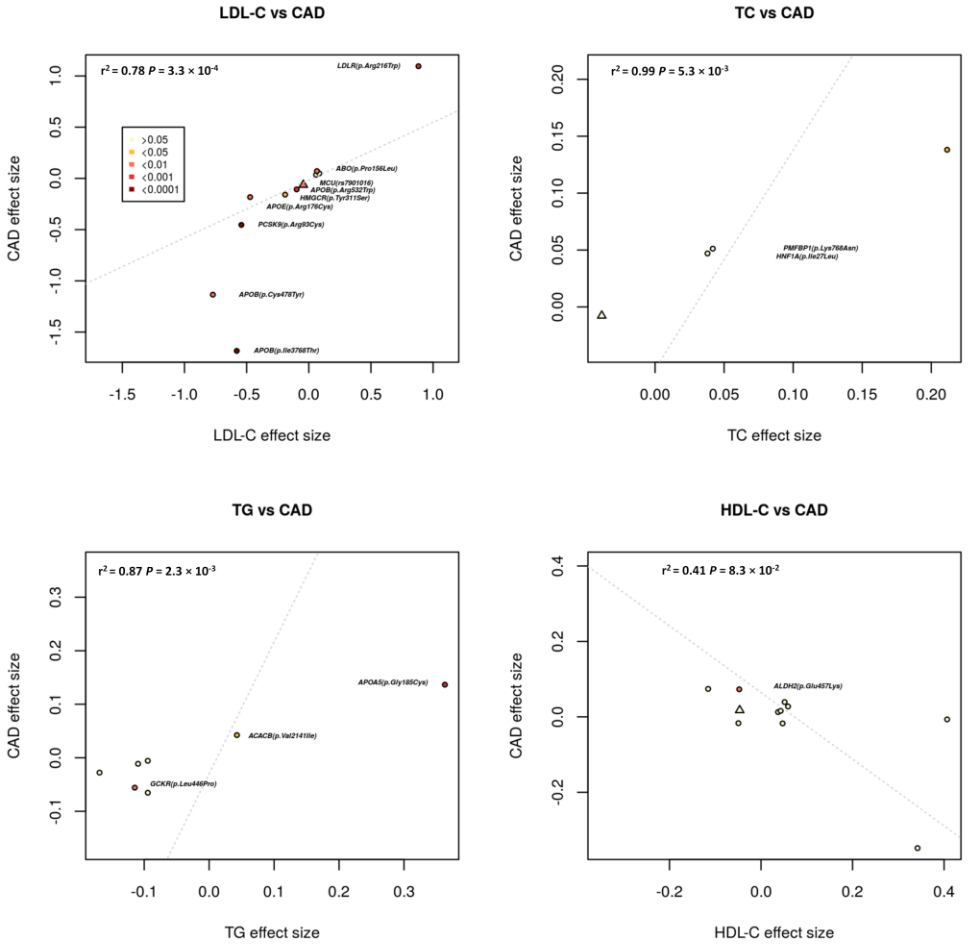
Supplementary Figures

Supplementary Figure 1. Genezoom plots for the 9 genes that reached gene-based significance ($P < 2.8 \times 10^{-6}$) with blood lipid levels



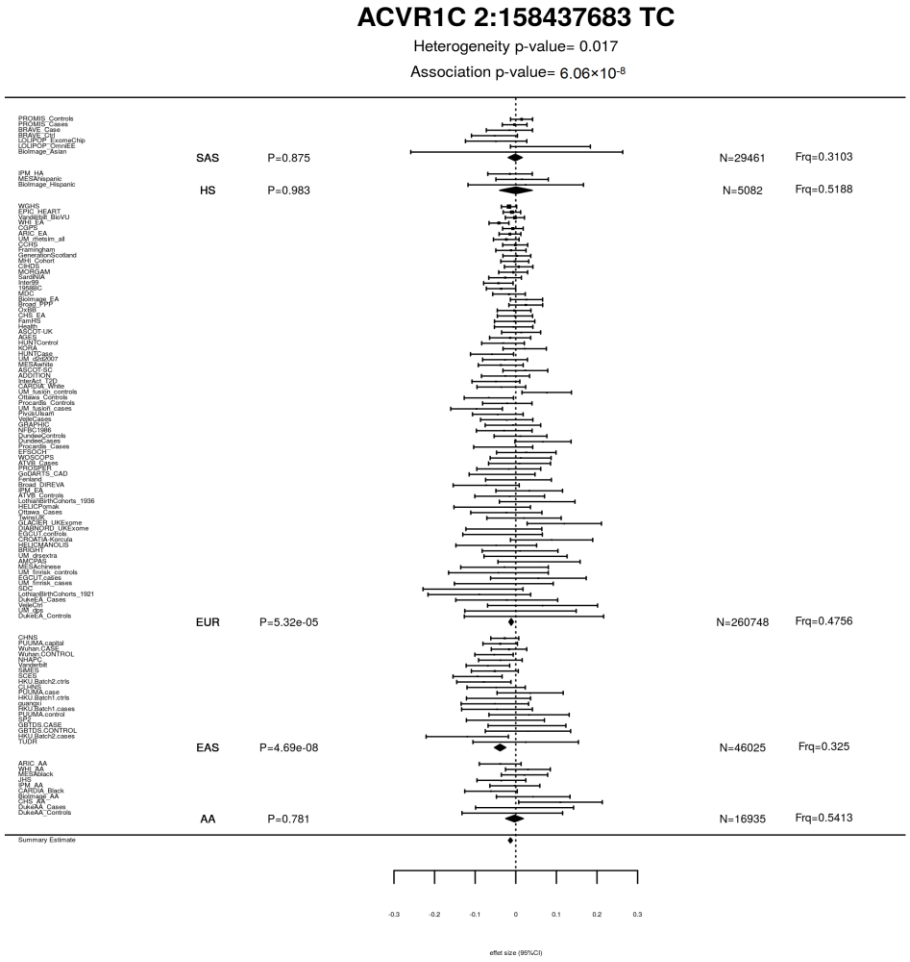
Supplementary Figure 2. Relationship between the effect sizes on CAD and lipid levels for the novel and potential function variants identified in East Asian population

All lipid and CAD effect sizes estimated by the Chinese samples were oriented to the alternate allele (hg19). Lipid effect sizes were transformed into SD units. Circles represent 31 potential function variants while triangles denote novel variants.



Supplementary Figure 3. Forest plots for the novel variants.

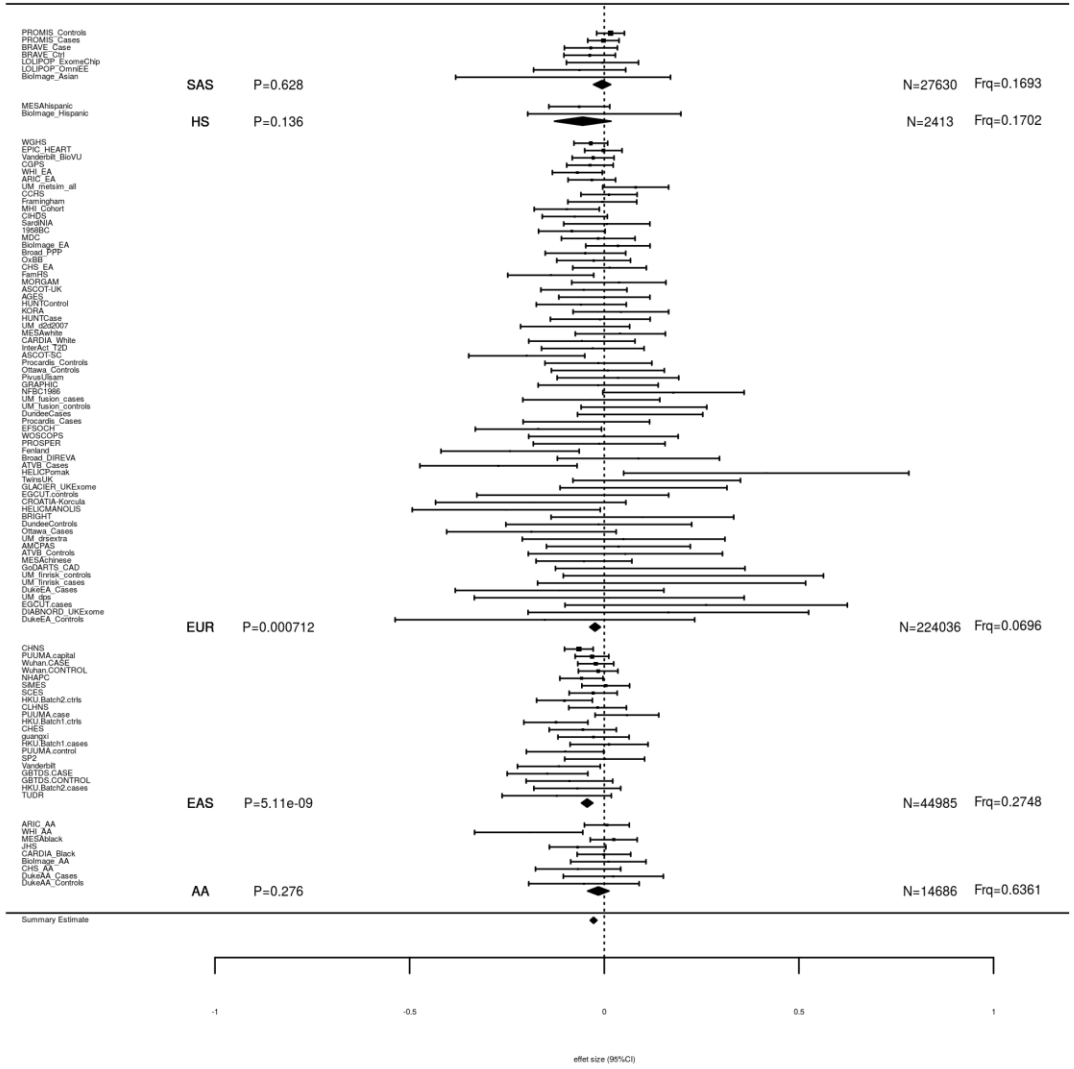
GLGC samples(AA: African American; EUR: European; HS: Spanish; SAS: South Asian); EAS: East Asian



MCU 10:74637326 LDL

Heterogeneity p-value= 0.00471

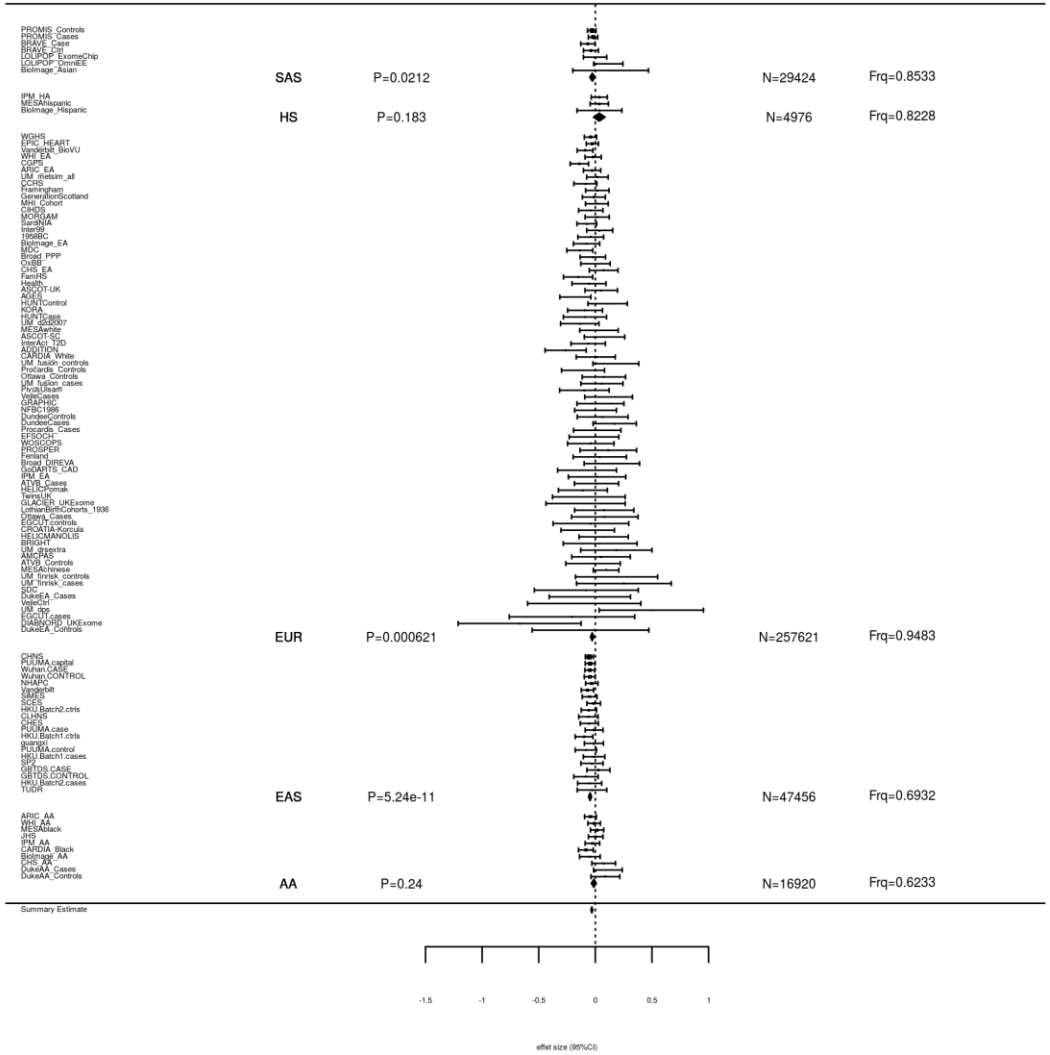
Association p-value= 2.21×10^{-9}



CD163 12:7649484 HDL

Heterogeneity p-value= 0.0772

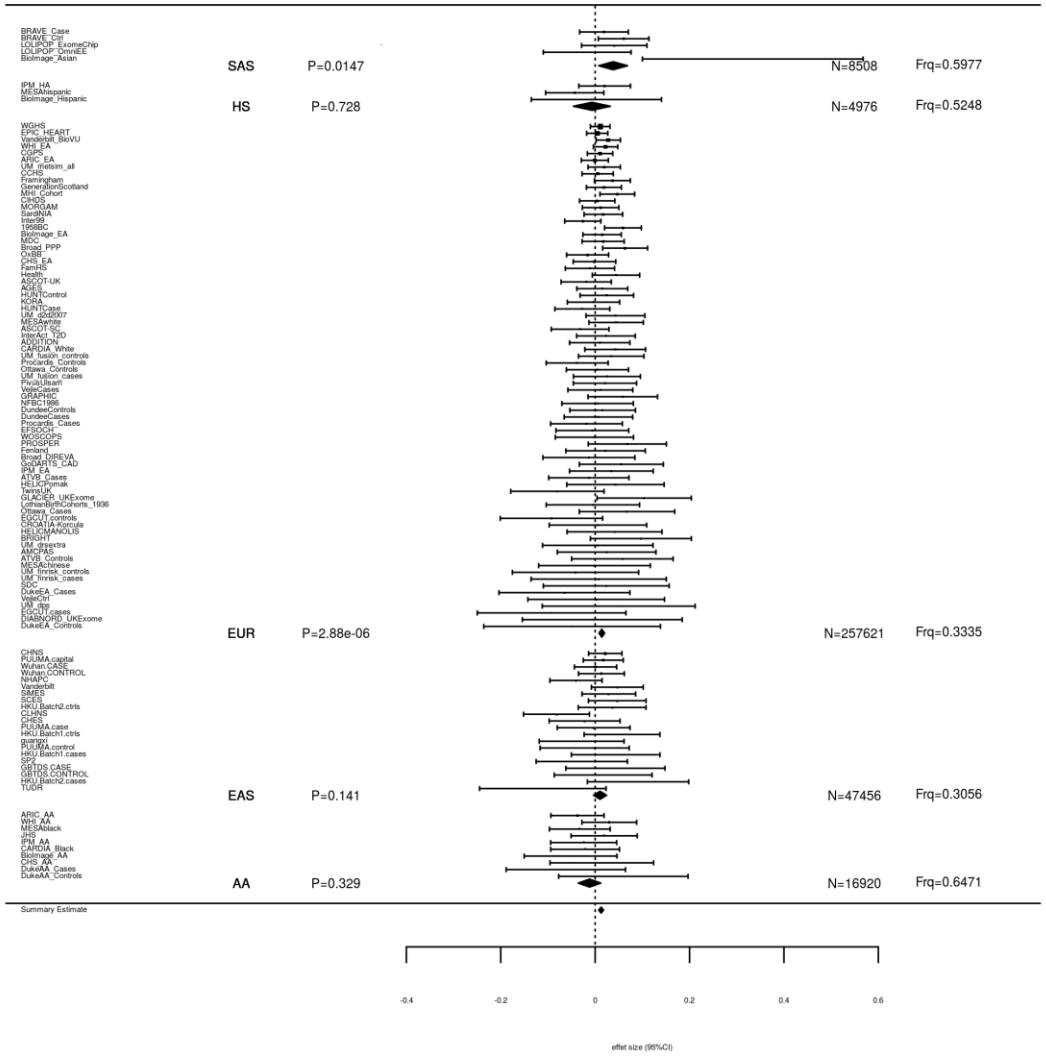
Association p-value= 6.30×10^{-13}



PDGFC 4:157720124 HDL

Heterogeneity p-value= 0.449

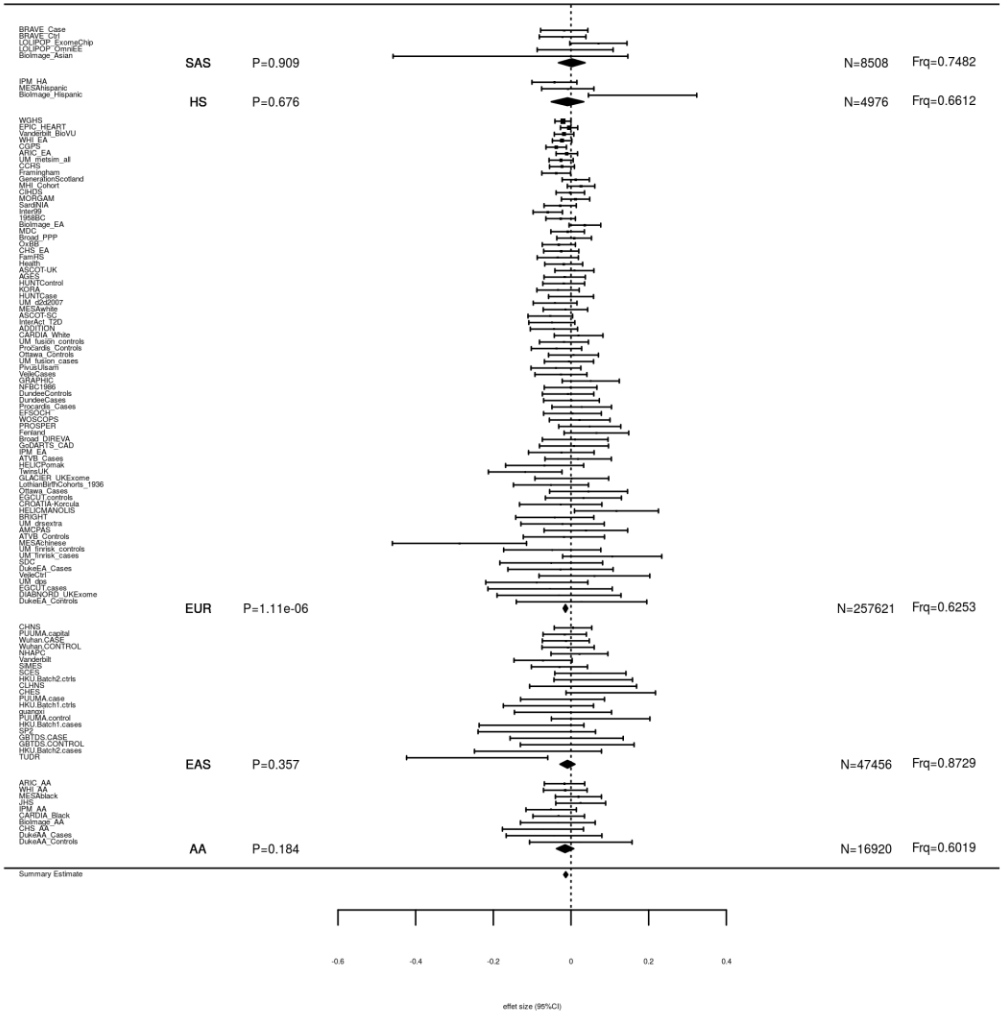
Association p-value= 1.07×10^{-7}



FAM114A2 5:153413390 HDL

Heterogeneity p-value= 0.124

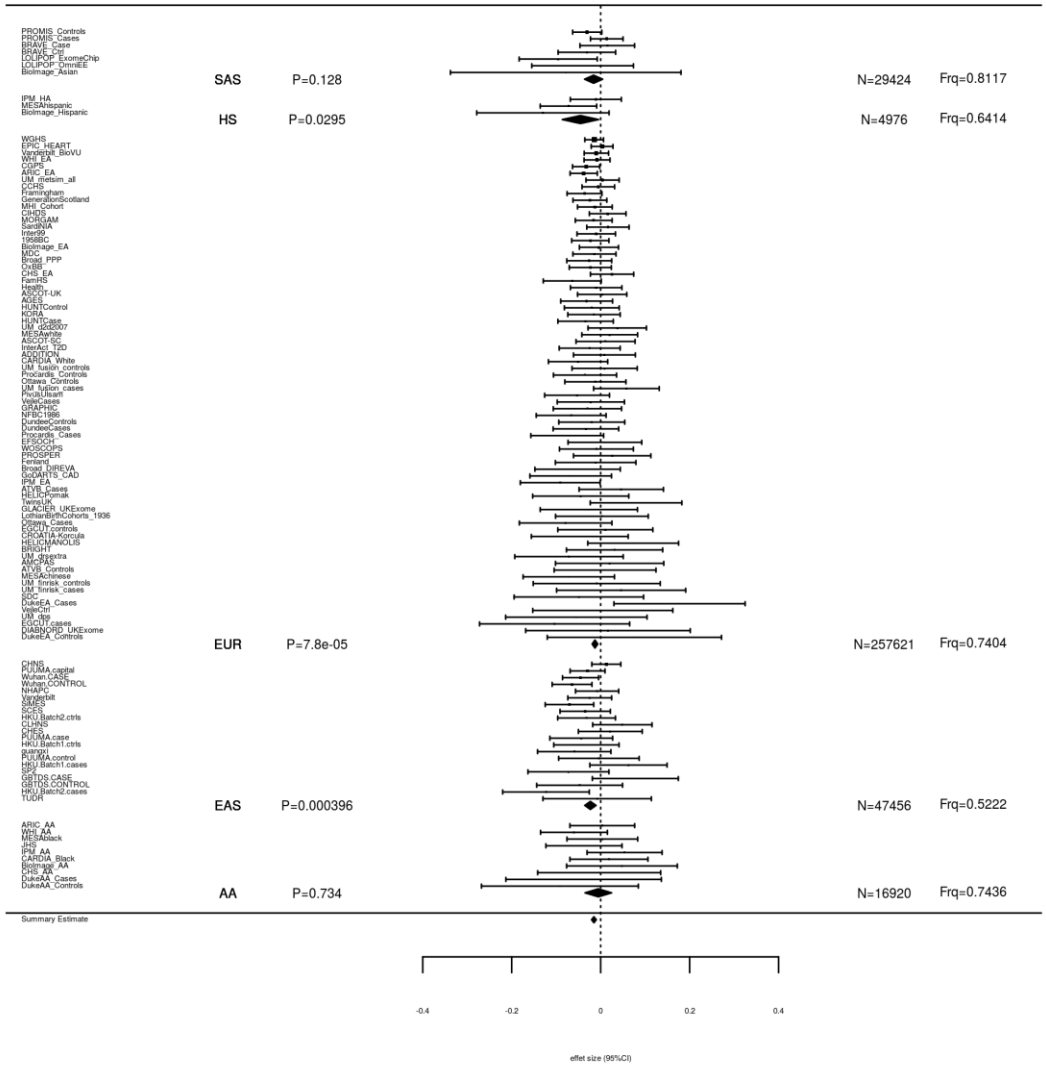
Association p-value= 1.74×10^{-7}



MGAT1 5:180218668 HDL

Heterogeneity p-value= 0.383

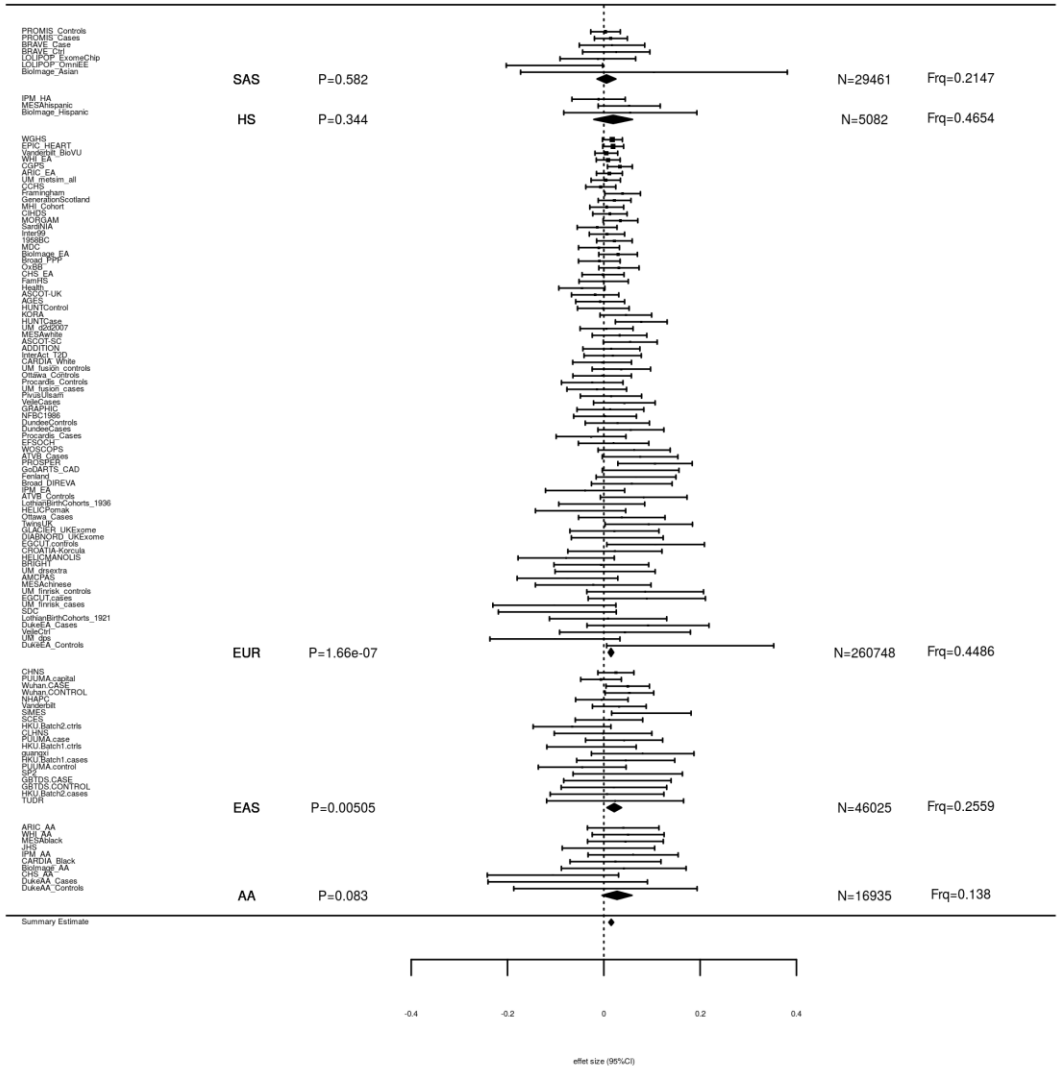
Association p-value= 9.36×10^{-8}



ASCC3 6:101296389 TC

Heterogeneity p-value= 0.214

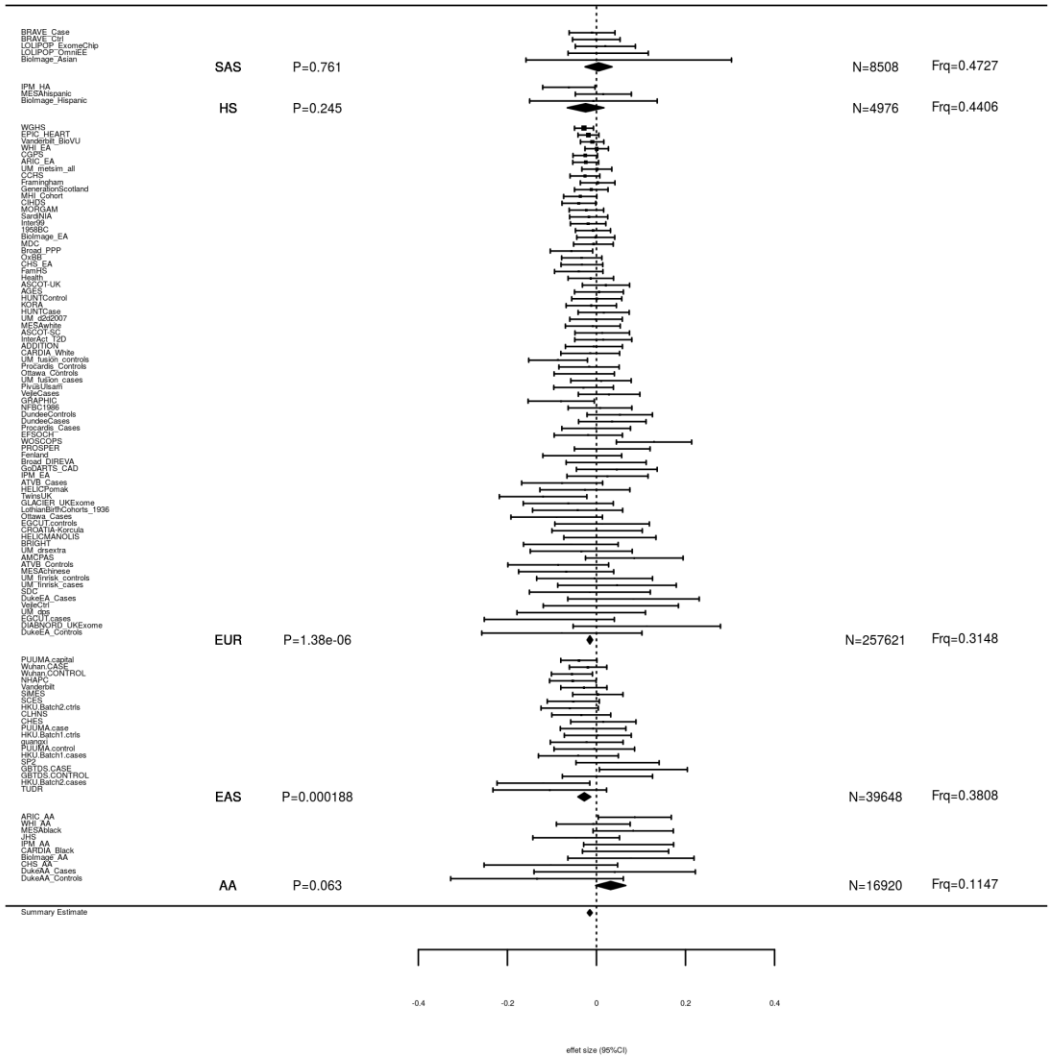
Association p-value= 5.22×10^{-9}

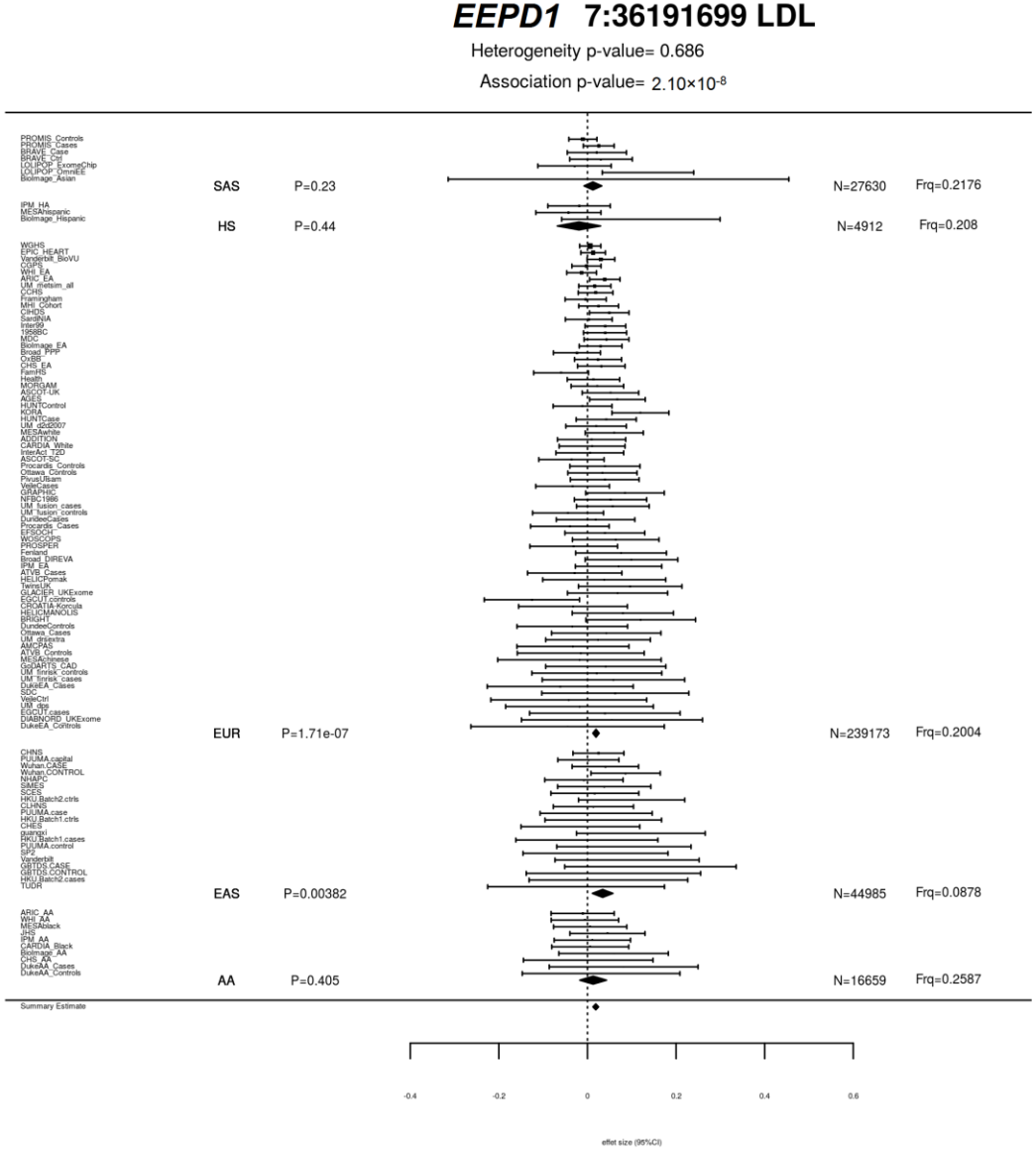


LOC100996634 6:109574095 HDL

Heterogeneity p-value= 0.139

Association p-value= 1.45×10^{-8}

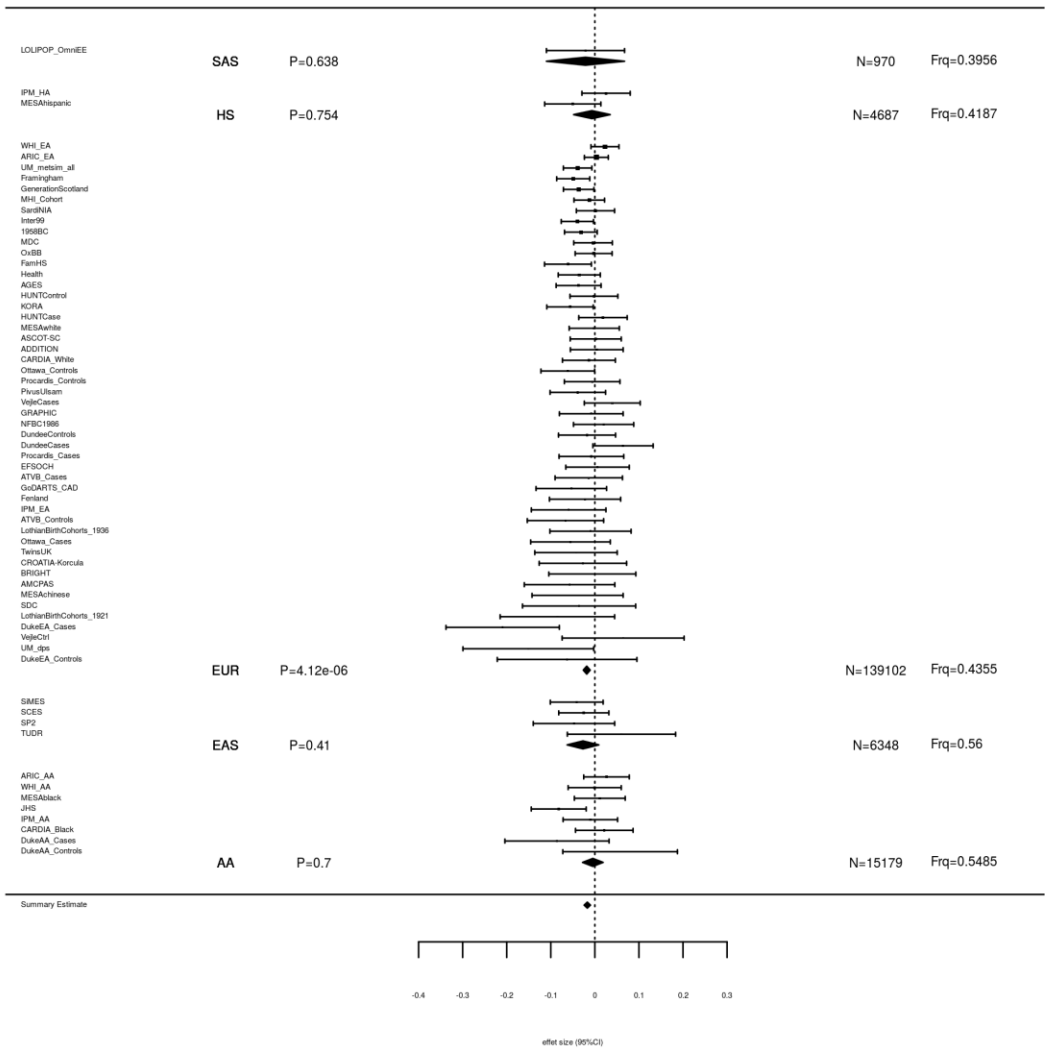



EEPD1 7:36191699 LDL
Heterogeneity p-value= 0.686
Association p-value= 2.10×10-8
PROMIS_Controls
PROMIS_Cases
BRAVE_Case
BRAVE_Control
LOLIPOP_ExomeChip
LOLIPOP_OmniEE
Biolmage_Asian
SAS
P=0.23
N=27630
Frq=0.2176
IPM_HA
MESAhispanic
Biolmage_Hispanic
HS
P=0.44
N=4912
Frq=0.208
WGHS
EPIC_HEART
Vanderbilt_BioVU
CGPS
WHI_EA
ARIC_EA
UM_metaim_all
CCHS
Framingham
MHI_Cohort
CHHS
SardiNIA
InterB6
MDCSC
MPP
Biolmage_EA
Broad_PPP
OxBB
CHS_EA
FamHS
Health
MORGAM
ASCOT-UK
AGES
HUNTControl
KORA
HUNTCase
UM_gwas2007
MESAwhite
ADDITION
CARDIA_White
InterAct_T2D
ASCOT-SC
Procardis_Controls
Ottawa_Controls
PivusUfsam
VelieCases
GRAPHIC
NFBC1966
UM_fusion_cases
UM_fusion_controls
DundeeCases
PrudentCases
EPSGH
WOSCOPS
PROSPER
Fenland
Broad_DIREVA
IPM_EA
ATVB_Cases
HELICPomak
TwinsUK
GLACIER_UKExome
EGCUT_controls
CROATIA-Korcula
HELICMANOLIS
BRIGHT
DundeeControls
Ottawa_Cases
UM_dnsextra
AMCPAS
ATVB_Controls
MESAchinese
GoDARTS_CAD
UM_tmrisk_controls
UM_tmrisk_cases
DukeEA_Cases
SOC
VelieCtrl
UM_dps
EGCUT_cases
DIABNORD_UKExome
DukeEA_Controls
EUR
P=1.71e-07
N=239173
Frq=0.2004
CHNS
PUUMA_capital
Wuhan_CASE
Wuhan_CONTROL
NHAPC
SIMES
SCES
HKU_Batch2.ctrls
CLHNS
PUUMA_case
HKU_Batch1.ctrls
CHES
guangxi
HKUBatch1.cases
PUUMA_control
SP2
Vanderbilt
GBTDS_CASE
GBTDS_CONTROL
HKU_Batch2.cases
TUDR
EAS
P=0.00382
N=44985
Frq=0.0878
ARIC_AA
WHI_AA
MESAblack
JHS
IPM_AA
CARDIA_Black
Biolmage_AA
CHS_AA
DukeAA_Cases
DukeAA_Controls
AA
P=0.405
N=16659
Frq=0.2587
Summary Estimate
-0.4
-0.2
0
0.2
0.4
0.6
effet size (95%CI)

PLCE1 10:96039597 TC

Heterogeneity p-value= 0.112

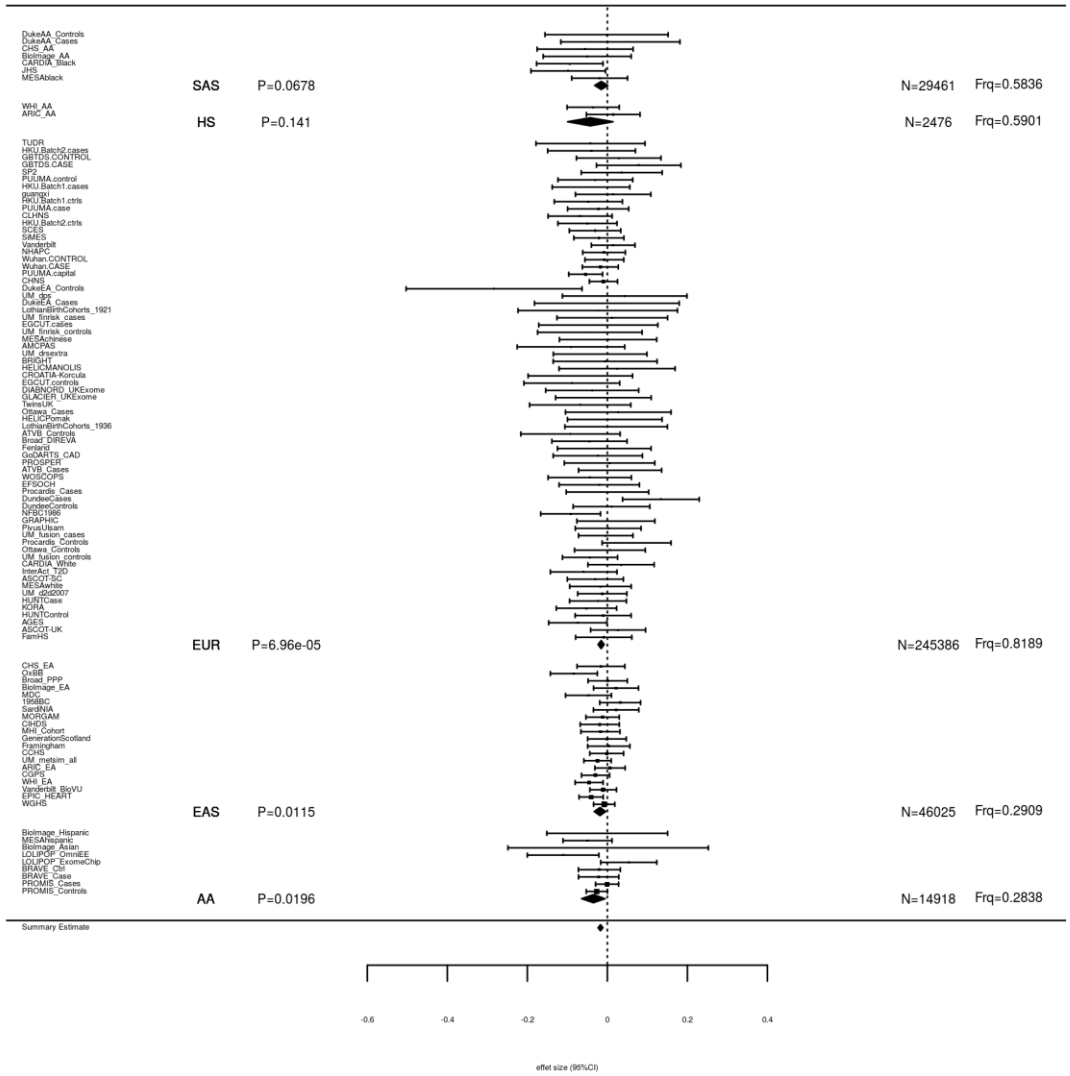
Association p-value= 9.92×10^{-8}



EIF4B 12:53393964 TC

Heterogeneity p-value= 0.684

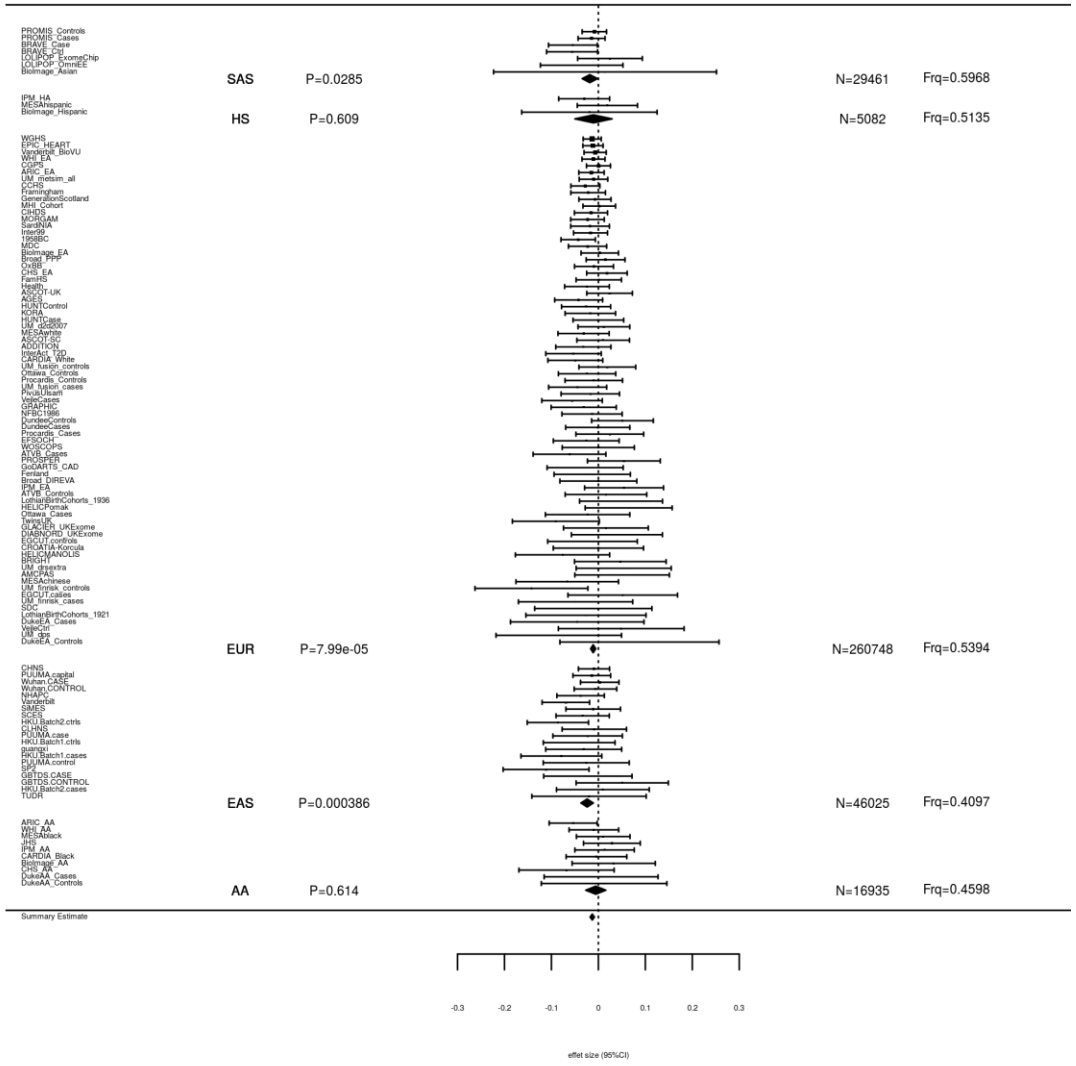
Association p-value= 5.36e-08



SLC17A8 12:100800193 TC

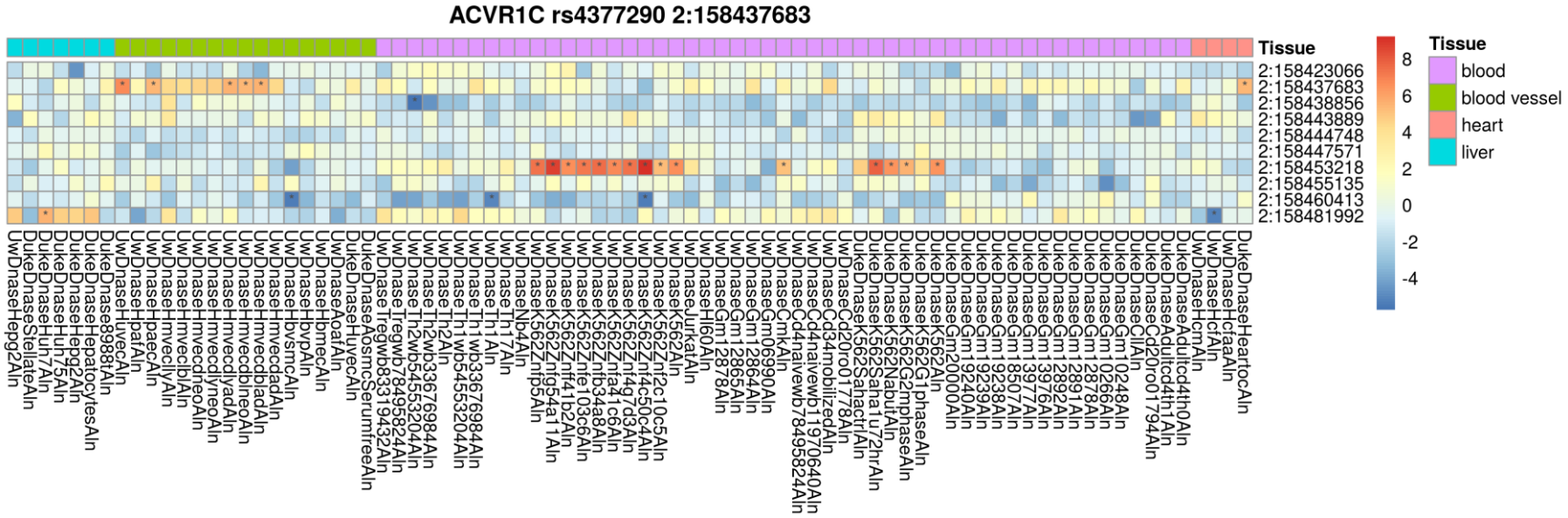
Heterogeneity p-value= 0.835

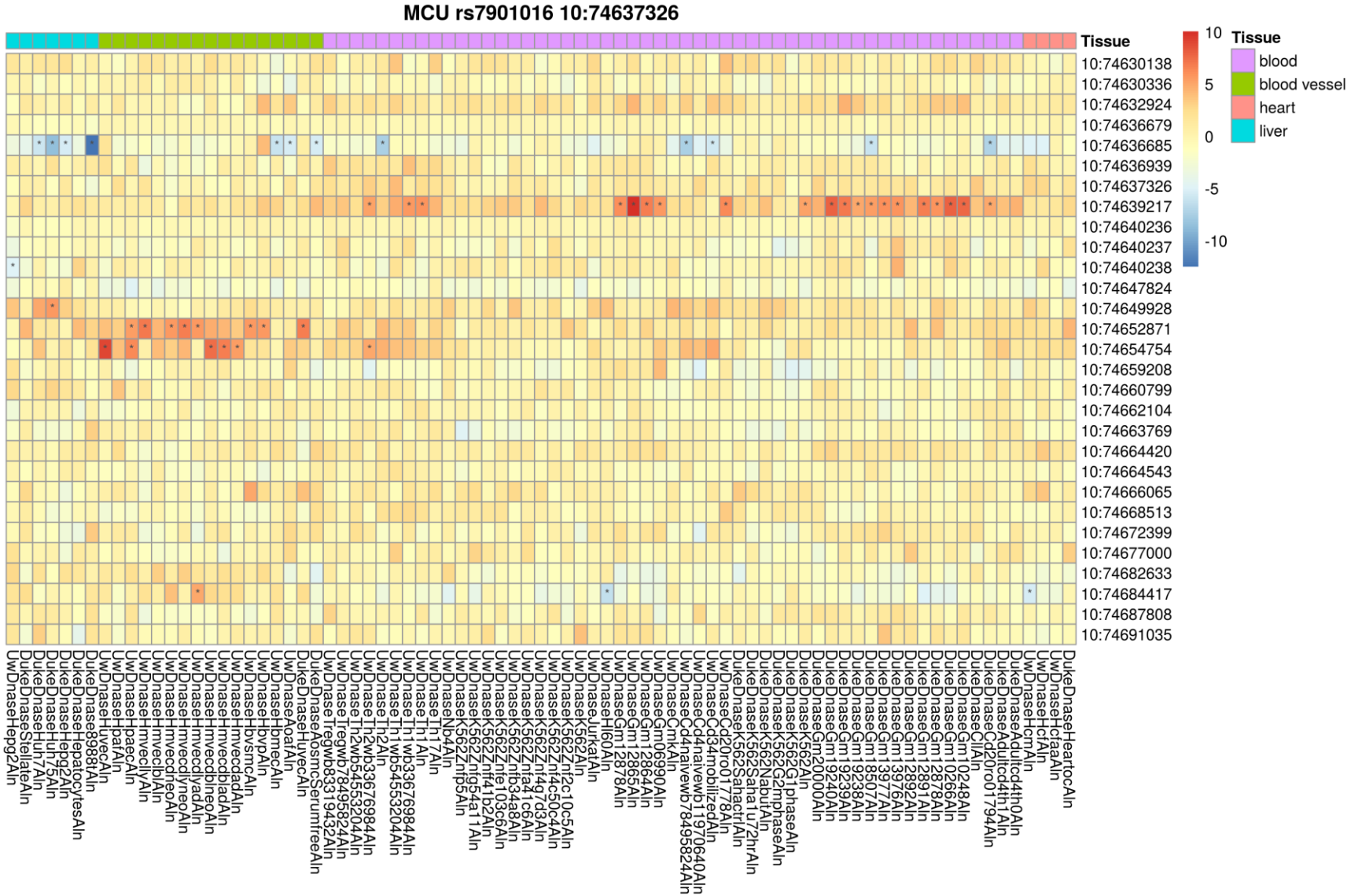
Association p-value= 8.28×10^{-9}



Supplementary Figure 4. Heatmaps of deltaSVM scores used to predict the impact of regulatory variants in noncoding regions

DeltaSVM uses a gapped k-mer support vector machine to estimate the effect of a variant in a cell-type-specific manner (Nat Genet. 2015 47(8):955-61). Precomputed weights were available from a total of 222 ENCODE DHS samples—99 from the Duke University (Duke) set and 123 from the University of Washington (UW) set (Nature. 2012;489(7414):75-82). For the current study, genetic variants were scored for deltaSVM in 81 cell lines from four tissues (blood, blood vessel, heart and liver). For each of the seven novel noncoding regions, all proxies (r^2 > 0.8) were identified using data from 1000 genome. The deltaSVM scores are represented as different color gradients, and the variants with deltaSVM score greater than an absolute value of 5 are highlighted with asterisk. The regulatory deltaSVM score of 5 is in the same range as previous predictions for known functional SNPs (Nat Genet. 2015 47(8):955-61).

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Tissue
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10:74630336
10:74632924
10:74636679
10:74636685
10:74636939
10:74637326
10:74639217
10:74640236
10:74640237
10:74640238
10:74647824
10:74649928
10:74652871
10:74654754
10:74659208
10:74660799
10:74662104
10:74663769
10:74664420
10:74664543
10:74666065
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10:74672399
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DukeDnaseHuh7Aln
DukeDnaseHuh75Aln
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DukeDnase8988tAln
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UwDnaseHbmecAln
UwDnaseAoafAln
DukeDnaseHuvecAln
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DukeDnaseAdultcd4th0Aln
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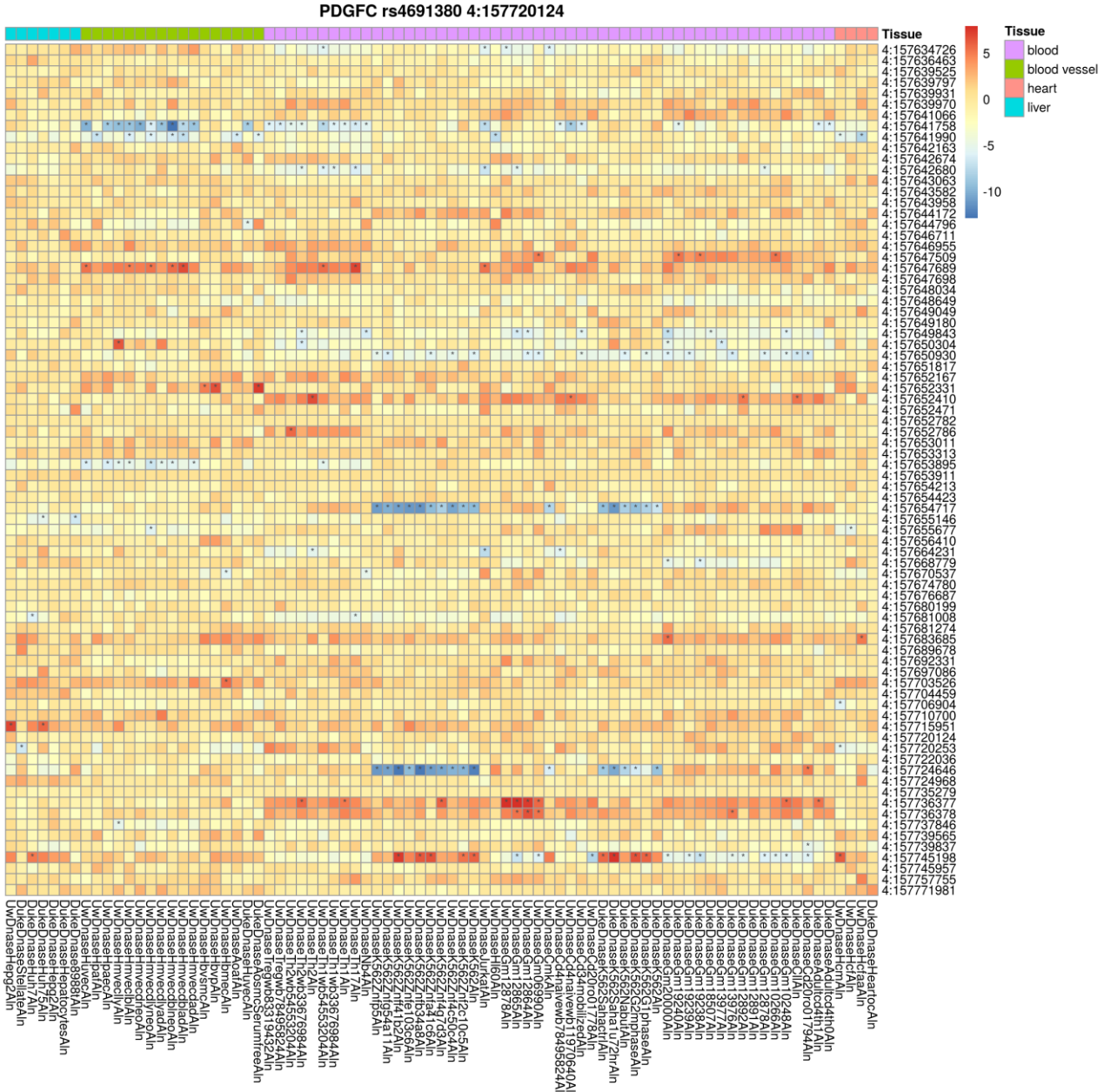
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blood vessel
heart
liver
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0
-5
-10
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4:157636463
4:157639525
4:157639797
4:157639931
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4:157641066
4:157641758
4:157641990
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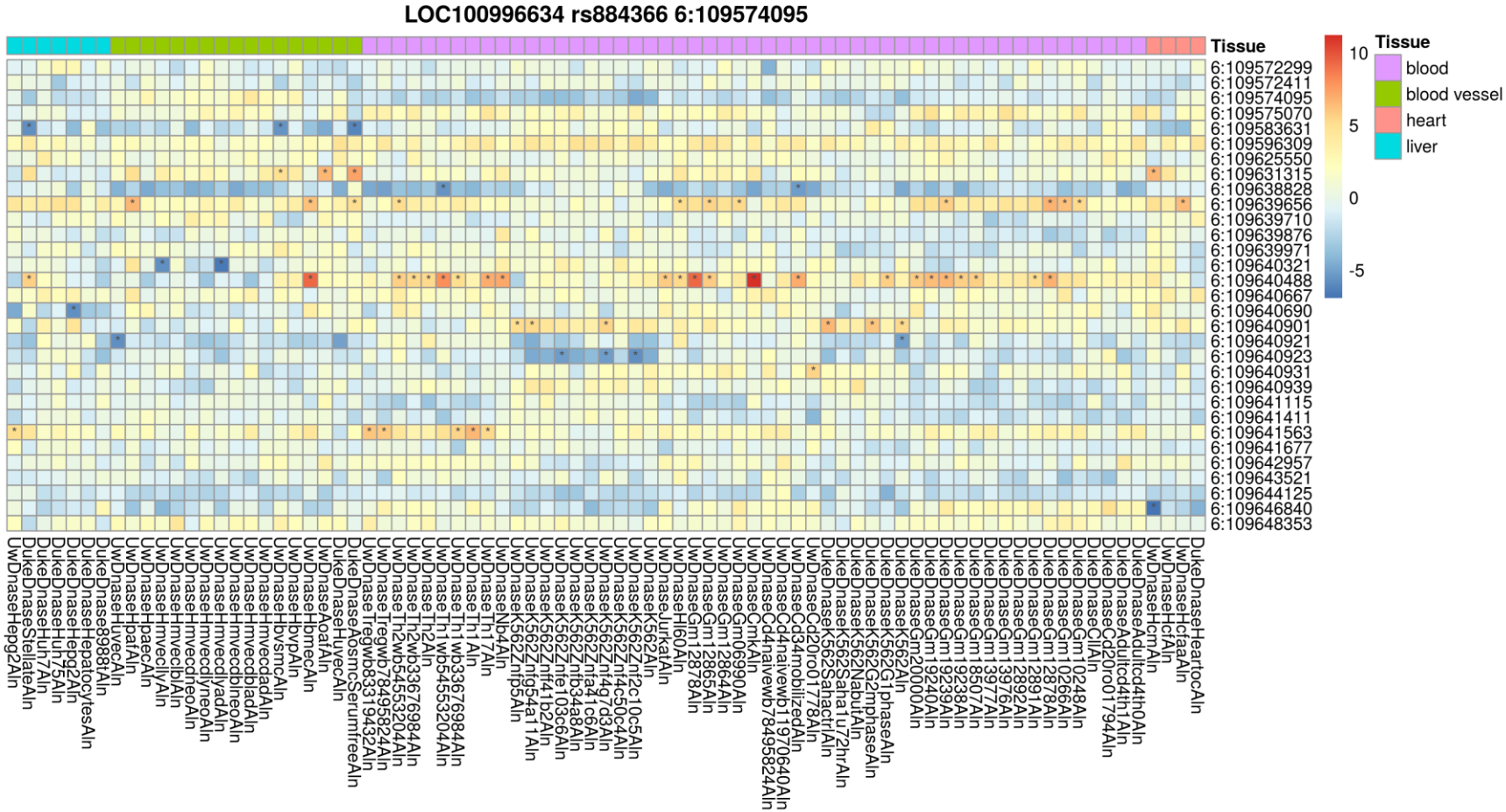
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blood vessel
heart
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DukeDnaseHuh7Aln
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DukeDnaseHepatocytesAln
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UwDnaseHuvecAln
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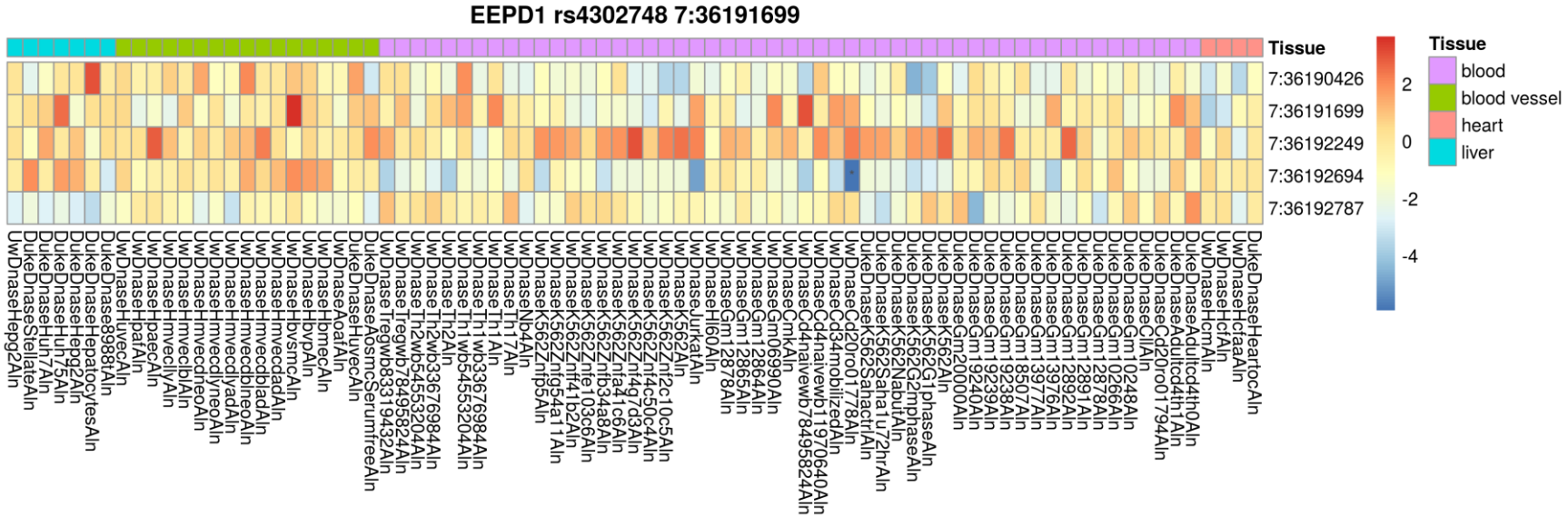
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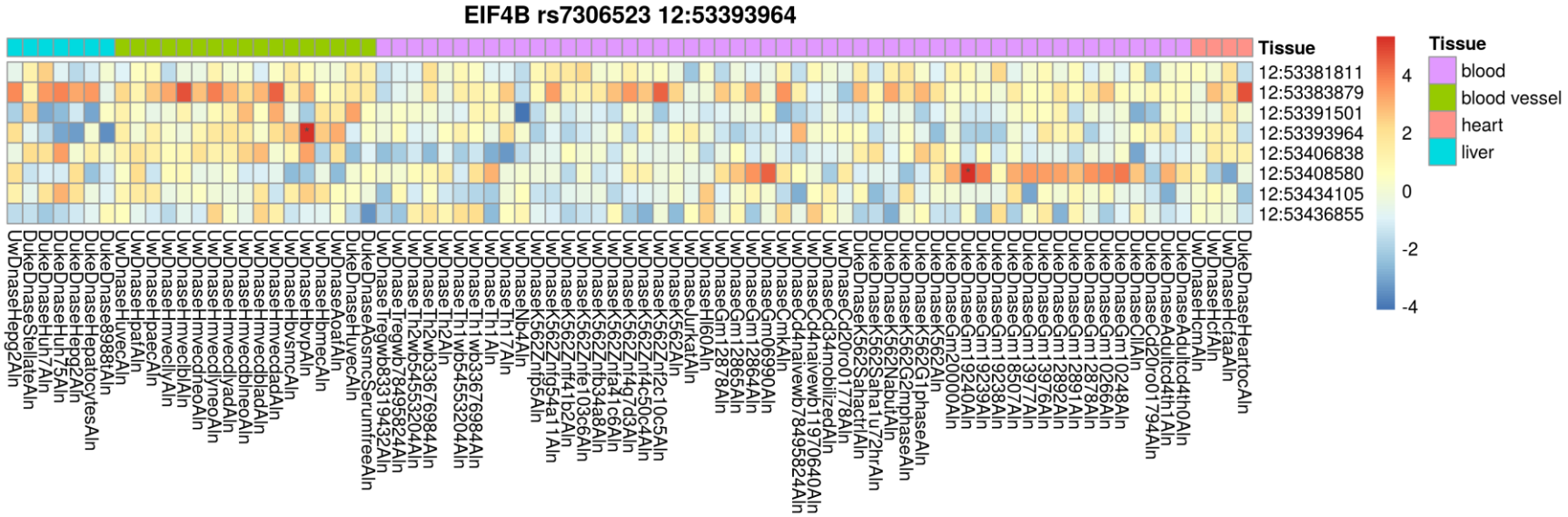
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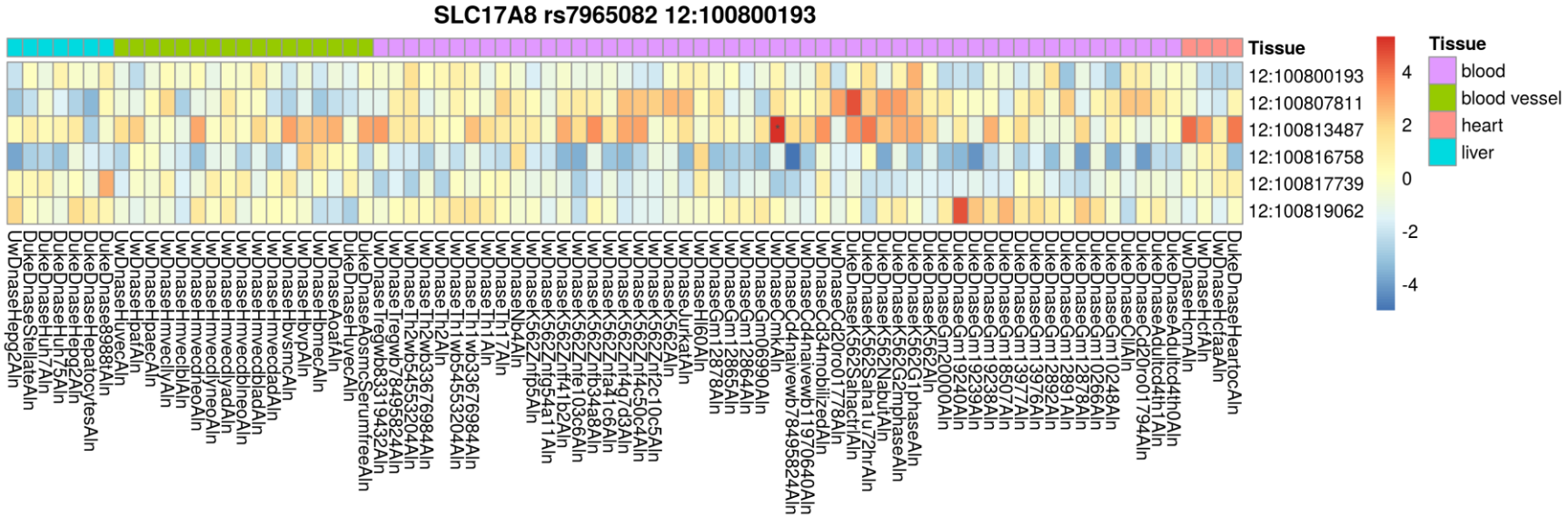
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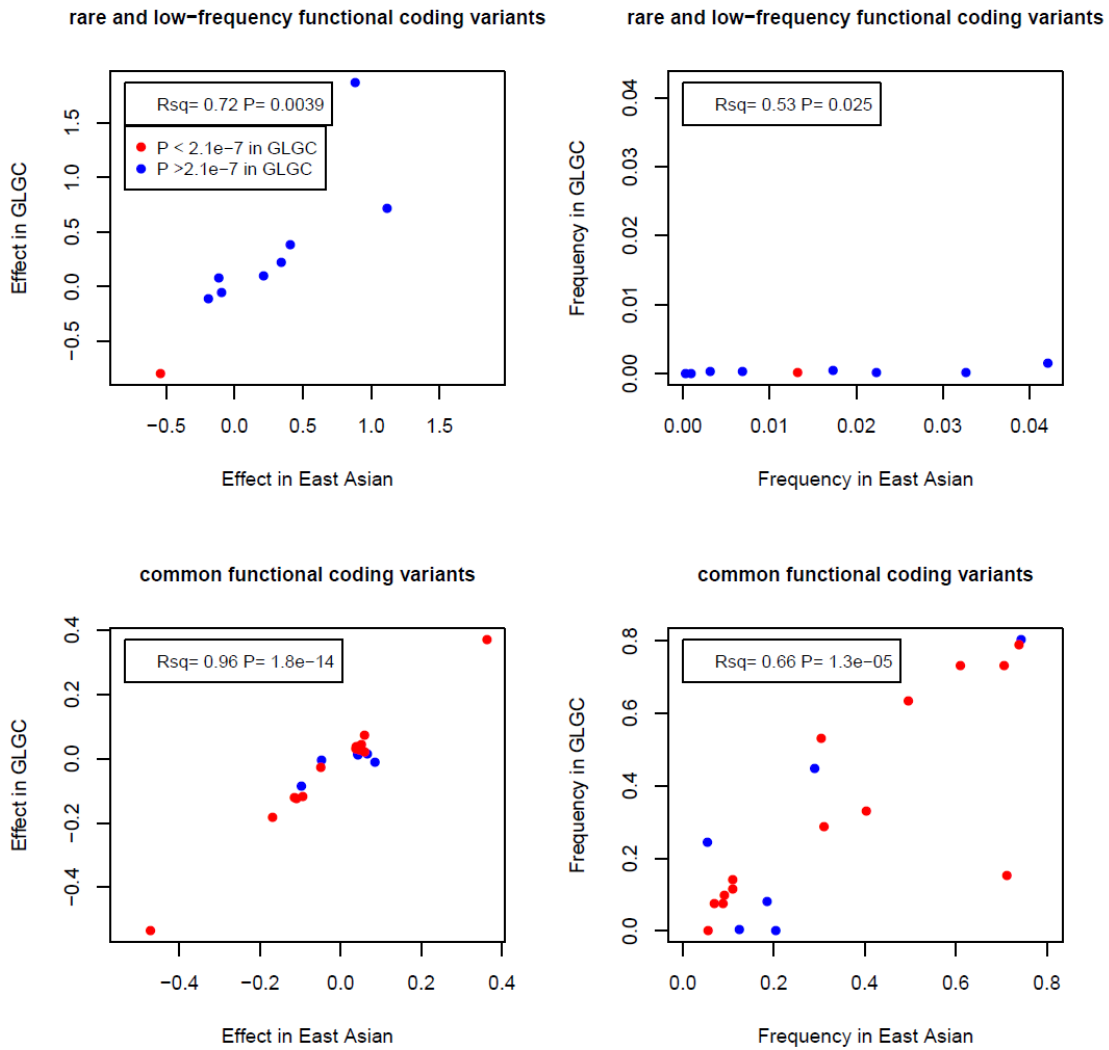
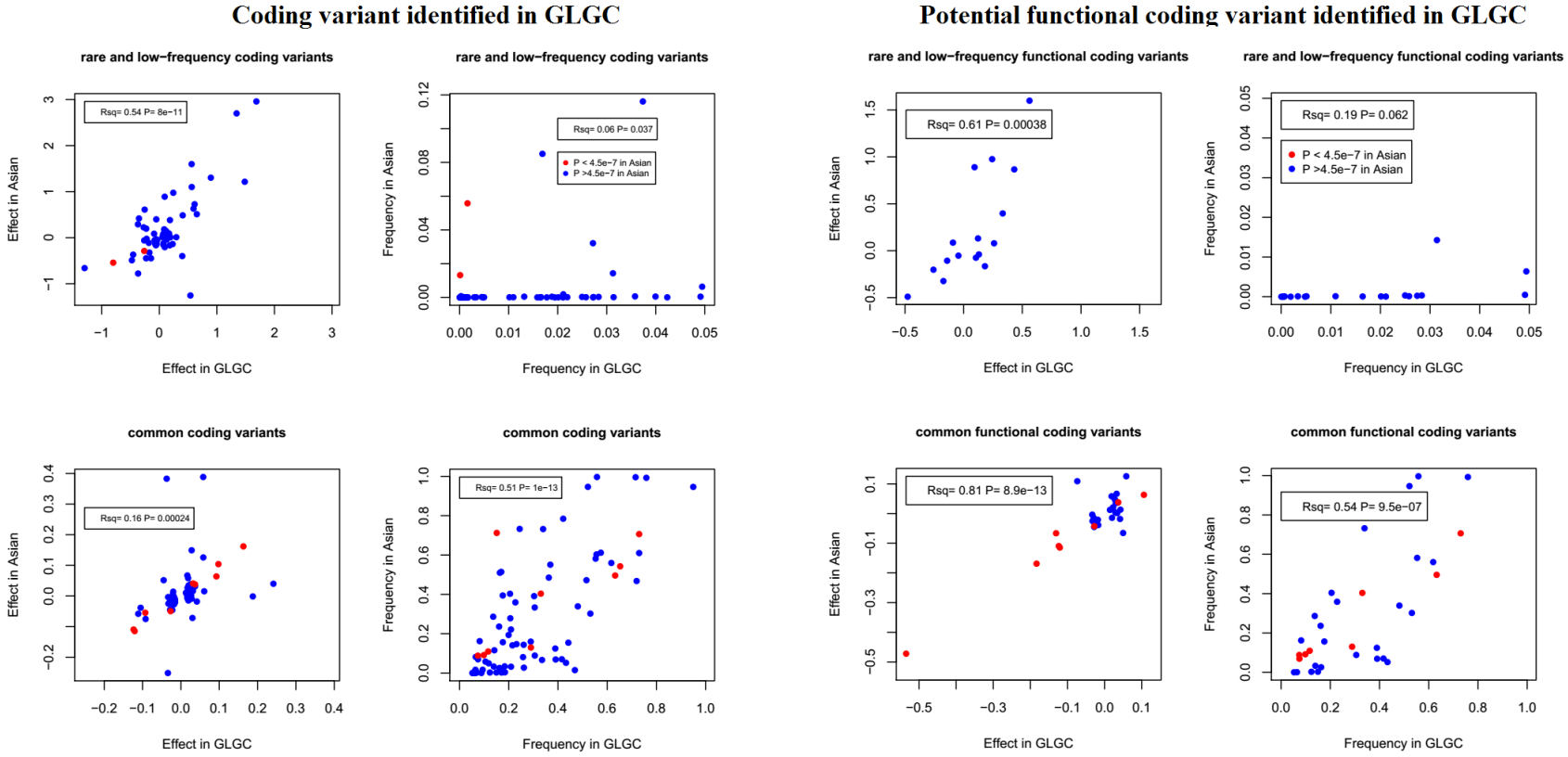
Supplementary Figure 5. Comparison of effect sizes and frequency between East Asian and GLGC for 31 functional coding variants identified in East Asian population



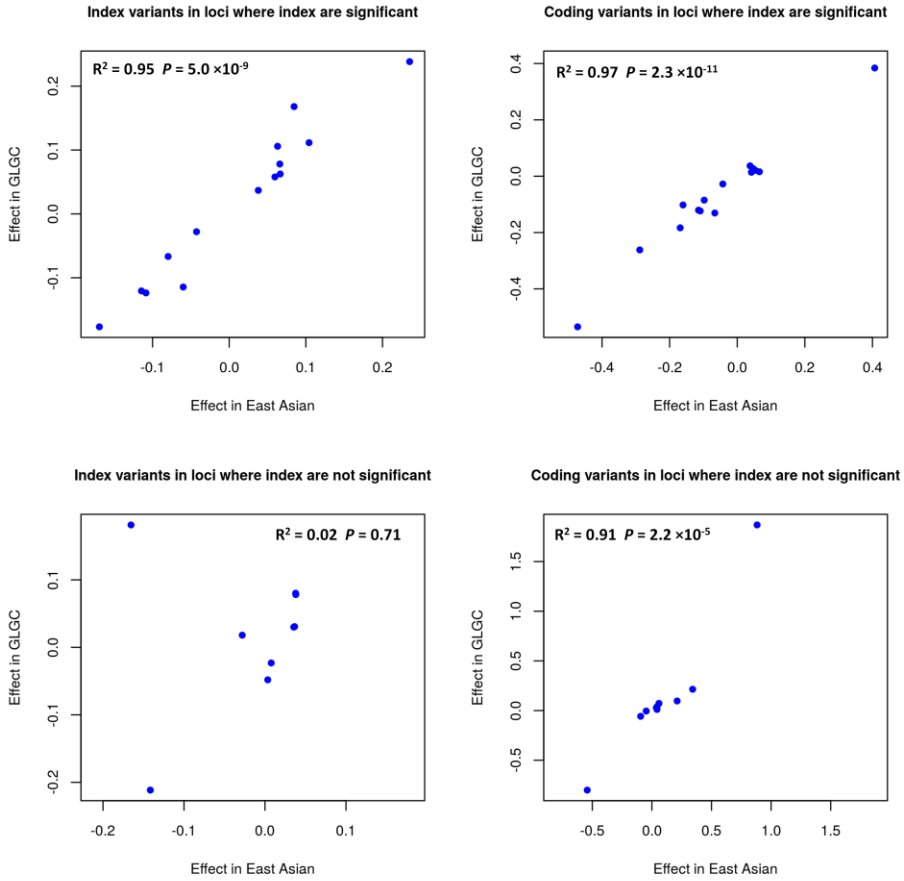
Supplementary Figure 6. Comparison of effect sizes and frequencies between East Asian and GLGC for coding variants identified in GLGC.

Among 156 independent coding variants in the known loci in GLGC samples (Supplementary table 11), 77 are low-frequency and rare coding variants (MAF < 0.05), and 60 (77.9%) show at least 10 fold lower frequency or are monomorphic in East Asian samples. Among 19 low-frequency and rare putative functional variants identified in GLGC samples (Supplementary Table 11), 17 (89.5%) were extremely rare or monomorphic in East Asian samples.



Supplementary Figure 7. Comparison of effect sizes of GWAS index and the corresponding potential functional variants across ethnic groups

Among 25 loci harboring both GWAS index and the corresponding potential functional variants, the GWAS index variants in 9 loci do not reached significant in East Asians. For the GWAS index variants that could not be replicated in East Asian samples, effect sizes are not related (r^2 = 0.02, P = 0.71) between East Asian and Europeans, while the effect sizes of the corresponding coding variants are strongly related (r^2 = 0.91, P = 2.2 ×10^{-5}). We also observed that the effect sizes of coding variants were larger than those of index variants, even for the loci where the initial GWAS index variants showed significance in East Asian samples.



Supplementary Figure 8. Quantile-quantile plots of association *P*-values for TG, HDL-C, LDL-C and TC.

Red points represent the p-value distribution of the variants in the 175 known loci (±1Mb) while blue points denote the distribution after removal of variants mapping to the known loci.