Supplementary Information

Supplementary Note

Supplementary Tables

Supplementary Table 1: (a) Study-specific *sample* quality control exclusions and baseline characteristics of the studies with *de novo* genotyping. (b) Study-specific definitions of disease outcome (CAD).

Supplementary Table 2: Summary of study-specific *SNP genotype* quality control of the studies with *de novo* genotyping.

Supplementary Table 3: Inflation factors for the studies with *de novo* genotyping.

Supplementary Table 4: Results of CAD association tests from the European and All ancestry meta-analyses for SNPs with $P<5x10^{-8}$ at the new loci.

Supplementary Table 5: Results of meta-analyses across the studies (including all samples) with *de novo* genotyping at the new CAD-associated SNPs reported in Supplementary Table 4.

Supplementary Table 6 Summary of *P*-values for the null and associated sets used in the modified MAGENTA pathway analyses with the hypergeometric tests.

Supplementary Table 7 Pathways with enrichment of CAD associated variants from the all ancestry meta-analyses identified using modified MAGENTA.

Supplementary Table 8 Ingenuity pathway analysis results. (a) identified canonical pathways (b) identified upstream regulators.

Supplementary Table 9 Co-ordinates for the genomics regions used for each new CAD locus

Supplementary Table 10 eQTL look ups of the 15 new CAD-associated regions.

Supplementary Table 11 Haploreg enrichment analyses of H3K27ac enhancer marks.

Supplementary Table 12: Association results for the established CAD loci.

Supplementary Figures

Supplementary Figure 1 QQ plots illustrating array-wide inflation for each of the studies with *de novo* genotyping.

Supplementary Figure 2 Manhattan plot showing the association of ~79,000 variants with CAD from the European meta-analysis in up to ~221,000 individuals.

Supplementary Figure 3 Forest plots from the all studies meta-analysis for the 15 sentinel CAD-associated SNPs.

Supplementary Figure 4 Regional association plots for novel CAD associated loci (a) from the all ancestry meta-analysis for 13 loci and the European meta-analysis for *GOSR* and *SERPINH1*. (b) from the publicly available CARDIoGRAMplusC4D 1000G imputed GWAS results[1].

Supplementary Figure 5 Manhattan plot for the association of the Metabochip SNPs in the studies with *de novo* genotyping.

Supplementary Figure 6 *SCARB1* regional association plots with (a) CAD (b) HDL[2] (c) LDL[2] and (d) triglycerides[2]. Physical position is given for GRCh37.

Supplementary Figure 7 Annotation of the *SCARB1* region using publicly available transcriptomic and epigenomic reference data sets

Supplementary Figure 8 Association of the PROCR gene region

Study descriptions

Baseline characteristics of the contributing studies are summarized in **Supplementary Table 1.**

The Copenhagen Ischaemic Heart Disease Study (CIHDS)

This study comprised 2,724 cases with myocardial infarction and other major acute coronary syndromes and 2,815 controls matched by age and sex from the Copenhagen General Population Study (CGPS) described below. The cases were recruited from Copenhagen University Hospital during the period from 1991 to 2009. 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, as previously described[3].

The Copenhagen General Population Study (CGPS)

The CGPS is a population-based prospective study initiated in 2003 with ongoing enrolment[3]. Participants were selected on the basis of the national Danish Civil Registration System to reflect the adult Danish population age 20 to ≥80 years. Data were obtained from a questionnaire, a physical examination, and blood samples including deoxyribonucleic acid extraction. Follow-up was 100% complete; that is, no participant was lost to follow-up. As noted above, individuals free of coronary heart disease at the time of examination were selected to serve as controls for CIHDS (Copenhagen Ischemic Heart Disease Study).

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[4]. Selection of individuals for the CCHS was based on the same criteria as for the CGPS. Information on diagnosis of CAD (defined as WHO ICD 8 410 to 414 and WHO-ICD 10 I20 to I25) was collected and verified from 1976 until 2010 by reviewing all hospital admissions and diagnoses entered in the national Danish Patient Registry, and by reviewing all causes of death entered in the national Danish Causes of Death Registry[4,5]. Again, follow-up was 100% complete for both non-fatal coronary outcomes and mortality.

European Investigation into Cancer and Nutrition-CVD (EPIC-CVD)

EPIC is a multi-centre prospective cohort study[6] 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. Participants were invited mainly from population-based registers (Denmark, Germany, certain Italian centres, the Netherlands, Norway, Sweden, UK)[7]. 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)[7]. About 97% of the participants were of white European ancestry. Prevalent CAD was ascertained through self-reported history of MI or angina, or registry-ascertained CAD event prior to baseline. EPIC-CVD employs a nested case-cohort design, analogous to the EPIC-InterAct study for type-2 diabetes[8] which established a common set of referents through selection of a random sample of the entire cohort ("subcohort"). Incident CAD cases

have been defined as fatal and non-fatal MI and other major acute coronary events, according to ICD-10 codes I20-I25. All centres have recorded cause-specific mortality through mortality registries and/or active follow-up, and have ascertained and validated incident fatal and non-fatal CAD through a combination of methods (eg, morbidity registers, general practice records, MONICA registries, self-report, clinical records[7]).

Bangladesh Risk of Acute Vascular Events (BRAVE)

BRAVE is a retrospective case-control study of first-ever confirmed acute myocardial infarction (MI) in Bangladesh. 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 if they fulfilled all of the following criteria: i) presented within 24 hours of the onset of sustained clinical symptoms suggestive of MI lasting longer than 20 minutes, including chest pain and breathlessness; ii) had ECG changes indicative of MI (new pathologic Q waves, at least 1 mm ST elevation in any 2 or more contiguous limb leads or a new left bundle branch block, or new persistent ST-T wave changes diagnostic of a non-Q wave MI) with a subsequent confirmation by troponin-I measurements; and iii) had no previous cardiovascular diseases; defined as self-reported history of angina, MI, coronary revascularisation, transient ischaemic attack, stroke or evidence of CAD on prior ECG or in other medical records. Participants were not recruited into BRAVE if any of the following features had been evident: i) a previous history of cardiovascular disease (including self-reported MI, angina, coronary revascularization, stroke, transient ischaemic attack, or peripheral vascular disease, and, in cases, presence of cardiogenic shock); ii) a history of a viral or bacterial infection in the previous 2 weeks; iii) current hospitalization for acute cerebrovascular events; iv) MI secondary to any surgery; v) documented chronic conditions, such as malignancy, any chronic infection, leprosy, malaria or other bacterial/parasitic infections, chronic inflammatory disorders, hepatitis or renal failure on past medical history; vi) pregnancy or related conditions; or vii) unable to provide consent. 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.

Pakistan Risk of Myocardial Infarction Study (PROMIS)

PROMIS is an ongoing retrospective case-control study of first-ever confirmed acute MI in Pakistan. Since 2005, the study has enrolled close to 18,500 MI cases and equivalent number of controls; the present investigation has included all MI cases and controls that had been enrolled until 2011. Patients aged 30-80 years who were admitted to the emergency rooms of nine recruitment centres across Pakistan [9] were eligible for inclusion as cases if they fulfilled all of the following criteria: symptoms within 24 hours of hospital presentation; typical ECG changes; and positive troponin-I test. To identify referents from approximately the same source population as the cases, controls were identified contemporaneously in the same hospitals as the index cases and selected from among people who had no history of CVD and who were: visitors of patients attending the outpatient department; patients attending outpatient departments for routine non-cardiac complaints; or non-blood relatives visiting index MI cases. Controls were frequency-matched to MI cases by sex and age (5-year bands). People with recent illnesses or infections were not eligible.

ARIC

The ARIC study is a multi-center cohort and community surveillance investigation in predominantly bi-racial populations (white and African Americans)[10]. ARIC recruited 15,792 individuals of which,

4,266 were African Americans. Individuals were aged 45-64 years and from four communities in Forsyth County, N.C., Jackson, M.S., Minneapolis, M.N., and Washington County, M.D. Baseline examination occurred between 1987-1989, with four follow-up examinations. Annual follow-up and community surveillance identified CAD events including hospitalizations and deaths which were then classified by an expert panel of physicians based on review of hospital records, death certificates and interviews of next of kin[10]. CAD events were defined as acute hospitalized MI (definitive or probable), definite fatal CAD, or ECG diagnosis of MI. Acute MI was defined based on criteria that included cardiac pain, cardiac markers and ECG readings. Events through December 31st, 2007 are included. After genotyping quality control and exclusion of prevalent CAD cases, 3204 African American participants 366 of which had incident CAD events were included in this study. All participants included in these analyses gave consent for genetic studies and data sharing.

WHI

WHI is a prospective study investigating post-menopausal women's health in the U.S[11]. A total of 161,838 women aged 50–79 years old were recruited from 40 US clinical centers between 1993 and 1998 to participate in an observational study (OS) and in three clinical trials (CT). Annual (OS) and semi-annual (CT) follow-up identified self-reported events which were then classified by an expert panel of physicians based on review of hospital records, death certificates and interviews of next of kin[12]. A subset of 2,200 WHI African American women was selected to be genotyped with the CardioMetaboChip by the Population Architecture using Genomics and Epidemiology (PAGE) study[13] investigators. Women were selected for genotyping on the basis of DNA and biomarker availability, and consent. CAD was defined as acute hospitalized MI (definitive or probable) and definite fatal CAD. Acute MI was defined based criteria that included cardiac pain, cardiac markers and ECG readings. Follow-up of events in WHI were through August 2009. The final sample after genotyping quality control and exclusion of prevalent self-reported CAD was up to 1954 with 99 incident CAD events. All participants included in these analyses gave consent for genetic studies and data sharing. Additional study descriptions are shown in Supplementary Table 1.

MIGen

Involves a conglomerate of six MIGen studies focused exclusively on African American (AA) ancestry and included: 565 from Multi-ethnic Study of Atherosclerosis (MESA); 700 from the Cleveland Clinic GeneBank; 410 from the International Verapamil SR/Trandolapril Study (INVEST); 324 from Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status (TRIUMPH); 469 from Penn Medicine Biobank, and 315 from Emory GeneBank .[14]

TAIwan metaboCHIp Consortium (TAICHI)

The TAICHI consortium is formed of seven studies through a collaborative effort between investigators based in the U.S. and Taiwan. The main U.S academic sites participating in the TAICHI consortium include Stanford University School of Medicine in Stanford, California; Hudson-Alpha Biotechnology Institute in Huntsville, Alabama; and Harbor-UCLA in Los Angeles, California. The main academic sites in Taiwan include National Health Research Institute (NHRI); National Taiwan University Hospital (NTUH); Taipei and Taichung Veteran's General Hospitals (VGH) and Tri-Service General Hospital (TSGH). These investigators have assembled a large, well-phenotyped sample set consisting of >13,000 Han Chinese from seven existing studies[15-19]. The consortium aims to identify genetic determinants of atherosclerosis and diabetes related traits in East Asians and to fine map validated loci identified in other race/ethnic groups.

A majority of coronary artery disease (CAD) cases in TAICHI were ascertained through hospital based studies enrolling subjects admitted for coronary angiography and/or clinical complications of CAD. These subjects were labelled as a case if a chart review by a qualified MD (most often a cardiologist) revealed that the subject either currently or in the past was suffering from a myocardial infarction, an acute coronary syndrome, angina, or demonstrated at least one epicardial coronary artery obstruction of >50% on coronary angiogram. A small minority of cases were identified among the non-hospital based prospective cohort studies through a self-report of either having suffered an MI, having undergone one or more procedures related to clinical complications of CAD, or having an ECG diagnostic of a prior q wave myocardial infarction or an ongoing ST-segment elevation MI based on the Minnesota Code[20]. Subjects who had no previous history of clinical CAD who were found to have sub-occlusive disease on angiogram (*i.e.* some evidence of atherosclerosis but no epicardial coronary artery obstruction of >50%) were excluded (*i.e.* they were neither considered a case or a control). All other subjects were considered controls.

1. **Taiwan Coronary Artery Disease GENetic (TCAGEN) study (PI - Dr. Jyh-Ming Juang)** is an ongoing cohort study that has been enrolling patients undergoing coronary angiography or percutaneous intervention at the National Taiwan University Hospital (NTUH) in the setting of either stable angina pectoris or prior myocardial infarction[19]. Participants are from both the north of Taiwan where the main NTU medical school/hospital is located, and from the Yulin branch of NTUH, located in south/central Taiwan. The hospital uses an elaborate electronic medical record system that provides access to clinic visit notes, diagnostic codes of clinic encounters, prescriptions, and laboratory data in a searchable form. Fasting blood samples were collected before cardiac catheterization while peripheral blood was collected in the catheter lab specifically for buffy coat isolation and DNA extraction.
2. **Taichung CAD (TCAD) study (PI - Dr. Wayne Huey-Herng Sheu)** includes patients with a variety of cardiovascular diseases receiving care at the Taichung Veterans General Hospital. Specifically, individuals who were hospitalized for diagnostic and interventional coronary angiography examinations and treatment are included in TAI CHI[16]. Also included in TAI CHI are subjects with a history of myocardial infarction or revascularization of any type (percutaneous coronary intervention or coronary artery bypass).
3. **TAiwan Coronary and Transcatheter intervention (TACT) cohort study (PI Dr. Tzung-Dau Wang)** enrolled patients with angina pectoris and objective documentation of myocardial ischemia who underwent diagnostic coronary angiography and/or revascularization any time after October 2000 at the National Taiwan University Hospital (NTUH)[18]. This cohort is very similar to TCAGEN but was collected independently. Participants provided clinically relevant information including use of cardiovascular related medication through a standardized questionnaire. Clinically relevant information is also available through a comprehensive electronic medical records database that includes information on drug use and surgical interventions. Fasting blood samples were collected before cardiac catheterization.
4. **Taiwan Diabetes and RelAted Genetic COmplicatioN (Taiwan DRAGON) cohort study (PI - Dr. Wayne Huey-Herng Sheu)** of type 2 diabetes (T2D) at the Veteran's General Hospital in Taichung, Taiwan (Taichung VGH)[17]. Participants include individuals with either newly diagnoses or established diabetes who visit the diabetes outpatient clinic on a regular basis. Subjects with hyperglycemia who do not meet criteria for T2D defined by IDF are not included. Individuals participate in a health examination program at Taichung VGH are also interviewed. Specialized tests include an oral glucose tolerance tests (OGTT) in subjects without an established diagnosis of diabetes.

5. **Taiwan USA Diabetes Retinopathy (TUDR) cohort study (PI - Dr. Wayne Huey-Herng Sheu)** enrolled subjects with T2D receiving care at Taiching Veteran's General Hospital, a small number of subjects were included from Tri-Service General Hospital (TSGH)[17]. All TUDR subjects underwent a complete fundoscopic examination to carefully document the presence and extent of retinopathy. To date, a total of 2,222 unrelated T2D subjects with and without retinopathy were ascertained and have undergone metabochip genotyping. Of the 2,222 subjects, 1,201 were T2D without eye diseases, 479 were T2D with NPDR and 542 T2D with PDR. In addition to DNA and buffy coats, fasting blood for future measurement of serum/plasma biomarkers has also been banked. A variety of additional clinical related phenotypes are available. All 2,222 overlaps with the Taiwan Dragon Study.
6. **Healthy Aging Longitudinal Study in Taiwan (HALST) (PI – Dr. Agnes Chao Hsiung)** is a population based multi-site cohort study of ambulatory adults aged > 55 years living in 7 major geographic regions of Taiwan, established by the NHRI[21]. The aim of the study is to investigate the multidimensional determinants, including lifestyle, genetic, metabolic, and inflammatory factors, of an older Asian population. These 7 locations include both urban and rural areas: two are in the north (Taipei's Shilin District and Taoyuan County's Yangmei Township), two in central Taiwan (Miaoli City in Miaoli County and Changhua City in Changhua County), two in the south (Puzi, Chiayi County, and Kaohsiung's Lingya District), and one in the east (Hualien City/County). The only exclusion criteria are presence of highly contagious diseases, advanced illnesses with limited life span or bedridden status, dementia, other advanced neurological deficit, severe hearing loss, and institutionalization in a chronic care facility for any reason. Over 5000 subjects have been recruited over a five-year period (2008-2012) from seven recruitment sites across the country. Follow-up in person visits are currently ongoing and will continue throughout a second 5-year study cycle scheduled that began in 2013 (~1000 subjects / year). Within each wave, participants are to be followed up by telephone contact every year for vital status and for updates on health-related conditions. Medical records are requested to confirm the development of any new health conditions. Vital status, health claims, health care utilization data are being collected for the cohort on a regular basis by linking to the National Death Registry Database and the National Health Insurance Database. HALST served as one the main "control" cohorts for this study after exclusions of subjects with a self-report of CAD or a ECG diagnostic of prior MI.
7. **Stanford-Asian Pacific Program in Hypertension and Insulin Resistance (SAPPHIRe) family based study (PIs – Dr. Thomas Quertermous, Agnes Chao Hsiung, and Wayne Huey-Herng Sheu**) was established in 1995 with an initial goal of identifying major genetic loci underlying hypertension and insulin resistance through linkage in East Asian populations. SAPPHIRe was also one of four networks participating the NHLBI's Family Blood Pressure Program (FBPP)[15]. At the outset, SAPPHIRe involved recruitment sites in the San Francisco Bay Area, Hawaii, and Taiwan. However, a majority of the ~1,700 sibpairs in SAPPHIRe were recruited from 3 centers in Taiwan (NTUH, Taipei VGH and Taichung VGH) with NHRI being the DCC. Sibpairs were either highly concordant or discordant for blood pressure and a subset underwent an insulin suppression test. Many metabolic variables associated with blood pressure and insulin resistance were examined in the first 5-year investigative cycle funded by the NIH (1995-2000). Further extensive phenotyping through return visits and regular follow ups occurred between 2001 and 2008 in the Taiwanese SAPPHIRe participants which included echocardiographic and multi-detector row CT imaging procedures. These efforts were facilitated by a programmatic collaboration between the NHLBI's FBPP and the National Health Research Institute in Taiwan. Like

HALST, SAPPHIRe served predominantly as a “control” cohort in this study. Only one sib per family was included as a control in this study.

Two of the TAICHI studies (Taiwan DRAGON and TUDR) were T2D cohorts and so T2D cases that had been diagnosed with CAD were included as cases in the CAD analyses, while the remaining T2D samples were included as controls.

Pathway and network analyses

Modified MAGENTA

Given the Metabochip comprises a select set of SNPs and lacks complete genomic coverage[22], MAGENTA, which assumes random sampling of variants from across the genome, could not be directly implemented. Therefore a modified version of MAGENTA involving a hypergeometric test to account for the chip design was used to test for pathways that were enriched with CAD associated variants[23]. This approach requires defining two sets of variants; a null set of variants that are not associated with CAD and a set that are associated with CAD, referred to as the "associated set". Multiple variants can map to the same gene and still be included in the test. SNPs in LD were pruned out of the association results such that $r^2 < 0.2$ for all pairs of SNPs (based on 1,000 Genomes Project data[24]; www.1000genomes.org; Supplementary Table 6) prior to implementation of the modified MAGENTA. The null set was defined as the 1,000 remaining QT interval SNPs with the largest *P*-values (least evidence) for association with CAD. The associated set was defined as variants (after LD pruning) that showed evidence of association $P < 1x10^{-6}$. This approach was adopted to select the null and associated sets so as to limit the number of variants included in the hypergeometric cumulative mass function, as a large number of variants results in an intractable calculation for the binomial coefficients. The observed *P*-value from the hypergeometric test is compared to the *P*-values obtained from 10,000 random sets to compute an empirical enrichment *P*-value.

An analysis of European, and all ancestry meta-analyses are reported. A total of 47,468 SNPs (of which 2,937 were QT interval SNPs) mapped to 11,190 genes and could be included in the European analysis, whilst 61,223 SNPs (3,403 of which were QT interval SNPs) mapped to 11,904 genes were included in the all ancestry analysis. Within the null set of the European analysis 873 genes were covered by the 1,000 null SNPs, whilst within the associated set 73 genes were covered by 76 SNPs. For the all ancestry analysis, 887 genes were covered by the 1,000 null SNPs and 78 genes were covered by 85 SNPs in the associated set. Sensitivity analyses to specific parameters used in the modified MAGENTA analyses were assessed. Sensitivity to the *P*-value threshold for inclusion in the associated set of variants was tested at $P<10^{-5}$, $P < 10^{-7}$; the number of variants included in the null set of variants was set to 900 and 1,100; known CAD regions (identified in the NIH Catalog of Published Genome-Wide Association Studies, https://www.genome.gov/26525384) were removed; the newly identified CAD loci were removed; the *COL4A1* and *COL4A2* genes that appear in the associated sets for several enriched pathways were excluded and the number of random sets used to calculate the empirical enrichment *P*-value by was changed to 1,000 and 100,000 random sets.

Seven databases (BioCarta www.biocarta.com/genes/indexasp, Kyoto Encyclopedia of Genes and Genomes [KEGG], www.genome.jp.kegg, Ingenuity, www.ingenuity.com, Panther, Panther Biological Processes and Panther Molecular Functions www.pantherdb.org, and Reactome, www.reactome.org) comprising 1,558 pathways, were tested for enrichment of genes associated with CAD. There were 23 pathways (18 independent) with $P<0.01$ from the European only pathway analysis and 19 pathways (16 independent) with $P<0.01$ from the all ancestry pathway analysis. (A more stringent significance threshold of $p<0.01$ was used rather than the more conventional $P\leq0.05$ so as to minimise the number of enriched pathways identified.) Ten pathways were in common between these analyses. Independence of pathways were determined by pathway gene content, if a pathway was a subset of another then it was deemed dependent. For example, the Reactome cell surface interactions at the vascular wall pathway (93 genes) is contained in the Reactome hemostasis pathway (272 genes). The chylomicron mediated lipid transport pathway (17 genes) is contained in the

Reactome lipoprotein metabolism pathway (27 genes), which is itself contained in the Reactome metabolism of lipids and lipoproteins pathway (228 genes).

The strongest evidence for enrichment in the European only analysis was for the KEGG glycerolipid metabolism pathway (49 genes, $P<3x10^{-5}$). The strongest evidence for enrichment from the all ancestry analysis was shown by the Reactome lipoprotein metabolism pathway (27 genes, $P<3x10^{-5}$). Generally pathways involved in lipid metabolism were the most enriched (11 of the 32 with $P<0.01$ in the European or all ancestry analysis).

The sensitivity analyses revealed that changing the number of random sets to 1,000 or 100,000 instead of 10,000 as used in the main analysis, resulted in the same pathways being identified in the European and the all ancestry analyses ($P<0.01$). Exclusion of *COL4A1/2* from the associated set resulted in fewer pathways being enriched, however, all but one of those enriched for the all ancestry pathway analysis were identified by the main analyses. Inclusion of less ($P<10^{-7}$) associated variants resulted in the loss of several pathways that were identified by the main analysis. Use of less associated variants ($P<1x10^{-7}$) identified fewer pathways as expected, however, most of these were identified by the main analysis. A more liberal *P*-value threshold ($P<1x10^{-5}$) for inclusion of variants in the associated set produced more enriched pathways than the main analysis, with most of the pathways identified by the main analysis being detected. The all ancestry sensitivity analysis with more associated variants detected several unique pathways. Use of less null variants (N=900) generally identified the same pathways as the main analysis. However, inclusion of more variants in the null set (N=1,100) resulted in an attenuation of pathways that were enriched. Most pathways identified under this sensitivity were detected by the main analysis. Removal of known and novel CAD loci generally resulted in less pathways being identified. The pathways found to be enriched from the sensitivity analyses that were not detected by the main analyses did not give additional insights into novel biological pathways involved with CAD. Three positive control pathways were also tested for enrichment of variants associated with CAD (Supplementary Table 7). The CAC and CAD pathways were significantly enriched for variants associated with CAD (CAC pathway *P*-value range: $0.00\text{-}1x10^{-5}$; CAD pathway $P = 0.00$ for all analyses).

Ingenuity pathway analyses

We used the Core Analysis' function in the Ingenuity Pathway Analysis (IPA) software (Ingenuity Systems, Redwood City) to identify canonical pathways enriched with one or more SNPs with a low *P*-value in the all ancestry meta-analysis. IPA mapped 41,480 of the ~78,954 SNPs in our meta-analysis to ~8,894 RefSeq genes (*i.e.* the reference set of genes). Given the ~79,000 SNPs examined were primarily preselected candidate SNPs for association with CAD or its risk factors[22] and CAD has a complex genetic architecture the appropriate *P*-value cut-off to select SNPs for inclusion in the pathway analysis was unclear[25,26]. Therefore, six *P*-value thresholds ($5x10^{-7}$, $5x10^{-6}$, $5x10^{-5}$, 0.0005, 0.005, and 0.05) were considered. The number of focus genes increased as the *P*-value threshold was lowered (76, 142, 228, 402, and 909, 2,439 for the six *P*-value thresholds). IPA uses a right-tailed Fisher Exact Test to test for statistically significant over-representation of focus genes in a given canonical pathway among the genes with SNPs with low *P*-values compared to the reference set of genes.

We also used the IPA to identify potential upstream regulators of genes with SNP(s) with low *P*-values

[http://pages.ingenuity.com/rs/ingenuity/images/0812%20upstream_regulator_analysis_whitepaper.pdf]. Upstream regulators were not necessarily represented by SNPs on the Metabochip but could still be expected to play an important role in the pathogenesis of CAD.

The use of a liberal *P*-value thresholds in IPA revealed evidence of enrichment for the, sildenafil, PPARα/RXRα Activation, Protein Kinase A signaling, and the Axonal Guidance Signaling pathways (Supplementary Table 8). We note analyses of the CARDIoGRAM GWAS data with only partial overlap with subjects examined here and using a different gene-set enrichment analysis algorithm also identified the axonal guidance pathways as relevant to CAD[27]. While axon guidance pathways modulate diverse biological phenomena within the nervous system, there is growing evidence that neural guidance cues play important roles outside the nervous system. For example, Netrin-1 is secreted by macrophage foam cells in atherosclerotic plaques and acts to inhibit emigration of these cells out of lesions by causing dysregulation of the actin cytoskeleton[28] and semaphorin 3A, expressed in coronary artery endothelial cells, potently inhibits chemokine-directed migration of human monocytes[29,30].

The tests for enrichment of genes associated with CAD[23] (Supplementary Tables 6 and 7) and analyses using the Ingenuity Pathway Analysis (IPA) software (Supplementary Table 8) identified known CAD associated pathways, such as metabolism of lipids and lipoproteins, farnesoid X receptor (FXR)/retinoid X receptor (RXR) activation and liver X receptor (LXR)/RXR activation. Evidence of enrichment using IPA with a P=0.05 cut-off was obtained for a number of pathways including the PPARα/RXRα Activation, and Protein Kinase A signaling pathways (P=3.98x10^{-11} and 3.16x10^{-11}, respectively) which could indicate new areas of biology to investigate.

Further information on the new CAD gene regions

ATP1B1

The sentinel CAD associated SNP, rs1892094, is located at intron 3 of the *ATP1B1* gene, encoding for the Na^+/K^+ ATPase beta subunit 1. Several GWASs have identified common variants at this locus associated with electrocardiographic parameters, including QT interval[31-33]. However, the implicated variants are not in LD with rs1892094 ($r^2<0.2$, 1000 Genomes EUR). The CAD SNP is however, associated with expression of *ATP1B1* in atherosclerotic root ($P=5.24x10^{-24}$)[34]. A recent study has reported an association of the region with pulse pressure[35] with a SNP (rs7519279) that is in LD with the CAD associated SNP ($r^2=0.44$, D'=0.98 in 1000Genomes EUR). In mouse, mutations in this gene have resulted in increased heart mass and cardiac hypertrophy, which could suggest a common mechanism. Together these findings make *ATP1B1* an interesting candidate gene.

Expression studies, however, also highlight *NME7* as a possible candidate. The CAD SNP rs1892094 is associated with *NME7* gene expression levels in LCLs ($P=4.82x10^{-13}$) adipose ($P=9.46x10^{-14}$)[36], aorta ($P=2.39x10^{-14}$)[37], peripheral blood mononuclear cells ($P=7.98x10^{-18}$)[38] and monocytes ($P=1.1\times10^{-11}$)[39]. *NME7* encodes the protein NME/NM23 family member 7 that is found in high abundance in many tissues including liver and kidney. However, there is no compelling cardiovascular phenotypes reported for this gene in mouse and its possible gene function with regards to the pathobiology of cardiovascular disease is elusive.

TNS1

The non-synonymous CAD associated SNP, rs2571445 (W1197R) has previously been associated with pulmonary function[40-42]. Repapi et al. (ref [40]), also showed *TNS1* was expressed in lung tissue, bronchial epithelial cells, airway smooth muscle cells and peripheral blood mononuclear cells in human. The CAD risk allele is associated with increased expression of TNS1 in adipose ($\beta=0.12$, $P=8.88x10^{-10}$)[36] and peripheral blood ($P=1.81x10^{-24}$)[43]. The encoded protein is found in many tissues including smooth muscle cells and heart. Animal models have shown that this gene causes abnormal kidney morphology, kidney failure and abnormal renal glomerulus morphology and decreased renal plasma flow rate.

ARHGAP26

The CAD risk allele, rs246600-T ($P=1.51x10^{-8}$; OR[95%CI]=1.04[1.03-1.06]) maps to an intron of Rho GTPase-Activating Protein 26 (*ARHGAP26*) a region that has been associated with triglycerides, type 2 diabetes and BMI. These variants however are not in LD with rs246600, the CAD associated SNP. However, this gene remains a very interesting candidate because the protein encoded by this gene is a GTPase activating protein that binds to focal adhesion kinase (FAK), a protein involved in the signaling cascades that regulate the organization of the actin-cytoskeleton, and mediates the activity of the GTP binding proteins RhoA and Cdc42[44], which represent proteins involved in the regulation and timing of cell division, morphology, migration and endocytosis. These processes may be relevant to the migration of fibroblasts and smooth muscle cells in the arterial vessel wall in response to the

deposition of vessel wall plaque as has been recently shown for the *TCF21* CAD susceptibility locus[45].

PARP12

We have shown that rs10237377-T confers protection from CAD (P=1.75x10^{-8}, OR[95%CI]=0.95[0.93-0.97]). This variant (or a tag r^2>0.8) has not been associated with another trait as GWS to date but it is an eQTL for Thromboxane A Synthase 1 (*TBXAS1*) in whole blood (P=3.09x10^{-71})[43]. TBXAS1, catalyzes the conversion of the prostaglandin endoperoxide into thromboxane A2, a potent vasoconstrictor and inducer of platelet aggregation[46]. *TBXAS1*, has been implicated in reduction of CAD complications in a recent trial[47]. The gene has also been associated with thromboxane synthetase deficiency a rare bleeding disorder (OMIM). In mouse, mutations in *TBXAS1* have resulted in increased bleeding and decreased platelet aggregation. Together these findings suggest that *TBXAS1* could be a candidate causal gene in the region through platelet aggregation mechanisms.

SERPINH1

rs590121-T maps to an intron of *SERPINH1* and we show is associated with increased risk of CAD (Table 1; OR=1.05[1.03-1.07], P=1.54x10^{-8}). This SNP is in LD with rs6704 (D'=1, r^2=0.86) which is an eQTL for *SERPINH1* in whole blood (P=3.3x10^{-22}). This gene encodes a member of the serpin superfamily of serine proteinase inhibitors. The encoded protein is found in smooth muscle cells, is localized to the endoplasmic reticulum and plays a role in collagen biosynthesis as a collagen-specific molecular chaperone. Autoantibodies to the encoded protein have been found in patients with rheumatoid arthritis.

The CAD associated SNP is also an eQTL for a neighbouring gene, *GDPD5*, in whole blood (P=8.69x10^{-10}) [43] and peripheral blood mononuclear cells (P=2.22x10^{-14})[38], however, the LD between the CAD associated SNP and the top eQTL is low r^2<0.1. GDPD5 protein is found in many tissues including liver and kidney.

C12orf43/HNF1A

The *C12orf43* region harbours three SNPs in the EUR studies and four in the all ancestry (five in total) that are associated with CAD at genome-wide significance (Supplementary Table 4). rs2258287, the sentinel SNP in EUR is located about 2Kb upstream of *C12orf43*. The A allele increases risk of CAD (OR[95% CI]=1.05[1.03-1.06], P=6x10^{-9}) and has previously been associated with increased LDL-C and total cholesterol levels (P=6.66x10^{-17})[2].

rs2258287 is also associated in the all ancestry analyses (P=2.18x10^{-8}) however rs2244608 has a modestly smaller P-value (P=1.57x10^{-8}). These SNPs are not in LD in African ancestries (r^2=0.12, D'=0.65, 1000G AFR), East Asians (r^2=0.14, D'=0.8, 1000G) or South Asians (r^2=0.38, D'=0.7 1000G SAS) and are in moderate LD in Europeans (r^2=0.68, D'=0.84 in 1000G EUR). These SNPs or strong proxies (r^2>0.8) were associated with decreased C-reactive protein (P=6.66x10^{-17}) [48,49], increased gamma glutamlytransferase levels (P=8.30x10^{-38}) [50] and activity (P=6.66x10^{-17})[51]. rs2244608 is intronic in the *HNF1A* gene. *HNF1A* encodes hepatocyte nuclear factor 1 homeobox A, a transcription factor highly expressed in the

digestive system and liver, which regulates many genes involved in a wide range of biological processes, including lipid and glucose transport and metabolism, and coagulation pathways. However, *HNF1A* is perhaps better known as a gene containing low-frequency variants causing maturity onset diabetes of the young (MODY3), a Mendelian form of diabetes caused by low-frequency dominant mutations. A tightly correlated missense variant in *HNF1A* (rs1169288, r^2=0.96, D'=0.99 with rs2244608 in 1000G EUR) is predicted to have functional effects on *HNF1A.*

SCARB1

The CAD and HDL associations in the *SCARB1* region are likely to be independent as neither of our CAD associated SNPs in *SCARB1* (rs11057830 and rs11057841) were in LD with the sentinel HDL-C associated SNP, rs838880, (r^2=0.02, D'=0.6 in 1000 Genomes CEU samples; Supplementary Fig. 6).

To further test the CAD and HDL associations, the summary statistics for major lipids[2] (joint analysis of metabochip and GWAS data http://csg.sph.umich.edu//abecasis/public/lipids2013/) made available by the Global Lipids Genetics Consortium were downloaded and used for the conditional analyses at the *SCARB1* region. The association of rs11057830 with CAD remained after conditioning on the HDL signal (P=1.30x10^{-8}: note, rs838880, a SNP in strong LD with the sentinel HDL SNP, r^2=0.83, D'=0.95 in the 1000G CEU samples, was used as rs838876 was not genotyped on the Metabochip). The association of rs838876 with HDL remained (P=1.15x10^{-35}, β=-0.049) after conditioning on the CAD associated SNP, rs11057830.

<u>The unconditional associations of the above mentioned SNPs with CAD, HDL, LDL and TG.</u>

	CAD SNP rs11057830 A/G	**Reported HDL SNP rs838876** G/A	**Metabochip Tag of HDL SNP rs838880** T/C	**Top TG SNP rs10846744** C/G
	β (*P*-value)			
CAD	0.0623 (1.34x10^{-8})	--	0.0153 (0.055)	0.0524 (5.857x10^{-7})
HDL	-0.0181 (0.0018)	-0.049 (7.33x10^{-33})	-0.048 (6.38x10^{-32})	-0.0145 (0.009)
LDL	0.0253 (2.58x10^{-5})	0.003 (0.44)	0.0006 (0.88)	0.0253 (4.654x10^{-5})
TG	0.0220 (8.34x10^{-5})	0.0052 (0.38)	0.0059 (0.31)	0.0236 (2.218x10^{-5})

Note the effect allele/non-effect alleles are listed after the SNP name.

In contrast, there is no evidence of association in the region after conditioning on the top CAD SNP rs11057830, which is also the top LDL SNP, in this region and is in high LD with the top TG SNP rs10846744 (r^2=0.94 in 1000 Genome phase 3 EUR samples). Given there is evidence of association with LDL-C and triglycerides at the CAD associated SNPs, this suggests that the *SCARB1* CAD association may be mediated via pro-atherogenic lipids.

DHX38

The *DHX38* region has previously been associated with increased total and LDL cholesterol[52]. Indeed, rs2000999-A, the cholesterol associated SNP, was associated with CAD in our data, but with less evidence (P=6.8x10^{-7}, OR[95% CI]=1.04[1.03-1.06]) than the SNPs that map to *DHX38* and was not convincingly associated with CAD after conditioning on rs1050362 (P>0.001). In addition to the cholesterol associations, the *DHX38* region has been reported to be associated with metabolites (tyrosine, phenylalanine/tyrosine ratio and glycoprotein)[53,54], ischemic stroke[55], atrial fibrillation[56] and Kawasaki disease[57], however the SNPs involved are not in LD with the CAD associated SNPs (r^2<0.15) suggesting these associations act through different causal pathways to the CAD association.

GOSR2

Within the *GOSR2* region, the CAD risk increasing allele rs17608766-C (OR[95% CI]=1.07[1.04-1.09]) has previously been reported to be associated with increased SBP[58] and increased pulse pressure.[59] It has also been associated with expression of *GOSR2* in liver[60,61] and reduced expression in brain, cerebellum and temporal cortex.[62] The association with CAD is likely to be through blood pressure and so the neighboring gene *WNT9B* also makes an interesting candidate. The kidney has an important role in blood pressure regulation. WNT9B protein shows highest expression in kidney (human protein atlas) and is implicated in kidney development. In mouse, mutation in the orthologous gene result in abnormal kidney development. Canonical Wnt9b signaling balances progenitor cell expansion and differentiation during kidney development.

PROCR

The CAD-associated SNP, rs867186 (or a SNP in strong LD r^2>0.8 in 1000G EUR) is associated with expression of *PROCR* across a range of tissues including, atherosclerotic aortic root[34], liver[60], skin and subcutaneaous adipose tissue[36] and transformed fibroblasts[37] (Supplementary Table 8, Supplementary Figure 8). While it is also in LD with the top eQTL for *EIF6*[63] and *ITGB4BP*[39] in monocytes, *PROCR* remains a plausible candidate gene for the CAD association.

The complexity underpinning the *PROCR* pathway is highlighted by its apparently paradoxical effects to reduce activity of the protein C pathway and increase risk of venous thrombosis, but *decrease* risk of CAD. Future studies will seek to elucidate this pathway, noting that previous studies have also highlighted a role of the EPCR in influencing vascular permeability and inflammation[64], which may be independent of its thrombotic effects.

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Acknowledgements

The TAICHI study was supported by a grant from the NHLBI grant HL087647. The Taiwan Dragon (TAICHI) was supported by grants from National Science Council (NSC 98-2314-B-075A-002-MY3) and Taichung Veterans General Hospital, Taichung, Taiwan (TCVGH-1013001C;TCVGH-1013002D). The TCAD (TAICHI) was supported by grants from National Science Council (NSC 98-2314-B-075A-002-MY3) and Taichung Veterans General Hospital, Taichung, Taiwan (TCVGH-1013001C;TCVGH-1013002D). The SAPPHIRe (TAICHI) was supported by grants from National Health Research Institutes (BS-094-PP-01 & PH-100-PP-03). The HALST (TAICHI) was supported by grants from National Health Research Institutes (PH-100-SP-01)

The Population Architecture Using Genomics and Epidemiology (PAGE) program is funded by the National Human Genome Research Institute (NHGRI), supported by U01HG004803 (CALiCo), U01HG004798 (EAGLE), U01HG004802 (MEC), U01HG004790 (WHI), and U01HG004801 (Coordinating Center), and their respective NHGRI ARRA supplements. The complete list of PAGE members can be found at http://www.pagestudy.org.

The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118-32119, 32122, 42107-26, 42129-32, and 44221. This manuscript was prepared in collaboration with investigators of the WHI, and has been approved by the WHI. WHI investigators are listed at http://www.whiscience.org/publications/WHI_investigators_shortlist.pdf.

The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C), R01HL087641, R01HL59367 and R01HL086694; National Human Genome Research Institute contract U01HG004402; and National Institutes of Health contract HHSN268200625226C. The authors thank the staff and participants of the ARIC study for their important contributions. Infrastructure was partly supported by Grant Number UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research.

JE funding is provided by the German Federal Ministry of Education and Research (BMBF) in the context of the e:Med program (e:AtheroSysMed and sysINFLAME) , the FP7 European Union project CVgenes@target (261123) and a grant from the Fondation Leducq (CADgenomics: Understanding Coronary Artery Disease Genes, 12CVD02. This study was also supported through the Deutsche Forschungsgemeinschaft (DFG) cluster of excellence 'Inflammation at Interfaces'.

We are thankful to all the study participants in Pakistan. Recruitment in PROMIS was funded through grants available to investigators at the Center for Non-Communicable Diseases, Pakistan (Danish Saleheen and Philippe Frossard) and investigators at the University of Cambridge, UK (Danish Saleheen and John Danesh). Field-work, genotyping, and standard clinical chemistry assays in PROMIS were principally supported by grants awarded to the University of Cambridge from the British Heart Foundation, UK Medical Research Council,

Wellcome Trust, EU Framework 6-funded Bloodomics Integrated Project, Pfizer. We would like to acknowledge the contributions made by the following individuals who were involved in the field work and other administrative aspects of the study: Mohammad Zeeshan Ozair, Usman Ahmed, Abdul Hakeem, Hamza Khalid, Kamran Shahid, Fahad Shuja, Ali Kazmi, Mustafa Qadir Hameed, Naeem Khan, Sadiq Khan, Ayaz Ali, Madad Ali, Saeed Ahmed, Muhammad Waqar Khan, Muhammad Razaq Khan, Abdul Ghafoor, Mir Alam, Riazuddin, Muhammad Irshad Javed, Abdul Ghaffar, Tanveer Baig Mirza, Muhammad Shahid, Jabir Furqan, Muhammad Iqbal Abbasi, Tanveer Abbas, Rana Zulfiqar, Muhammad Wajid, Irfan Ali, Muhammad Ikhlaq, Danish Sheikh and Muhammad Imran. The genetic and biomarker assays in this study (consumables and labour) were supported by grants from the British Heart Foundation (PG/09/035/27378), US National Institutes of Health (RC2HL101834 and RC1TW008485), Fogarty International Center (RC1TW008485), the Wellcome Trust (084711/Z/08/Z), and Pfizer, as well as by underpinning support from the UK Medical Research Council (MR/L003120/1), British Heart Foundation (RG/13/13/30194), and National Institute for Health Research Cambridge Biomedical Research Centre

We thank participants and staff of the Copenhagen City Heart Study, Copenhagen Ischemic Heart Disease Study, and the Copenhagen General Population Study for their important contributions.

CAD case ascertainment and validation, genotyping, and clinical chemistry assays in EPIC-CVD were principally supported by grants awarded to the University of Cambridge from the EU Framework Programme 7 (HEALTH-F2-2012-279233), the UK Medical Research Council (G0800270) and British Heart Foundation (SP/09/002), and the European Research Council (268834). We thank all EPIC participants and staff for their contribution to the study, the laboratory teams at the Medical Research Council Epidemiology Unit for sample management and Cambridge Genomic Services for genotyping, Sarah Spackman for data management, and the team at the EPIC-CVD Coordinating Centre for study coordination and administration.

The BRAVE study genetic epidemiology working group is a collaboration between the Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, UK, the Centre for Control of Chronic Diseases, icddr,b, Dhaka, Bangladesh and the National Institute of Cardiovascular Diseases, Dhaka, Bangladesh.

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30. Medical Research Council Epidemiology Unit, University of Cambridge, Cambridge, UK
31. Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, UK
32. School of Public Health, Imperial College London, UK
33. Cardiovascular Epidemiology Unit, Department of Public Health & Primary Care, University of Cambridge, UK
34. The National Institute for Health Research Blood and Transplant Unit (NIHR BTRU) in Donor Health and Genomics at the University of Cambridge, UK
35. Wellcome Trust Sanger Institute, Genome Campus, Hinxton, UK

Supplementary Tables

Supplementary Table 1 (a) Study-specific sample quality control exclusions and baseline characteristics of the studies with *de novo* genotyping. **(b)** Study-specific definitions of disease outcome (CAD).

Collection	Recruitment Country	Study design	Disease Outcome	N samples failed QC	N related samples removed	N ancestry outliers removed	N cases (% male)	N controls (% male)	Mean (SD) age
European									
EPIC-CVD	UK, Germany, Netherlands, Sweden, Norway, France, Spain, Greece, Italy	Case-cohort	CAD	231	475	616	11,391 (60) **	7,251 (35) **	59.3 (8.9) [56.5 (10.1)]*
CCHS	Denmark (Copenhagen)	Prospective	CAD	122	212	13	1,999 (52)	6,562 (42)	66.1 (10.8) [57.9 (15.1)]*
CIHDS	Denmark (Copenhagen)	Case series	ACS	106	163	8	2,703 (73)	NA	60.4 (11.8)*
CGPS	Denmark (Copenhagen)	Prospective	N/A	120	58	6	NA	2,803 (44)	58.0 (12.6)
South Asian									
PROMIS	Pakistan (8 centres)	Case/Control	AMI	385	264	2	5,833 (84) **	5,369 (81) **	53.2 (12.3)

BRAVE	Bangladesh (Dhaka)	Case/Control	AMI	63	111	9	1,821 (88)	1,645 (89)	48.5 (15.9)
African American									
ARIC (females)	USA	Prospective	CAD	NA	NA	NA	192 (0)	1840	53.3 (5.7)
ARIC (males)	USA	Prospective	CAD	NA	NA	NA	174 (100)	998	53.6 (6.0)
WHI	USA	Prospective	CAD	NA	0	2	99 (0)	1855	60.8 (6.8)
MIGen	USA	Case/Control	CAD	85	60	0	1,635 (NA)	1,053 (NA)	NA
East Asian									
TAICHI	Taiwan	Case/Control	CAD	797	1,312	4	4,129 (78)	6,369 (53)	66.6 (11.3) [64.4 (12.5)][*]

[*]Mean age at diagnosis of CAD rather than baseline age at recruitment is given. [**] These are the numbers of samples genotyped and passing QC. A subset of the PROMIS samples (3,704 CAD cases and 3,433 controls) and the EPIC-CVD samples (1,830 CAD cases and 449 controls) had been included in the CARDIoGRAMplusC4D discovery effort and were therefore not included in the meta-analyses with CARDIoGRAMplusC4D. Note, 21 samples were dropped from CIHDS and 12 from CGPS as they were identical to samples found in CCHS.

Supplementary Table 1(b)

Study	Case definition
MIGen	CAD defined as acute myocardial infarction, >50% stenosis in coronary artery on coronary angiography, abnormal stress test, or unstable angina diagnosis
ARIC	CAD, defined as acute hospitalized MI (definitive or probable), definite fatal CAD, or ECG diagnosis of MI, validated by review of hospital records, death certificates and interviews of next of kin
BRAVE	Acute MI within the preceding 24 hours
CCHS	CAD, defined as ICD10 I20-I25, from morbidity and mortality registries
CGPS	CAD, defined as ICD10 I20-I25, from morbidity and mortality registries
CIHDS	MI or other major acute coronary syndromes plus stenosis or atherosclerosis on coronary angiography and/or positive results on exercise electrocardiography.
EPIC-CVD	CAD, defined as ICD10 I20-I25, ascertained and validated through various methods (morbidity registers, general practice records, MONICA registries, self- report, clinical records)
PROMIS	Acute MI within the preceding 24 hours
TAICHI	CAD, defined as either currently or in the past suffering from an MI, an ACS, angina, or demonstrated at least one epicardial coronary artery obstruction of >50% on coronary angiogram.
WHI	CAD, defined as acute hospitalized MI (definitive or probable), definite fatal CAD, or ECG diagnosis of MI, validated by review of hospital records, death certificates and interviews of next of kin

ACS = acute coronary syndrome; CAD = coronary artery disease; ECG = electrocardiogram; MI = myocardial infarction. Similar CAD definitions were used by the CARDIoGRAMplusC4D: Supplementary Table 2 of reference 3.

Supplementary Table 2 Summary of study specific SNP genotype quality control for studies with *de novo* genotyping. The CardioMetabochip+ genotypes 209,818 SNPs, of which 209,529 map to the autosomes, while the CardioMetabochip includes 196,725 SNPs of which 196,479 map to the autosomes.

Collection	**Genotyping array**	**HWE *P*-value threshold**	**SNP call rate threshold**	**#SNPs with no calls**	**# monomorphic snps**	**Number of SNPs removed call rate/HWE/MAF<0.01**	**Number of SNPs passing QC**
European							
EPIC-CVD	CardioMetabo+	$1x10^{-6}$	0.97	1,403	25,192	48,322	134,612
CCHS	CardioMetabo+	$1x10^{-6}$	0.97	1,374	37,152	35,093	135,910
CIHDS/CGPS	CardioMetabo+	$1x10^{-6}$	0.97	1,387	42,708	29,307	136,127
South Asian							
PROMIS	CardioMetabo+	$1x10^{-6}$	0.97	1,149	21,302	55,491	131,587
BRAVE	CardioMetabo+	$1x10^{-6}$	0.97	1,019	52,407	25,485	130,618

African American							
ARIC (males)	CardioMetabo	$1x10^{-6}$	0.95	NA	NA	NA	143,615
ARIC (females)	CardioMetabo	$1x10^{-6}$	0.95	NA	NA	NA	143,473
WHI	CardioMetabo	$1x10^{-6}$	0.95	NA	NA	NA	145,132
MIGen	CardioMetabo	$1x10^{-6}$	0.97	535	10,940	37,019	148,231
East Asian							
TAICHI	CardioMetabo	$1x10^{-6}$	0.97	5,787 (<95%)	46,543	39,092	105,834

Supplementary Table 3 Inflation factors for studies with *de novo* genotyping. Lambda represents the inflation of the test statistics across all variants that passed QC in a study. Given that the CardioMetabochip was a customised genotyping array that included fine-mapping of previously established CAD loci and not a random selection of SNPs from across the genome, we also calculated inflation factors having excluded known CAD regions. The Lambda (noCAD) have had the variants that map to one of the 47 previously published CAD regions (or within 1Mb) of that region. QQ plots of the association statistics are provided in Supplementary Figure 1.

Collection	Association model	Lambda	Lambda (noCAD)	# PCs
European				
EPIC-CVD	LMM	1.03	0.99	5
CCHS	LMM	1.00	0.98	0
CIHDS/CGPS	LMM	1.05	0.99	1
South Asian	LMM	1.10	1.03	3
PROMIS	Logistic	1.07	1.03	1
BRAVE	Logistic	1.06	1.04	1
African American				
WHI	Logistic	0.97	0.97	10
MIGen	Logistic	1.06	1.05	10
ARIC (males)	Logistic	1.03	1.01	10
ARIC (females)	Logistic	1.04	1.04	10
East Asian				
TAICHI	LMM	1.09	1.05	5

LMM = linear mixed model as implemented in GEMMA. Logistic = logistic regression model

Supplementary Table 4 Results of CAD association tests from the European and All ancestry meta-analyses for SNPs with $P<5x10^{-8}$ at the new loci.

Closest gene(s)	SNP	Chr:Position	Effect allele (AF)	European collections			All collections			
				OR [95% CI]	*P*	P_{het}	OR [95% CI]	*P*	P_{het}	$log_{10}BF$
ATP1B1	rs1892094C>T	1:169094459	T (0.50;0.48)	**0.96 [0.94-0.97]**	**$3.99x10^{-8}$**	**0.86**	0.96 [0.94-0.97]	$2.25x10^{-8}$	0.83	6.33
	rs10919065G>T	1:169093557	T (0.43;0.43)	**1.05 [1.03-1.06]**	**$1.57x10^{-8}$**	**0.72**	1.04 [1.02-1.05]	$9.28x10^{-7}$	0.11	5.06
	rs1200159C>T	1:169100241	T (0.43;0.42)	**1.05 [1.03-1.06]**	**$3.40x10^{-8}$**	**0.72**	1.04 [1.02-1.05]	$1.90x10^{-6}$	0.20	4.68
DDX59/CAMSAP 2	rs6700559C>T	1:200646073	T (0.47;0.47)	**0.96 [0.94-0.97]**	**$2.50x10^{-8}$**	**0.14**	0.96 [0.95-0.97]	$1.13x10^{-8}$	0.51	6.68
LMOD1	rs2820315C>T	1:201872264	T (0.30;0.29)	**1.05 [1.03-1.07]**	**$4.14x10^{-9}$**	**0.01**	1.05 [1.03-1.07]	$7.70x10^{-10}$	0.02	7.72
	rs2819348T>C	1:201884952	C (0.34;0.33)	**1.05 [1.03-1.06]**	**$2.83x10^{-8}$**	**0.02**	1.05 [1.03-1.06]	$1.77x10^{-8}$	0.01	6.42
(nsSNP) *TNS1*	rs2571445G>A	2:218683154	A (0.39;0.39)	1.04 [1.02-1.06]	$3.58x10^{-6}$	0.86	**1.05 [1.03-1.06]**	**$4.55x10^{-10}$**	**0.01**	**8.41**
ARHGAP26	rs246600C>T	5:142516897	T (0.48;0.46)	**1.05 [1.03-1.06]**	**$1.29x10^{-8}$**	**0.41**	1.04 [1.03-1.06]	$1.51x10^{-8}$	0.36	6.39
PARP12	rs10237377G>T	7:139757136	T (0.35;0.38)	0.95 [0.93-0.97]	$1.70x10^{-7}$	0.13	**0.95 [0.93-0.97]**	**$1.74x10^{-8}$**	**0.34**	**6.32**
PCNX3	rs12801636G>A	11:65391317	A (0.23;0.25)	0.95 [0.93-0.97]	$1.00x10^{-7}$	0.22	**0.95 [0.94-0.97]**	**$9.72x10^{-9}$**	**0.48**	**6.64**
SERPINH1	rs590121G>T	11:75274150	T (0.30;0.31)	**1.05 [1.03-1.07]**	**$1.54x10^{-8}$**	**0.47**	1.04 [1.03-1.06]	$9.32x10^{-8}$	0.05	5.80
C12orf43/HNF1A	**rs2258287C>A**	**12:121454313**	**A (0.34;0.37)**	**1.05 [1.03-1.06]**	**$6.00x10^{-9}$**	**0.10**	1.04 [1.03-1.06]	$2.18x10^{-8}$	0.13	6.40
	rs2708081C>T	12:121463288	T (0.48;0.47)	**0.96 [0.94-0.97]**	**$1.02x10^{-8}$**	**0.32**	0.96 [0.95-0.98]	$1.56x10^{-7}$	0.28	4.99
	rs3213545G>A	12:121471337	A (0.31;0.32)	**1.04 [1.03-1.07]**	**$2.50x10^{-8}$**	**0.22**	1.04 [1.03-1.06]	$4.81x10^{-8}$	0.43	6.13

	rs2244608A>G	**12:121416988**	**G (0.34;0.34)**	1.04 [1.03-1.06]	$1.96x10^{-7}$	0.30	**1.04 [1.03-1.06]**	**$1.57x10^{-8}$**	**0.71**	**6.42**
	rs1169288A>C	12:121416650	C (0.34;0.34)	1.05 [1.03-1.06]	$3.44x10^{-7}$	0.20	**1.05 [1.03-1.06]**	**$4.53x10^{-8}$**	**0.68**	**5.94**
SCARB1	rs11057830G>A	12:125307053	A (0.16;0.15)	**1.07 [1.05-1.10]**	**$5.65x10^{-9}$**	**0.56**	1.06 [1.04-1.09]	$1.34x10^{-8}$	0.78	6.49
	rs11057841C>T	12:125316743	T (0.15;0.16)	**1.07 [1.04-1.09]**	**$1.19x10^{-8}$**	**0.60**	1.05 [1.03-1.08]	$7.52x10^{-7}$	0.23	4.92
OAZ2/*RBPMS2*	rs6494488A>G	15:65024204	G (0.18;0.21)	0.95 [0.93-0.97]	$1.43x10^{-6}$	0.44	**0.95 [0.93-0.97]**	**$2.09x10^{-8}$**	**0.50**	**6.41**
DHX38	rs1050362C>A	16:72130815	A (0.38;0.39)	1.04 [1.03-1.06]	$2.32x10^{-7}$	0.59	**1.04 [1.03-1.06]**	**$3.52x10^{-8}$**	**0.60**	**6.16**
	rs2072142C>T	16:72132713	T (0.37;0.38)	1.05 [1.03-1.06]	$2.44x10^{-7}$	0.66	**1.05 [1.03-1.06]**	**$4.26x10^{-8}$**	**0.65**	**5.75**
GOSR2	rs17608766T>C	17:45013271	C (0.14;0.14)	**1.07 [1.04-1.09]**	**$4.14x10^{-8}$**	**0.99**	1.06 [1.04-1.09]	$2.10x10^{-7}$	0.74	5.30
PECAM1	rs1867624T>C	17:62387091	C (0.39;0.38)	0.96 [0.94-0.97]	$1.14x10^{-7}$	0.70	**0.96 [0.95-0.97]**	**$3.98x10^{-8}$**	**0.36**	**6.03**
	rs9892152C>T	17:62401965	T (0.47;0.46)	0.96 [0.95-0.98]	$2.73x10^{-7}$	0.41	**0.96 [0.95-0.98]**	**$5.00x10^{-8}$**	**0.75**	**5.92**
(nsSNP) *PROCR*	rs867186A>G	20:33764554	G (0.11;0.11)	**0.93 [0.91-0.96]**	**$1.26x10^{-8}$**	**0.61**	0.93 [0.91-0.96]	$2.70x10^{-9}$	0.74	7.11

Chr:Position = chromosome:position (build 37). AF= allele frequency in Europeans; allele frequency averaged across All ancestries. OR [95% CI] = odds ratio [95% confidence interval]. *P* = CAD association *P*-value. P_{het} is the *P*-value for heterogeneity from the meta-analysis. $\log_{10}$BF is the log base 10 of the Bayes factors obtained from the MANTRA analyses ($\log_{10}$BF≥6 is considered significant)

Supplementary Table 6 Summary of *P*-values for the null and associated sets used in the modified MAGENTA pathway analyses with the hypergeometric tests.

	Null set						**Associated set**					
		P-value distribution						*P*-value distribution				
Meta-analysis	*N*	*Min*	Q_1	*Median*	Q_3	*Max*	*N*	*Min*	Q_1	*Median*	Q_3	*Max*
EUR	1,000	0.6530	0.7370	0.8195	0.9041	0.9998	53	5.82×10^{-14}	1.585×10^{-6}	1.958×10^{-5}	4.296×10^{-5}	9.890×10^{-5}
EUR+SAS+AA+EAS+CG	1,000	0.6871	0.7696	0.8388	0.9153	0.9999	85	8.40×10^{-97}	4.86×10^{-11}	9.72×10^{-9}	8.04×10^{-8}	1.00×10^{-6}

N: number of variants contained in the set. *Min*: minimum. Q_1: first quartile. Q_3: third quartile. *Max* = maximum.

Supplementary Table 7 Pathways with enrichment of CAD associated variants from the all ancestry meta-analyses identified using modified MAGENTA.

				Europeans				All ancestry			
Category	**Database**	**Pathway**	**Genes**	*k*	*n*	P_{obs}	P_{enr}	*k*	*n*	P_{obs}	P_{enr}
Lipids / lipoproteins	Reactome	Lipoprotein metabolism	27	3	3	0.00034	0.0004	4	4	0.00004	0.0000
	KEGG	Glycerolipid metabolism	49	4	4	0.00002	0.0000	3	3	0.00047	0.0002
	Reactome	Metabolism of lipids and lipoproteins	228	6	11	0.00004	0.0001	7	15	0.00005	0.0003
	Reactome	Chylomicron mediated lipid transport	17	1	1	0.07063	1.0000	3	3	0.00047	0.0003
	Ingenuity	FXR/RXR activation	57	3	6	0.00581	0.0047	4	6	0.00047	0.0006
	Panther BP	Lipid and fatty acid transport	111	3	11	0.03701	0.0378	5	11	0.00083	0.0016
	Ingenuity	LXR/RXR activation	40	1	2	0.13634	1.0000	3	4	0.00176	0.0020
	Panther MF	Apolipoprotein	23	1	2	0.13634	1.0000	2	2	0.00607	0.0050
	Panther MF	Lipase	19	1	1	0.07063	1.0000	2	2	0.00607	0.0069
	KEGG	Glycerophospholipid metabolism	77	3	5	0.00306	0.0029	1	5	0.33548	1.0000
	Reactome	HDL mediated lipid transport	11	2	2	0.00493	0.0041	1	1	0.07834	1.0000
Immune system / thrombosis	Reactome	Signaling by platelet derived growth factor (PDGF)	64	4	10	0.00349	0.0026	4	7	0.00103	0.0009
	BioCarta	Platelet amyloid precursor protein (APP)	14	3	5	0.00306	0.0034	3	4	0.00176	0.0019

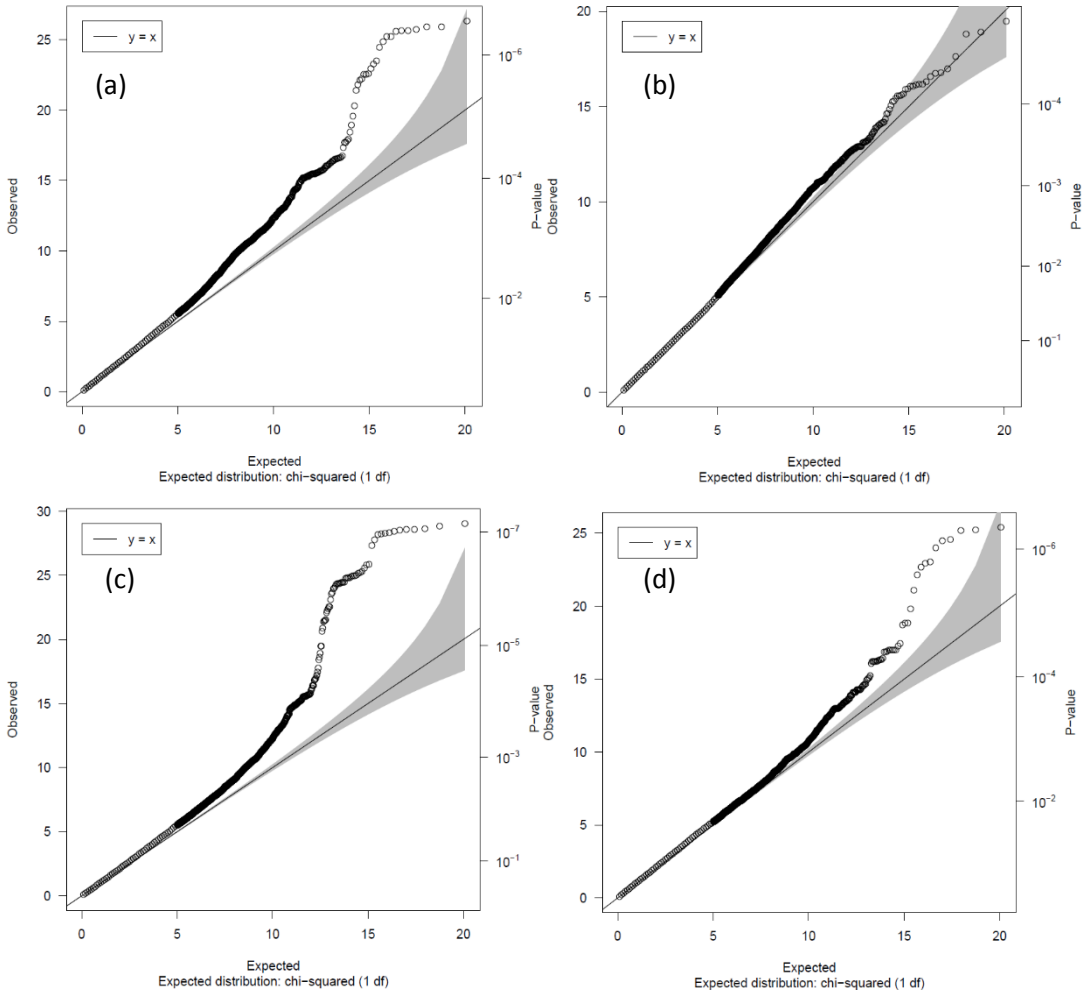
	BioCarta	Intrinsic prothrombin activation	23	2	2	0.00493	0.0049	2	3	0.01728	0.0167
	Reactome	Formation of platelet plug	185	5	16	0.00364	0.0045	3	15	0.10636	0.1037
	Reactome	Platelet activation	166	5	16	0.00364	0.0033	3	15	0.10636	0.1048
	Reactome	G alpha Q signalling events	155	4	12	0.00737	0.0072	2	8	0.12471	0.1172
Heart / cardiac function	BioCarta	Acute myocardial infarction (AMI)	20	3	4	0.00129	0.0004	3	4	0.00176	0.0011
	BioCarta	Angiotensin-converting enzyme (ACE) 2	13	2	2	0.00493	0.0041	2	2	0.00607	0.0073
Blood	Panther	Endothelin signaling pathway	19	3	4	0.00129	0.0013	3	4	0.00176	0.0019
	Reactome	Hemostasis	272	7	21	0.00035	0.0006	5	21	0.01959	0.0206
Vitamin C	BioCarta	Vitamin C in the brain	11	2	2	0.00493	0.0047	2	2	0.00607	0.0052
Phosphatase	Panther MF	Phosphatase modulator	19	1	1	0.07063	1.0000	2	2	0.00607	0.0058
DNA/RNA modification	Reactome	Elongation and processing of capped transcripts	133	1	1	0.07063	1.0000	2	2	0.00607	0.0069
Cell structure / interactions	Panther MF	Cation transporter	112	3	11	0.03701	0.0345	4	11	0.00757	0.0076
	Reactome	mRNA splicing	107	1	1	0.07063	1.0000	2	2	0.00607	0.0077
	Reactome	Integrin cell surface interactions	81	4	6	0.00031	0.0006	3	8	0.01948	0.0169
	Reactome	Cell surface interactions at the vascular wall	93	4	8	0.00130	0.0006	3	8	0.01948	0.0227
	KEGG	ECM receptor interaction	84	3	6	0.00581	0.0057	2	7	0.09840	0.0959

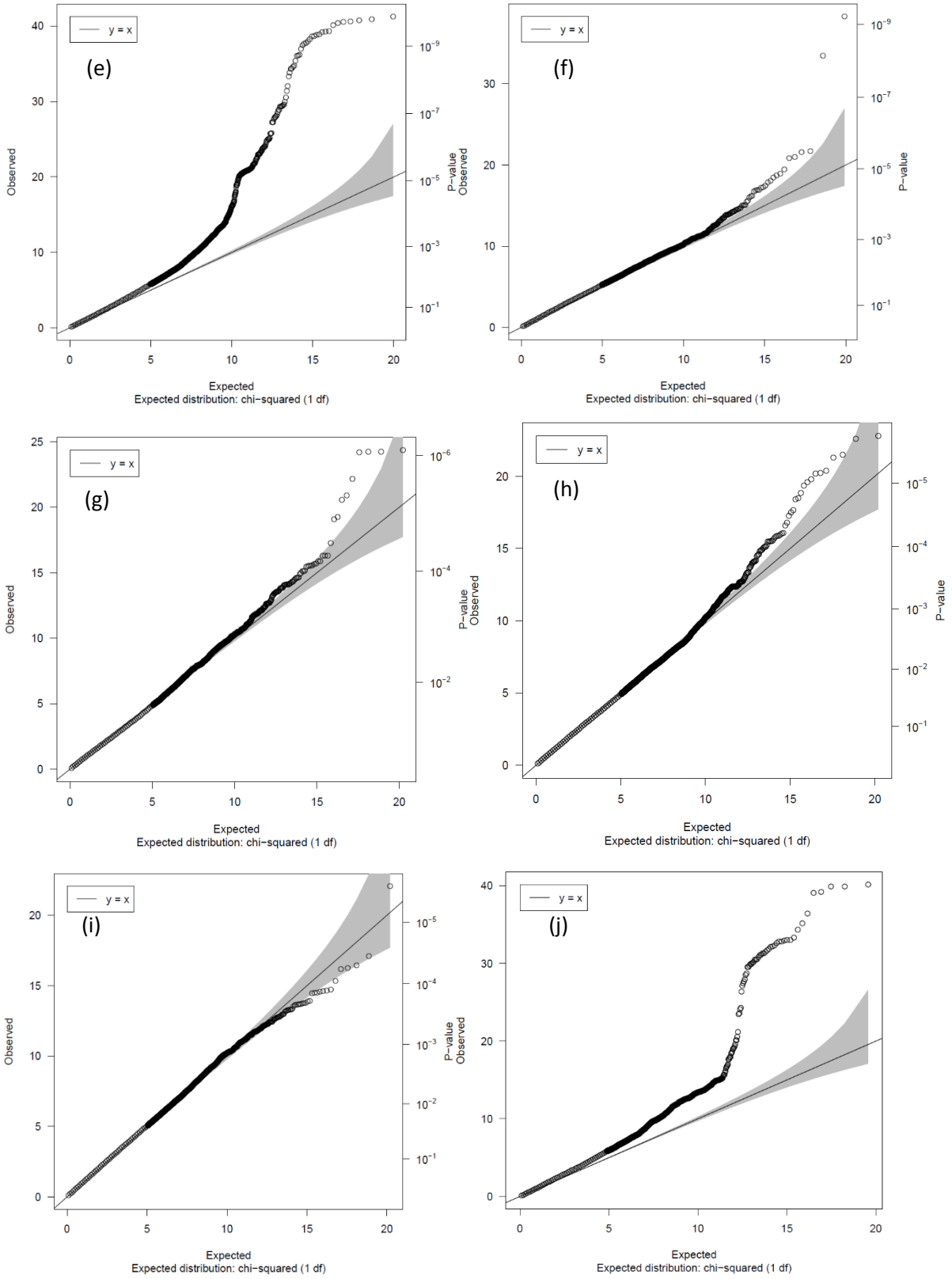
SNARE protein	Panther MF	SNARE protein	36	2	2	0.00493	0.0041	2	3	0.01728	0.0168
	KEGG	SNARE interactions in vesicular transport	37	2	2	0.00493	0.0040	2	3	0.01728	0.0173
Liver	Ingenuity	Hepatic fibrosis / hepatic stellate cell activation	83	4	11	0.00519	0.0068	3	10	0.03723	0.0397

For each hypergeometric test the empirical *P*-values displayed were calculated based on comparing the observed *P*-value to those obtained from 10,000 random sets. Seventy six SNPs formed the associated set for the European ancestry analysis and 85 for the All ancestry analysis. Genes: the number of genes that are listed for that pathway in the database. n: number of analyses for which this pathway showed evidence of enrichment at $P < 0.01$. *k:*number of variants in the associated set that were mapped to a gene listed in the pathway. [§] $P < 0.0001$, occurs when no random set hypergeometric test *P*-values are less than or equal to the observed *P*-value.

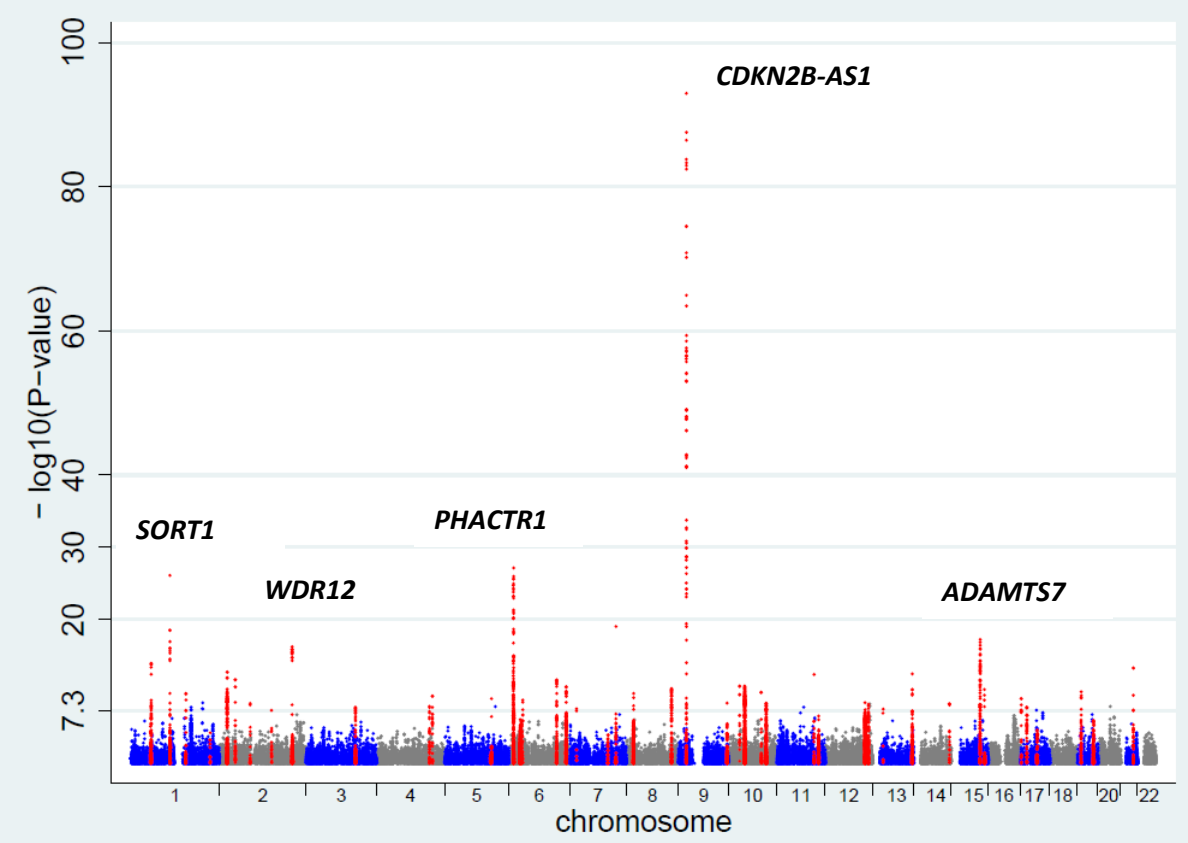
Supplementary Figures

Supplementary Figure 1: QQ plots illustrating array-wide inflation for each of the studies with *de novo* genotyping. **(a)** CIHDS/CGPS studies analysed using a mixed effects model at 136,127 SNPs **(b)** CCHS study analysed at 135,910 SNPs **(c)** EPIC-CVD analysed using a mixed model at 134,533 SNPs **(d)** EPIC-CVD-Umea analysed using a mixed model at 133,849 SNPs **(e)** South Asian studies PROMIS and BRAVE combined in a mixed model analysis of 127,114 SNPs **(f)** MIGen analysed using a logistic regression model at 123,885 SNPs (note the two SNPs with $P < 1x10^{-8}$, only passed QC in MIGen and consequently are likely to be genotype clustering artefacts and were excluded from all meta analyses) **(g)** WHI analysed at 145,132 SNPs **(h)** ARIC males analysed using a logistic regression model at 143,615 SNPs **(i)** ARIC females analysed using logistic regression at 143,473 SNPs (**j**) TAICHI using linear a mixed model at 103,238 SNPs. Inflation factors are reported in Supplementary Table 3.

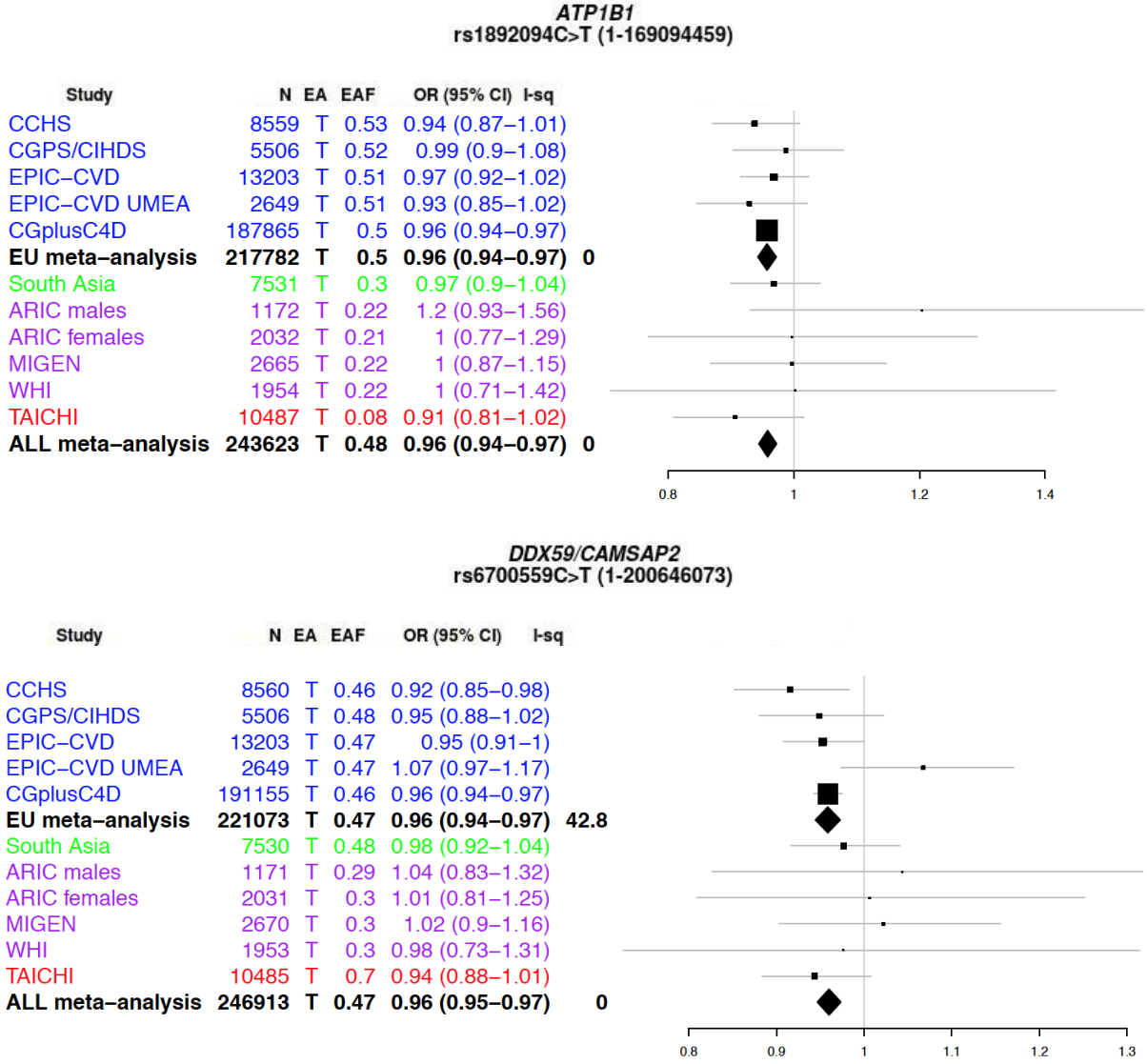



(e)
y = x
Observed
P−value
Observed
Expected
Expected distribution: chi−squared (1 df)
(f)
y = x
P−value
Expected
Expected distribution: chi−squared (1 df)
(g)
y = x
Observed
P−value
Observed
Expected
Expected distribution: chi−squared (1 df)
(h)
y = x
P−value
Expected
Expected distribution: chi−squared (1 df)
(i)
y = x
Observed
P−value
Observed
Expected
Expected distribution: chi−squared (1 df)
(j)
y = x
P−value
Observed
Expected
Expected distribution: chi−squared (1 df)

Supplementary Figure 2: Manhattan plot showing the association of ~79,000 variants with CAD from the European meta-analysis in up to ~221,000 individuals. Red dots represent SNPs that map to LD blocks that include the previously published (known) CAD regions. The SNP with the most evidence of association in this meta-analysis was rs133045 in the 9p21 region (P=1x10^{-93}). -log(P=5x10^{-8})~7.3

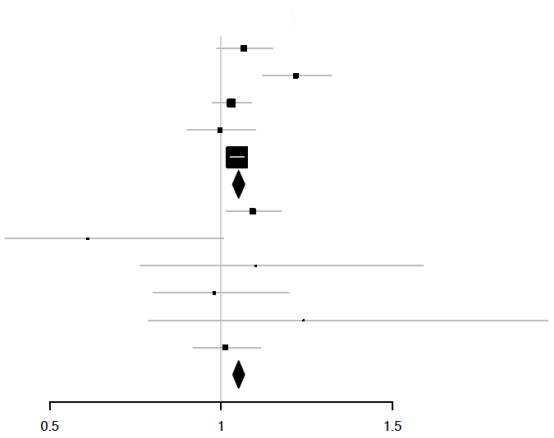


Supplementary Figure 3: Forest plots from the all studies meta-analysis for the 15 sentinel CAD-associated SNPs. N = number of subjects, EA= effect allele, EAF= effect allele frequency, OR = odds ratio, CI = confidence interval.



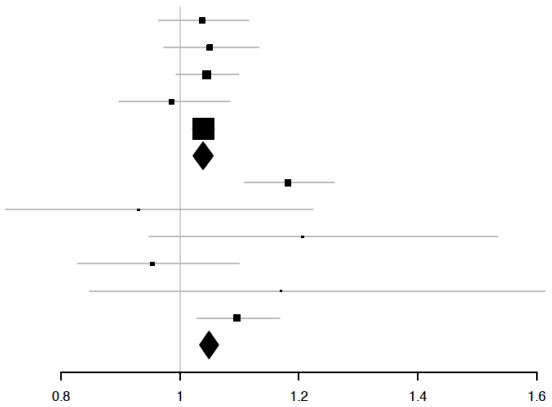
LMOD1
rs2820315C>T (1-201872264)

Study	N	EA	EAF	OR (95% CI)	I-sq
CCHS	8558	T	0.31	1.07 (0.99–1.15)	
CGPS/CIHDS	5503	T	0.3	1.22 (1.12–1.32)	
EPIC–CVD	13202	T	0.28	1.03 (0.97–1.09)	
EPIC–CVD UMEA	2649	T	0.31	1 (0.9–1.1)	
CGplusC4D	184932	T	0.31	1.05 (1.03–1.07)	
EU meta–analysis	**214844**	**T**	**0.3**	**1.05 (1.03–1.07)**	**72.3**
South Asia	7528	T	0.25	1.09 (1.01–1.18)	
ARIC males	1172	T	0.08	0.61 (0.37–1.01)	
ARIC females	2031	T	0.08	1.1 (0.76–1.59)	
MIGEN	2670	T	0.09	0.98 (0.8–1.2)	
WHI	1953	T	0.1	1.24 (0.79–1.95)	
TAICHI	10487	T	0.11	1.01 (0.92–1.11)	
ALL meta–analysis	**240685**	**T**	**0.29**	**1.05 (1.03–1.07)**	**53.8**



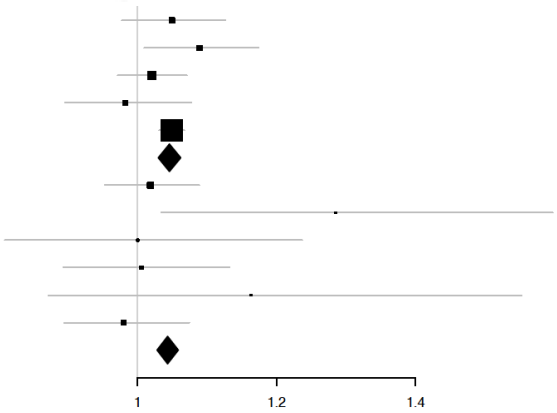
TNS1
rs2571445G>A (2-218683154)

Study	N	EA	EAF	OR (95% CI)	I-sq
CCHS	8561	A	0.38	1.04 (0.96–1.11)	
CGPS/CIHDS	5506	A	0.39	1.05 (0.97–1.13)	
EPIC–CVD	13190	A	0.38	1.05 (0.99–1.1)	
EPIC–CVD UMEA	2649	A	0.41	0.99 (0.9–1.08)	
CGplusC4D	164348	A	0.4	1.04 (1.02–1.06)	
EU meta–analysis	**194254**	**A**	**0.39**	**1.04 (1.02–1.06)**	**0**
South Asia	7525	A	0.44	1.18 (1.11–1.26)	
ARIC males	1161	A	0.19	0.93 (0.71–1.22)	
ARIC females	2011	A	0.19	1.21 (0.95–1.53)	
MIGEN	2655	A	0.2	0.95 (0.83–1.1)	
WHI	1954	A	0.21	1.17 (0.85–1.61)	
TAICHI	10487	A	0.36	1.1 (1.03–1.17)	
ALL meta–analysis	**220047**	**A**	**0.39**	**1.05 (1.03–1.06)**	**54.8**



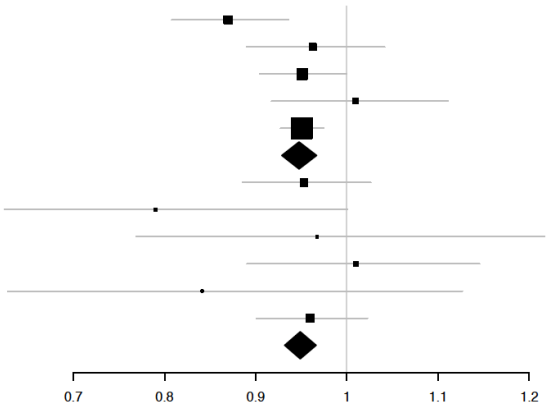
ARHGAP26
rs246600C>T (5-142516897)

Study	N	EA	EAF	OR (95% CI)	I-sq
CCHS	8559	T	0.5	1.05 (0.98–1.13)	
CGPS/CIHDS	5506	T	0.5	1.09 (1.01–1.17)	
EPIC–CVD	13205	T	0.5	1.02 (0.97–1.07)	
EPIC–CVD UMEA	2649	T	0.5	0.98 (0.9–1.08)	
CGplusC4D	180461	T	0.48	1.05 (1.03–1.07)	
EU meta–analysis	**210380**	**T**	**0.48**	**1.05 (1.03–1.06)**	**0**
South Asia	7530	T	0.35	1.02 (0.95–1.09)	
ARIC males	1172	T	0.32	1.29 (1.03–1.6)	
ARIC females	2030	T	0.33	1 (0.81–1.24)	
MIGEN	2669	T	0.32	1.01 (0.89–1.13)	
WHI	1954	T	0.34	1.16 (0.87–1.55)	
TAICHI	10488	T	0.12	0.98 (0.89–1.07)	
ALL meta–analysis	**236223**	**T**	**0.46**	**1.04 (1.03–1.06)**	**8.5**



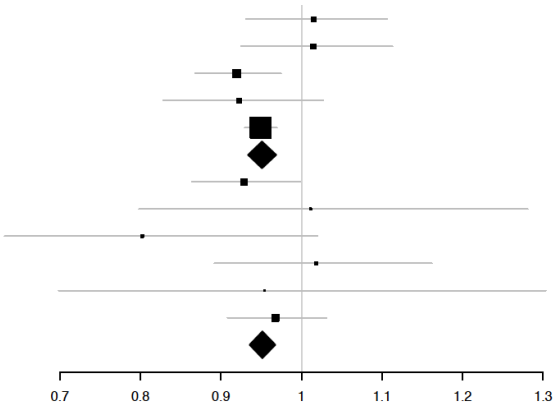
PARP12
rs10237377G>T (7-139757136)

Study	N	EA	EAF	OR (95% CI)	I-sq
CCHS	8557	T	0.36	0.87 (0.81–0.94)	
CGPS/CIHDS	5506	T	0.36	0.96 (0.89–1.04)	
EPIC–CVD	13204	T	0.38	0.95 (0.9–1)	
EPIC–CVD UMEA	2649	T	0.35	1.01 (0.92–1.11)	
CGplusC4D	151643	T	0.34	0.95 (0.93–0.97)	
EU meta–analysis	**181559**	**T**	**0.35**	**0.95 (0.93–0.97)**	**44.1**
South Asia	7529	T	0.24	0.95 (0.89–1.03)	
ARIC males	1172	T	0.73	0.79 (0.62–1)	
ARIC females	2031	T	0.72	0.97 (0.77–1.22)	
MIGEN	2667	T	0.71	1.01 (0.89–1.15)	
WHI	1954	T	0.7	0.84 (0.63–1.13)	
TAICHI	10487	T	0.6	0.96 (0.9–1.02)	
ALL meta–analysis	**207399**	**T**	**0.38**	**0.95 (0.93–0.97)**	**11**



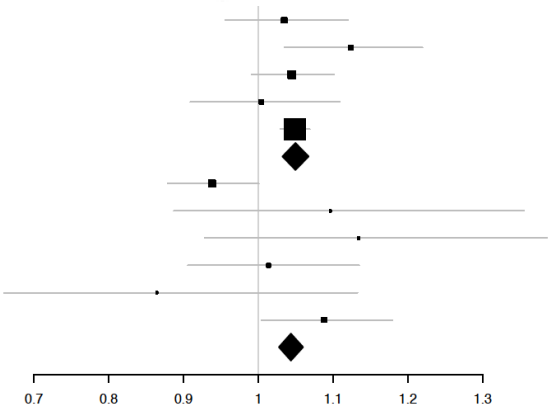
PCNX3
rs12801636G>A (11-65391317)

Study	N	EA	EAF	OR (95% CI)	I-sq
CCHS	8559	A	0.22	1.01 (0.93–1.11)	
CGPS/CIHDS	5506	A	0.21	1.01 (0.92–1.11)	
EPIC–CVD	13188	A	0.22	0.92 (0.87–0.97)	
EPIC–CVD UMEA	2649	A	0.24	0.92 (0.83–1.03)	
CGplusC4D	181250	A	0.23	0.95 (0.93–0.97)	
EU meta–analysis	**211152**	**A**	**0.23**	**0.95 (0.93–0.97)**	**29.8**
South Asia	7530	A	0.27	0.93 (0.86–1)	
ARIC males	1171	A	0.27	1.01 (0.8–1.28)	
ARIC females	2029	A	0.26	0.8 (0.63–1.02)	
MIGEN	2663	A	0.25	1.02 (0.89–1.16)	
WHI	1954	A	0.25	0.95 (0.7–1.3)	
TAICHI	10486	A	0.4	0.97 (0.91–1.03)	
ALL meta–analysis	**236985**	**A**	**0.25**	**0.95 (0.94–0.97)**	**0**



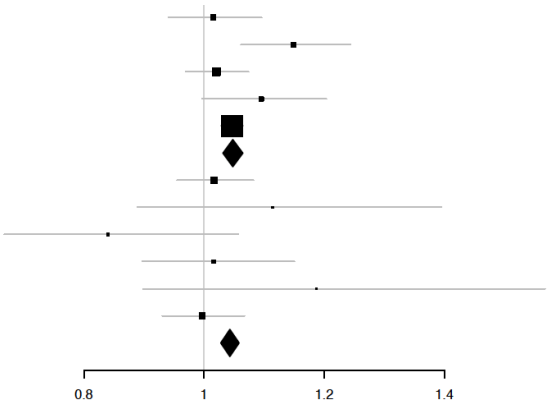
SERPINH1
rs590121G>T (11-75274150)

Study	N	EA	EAF	OR (95% CI)	I-sq
CCHS	8555	T	0.28	1.03 (0.96–1.12)	
CGPS/CIHDS	5498	T	0.28	1.12 (1.03–1.22)	
EPIC–CVD	13175	T	0.3	1.04 (0.99–1.1)	
EPIC–CVD UMEA	2646	T	0.33	1 (0.91–1.11)	
CGplusC4D	177552	T	0.3	1.05 (1.03–1.07)	
EU meta–analysis	**207426**	**T**	**0.3**	**1.05 (1.03–1.07)**	**0**
South Asia	7526	T	0.41	0.94 (0.88–1)	
ARIC males	1168	T	0.46	1.1 (0.89–1.36)	
ARIC females	2029	T	0.45	1.13 (0.93–1.39)	
MIGEN	2661	T	0.46	1.01 (0.91–1.13)	
WHI	1954	T	0.45	0.86 (0.66–1.13)	
TAICHI	10482	T	0.17	1.09 (1–1.18)	
ALL meta–analysis	**233246**	**T**	**0.31**	**1.04 (1.03–1.06)**	**45.8**



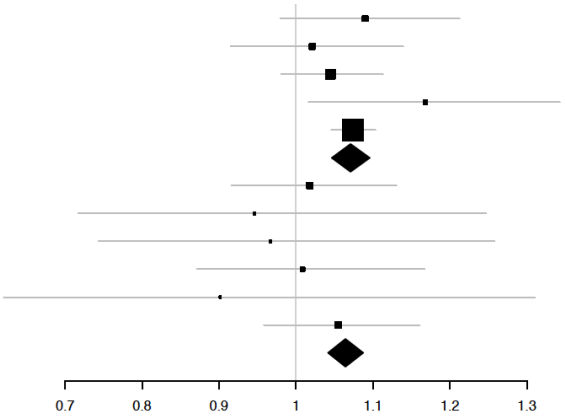
C12orf43
rs2258287C>A (12-121454313)

Study	N	EA	EAF	OR (95% CI)	I-sq
CCHS	8558	A	0.32	1.02 (0.94–1.1)	
CGPS/CIHDS	5504	A	0.32	1.15 (1.06–1.24)	
EPIC–CVD	13200	A	0.33	1.02 (0.97–1.07)	
EPIC–CVD UMEA	2649	A	0.39	1.1 (1–1.2)	
CGplusC4D	191157	A	0.34	1.05 (1.03–1.07)	
EU meta–analysis	**221068**	**A**	**0.34**	**1.05 (1.03–1.06)**	**48.4**
South Asia	7525	A	0.5	1.02 (0.95–1.08)	
ARIC males	1172	A	0.3	1.11 (0.89–1.4)	
ARIC females	2031	A	0.29	0.84 (0.67–1.06)	
MIGEN	2667	A	0.3	1.02 (0.9–1.15)	
WHI	1954	A	0.3	1.19 (0.9–1.57)	
TAICHI	10484	A	0.74	1 (0.93–1.07)	
ALL meta–analysis	**246901**	**A**	**0.37**	**1.04 (1.03–1.06)**	**33.9**



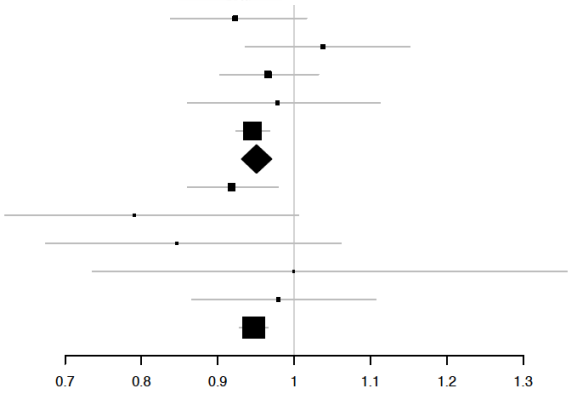
SCARB1
rs11057830G>A (12-125307053)

Study	N	EA	EAF	OR (95% CI)	I-sq
CCHS	8561	A	0.13	1.09 (0.98–1.21)	
CGPS/CIHDS	5506	A	0.14	1.02 (0.91–1.14)	
EPIC–CVD	13205	A	0.18	1.04 (0.98–1.11)	
EPIC–CVD UMEA	2649	A	0.13	1.17 (1.02–1.34)	
CGplusC4D	147629	A	0.16	1.07 (1.05–1.1)	
EU meta–analysis	**177550**	**A**	**0.16**	**1.07 (1.05–1.1)**	**0**
South Asia	7531	A	0.1	1.02 (0.92–1.13)	
ARIC males	1172	A	0.18	0.95 (0.72–1.25)	
ARIC females	2032	A	0.18	0.97 (0.74–1.26)	
MIGEN	2667	A	0.18	1.01 (0.87–1.17)	
WHI	1954	A	0.16	0.9 (0.62–1.31)	
TAICHI	10488	A	0.11	1.05 (0.96–1.16)	
ALL meta–analysis	**203394**	**A**	**0.15**	**1.06 (1.04–1.09)**	**0**



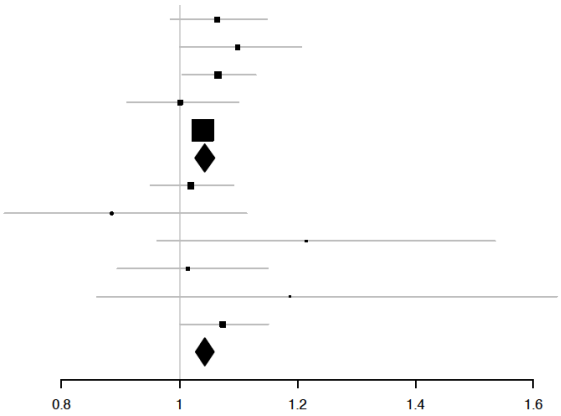
OAZ2/RBPMS2
rs6494488A>G (15-65024204)

Study	N	EA	EAF	OR (95% CI)	I-sq
CCHS	8560	G	0.16	0.92 (0.84–1.02)	
CGPS/CIHDS	5503	G	0.16	1.04 (0.94–1.15)	
EPIC–CVD	13179	G	0.16	0.97 (0.9–1.03)	
EPIC–CVD UMEA	2648	G	0.15	0.98 (0.86–1.11)	
CGplusC4D	175520	G	0.18	0.95 (0.92–0.97)	
EU meta–analysis	**205410**	**G**	**0.18**	**0.95 (0.93–0.97)**	**0**
South Asia	7527	G	0.46	0.92 (0.86–0.98)	
ARIC males	1171	G	0.69	0.79 (0.62–1.01)	
ARIC females	2030	G	0.69	0.85 (0.68–1.06)	
WHI	1954	G	0.65	1 (0.74–1.36)	
TAICHI	10486	G	0.06	0.98 (0.87–1.11)	
ALL meta–analysis	228578	G	0.21	0.95 (0.93–0.97)	



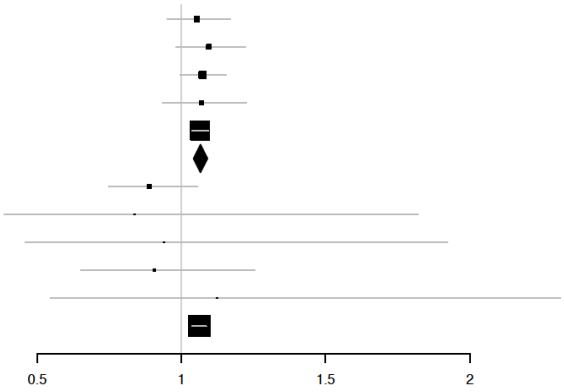
DHX38
rs1050362C>A (16-72130815)

Study	N	EA	EAF	OR (95% CI)	I-sq
CCHS	8558	A	0.37	1.06 (0.99–1.15)	
CGPS/CIHDS	5504	A	0.37	1.1 (1–1.21)	
EPIC–CVD	13203	A	0.37	1.06 (1–1.13)	
EPIC–CVD UMEA	2647	A	0.42	1 (0.91–1.1)	
CGplusC4D	186113	A	0.39	1.04 (1.02–1.06)	
EU meta–analysis	**216025**	**A**	**0.38**	**1.04 (1.03–1.06)**	**0**
South Asia	7526	A	0.47	1.02 (0.95–1.09)	
ARIC males	1171	A	0.69	0.89 (0.7–1.11)	
ARIC females	2031	A	0.7	1.22 (0.96–1.53)	
MIGEN	2666	A	0.69	1.01 (0.89–1.15)	
WHI	1954	A	0.7	1.19 (0.86–1.64)	
TAICHI	10485	A	0.26	1.07 (1–1.15)	
ALL meta–analysis	**241858**	**A**	**0.39**	**1.04 (1.03–1.06)**	**0**



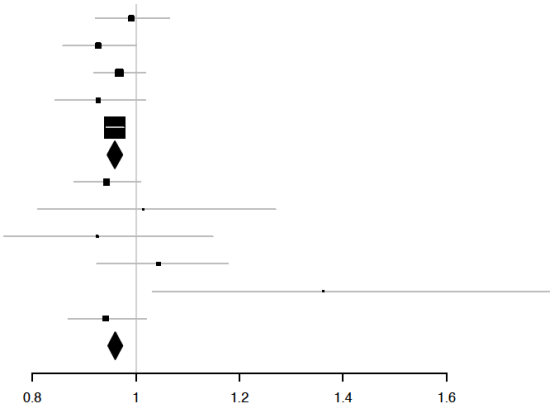
GOSR2
rs17608766T>C (17-45013271)

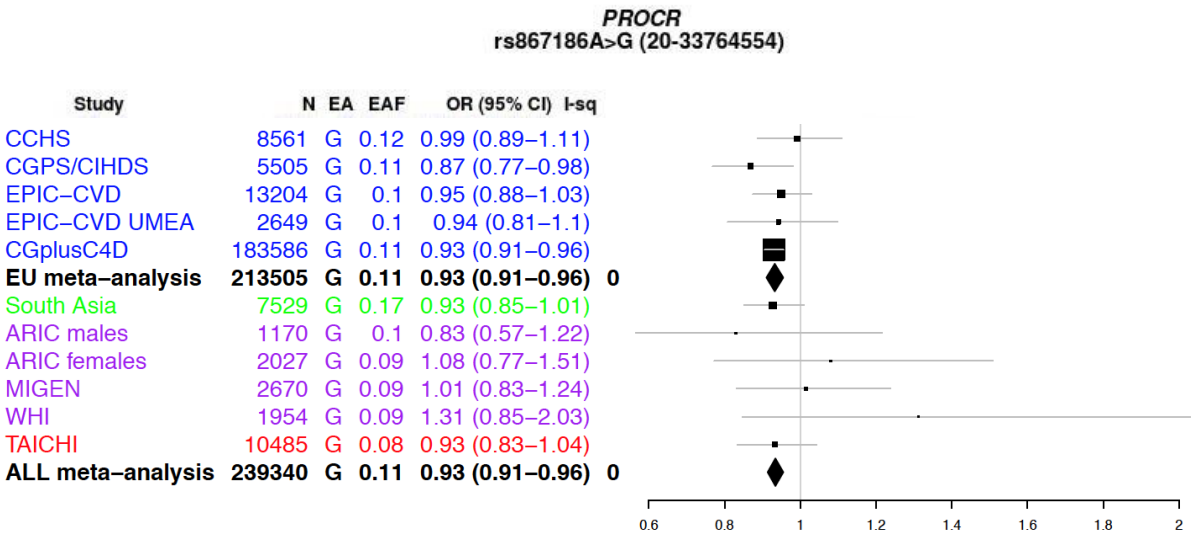
Study	N	EA	EAF	OR (95% CI)	I-sq
CCHS	8559	C	0.14	1.05 (0.95–1.17)	
CGPS/CIHDS	5500	C	0.14	1.09 (0.98–1.22)	
EPIC–CVD	13199	C	0.13	1.07 (1–1.16)	
EPIC–CVD UMEA	2649	C	0.14	1.07 (0.93–1.22)	
CGplusC4D	185950	C	0.14	1.06 (1.04–1.09)	
EU meta–analysis	**215857**	**C**	**0.14**	**1.07 (1.04–1.09)**	**0**
South Asia	7530	C	0.04	0.89 (0.75–1.05)	
ARIC males	1172	C	0.02	0.84 (0.38–1.82)	
ARIC females	2031	C	0.02	0.94 (0.46–1.92)	
MIGEN	2669	C	0.03	0.9 (0.65–1.25)	
WHI	1954	C	0.03	1.12 (0.55–2.31)	
ALL meta–analysis	231213	C	0.14	1.06 (1.04–1.09)	



PECAM1
rs1867624T>C (17-62387091)

Study	N	EA	EAF	OR (95% CI)	I-sq
CCHS	8561	C	0.41	0.99 (0.92–1.07)	
CGPS/CIHDS	5503	C	0.4	0.93 (0.86–1)	
EPIC–CVD	13202	C	0.36	0.97 (0.92–1.02)	
EPIC–CVD UMEA	2649	C	0.38	0.93 (0.84–1.02)	
CGplusC4D	190916	C	0.39	0.96 (0.94–0.98)	
EU meta–analysis	**220831**	**C**	**0.39**	**0.96 (0.94–0.97)**	**0**
South Asia	7527	C	0.33	0.94 (0.88–1.01)	
ARIC males	1172	C	0.3	1.01 (0.81–1.27)	
ARIC females	2032	C	0.31	0.92 (0.74–1.15)	
MIGEN	2670	C	0.31	1.04 (0.92–1.18)	
WHI	1954	C	0.32	1.36 (1.03–1.8)	
TAICHI	10488	C	0.18	0.94 (0.87–1.02)	
ALL meta–analysis	**246674**	**C**	**0.38**	**0.96 (0.95–0.97)**	**8.6**




PROCR
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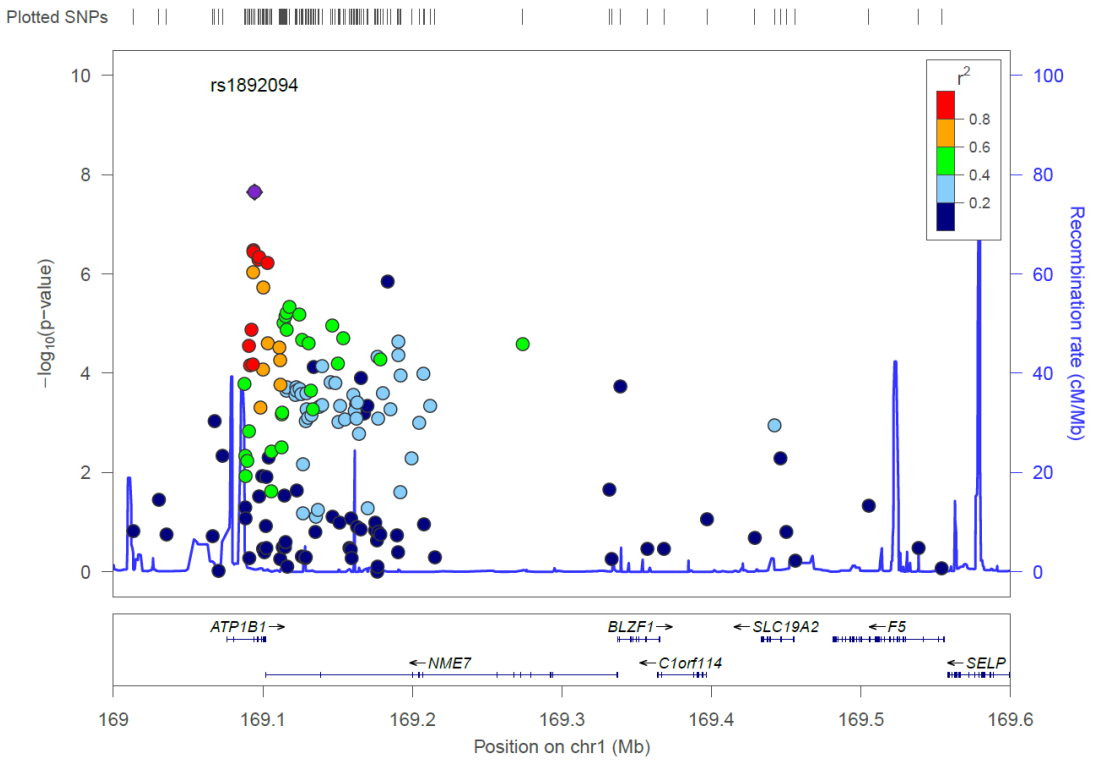
Study N EA EAF OR (95% CI) I-sq
CCHS 8561 G 0.12 0.99 (0.89–1.11)
CGPS/CIHDS 5505 G 0.11 0.87 (0.77–0.98)
EPIC–CVD 13204 G 0.1 0.95 (0.88–1.03)
EPIC–CVD UMEA 2649 G 0.1 0.94 (0.81–1.1)
CGplusC4D 183586 G 0.11 0.93 (0.91–0.96)
EU meta–analysis 213505 G 0.11 0.93 (0.91–0.96) 0
South Asia 7529 G 0.17 0.93 (0.85–1.01)
ARIC males 1170 G 0.1 0.83 (0.57–1.22)
ARIC females 2027 G 0.09 1.08 (0.77–1.51)
MIGEN 2670 G 0.09 1.01 (0.83–1.24)
WHI 1954 G 0.09 1.31 (0.85–2.03)
TAICHI 10485 G 0.08 0.93 (0.83–1.04)
ALL meta–analysis 239340 G 0.11 0.93 (0.91–0.96) 0
0.6
0.8
1
1.2
1.4
1.6
1.8
2

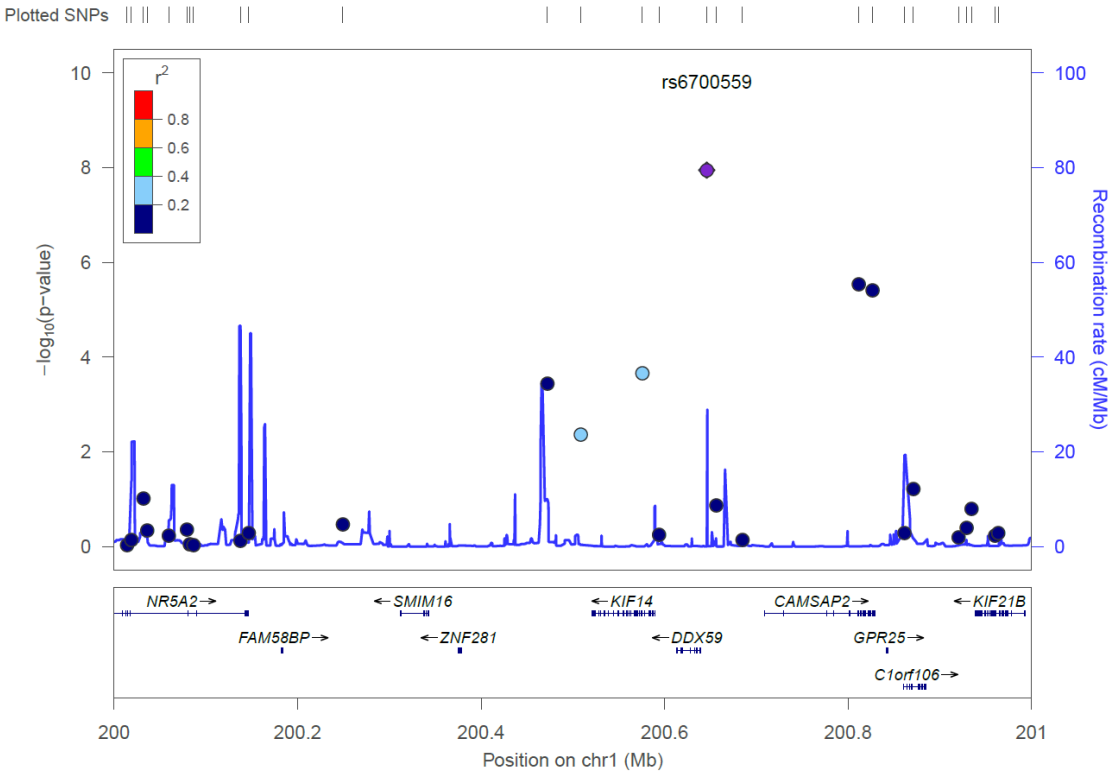
Supplementary Figure 4: Regional association plots for novel CAD associated loci (a) from the all ancestry meta-analysis for 13 loci and the European meta-analysis for *GOSR* and *SERPINH1*. (b) from the publicly available CARDIoGRAMplusC4D 1000G imputed GWAS results[1]. The r^2 information was calculated from the phased genotypes of 1000 Genome phase3 v5 (11/04/2014) super-populations (*PROCR* is given in Supplementary Figure 8).

Supplementary Figure 4(a)

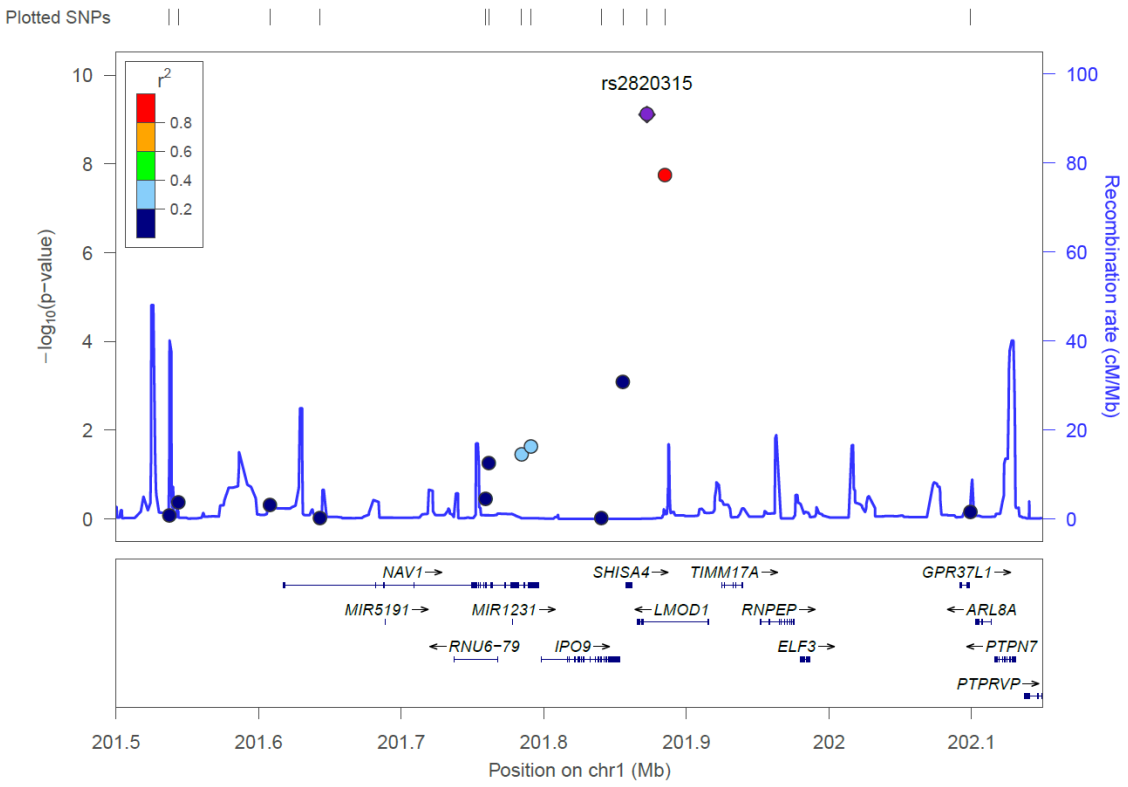
ATP1B1



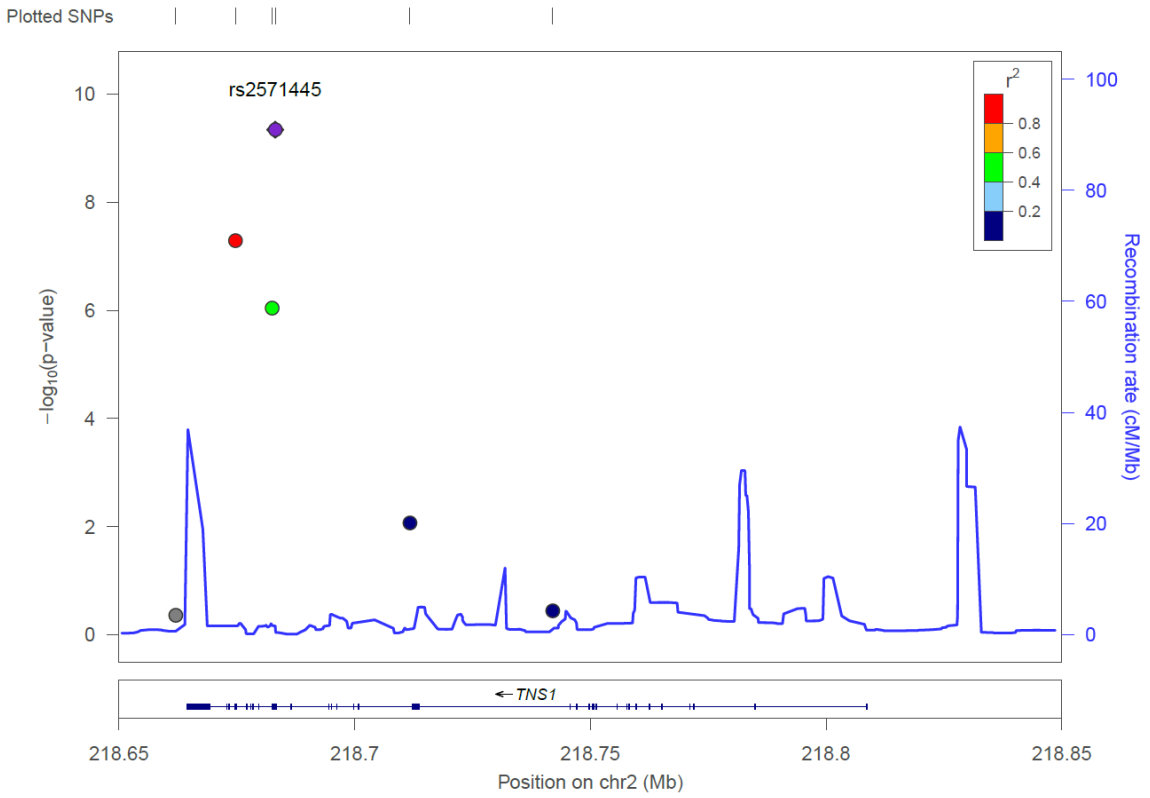
DDX59/CAMSAP2



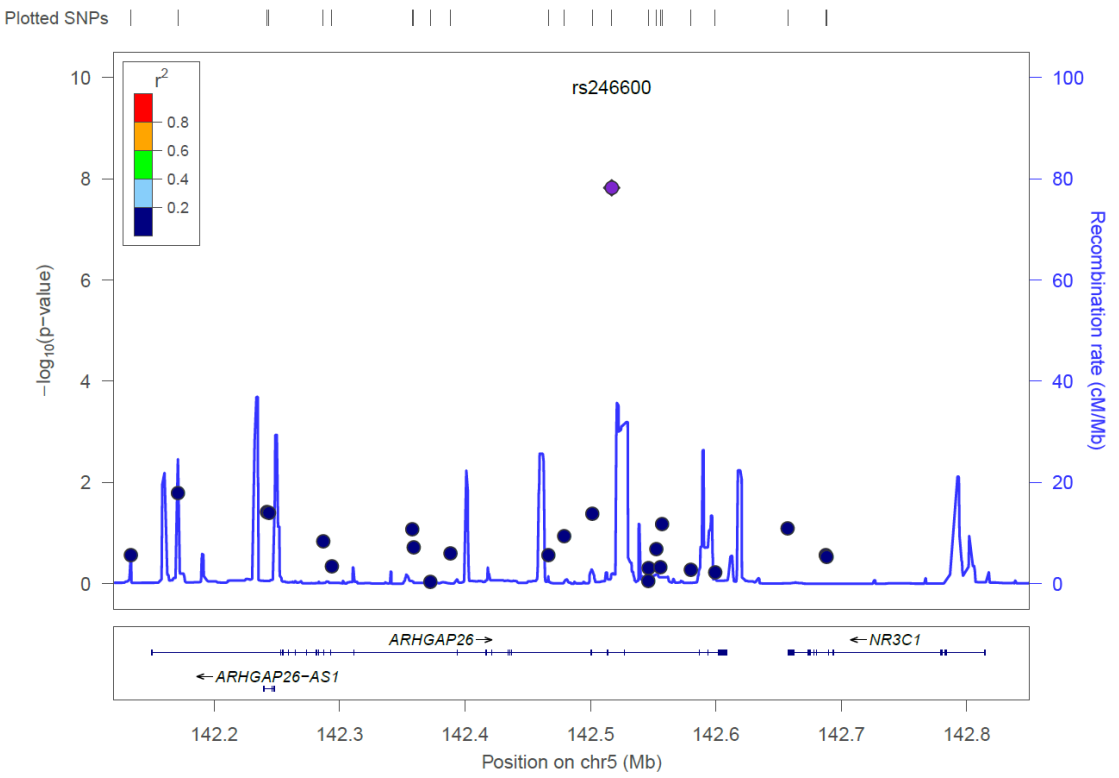
LMOD1



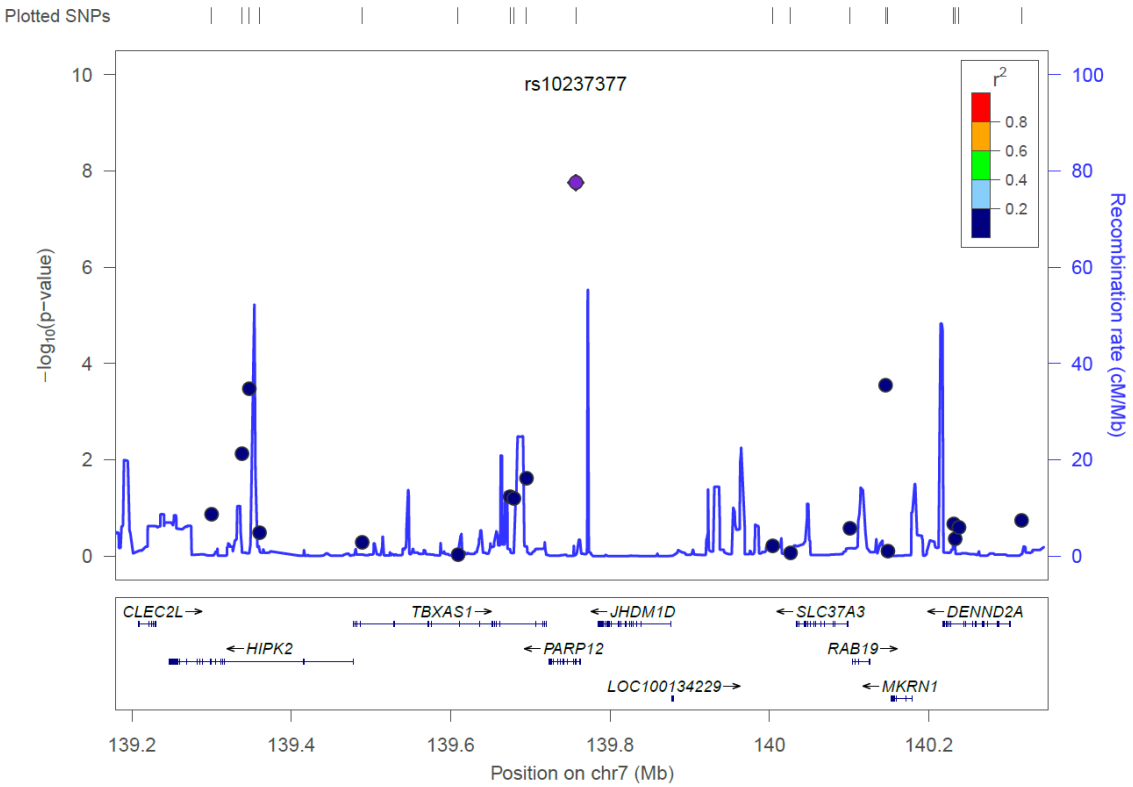
TNS1



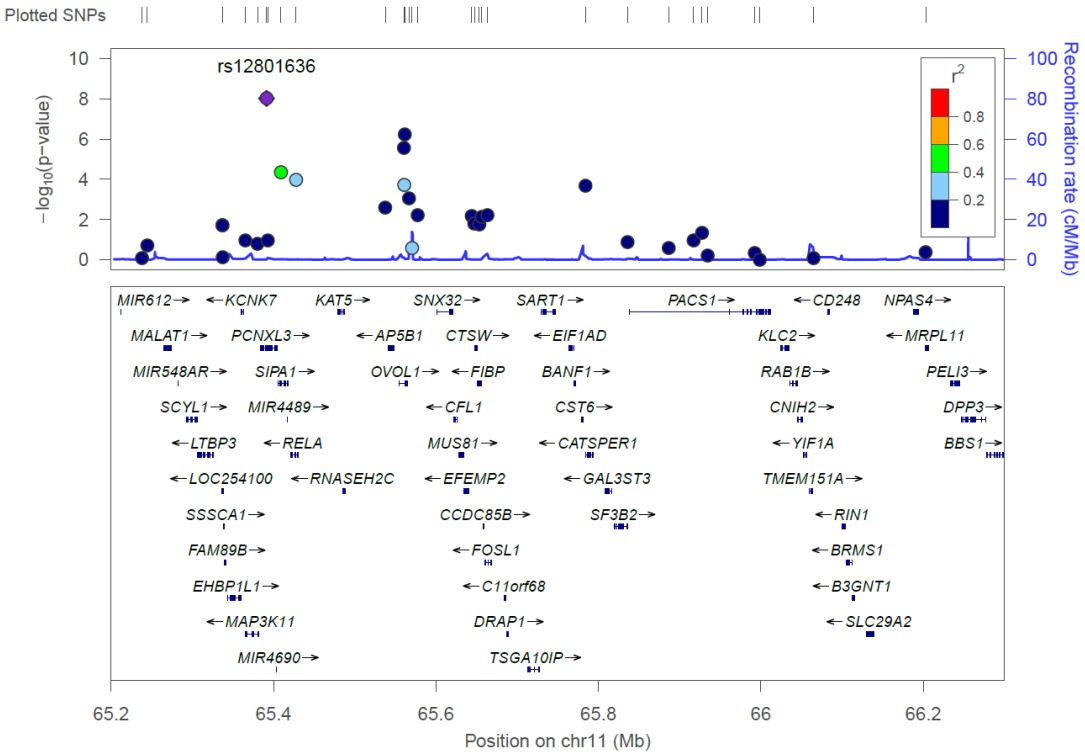
ARHGAP26



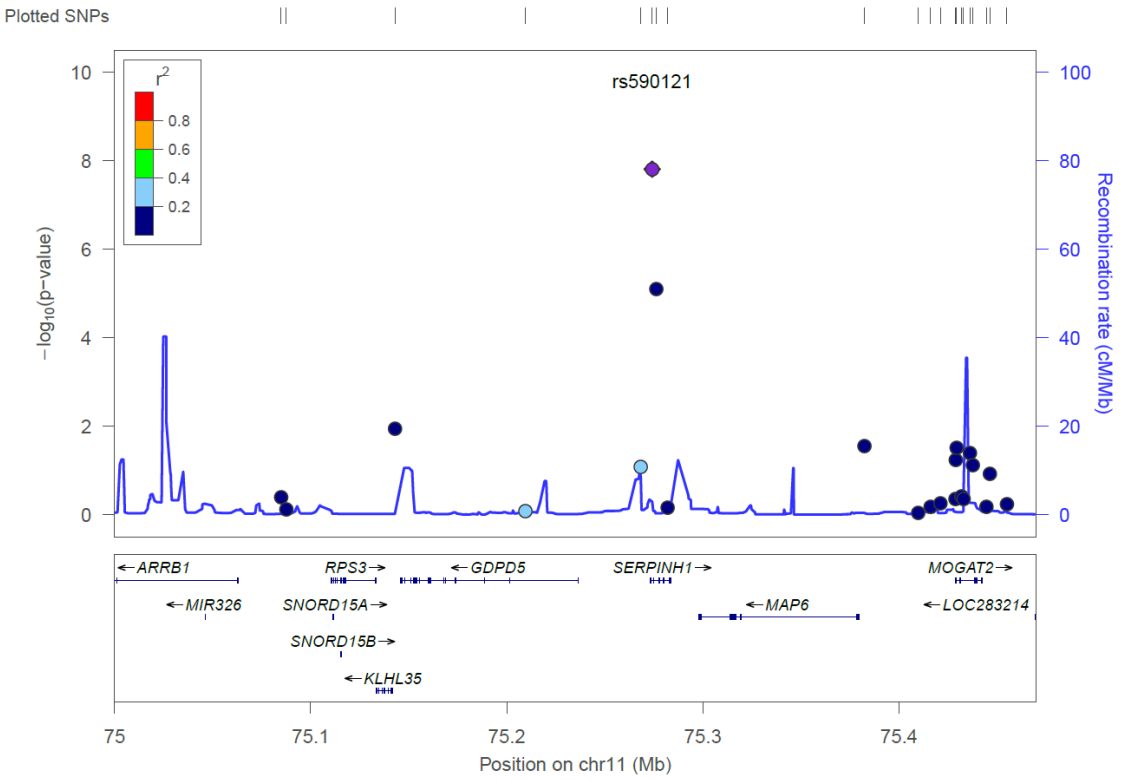
PARP12


Plotted SNPs
rs10237377
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
CLEC2L→
TBXAS1→
←JHDM1D
←SLC37A3
←DENND2A
←HIPK2
←PARP12
RAB19→
LOC100134229→
←MKRN1
Position on chr7 (Mb)

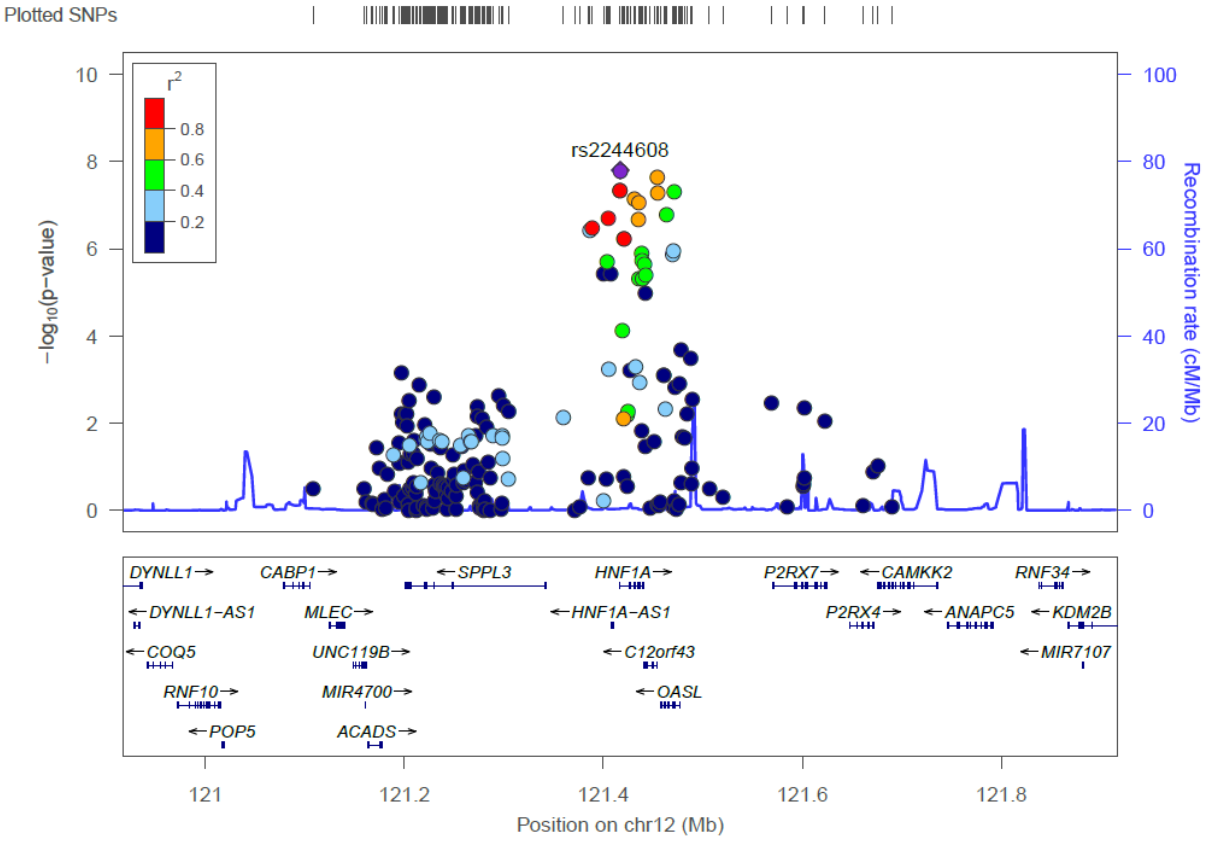
PCNX3


Plotted SNPs
rs12801636
r2
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
MIR612→
←KCNK7
KAT5→
SNX32→
SART1→
PACS1→
←CD248
NPAS4→
MALAT1→
PCNXL3→
←AP5B1
CTSW→
←EIF1AD
KLC2→
←MRPL11
MIR548AR→
SIPA1→
OVOL1→
←FIBP
BANF1→
RAB1B→
PELI3→
SCYL1→
MIR4489→
←CFL1
CST6→
CNIH2→
DPP3→
←LTBP3
←RELA
MUS81→
←CATSPER1
←YIF1A
BBS1→
←LOC254100
←RNASEH2C
←EFEMP2
←GAL3ST3
TMEM151A→
SSSCA1→
CCDC85B→
SF3B2→
←RIN1
FAM89B→
←FOSL1
←BRMS1
EHBP1L1→
←C11orf68
←B3GNT1
←MAP3K11
DRAP1→
←SLC29A2
MIR4690→
TSGA10IP→
Position on chr11 (Mb)

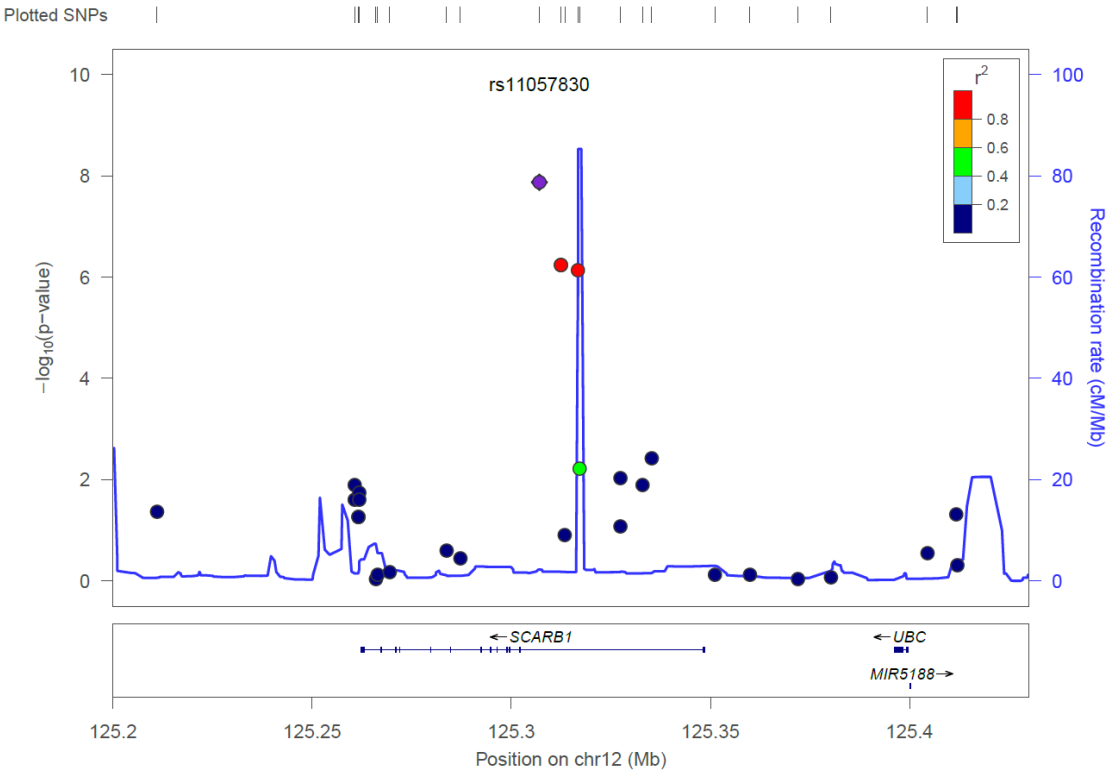
SERPINH1



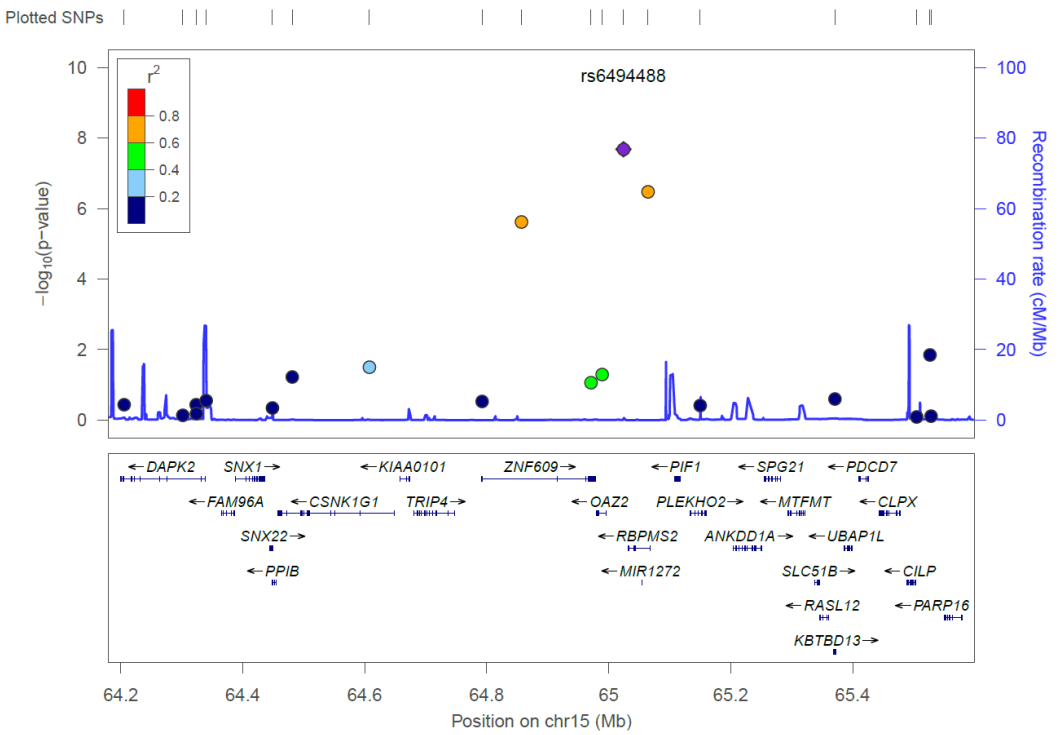
C12orf43/HNF1A



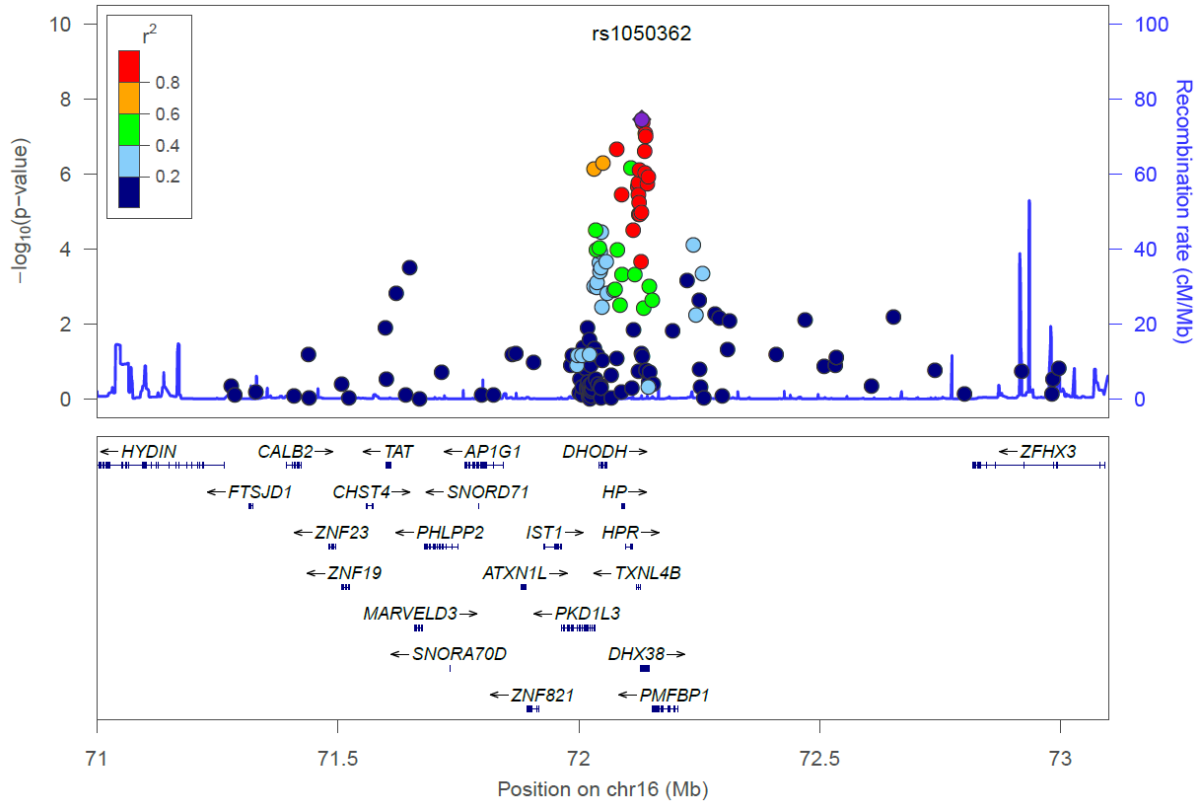
SCARB1



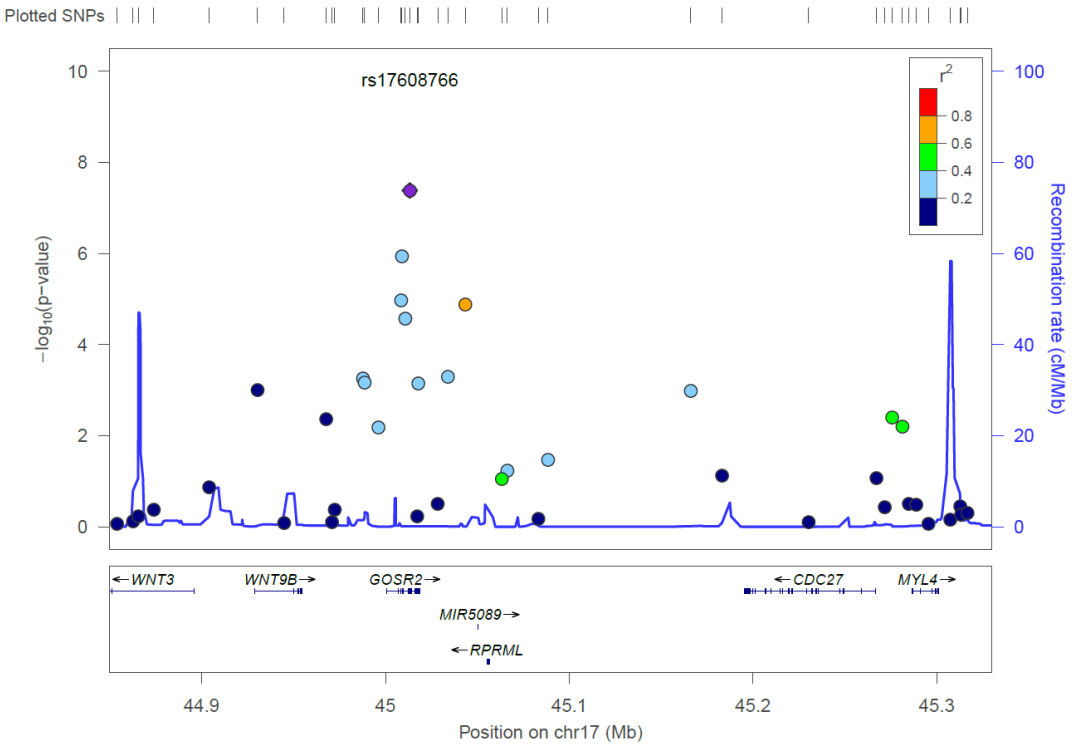
OAZ2, RBPMS2



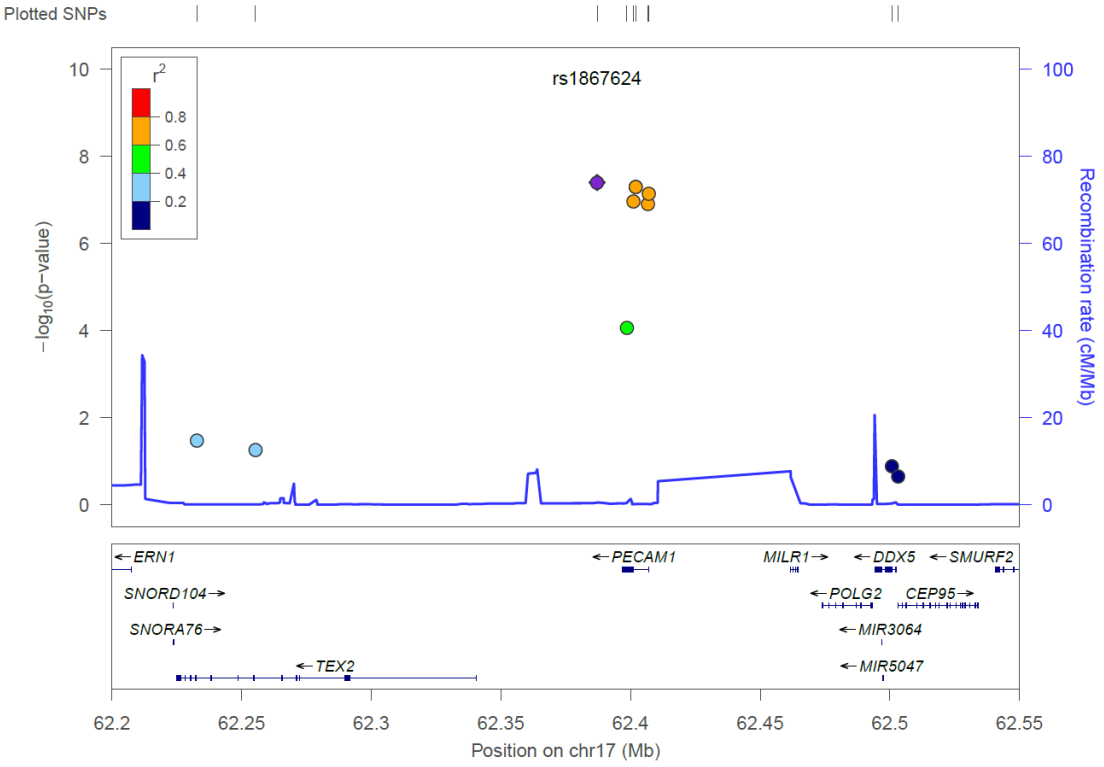
DHX38



GOSR2

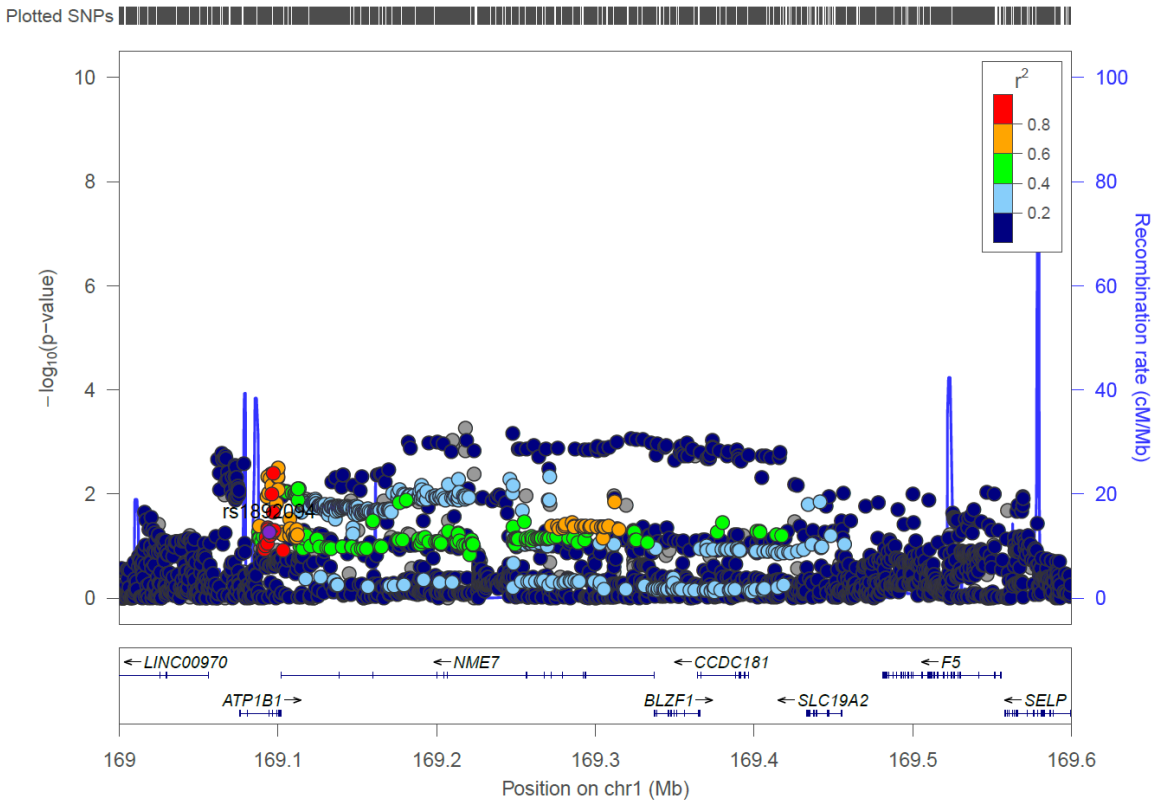


PECAM1

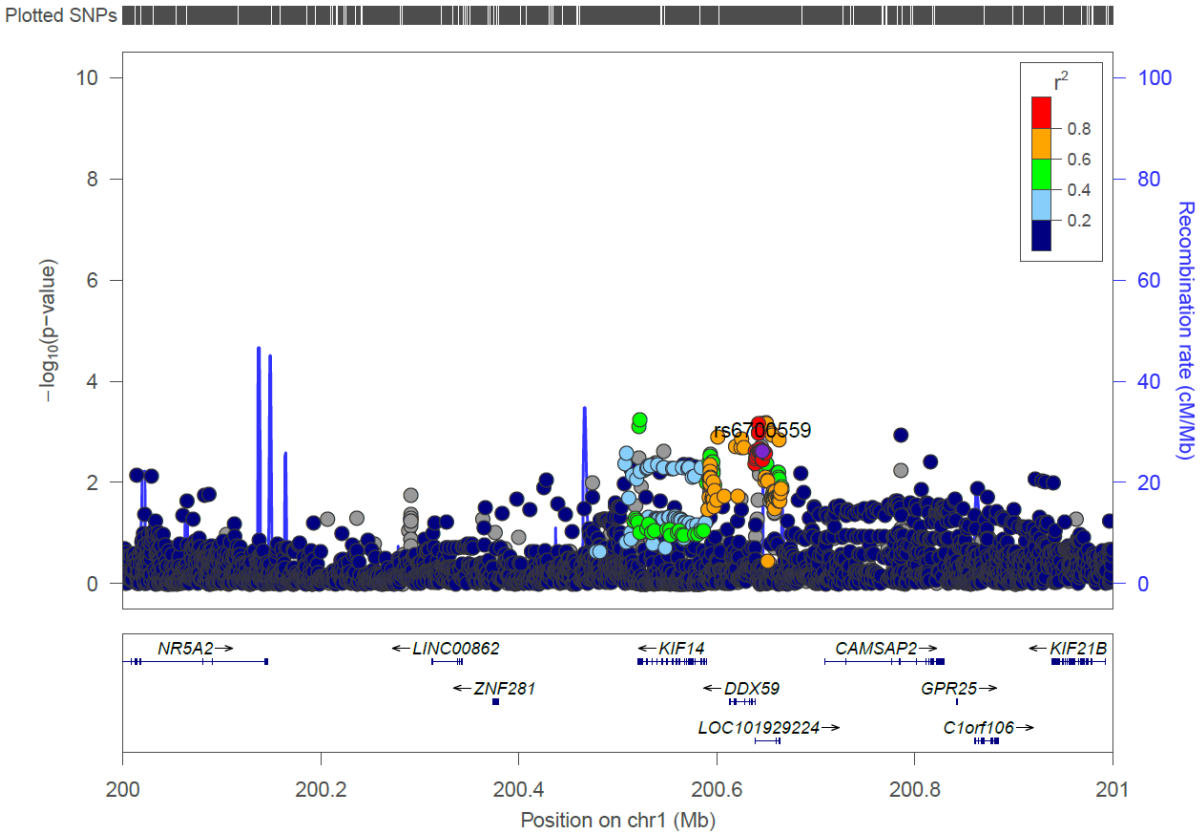


Supplementary Figure 4(b)

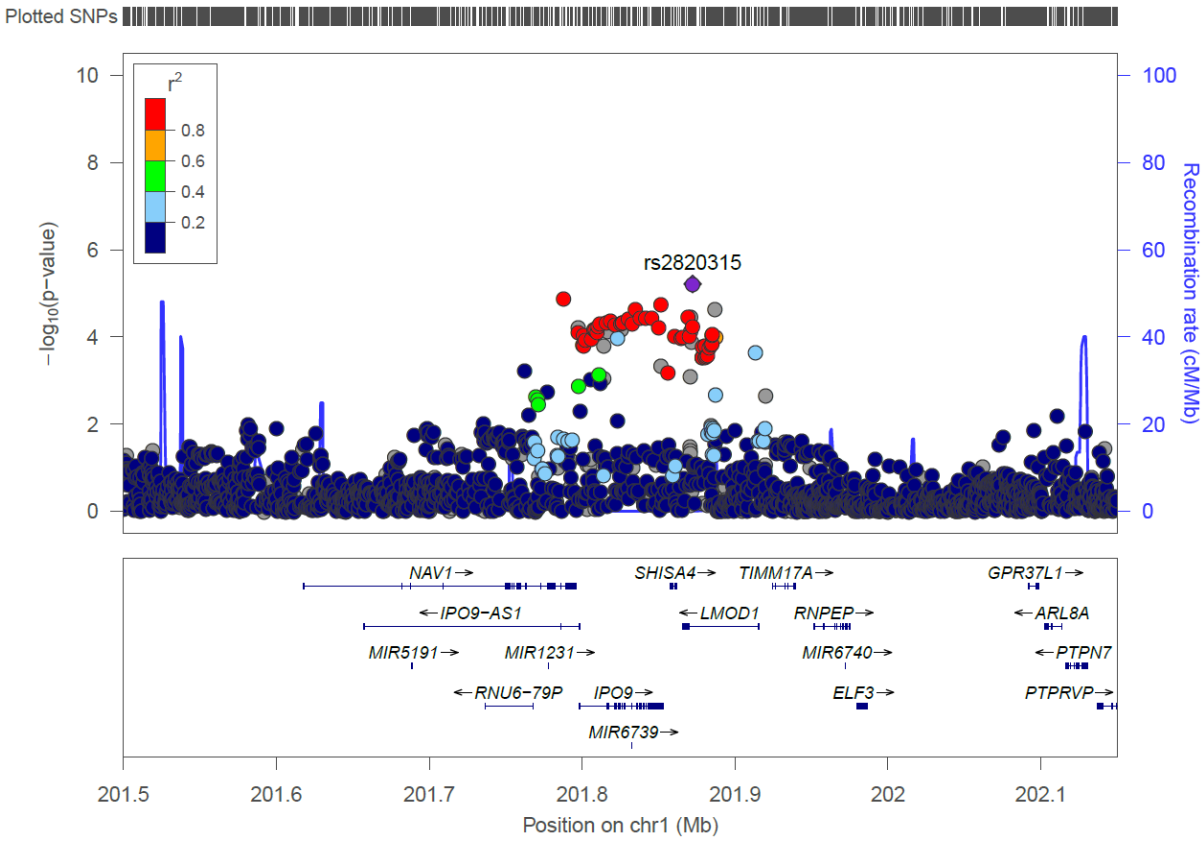
ATP1B1 (1000G)



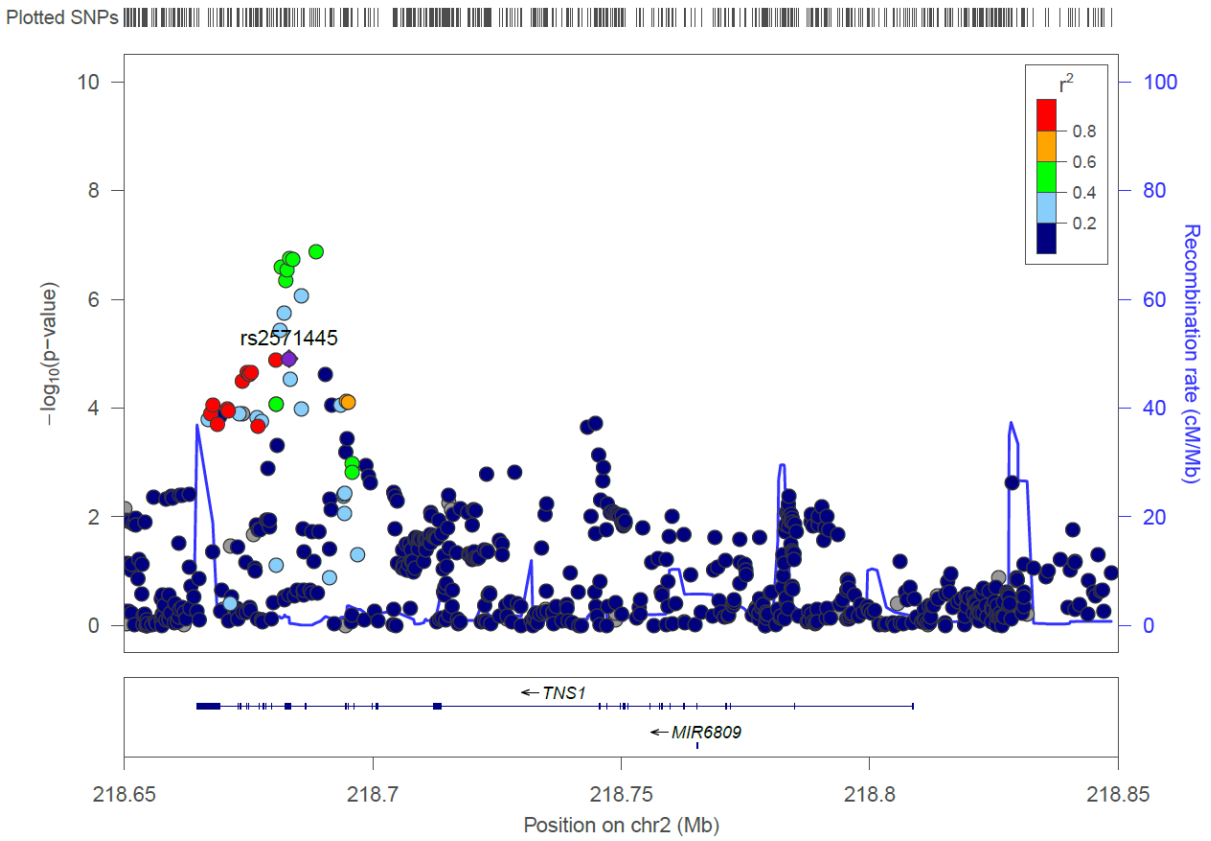
***DDX59/CAMSAP2* (1000G)**



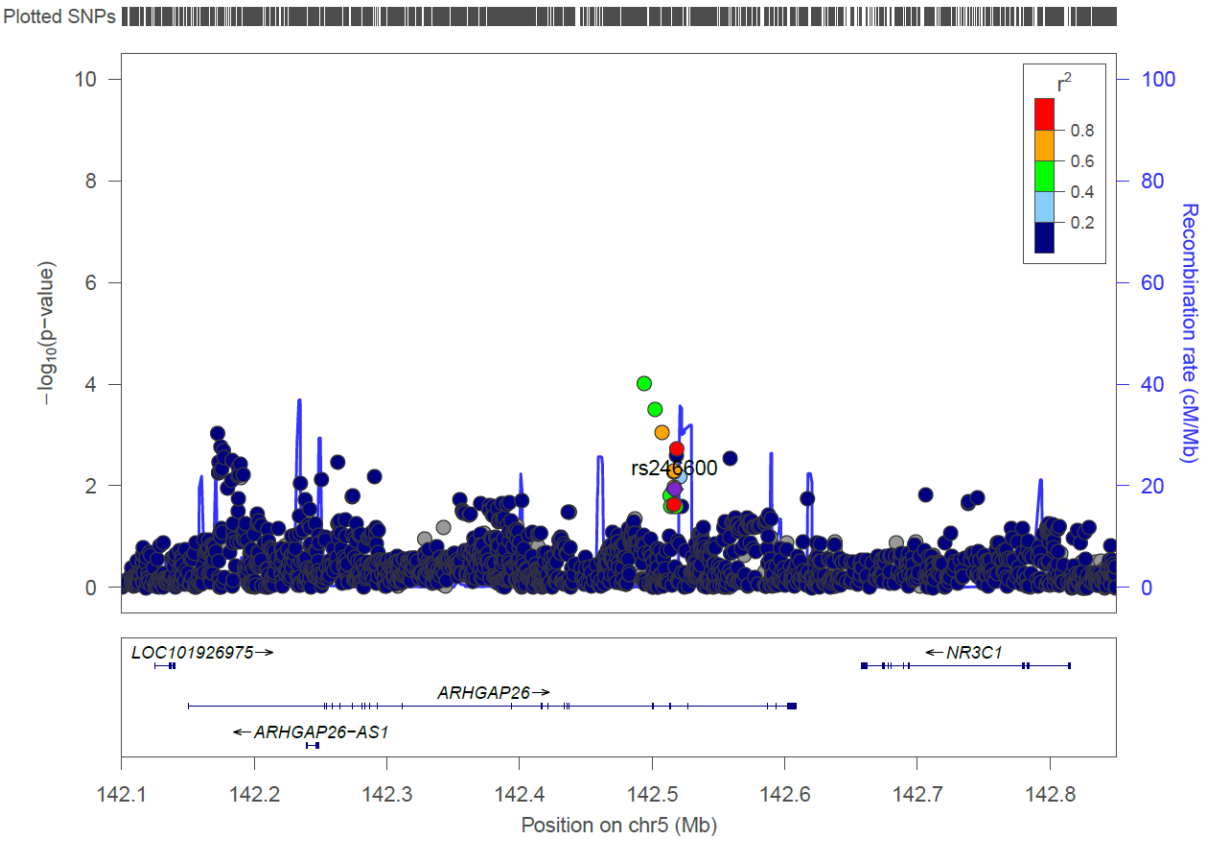
***LMOD1* (1000G)**



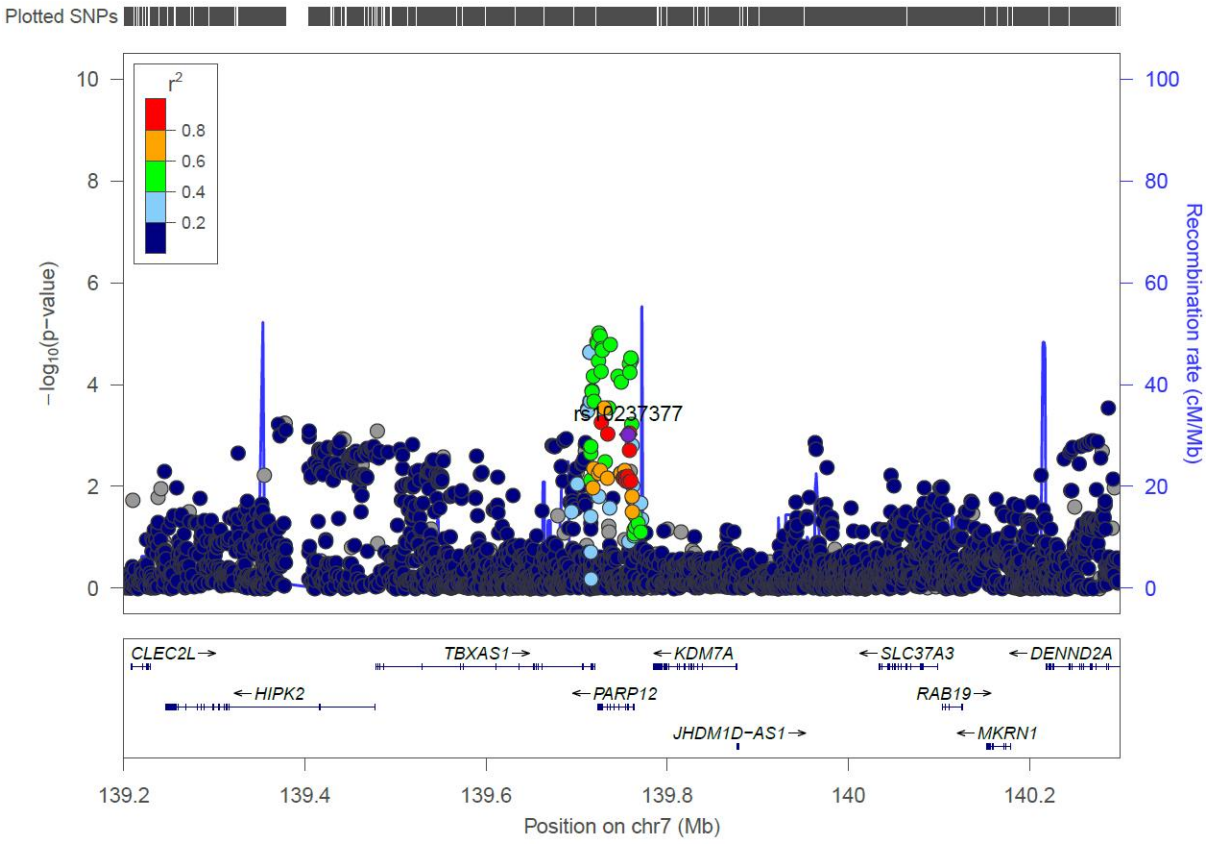
***TNS1* (1000G)**



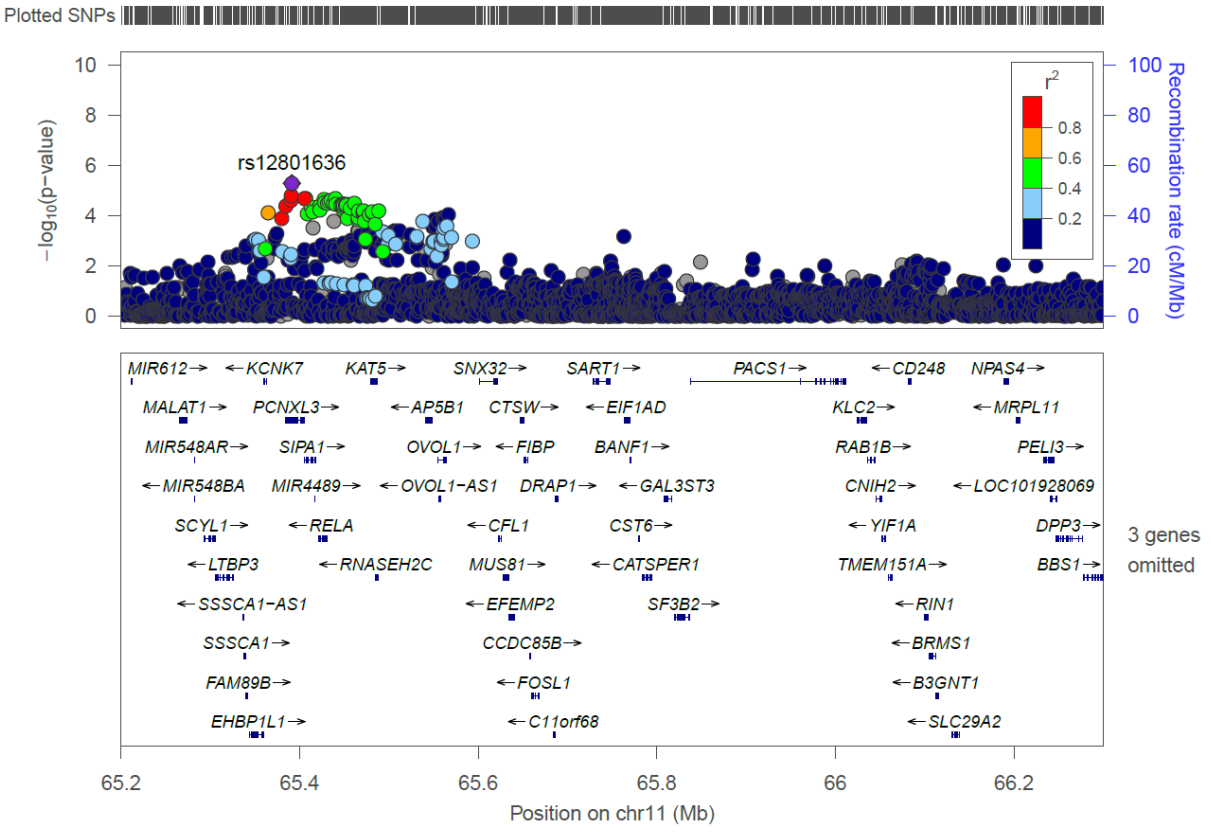
***ARHGAP26* (1000G)**



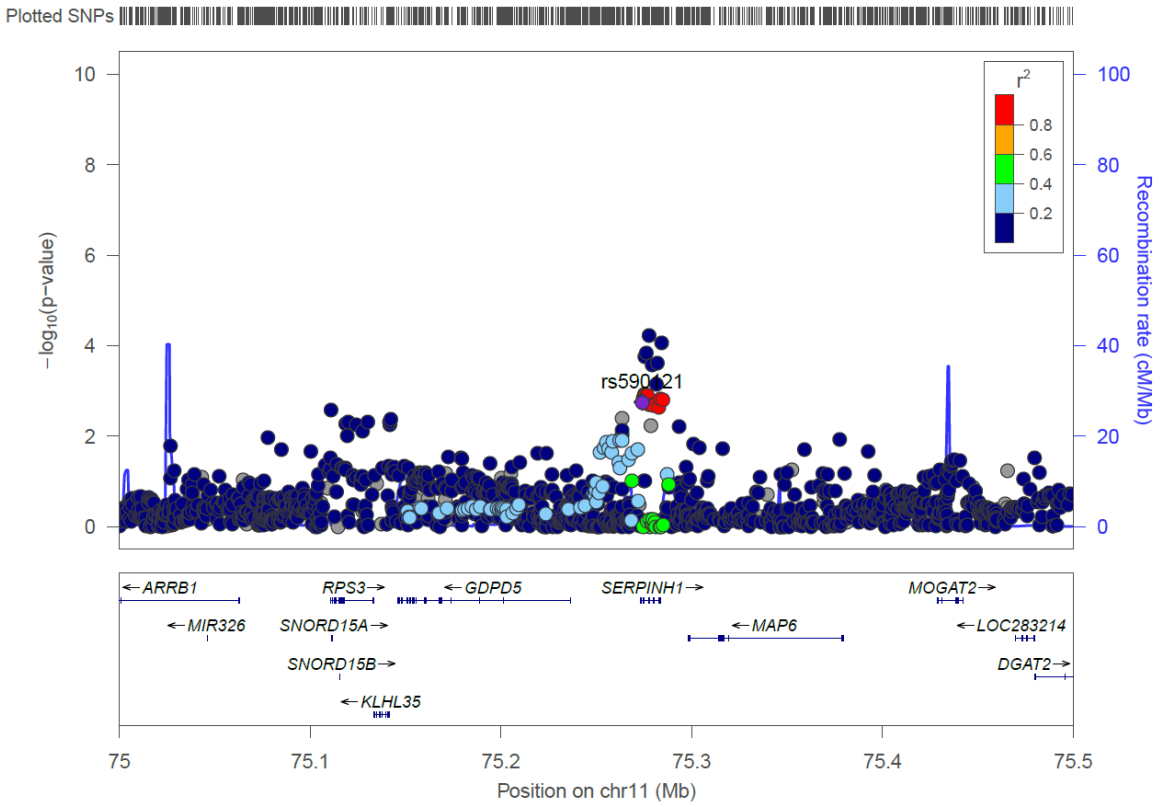
***PARP12* (1000G)**



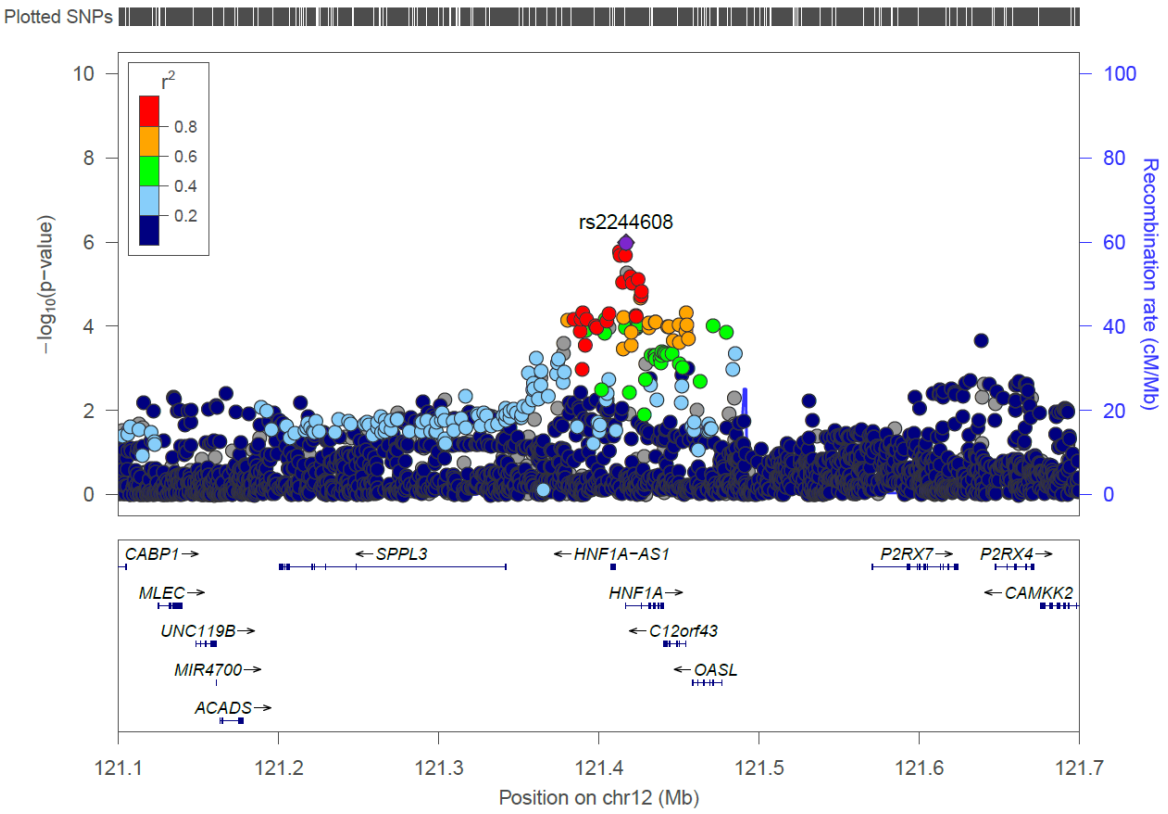
***PCNX3* (1000G)**



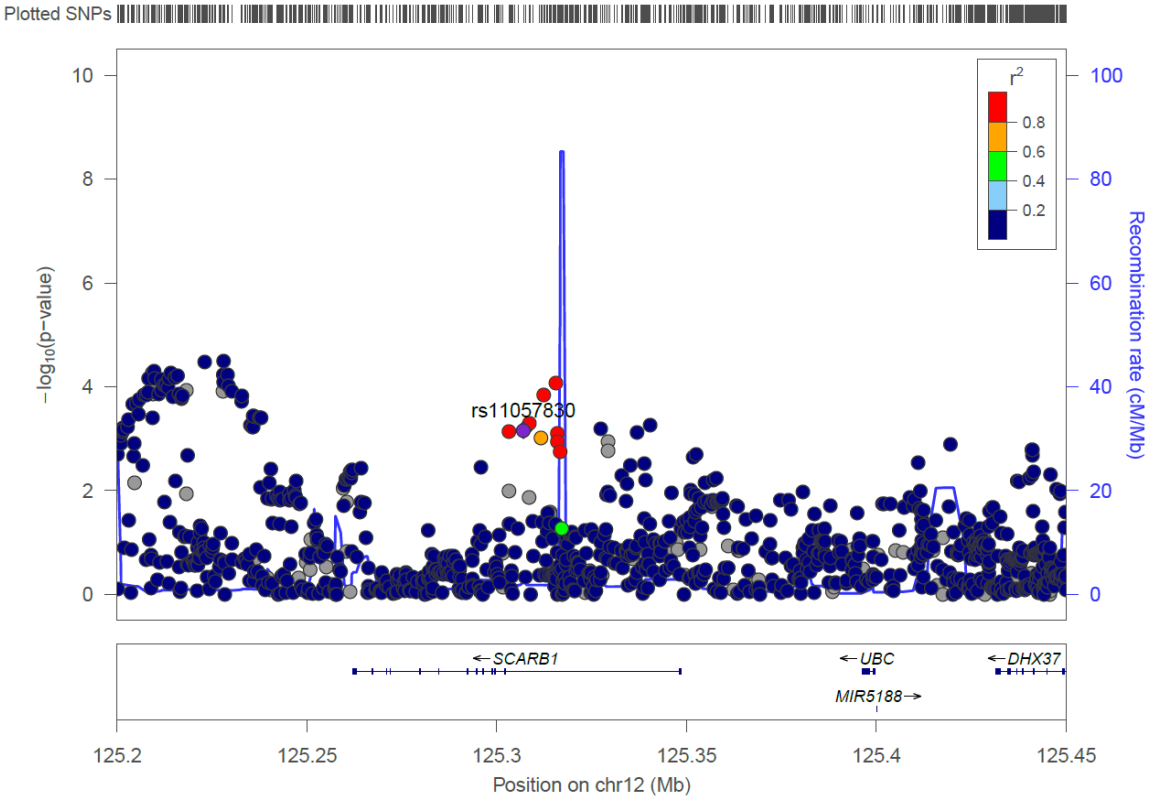
SERPINH1 (1000G)



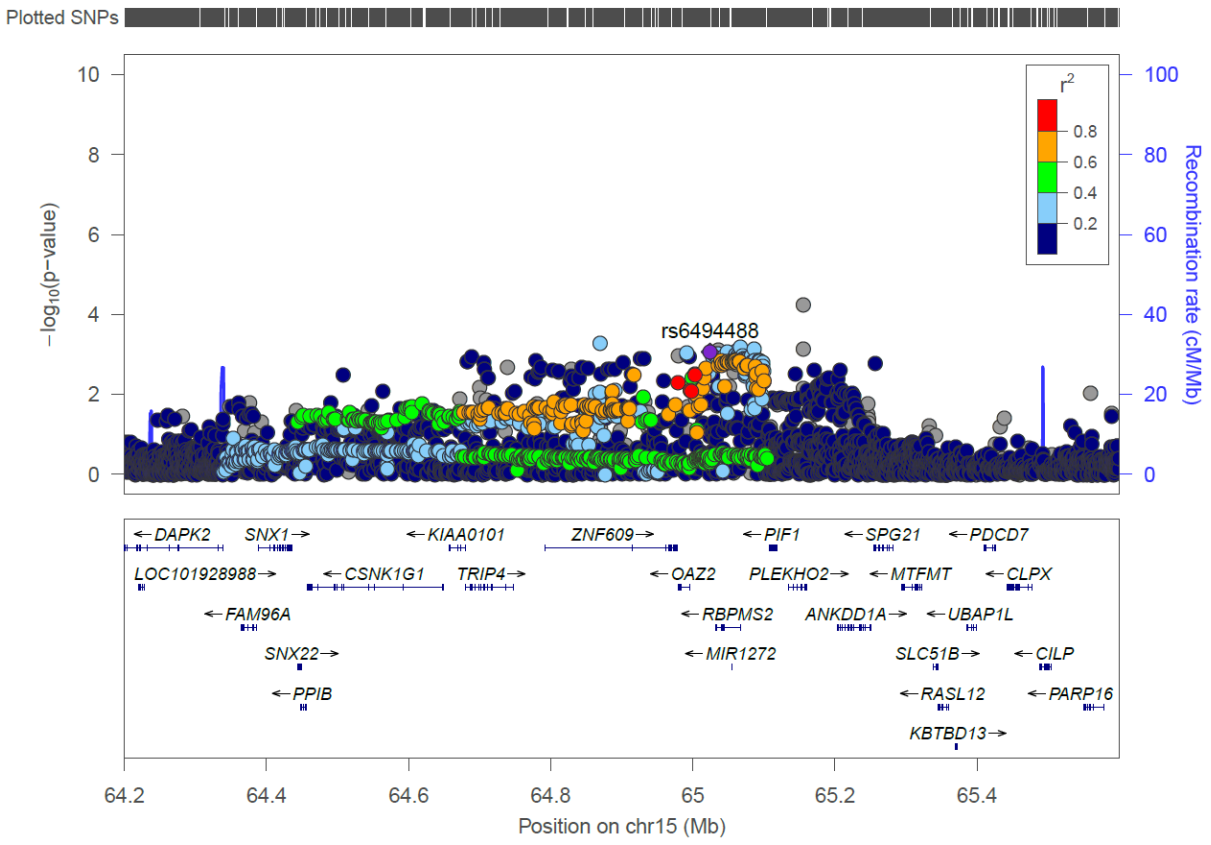
C12orf43/HNF1A (1000G)



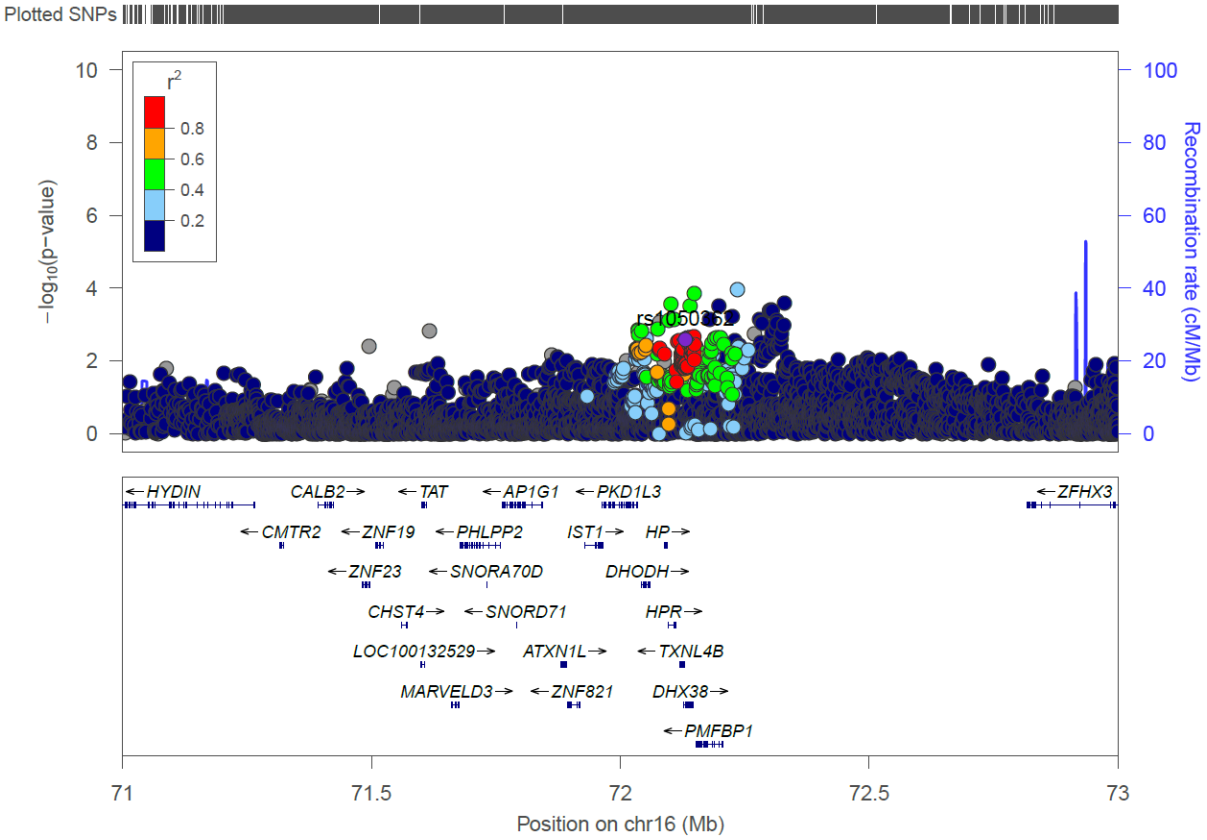
***SCARB1* (1000G)**



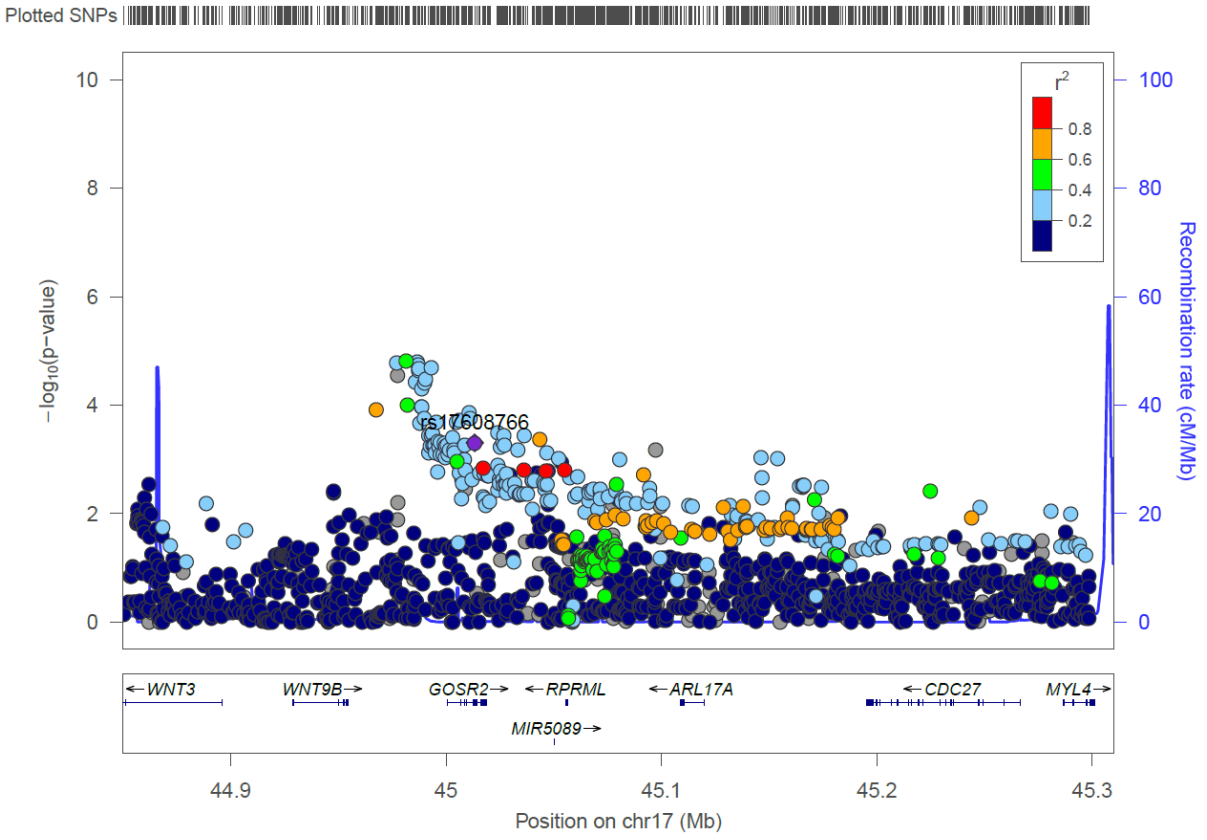
***OAZ2, RBPMS2* (1000G)**



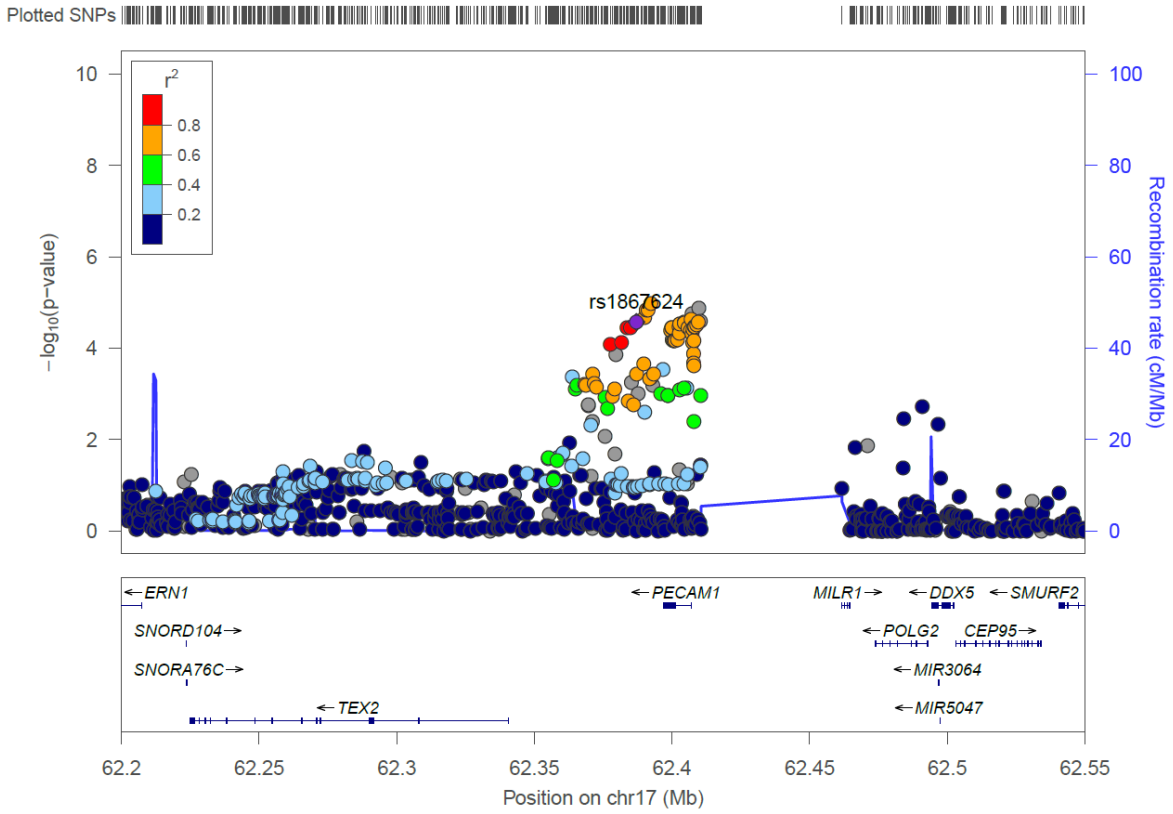
***DHX38* (1000G)**



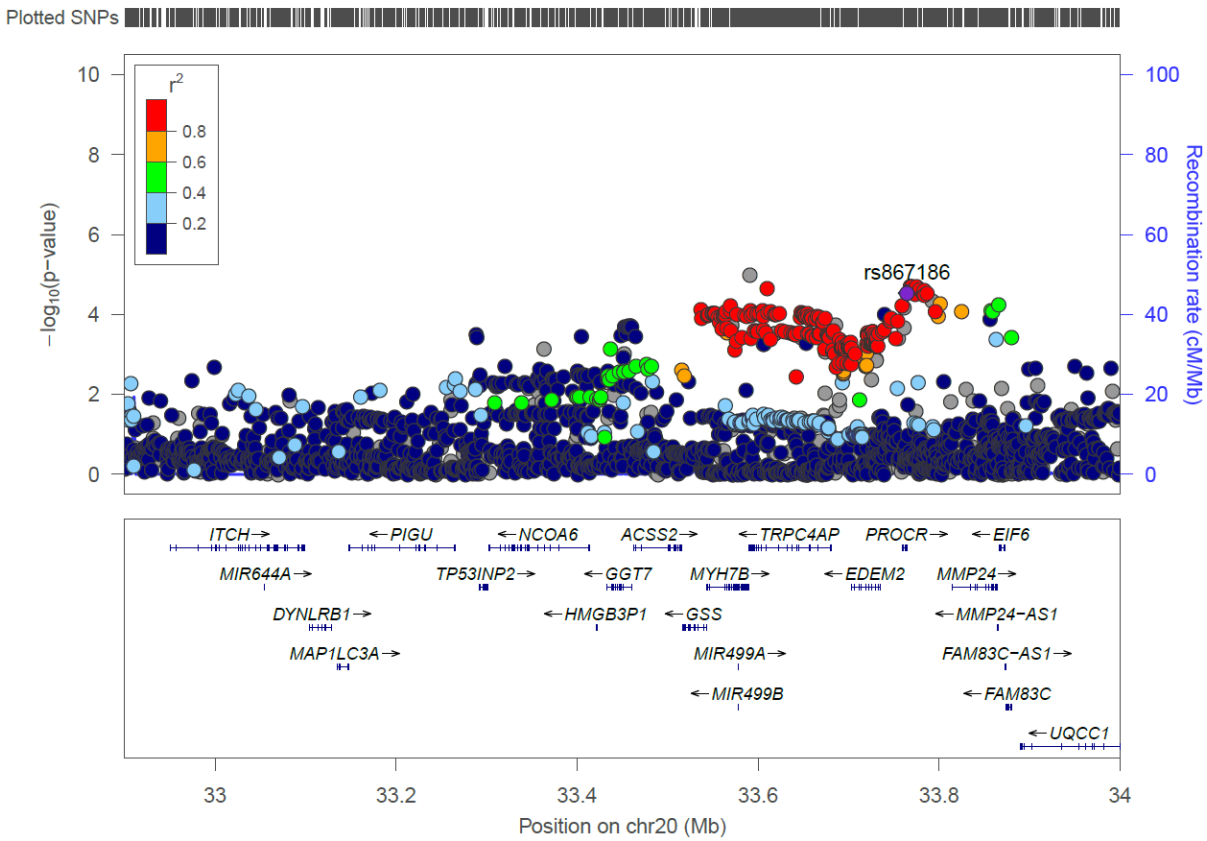
***GOSR2* (1000G)**



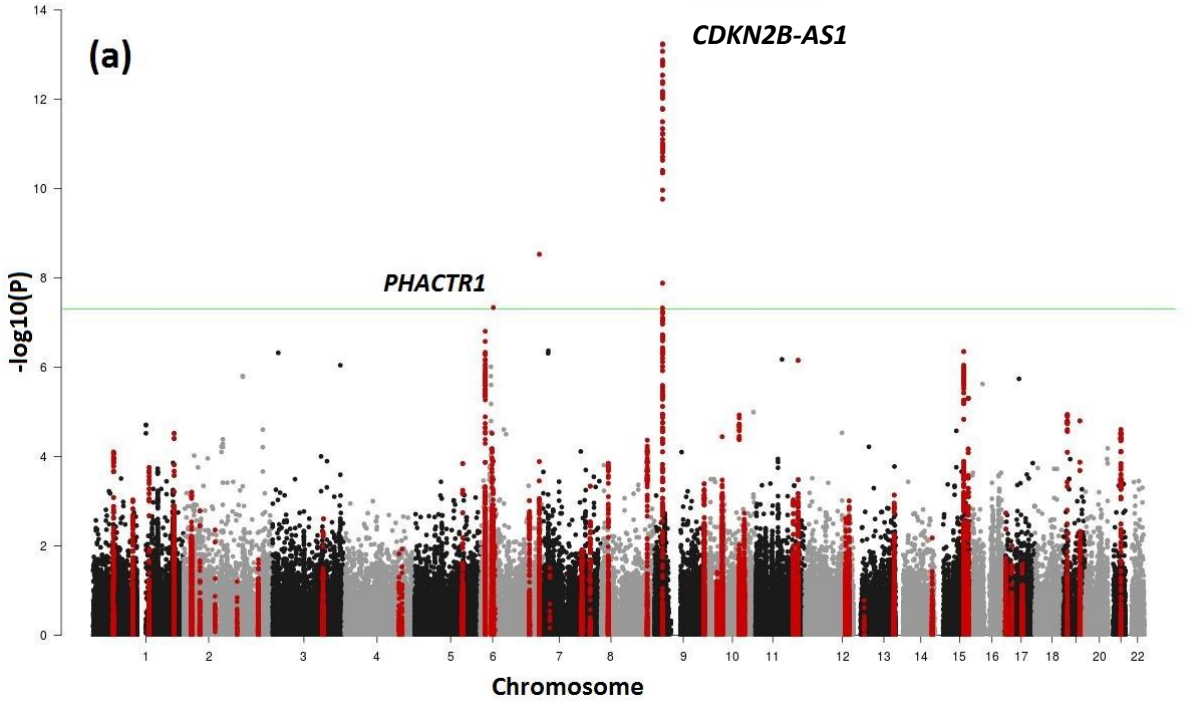
***PECAM1* (1000G)**

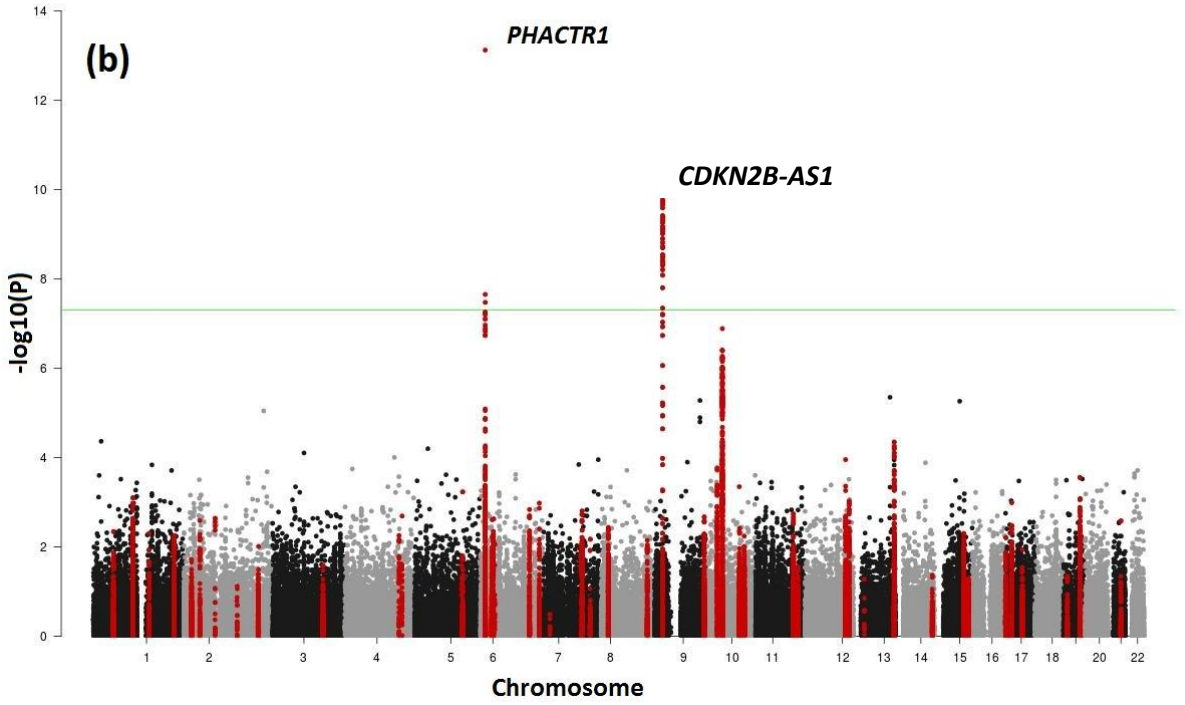


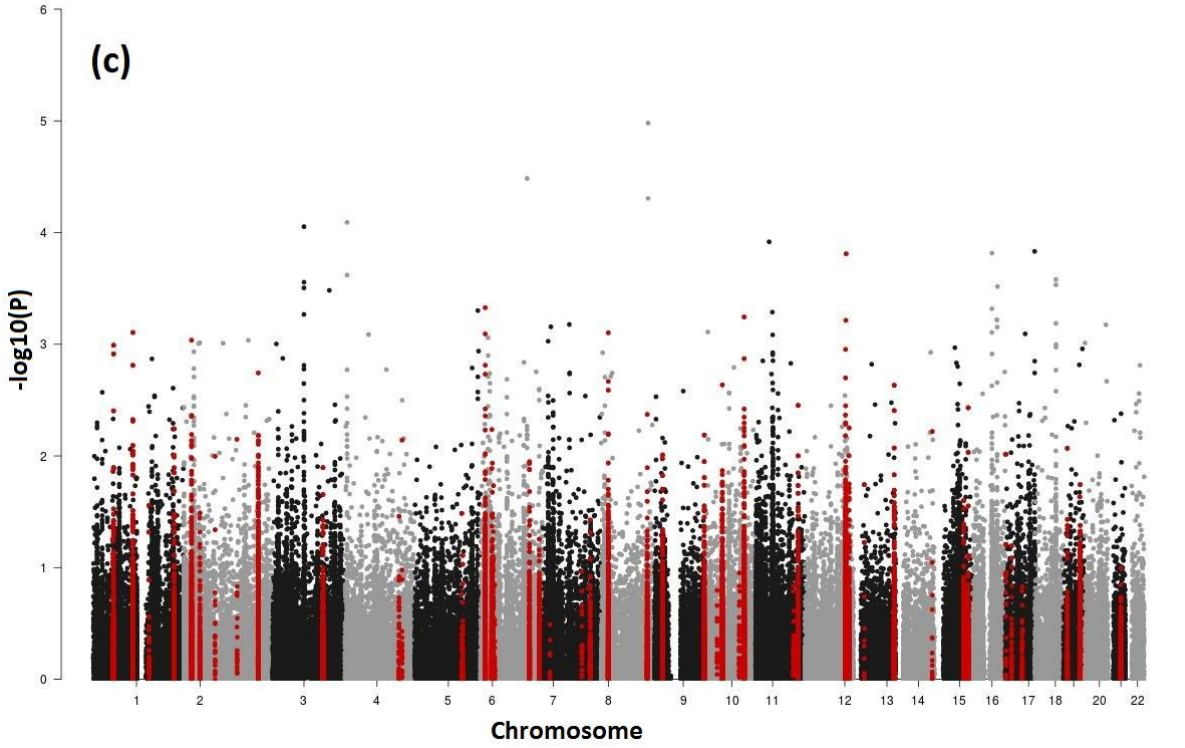
***PROCR* (1000G)**

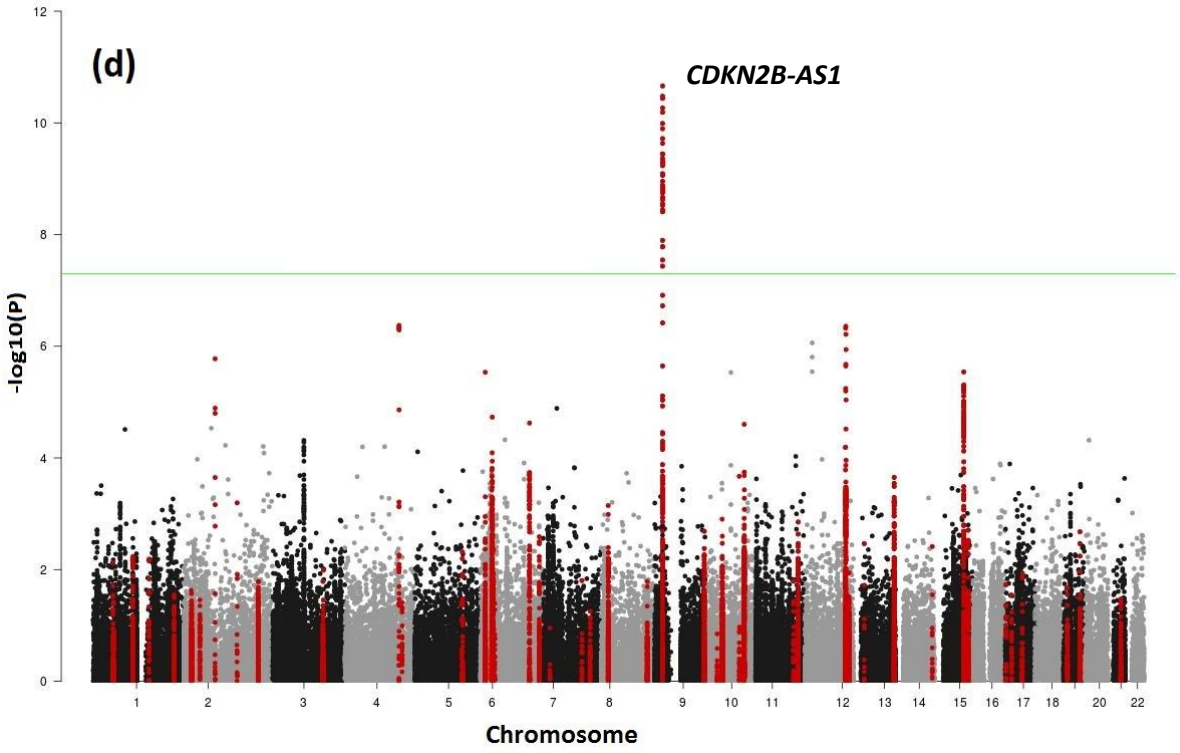


Supplementary Figure 5: Manhattan plot for the association of the Metabochip SNPs in the studies with *de novo* genotyping (a) European studies, CGPS/CIHDS, CCHS, EPIC-CVD, EPIC-Umea (b) the South Asian studies, BRAVE and PROMIS (c) the African American samples from MIGEN, WHI, and ARIC (d) the East Asian studies, TAICHI. -log(P=5x10^{-8})~7.3. Note these plots are across the whole CardioMetabochip and excluded the published CARDIoGRAMplusC4D data.

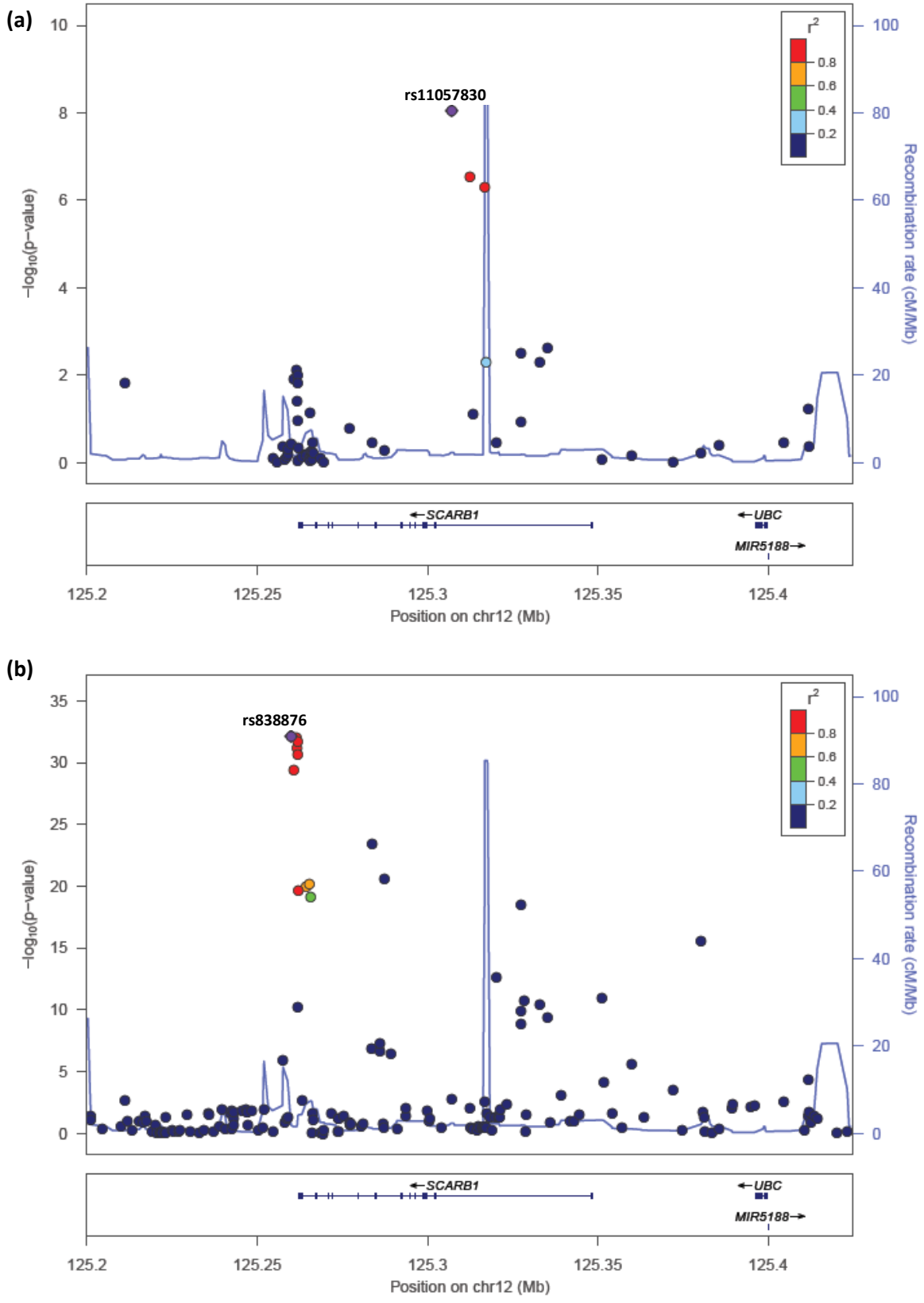



(b)
PHACTR1
CDKN2B-AS1
-log10(P)
Chromosome

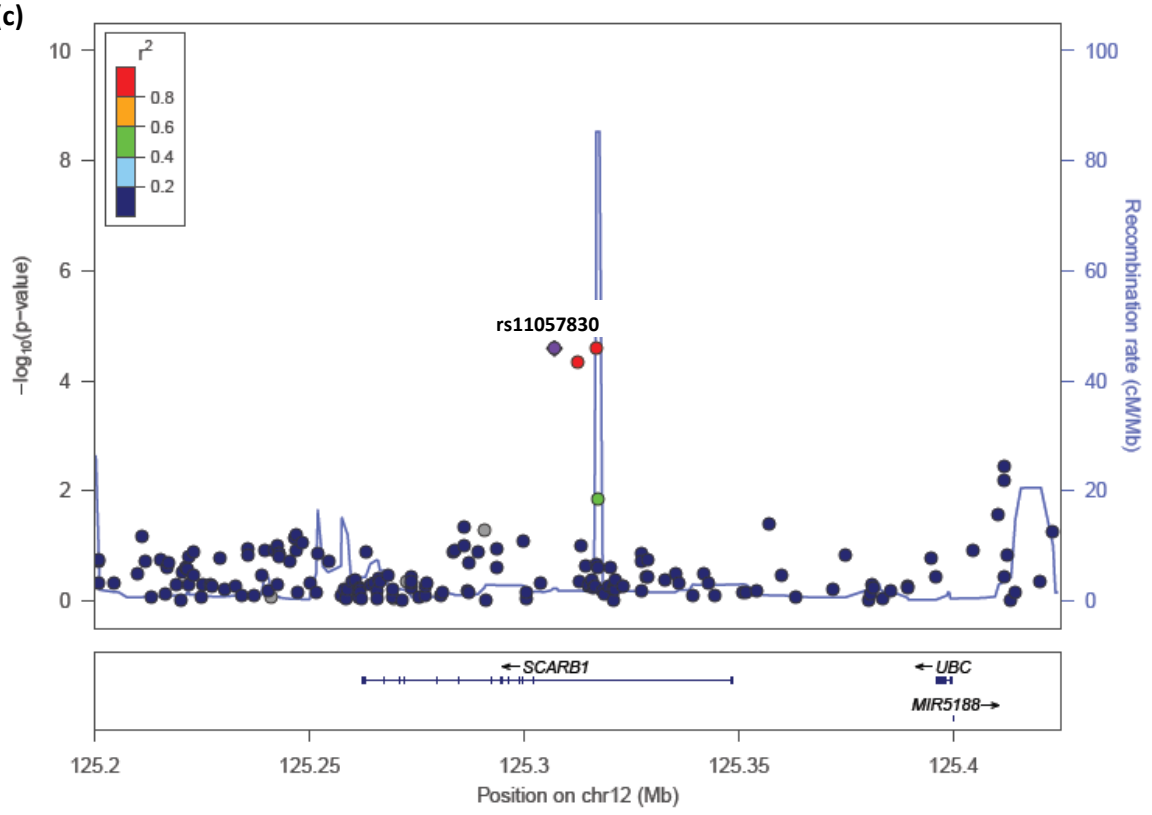

(c)
-log10(P)
Chromosome


(d)
CDKN2B-AS1
-log10(P)
Chromosome
0
2
4
6
8
10
12
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
20
22

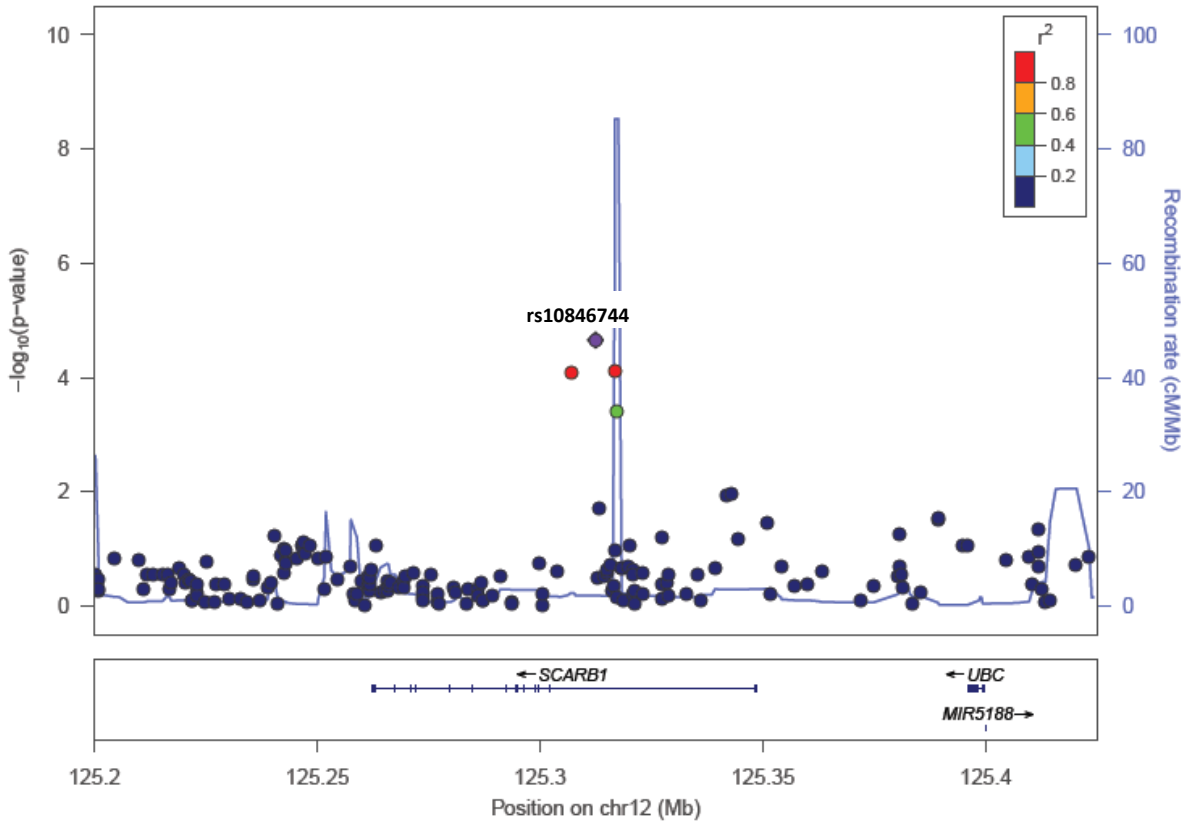
Supplementary Figure 6 *SCARB1* regional association plots with (a) CAD (b) HDL[2] (c) LDL[2] and (d) triglycerides[2]. Physical position is given for GRCh37. The r^2 information was from the 1000 Genome phase3 v5 EUR samples.



(c)

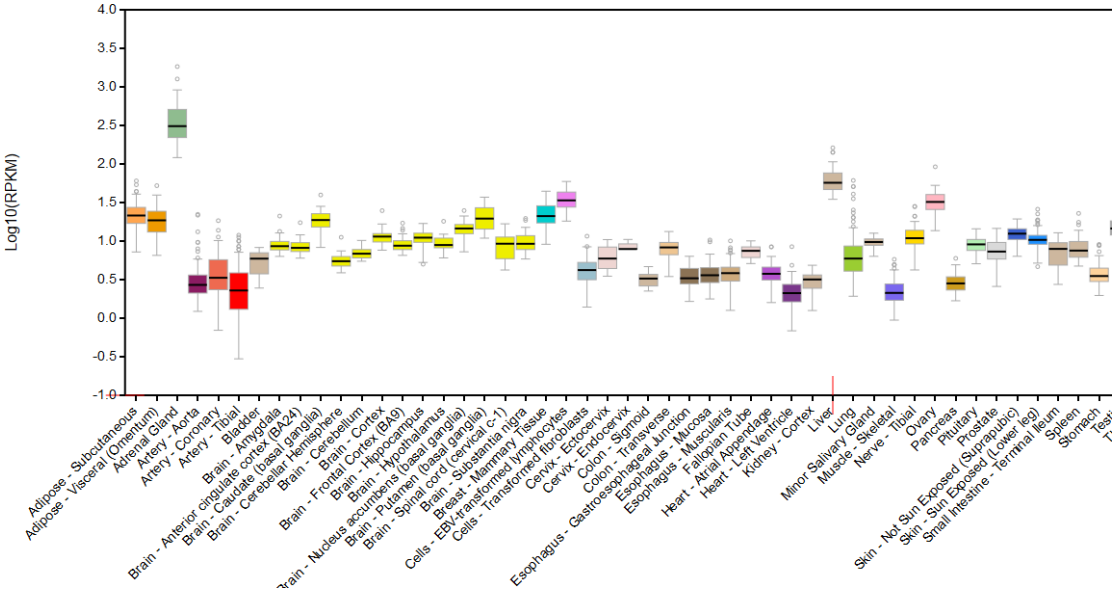

r²
0.8
0.6
0.4
0.2
rs11057830
−log10(p−value)
Recombination rate (cM/Mb)
SCARB1
UBC
MIR5188
125.2
125.25
125.3
125.35
125.4
Position on chr12 (Mb)

(d)


r²
0.8
0.6
0.4
0.2
rs10846744
−log10(p−value)
Recombination rate (cM/Mb)
SCARB1
UBC
MIR5188
125.2
125.25
125.3
125.35
125.4
Position on chr12 (Mb)

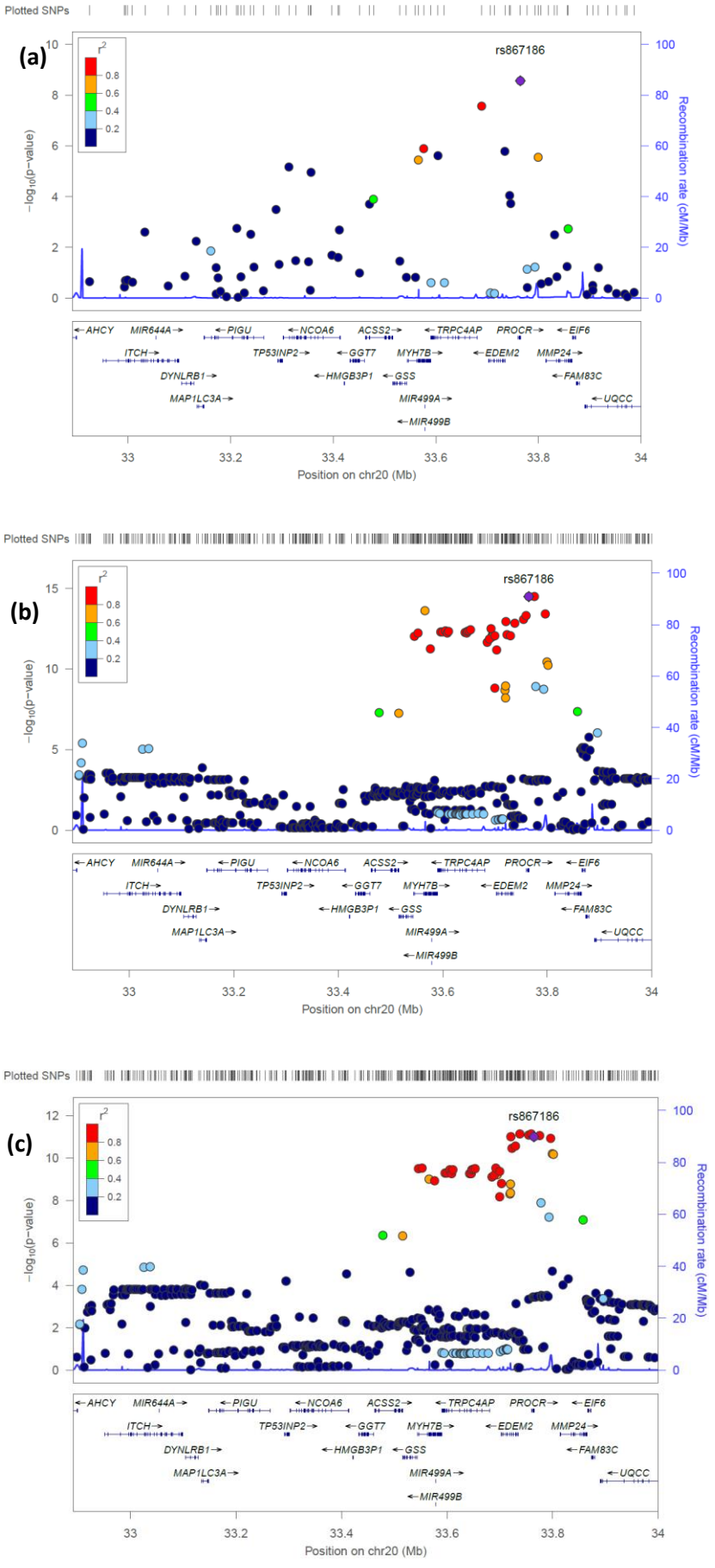
Supplementary Figure 7 Annotation of the *SCARB1* gene locus using publicly available transcriptomic and epigenomic reference data sets. **(a)** Gene expression profile of *SCARB1* in the GTEx data set (release V4; dbGaP accession phs000424.v4.p1). Among the profiled tissues, *SCARB1* is most highly expressed in adrenal gland and liver tissues. **(b)** Annotation of epigenomic features at the *SCARB1* locus (chr12:125,259,174–125,348,519; hg19) using the WashU Epigenome Browser v40.0.0 (http://epigenomegateway.wustl.edu/browser/). In the top panel, we show the two correlated variants rs11057830 and rs11057841 associated with CAD, as well as the variant rs838880 associated the HDL levels. RefSeq genes are shown at the bottom panel. A total of 23 epigenomic reference tracks (i.e. chromatin state maps) provided by the NIH Roadmap Epigenomics Project are displayed. Specifically, we show primary chromatin state maps in all available adult cell types/tissues (blood, bone, brain, fat and muscle tissues were excluded). All three highlighted genetic variants map to enhancers active in primary liver tissue.

A

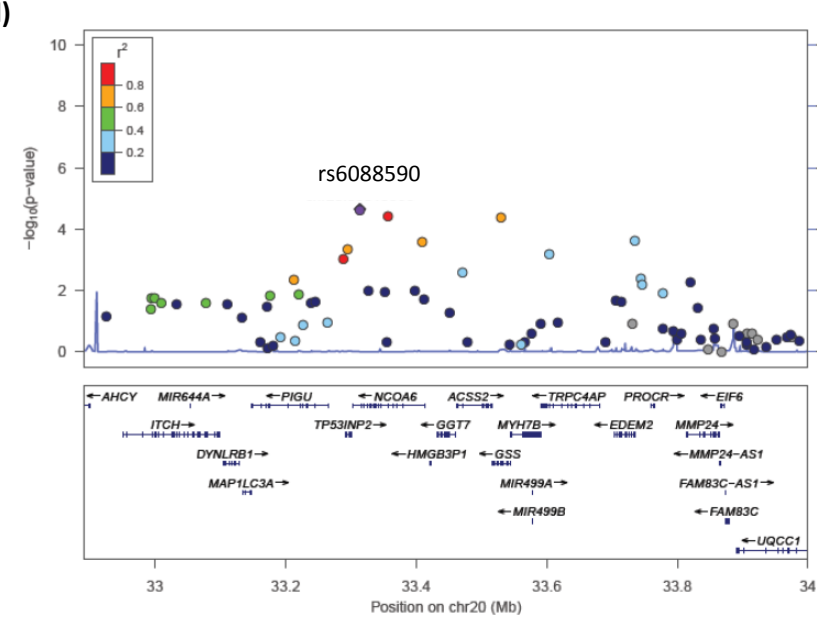


B

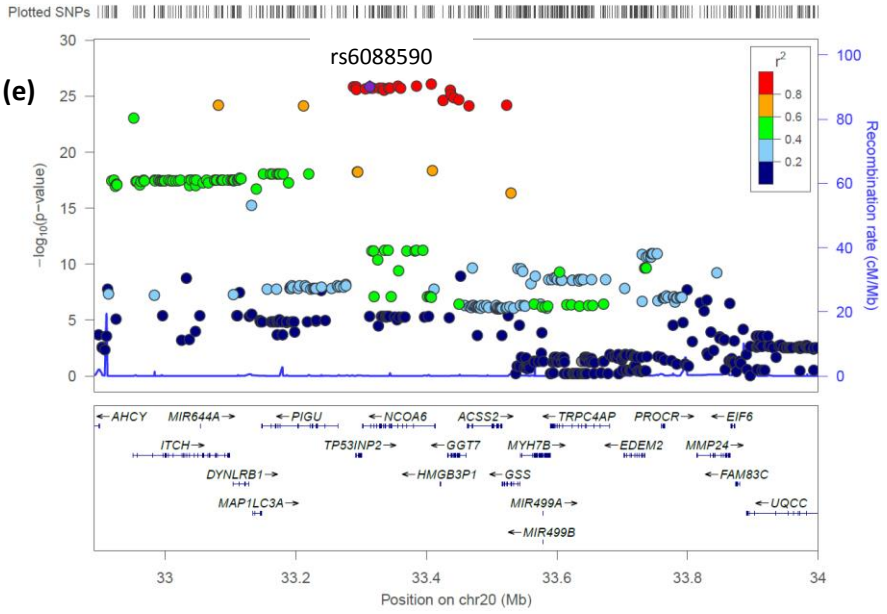
Supplementary Figure 8 Association of the PROCR gene region. (a) with CAD (b) with *PROCR* expression QTLs in subcutaneous adipose tissue from MuTHER (c) *PROCR* expression QTLs in skin tissue from MuTHER (d) CAD-association of the *PROCR* region conditional on the sentinel SNP, rs867186 (e) *GGT7* expression QTLs in subcutaneous adipose tissue from MuTHER (f) *GGT7* expression QTLs in skin tissue from MuTHER. Physical position is given for GRCh37. r^2 is calculated using 1000G EUR samples and reported relative to the sentinel CAD SNP, rs867186, in (a), (b) & (c) and to the second CAD-associated SNP, rs6088590, in (d), (e) and (f).



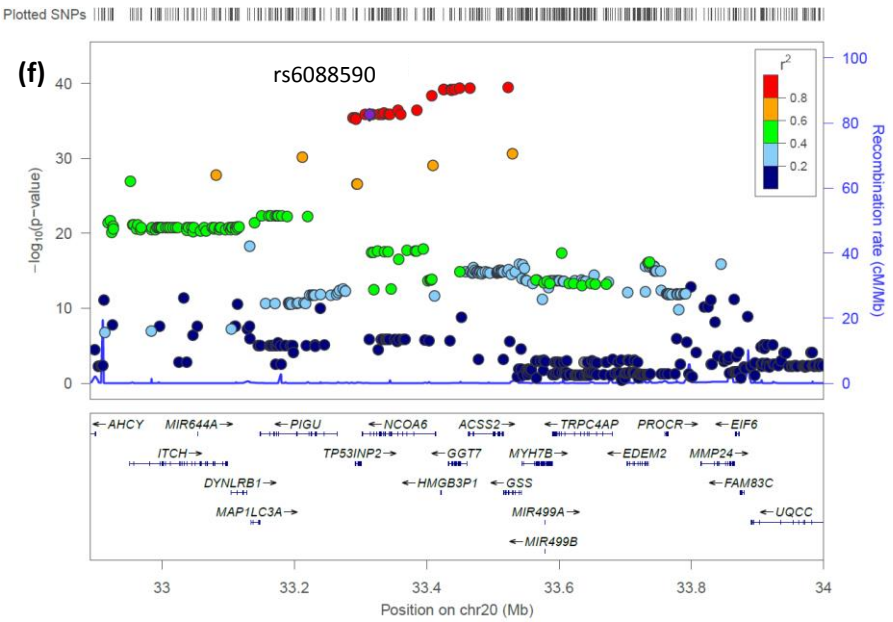
(d)


rs6088590
r²
0.8
0.6
0.4
0.2
−log10(p−value)
AHCY
MIR644A
PIGU
NCOA6
ACSS2
TRPC4AP
PROCR
EIF6
ITCH
TP53INP2
GGT7
MYH7B
EDEM2
MMP24
DYNLRB1
HMGB3P1
GSS
MMP24-AS1
MAP1LC3A
MIR499A
FAM83C-AS1
MIR499B
FAM83C
UQCC1
Position on chr20 (Mb)

(e)


Plotted SNPs
rs6088590
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
AHCY
MIR644A
PIGU
NCOA6
ACSS2
TRPC4AP
PROCR
EIF6
ITCH
TP53INP2
GGT7
MYH7B
EDEM2
MMP24
DYNLRB1
HMGB3P1
GSS
FAM83C
MAP1LC3A
MIR499A
UQCC
MIR499B
Position on chr20 (Mb)

(f)


Plotted SNPs
rs6088590
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
AHCY
MIR644A
PIGU
NCOA6
ACSS2
TRPC4AP
PROCR
EIF6
ITCH
TP53INP2
GGT7
MYH7B
EDEM2
MMP24
DYNLRB1
HMGB3P1
GSS
FAM83C
MAP1LC3A
MIR499A
UQCC
MIR499B
Position on chr20 (Mb)