Identification of *ADAMTS7* as a novel locus for coronary atherosclerosis and association of *ABO* with myocardial infarction in the presence of coronary atherosclerosis: two genome-wide association studies

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WEBAPPENDIX SUPPLEMENTARY MATERIALS

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eMETHODS

STUDY SAMPLES:

Discovery Study Samples

PennCath: PennCath is a University of Pennsylvania (U. Penn) Medical Center based coronary angiographic study that has been used previously for replication of novel genes and risk factors for atherosclerotic CVD and type-2 diabetes(1-10). Briefly, PennCath, recruited between July 1998 and March 2003, provides an ongoing focus for analyzing the association of biochemical and genetic factors with coronary atherosclerosis in a consecutive cohort of patients undergoing cardiac catheterization and coronary angiography. A total of 3,850 subjects provided written informed consent in a Penn Institutional Review Board approved protocol. Enrollment criteria included any clinical indication for cardiac catheterization and ability to give informed consent. The following data were extracted from the medical record; age, gender, self-reported race/ethnicity, past medical (including diabetes, hypertension, dyslipidemia, prior MI and cardiac events), social, family and medication history, cardiovascular risk factors, physical exam including vital signs, weight and height (for BMI). Ethnicity information was self-reported. Coronary angiograms were scored at the time of procedure by the interventional cardiologist. Blood was drawn in a fasting state, DNA (buffy coats) and plasma was isolated, and lipoproteins and glucose were assayed on all samples.

A nested case-control GWAS was performed in PennCath (N=1,401 Caucasians) composed of controls (N=468) who on coronary angiography showed no or minimal (<10% stenosis of any vessel) evidence of CAD and angiographic CAD (AngCAD) cases (N=933) with one or more coronary vessels with ≥50% stenosis. AngCAD cases were equally selected for cases with MI (AngCADMI+ cases; N=470) and cases without history or presentation with MI (AngCADMI- cases; N=463). Controls were aged over 40 in men and 45 in women. Cases were selected to be young ≤60 for males and ≤65 for females. Limited data from the PennCath GWAS has been used for replication of novel loci for atherosclerotic CVD and its risk factors(6, 7).

MedStar: The MedStar study, conducted by the Cardiovascular Research Institute of the MedStar Health Research Institute, is a Washington Hospital Center based angiographic study of 1,500 subjects specifically designed for biomarker and genetic association studies of acute and chronic coronary atherosclerosis. Briefly, the MedStar study is a cross sectional study of coronary atherosclerosis in a consecutive cohort of selected patients undergoing cardiac catheterization at Washington Hospital Center between August 2004 and March 2007. All subjects were enrolled in a MedStar Health Research Institute Institutional Review Board approved protocol and all subjects gave written informed consent. Enrollment criteria included any clinical indication for cardiac catheterization and ability to give informed consent. The following data was extracted from the medical record; age, gender, race/ethnicity, past medical, social, family and medication history, cardiovascular risk factors (diabetes, smoking, and hypertension), physical exam including vital signs, weight and height (for BMI), and cardiovascular findings. Ethnicity information was self-reported. Coronary angiograms were scored on the day by the interventional cardiologist who performed the procedure and reviewed by a second cardiologist. Blood was drawn in a 12-hour fasting state (except in those with acute MI), at the time of the initial catheter insertion prior to the administration of any contrast dye for plasma, for serum separation and Buffy coat DNA isolation.

A case-control GWAS similar to PennCath was performed in MedStar (N=1,322 Caucasians) composed of controls (N=447) who on coronary angiography showed no evidence of CAD and CAD (AngCAD) cases (N=875) with one or more coronary vessels with ≥50% stenosis divided into AngCADMI+ cases (N=421) and AngCADMI- cases (N=454). Controls were aged over 45 in men and women. Cases were selected to be young with age at diagnosis of CAD ≤55 for males and ≤60 for females. MedStar genotyping was performed with PennCath samples at U. Penn. Limited data from the MedStar GWAS has been used previously for replication of novel genes for atherosclerotic CVD and its risk factors(6, 7).

Additional Studies that Applied Angiographic Ascertainment of Coronary Artery Disease

The Wellcome Trust Case-Control Consortium (WTCCC) Study: The WTCCC design and findings for CAD have been described in detail in prior publications(11, 12). For the analysis of CAD vs. CAD-free controls in the present manuscript, we restricted analysis to CAD cases that had undergone coronary artery bypass graft (CABG) surgery or percutaneous coronary revascularization (PCI) indicating significant angiographic CAD. This represented 1,318 AngCAD cases selected from the total 1,926 CAD cases in WTCCC.

The Ottawa Heart Genomics Study (OHGS): The Ottawa Heart Genomics Study (OHGS) is a GWAS using the Affymetrix 500K and 6.0 arrays designed to detect genes associated with CAD(13-15). The population was enriched for genetic predisposition by selecting cases that exhibited symptomatic CAD before the age of 55 years in males and 65 in females. CAD, defined as greater than 50% stenosis of a coronary artery, was defined by coronary angiography. Cases with a history of diabetes were excluded. Since CAD onset is both age and gender dependent, occurring at least 10 years later in females than in males, asymptomatic elderly individuals were selected as controls (≥ 65 for males, ≥ 70 for females). Controls recruited via an extensive newspaper and television advertising campaign in the Ottawa community were interviewed by a physician or nurse to ascertain that they were free of symptoms of ischemic arterial disease and had no history of cardiovascular symptoms. For the analysis in the present manuscript, we restricted controls to those aged ≤75 in order to reduce differences between OHGS and other angiographic CAD studies. This represented 886 of the total 1,455 available OHGS controls.

The Atherosclerotic Disease VAscular functioN and genetiC Epidemiology study (ADVANCE): Detailed descriptions of the eligibility criteria and the source population for all groups in the multi ethnic ADVANCE study are provided elsewhere(16-19). Briefly, between October 28, 2001 and December 31, 2003, 3,179 member of the Kaiser Permanente of Northern California health maintenance organization were enrolled into three CAD groups and two control groups. The case groups included subjects with "early onset" CAD (as defined by a CAD qualifying event captured by the electronic databases at any time after Jan 1, 1999 including MI,

angina with at least one angiographic stenosis of >50%, or revascularization procedure in men 18 to 45 or women 18 to 55 years of age at the time of the event), incident stable exertional angina at an older age, and incident non fatal MI at an older age. The young control group included *de novo* recruited subjects between the ages of 30 and 45 for men or 30 and 55 for women as well as a subset of 479 participants in the same age range from the Coronary Artery Risk Development in Young Adults (CARDIA) study originally recruited at the Oakland field center and attending the study's Year 15 examination in 2000–2001(20). Older controls included men and women aged 60–69 years at the time of identification in June, 2001. All controls were free of clinical CAD, cerebrovascular disease and peripheral arterial disease at the time of recruitment. Thus, the total study sample included 3658 subjects.

From this sample, a subset of cases and controls underwent GWAS genotyping (N = 513 cases and 527 controls). These subjects included 278 European-ancestry cases with the earliest onset of disease as well as 312 European-ancestry controls frequency matched as much as possible to age and gender of the cases. Among the 278 cases, 31 self-reported a CAD event that may have occurred prior to enrollment at Kaiser or outside of Kaiser. These subjects were not included in the final AngCADMI+ (N=140) vs. AngCADMI- (N=107) analysis in the current report.

The CADomics Study: CADomics (**C**oronary **A**rtery **D**isease and gen**omics**) is a German-based case-control study of CAD. It is a pooled study from the population-based Gutenberg-Heart Study (GHS) and the hospital (cath-lab)-based Atherogene Registry(21-23). The GHS is a population-based, prospective, observational single-center cohort study in the Rhein-Main-Region in western mid-Germany. The primary aim of GHS is to evaluate and improve cardiovascular risk stratification. The sample was drawn randomly from the governmental local registry offices which contains all citizens in the city of Mainz and the district of Mainz-Bingen. Individuals between ages 35 and 74 were enrolled and enrollment was stratified for gender, residence (urban and rural) and decade of age. Exclusion criteria were insufficient knowledge of the German language, and physical or psychological inability to participate. Cardiovascular risk factors were assessed by a computer-assisted personal interview, from laboratory analyses of a venous blood sample in a fasting state, blood pressure and anthropometric measurements. Information about coronary angiography was extracted from medical records and angiograms were scored at the time of procedure by an interventional cardiologist. The data included in the present work are from the first 3,500 participants recruited from April 2007 to April 2008. The Atherogene Registry has been described elsewhere(21). Briefly, between June 1999 and February 2004, patients with documented CAD referred to the Department of Medicine II of the Johannes Gutenberg-University in Mainz, Germany and the Department of Medicine of the German Federal Armed Forces Central Hospital, Koblenz, were enrolled in the AtheroGene study registry. All participants had coronary angiography. Information on cardiovascular risk factors and coronary angiography were extracted from medical records. The angiograms were scored at the time of procedure by an interventional cardiologist.

For the current analysis, a customized nested GWAS (N=1,804) was performed in CADomics using criteria broadly similar to PennCath. Individuals with a history of a history of MI and with a documented stenosis of >30% in one or more coronary vessels in the angiography were categorized as Ang-CADMI+ cases (N=1,214) and individuals without history of MI, but an angiographically documented stenosis of >50% in one or more coronary vessels were categorized as AngCADMI- cases" (N=592).

The Emory Genebank Study (Atlanta, Georgia, USA): Study participants were enrolled at the Emory University Hospital, Crawford Long Hospital, the Emory Clinic and Grady Memorial Hospital, all in Atlanta, Georgia. The Emory Genebank Study was designed to investigate the association of biochemical and genetic factors for CAD in subjects undergoing cardiac catheterization(5, 8). For the purpose of the current study, angiographic CAD cases and controls were defined according to PennCath criteria. Cases with angiographic CAD with or without MI were aged ≤60 for males and ≤65 for females. Controls, aged over 40 in men and 45 in women, were subjects with no or minimal CAD on cardiac catheterization and no prior history of MI or CAD. Genotyping of specific SNPs for replication was performed on the GenomeLab SNPstream Genotyping System (Beckman Coulter, Inc., Fullerton, CA) at the Emory Biomarker Service Center Emory University.

The Intermountain Heart Collaborative Study (IHCS): Since 1994, patients undergoing coronary angiography within Intermountain Healthcare tertiary care hospitals including Intermountain Medical Center (IMC), LDS Hospital, and McKay-Dee Hospital have been recruited to the IHCS (http://clinicaltrials.gov/ct2/show/NCT00406185). Subjects provide written informed consent to bank DNA and plasma samples. As of December 2009, over 16,000 patients were enrolled. The population of this region is primarily Caucasian, ethnically homogeneous and highly representative of US Caucasians. With angiographic data, medical history, full clinical diagnosis information, and longitudinal follow-up data, a wealth of CVD traits are available. Incident CVD events and death are ascertained through survey of all hospitalizations (single provider system) and death records. The value of the IHCS resource for longitudinal and genetic studies of CVD is well established(24-26).

Penn investigators have an established collaboration with the IHCS Group for genetic studies of CVD traits. For this study, AngCAD cases and controls were selected for replication from the larger IHCS dataset according to PennCath criteria. Cases with AngCAD with or without MI were aged ≤60 for males and ≤65 for females. Controls, aged over 40 in men and 45 in women, were subjects with no or minimal CAD on cardiac catheterization and no prior history of MI or CAD. Genotyping of specific SNPs for replication was performed at U. Penn on the Sequenom iPLEX MassARRAY platform.

The Verona Heart Study (VHS): The VHS is an ongoing study aimed at identifying new risk factors for CAD and MI in a sample of subjects with coronary angiography. The application of VHS to genetic studies has been published previously(7, 8, 27, 28). Briefly, the CAD group had severe coronary atherosclerosis documented at angiography, the majority of them being candidates for CABG surgery or PCI procedures. Control subjects were selected such that they had normal coronary arteries, being submitted to coronary angiography for reasons other than CAD. Controls with history or clinical evidence of atherosclerosis in vascular territories beyond the coronary bed were excluded. Information on MI diagnoses was gathered through medical records showing diagnostic electrocardiogram and enzyme changes, and/or the typical sequelae of MI on ventricular angiography and on echocardiography.

Genotyping of specific SNPs for replication was performed at the Broad Institute on the Sequenom iPLEX MassARRAY platform as described(7).

The Cleveland Clinic GeneBank Study (Cleveland, Ohio, USA): The Cleveland Clinic GeneBank study is a hospital-based angiographic study of ~10,000 subjects that has been used previously for discovery and replication of novel genes and risk factors for atherosclerotic CVD(29-32). Briefly, subject recruitment into GeneBank occurred between 2004 and 2008 and provides an ongoing focus for analyzing the association of biochemical and genetic factors with coronary atherosclerosis in a consecutive cohort of patients undergoing elective cardiac evaluation. Enrollment criteria included stable patients undergoing elective coronary angiography without known myocardial infarction at time of enrollment and ability to give informed consent. Extensive clinical, demographic, laboratory and angiographic data were collected from electronic medical record. Ethnicity information was self-reported. Fasting blood was drawn and plasma, serum, and DNA were isolated. Lipid profile and complete metabolic panel were assayed on all samples. The Cleveland Clinic GeneBank study is supported by P01 HL076491-06 and 1P01 HL098055-01 to S.L.H.

A nested analysis was performed in 2994 GeneBank subjects (all of Caucasian ancestry) in order to identify genes for MI and CAD as well as in-stent coronary restenosis. CAD cases (N=2660) were those subjects with angiographic evidence of CAD (AngCAD cases), defined as ≥50% stenosis in one or more coronary vessels, at the time of enrollment into GeneBank. The distribution of those cases with prior history of MI (AngCADMI+; N=1346) and those without history of MI (AngCADMI-; N=1314) was approximately equal. Specifically, an AngCADMI+ subject was defined as having angiographic CAD as well as positive history of MI at GeneBank enrollment whereas an AngCADMI- subject was defined as having angiographic evidence of CAD but no history of MI at enrollment. Control subjects (N=334) were intentionally selected to be older (>50 years old) and exhibited no or minimal evidence of CAD upon angiography.

Genome-wide data was obtained from the Affymetrix Genome-Wide Human SNP Array 6.0 platform (genotyped at the University of Ottawa). For study A, SNP data for the *ADAMTS7* SNP rs1994016 was obtained and analyzed for association of AngCAD (all cases) vs. angiographic control. *ADAMTS7* variants were tested for Hardy-Weinberg equilibrium using χ^2 test prior to analysis. For Study B, after QC, SNP imputation and filtering, ~2.4 million SNPs were analyzed for association with AngCADMI+ vs. AngCADMI- in patients with AngCAD cases assuming an additive genetic model with adjustment for age at CAD diagnosis and gender.

Studies that Ascertained for Early-Onset Myocardial Infarction

Myocardial Infarction Genetics Consortium (MI-GEN): Study design for MI-GEN has been described recently(7). MI-GEN consisted of cases with early-onset myocardial infarction (MI) and matched controls from six studies. All participants were of European ancestry. The six studies were: i) Italian Atherosclerosis Thrombosis and Vascular Biology (IATVB); ii) Heart Attack Risk in Puget Sound (HARPS); iii) Registre Gironi del COR (Gerona Heart Registry or REGICOR); iv) Massachusetts General Hospital Premature Coronary Artery Disease (MGH PCAD); v) FINRISK; and vi) Malmo Diet and Cancer Study (MDC). Genotyping was performed on Affymetrix Genome-Wide Human SNP Array 6.0 platform at the Broad Institute. For this study, SNP data for the specific SNPs (e.g., *ADAMTS7* rs1994016) was analyzed for association with early onset MI vs. control.

German MI Family Studies (GerMIFS): GerMIFS I: As described previously, cases from the GerMIFS I (n=875) study had a strong positive family history for CAD and an early onset of disease, i.e. were enriched for a strong genetic component. Population-based subjects were entered as controls(12). GerMIFS II: All 1,222 patients had a validated MI with a strong genetic component as documented by an early age of onset (prior to the age of 60 years) and a positive family history for CAD in 59.4% of patients. Patients were identified following their admission for acute treatment of MI or in cardiac rehabilitation clinics. Population-based controls were derived from the MONICA/KORA Augsburg survey F4 (n=820) and the PopGen blood donor sample 2 (PopGen-BSP) (n=478)(23). GerMIFS III (KORA): We identified 1,630 cases of nonfatal MI in the KORA registry with DNA available, of whom 1,157 were included in this study. Hospitalized survivors of MI who are 25 to 74 years of age are routinely entered into this registry(33). The diagnosis of a MI was made with use of the algorithm of the World Health Organization's Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project(34). Controls were from the population-based Augsburg KORA S4/F4 study (n=996)(35) and PopGen (n=752)(36). For this study, SNP data for the specific SNPs (e.g., *ADAMTS7* rs1994016) was analyzed for association with early onset MI vs. control.

Informed consent. All participants in the each study included gave written informed consent in accordance with the guidelines of local ethical committees. Study protocols and procedure were reviewed and approved by the appropriate regulatory authorities in each country for each study.

GENOTYPING IMPUTATION AND QUALITY CONTROL

PennCath and MedStar samples were genotyped **(eTable 4)** using Affymetrix 6.0 GeneChip and genotypes were called using the Birdseed calling algorithm(37). We applied quality control (QC) filters to exclude unreliable samples. A sample was excluded if the genotype call rate was <95% or if the sample showed excess or deficient heterozygosity (inbreeding coefficient $|F| > 0.1$). Cryptic relatedness or erroneous duplicates were evaluated using pair-wise identity-by-descent estimation, and the sample with lower genotype call rate was removed from each identified relative pair. Population structure (genetic differences within an apparently homogeneous population) was investigated by using principal components (PCs) obtained from multidimensional scaling analysis(11). After QC filtering, 1,401 and 1,322 individuals remained in PennCath and MedStar, respectively. The overall genotype call rate was 98.1%. All analyses were conducted using software package PLINK(38). For the analysis reported here, we eliminated

SNPs with genotype call rate <95%, with minor allele frequency (MAF) <1% in either cases or controls or if there was significant departure from Hardy-Weinberg equilibrium ($p < 10^{-6}$). A total of 659,760 SNPs for PennCath samples and 678,707 SNPs for MedStar samples passed QC and were included in analysis. In addition, we used these genotyped SNPs and 120 phased chromosomes from the HapMap CEU samples (HapMap r22 release, NCBI build 36) to impute genotypes for untyped SNPs using MACH 1.0 software(39). Imputed SNPs with MAF <0.01 in either cases or controls and SNPs with poor imputation quality (r^2 <0.3) were excluded. Together with genotyped SNPs, a total of 2,426,375 and 2,433,405 SNPs remained for final analysis in PennCath and MedStar, respectively.

In stage-1 of Study A examining Angiographic CAD vs. control (AngCAD vs. control), genotyped and imputed SNPs passing QC in PennCath and MedStar were analyzed **(eTable 4A)**. In stage-2 of Study A, genotyping on either the Affymetrix (Mapping 500K Array Set, Genome-Wide Human SNP Array 5.0/6.0) or Illumina (550k v3, HH300/HHCNV370) was followed by imputation of HapMap SNPs using either IMPUTE or MACH 1.0 software (eTable 4A). In stage-3 of Study A, genotyping was performed in three studies using the Sequenom iPLEX MassARRAY platform (at Penn for Utah IHCS and at the Broad Institute for VHS samples) and the SNPstream platform (at Emory for Emory Genebank Study). SNPs were selected for this wet-lab genotyping based on (a) having $P < 1x10^{-5}$ in meta-analysis of Stages 1&2 (25 SNPs) or (b) published GWAS data supporting an association with MI or CAD (10 SNPs) (7, 12).

In stage-1 (six-study meta-analysis) of Study B examining myocardial infarction in patients with angiographic CAD (AngCADMI+ vs. AngCADMI-), genotyping was performed on either the Affymetrix (Mapping 500K Array Set, Genome-Wide Human SNP Array 5.0/6.0) or Illumina (550k v3, HH300/HHCNV370) platforms **(eTable 4B)**. In stage-2 of Study B (Cleveland Clinic GeneBank), genotyping was on Affymetrix 6.0. Imputation (HapMap r22 release, NCBI build 36) used MACH 1.0, IMPUTE or BimBam software and quality control of samples and SNPs were performed both locally and centrally at Penn as summarized in **eTable 4B**.

Genotyping in wet-lab replication studies

Sequenom iPLEX MassARRAY genotyping: In stage-3 of Study A, SNP rs numbers were submitted to the Genetics Services Lab at Sequenom for design, assays were plexed into 2 panels and genotyping was performed at the Molecular Diagnosis and Genotyping Facility (http://www.med.upenn.edu/rpd/core_sect1#mdgf) at the U. Penn (for Utah IHCS samples) and the Broad Institute (for VHS samples). Samples were run in 384-well plates. Multiplex PCR was performed followed by the addition of SAP to remove any remaining nucleotides. A single base pair extension reaction was performed using the iPLEX chemistry, MALDI TOF MS was applied to analyze the primer extension products, and the data was analyzed using the MassArray Typer 4.0 software. Samples with call rates <60% across the SNPs were eliminated while SNPs with call rates <95% or with Hardy Weinberg Equilibrium P-values <0.001 were also eliminated from the dataset.

Beckman SNPstream Genotyping: In stage-3 of Study A for Emory Samples, sequence information (SNP rs#, or flanking sequences for those SNPs without rs#) was entered into www.autoprimer.com for primer design at the Emory genotyping core facility. Three primers, two for PCR and one for single-base extension were designed for each SNP, and grouped into 48-plexed panels. Using 2-10ng of genomic DNA, a 48-plex PCR was carried out in 384-well format to amplify a ~100 bp region flanking each SNP. The PCR reaction was treated with ExoSAP reagent to remove any left-over PCR primers and dNTPs. The 48-plex extension primer pool was then added to the same PCR plate. A single-base extension reaction was performed to incorporate a differentially labeled fluorescent dNTP to the SNP position. The extension reaction was transferred to a Tag Array and spatially resolved to distinguish the SNPs. All reagents are pre-formulated and included in the GenomeLab SNPware Reagent kit. The GenomeLab SNPstream Genotyping System Software Suite v2.3 (Beckman Coulter, Inc., Fullerton, CA) was used for array imaging and genotype calling. The genotype data was exported for further analysis. To ensure genotyping accuracy and reproducibility two internal quality control samples were included, each run in triplicate, on each of the 384-well arrays.

STATISTICAL ANALYSIS

Power calculations: Power calculation was conducted using Genetic Power Calculator(40) (http://pngu.mgh.harvard.edu/~purcell/gpc/). For Study A, we assumed the prevalence of obstructive CAD in the population is 10%, and estimated power for a range of disease allele frequencies using an additive genetic model. For example, in stages 1-3 combined, 9,706 cases and 7,050 controls provided >80% power to detect a genotype relative risk (GRR) as low as 1.15 for disease allele frequency of 0.5 and 1.32 for disease allele frequency of 0.05 at significance level 5×10^{-8} (adjusting for 1 million independent tests). We also calculated the power within the stage-3 sample replication. With 5,078 cases and 2,311 controls, we had >80% power to detect GRR as low as 1.15 for disease allele frequency of 0.5 and 1.33 for disease allele frequency of 0.05 at significance level 0.0014 (adjusting for 35 independent tests).

For Study B, we assumed 10% prevalence of MI in the population with CAD and estimated power for a range of disease allele frequencies using an additive genetic model. For stage-1, 4,572 cases and 2,739 controls provided >80% power to detect a GRR of 1.24 for disease allele frequency of 0.5 and ≥1.53 for disease allele frequency of 0.05 at significance level 5×10^{-8}. For stage-2 replication, with 1,211 cases and 905 controls, we had >80% power to detect a GRR of 1.27 for disease allele frequency of 0.5 and ≥1.56 for disease allele frequency of 0.05 (adjusting for 12 independent tests at 49 SNPs).

Analysis of ABO blood groups and conditional analysis of ABO SNPs and blood groups: In study B, SNPs at the *ABO* locus had genome-wide significant associations with myocardial infarction in patients with angiographic CAD (AngCADMI+). Therefore, in

PennCath we inferred *ABO* blood group genotypes and analyzed blood group association with several angiographic CAD (AngCAD) phenotypes. To infer ABO blood group genotypes, we used three SNPs rs8176672, rs612169 and rs8176704. The A allele of rs8176672 tags the B blood-group allele, the A allele of rs612169 tags the O blood-group allele, the A allele of rs8176704 tags the A1 blood-group, and the haplotype GGG of these three SNPs tags the A2 blood-group allele(41) (eTable 7A). Haplotype phasing was obtained using software package PHASE(42), and we only kept phased haplotypes with maximum posterior probability greater than 0.9. Stratified and conditional analyses were performed in PennCath to examine whether the top *ABO* SNPs for myocardial infarction in patients with angiographic CAD (AngCAD+MI) were independent of ABO blood groups and distinct *ABO* SNPs.

The ABO blood group antigens are known to vary in frequency among Caucasians(43). Although there was no evidence for population stratification within any individual study (eTable 4B), we probed this further in the PennCath sample. Correction for the top two principal components (PC) obtained from the multidimensional scaling analysis in PennCath had no impact on the association of rs514659A allele with AngCADMI+ (OR 1.37 and 1.36 before and after PC adjustment) suggesting no residual admixture within this Caucasian sample.

eRESULTS

The ABO genetic association with myocardial infarction in patients with angiographic CAD (AngCADMI+) is similar to that for venous thromboembolism but appears to be distinct from ABO association with multiple other cardiovascular risk factor traits. Recent GWAS have shown that SNPs in *ABO* are associated with venous thromboembolism (VTE)(44), serum LDL-C and LDL particle size(45) and plasma levels of inflammatory biomarkers, E-selectin, P-selectin, and intercellular adhesion molecule-1 (ICAM-1)(46-48) as well as angiotensin-converting enzyme (ACE) activity(49). We compared our top SNP for AngCADMI+ **(Table 3)** to those reported for these GWAS traits (**see Figure 4**). The SNPs associated with VTE (rs657152, rs505922, rs630014) were in high LD with our top SNPs for AngCADMI+ (e.g., $r^2 = 1.0$ with rs514659) and had strong association with AngCADMI+ in our data (e.g., rs505922; $P = 1.032 \times 10^{-8}$). Further, the top SNPs (rs687621 and rs687289) in a recent GWAS of plasma VWF and Factor VIII(50) are in complete LD with rs514659 and blood group O and also reach genome-wide significance in our analysis of AngCADMI+ **(Table 3)**. This is consistent with a common ABO blood group O effect on both AngCADMI+ and VTE, perhaps due to lack of glycomic modification of VWF by the ABO glycotransferase-deficient O isoform; this results in greater access to and cleavage of VWF by ADAMTS13 and thus lower circulating levels of VWF and Factor VIII.

In contrast, a top GWAS SNP for plasma E-selectin (rs579459)(48), P-selectin and ICAM-1(47) had modest LD with our top SNPs (e.g., $r^2 = 0.36$ with rs514659) and had modest association with AngCADMI+ in our data (e.g., rs579459: $P = 0.00118$). The rs579459T allele partially tags the ABO O allele (estimated haplotype frequency 0.634) while the rs579459C allele is found with the blood group A1 allele (estimated haplotype frequency 0.194). The A allele of the top GWAS SNP (rs507666) for LDL-C(45), which is also associated with plasma ICAM-1(46) , almost perfectly tags the ABO blood group A1 allele. The rs507666 SNP had only moderate LD with our top AngCADMI+ SNP (e.g., $r^2 = 0.53$ with rs514659) and the rs507666G allele was found with blood groups B and A2 as well as O **(eTable 7C)**. Although rs507666 was neither genotyped nor imputed in our dataset, one genotyped SNP, rs651007, was in high LD with rs507666 ($r^2 = 0.88$ in the 1000 Genomes CEU samples) (http://www.sph.umich.edu/csg/abecasis/MACH/download/1000G-UoM-0908.html) but did not reach nominal significance ($P = 0.053$) for association with AngCADMI+. Finally, after conditioning on rs579459 or rs651007, SNPs associated with inflammatory CVD risk factors and LDL-C, the association of rs514659 with AngCADMI+ in PennCath remained significant (OR 1.42; $P = 0.005$). This suggests that the genetic and molecular effect of *ABO* on AngCADMI+ may be independent of *ABO's* association with LDL-c and inflammatory CVD risk factors but similar to that for ABO's association with VTE.

eFIGURE LEGENDS

eFigure 1: Study A; The 15q25.1 *ADAMTS7* locus harbors the rs1994016 SNP associated with angiographic coronary artery disease (AngCAD vs. control). The upper panel presents linkage disequilibrium (r^2) and recombination rates at top SNP rs1994016 in *ADAMTS7* using HapMap CEU data; vertical dashed lines demarcate a linkage-disequilibrium block in which $r^2 > 0.8$, and horizontal dashed line shows $r^2 > 0.2$. The lower panel shows the top associated SNP and linkage disequilibrium structure around *ADAMTS7*. The position of rs1994016 is highlighted.

eFigure 2: Study B; Manhattan (A) and QQ plots (B) of meta-analysis *P* values for association with myocardial infarction in patients with angiographic CAD (AngCADMI+ vs. AngCADMI-). (A) SNPs are plotted on the x-axis according to their physical positions on each chromosome. On the y-axis, the -log10 p-values are plotted for the association with myocardial infarction in patients with angiographic CAD. (B) Observed vs. expected meta-analysis *P* values. There was no evidence for population stratification within any individual study (genomic control λs of 0.99-1.01) or across the full meta-analysis (genomic control $\lambda = 1.01$). Data are shown for meta-analysis of all eight studies; PennCath, MedStar, Wellcome Trust Case Control Consortium (WTCCC), Ottawa Heart Genomics Study (OHGS), Coronary artery disease and Genomics (CADomics), and the Atherosclerotic Disease VAscular functioN and genetiC Epidemiology study (ADVANCE) and the Cleveland Clinic GeneBank #1 & #2 studies.

eFigure 3: Study B; The 9q34.2 *ABO* locus harbors the top SNPs associated with myocardial infarction in patients with angiographic CAD. Linkage disequilibrium (r^2) and recombination rates are presented for the region around the top ABO SNP, rs514659, using HapMap CEU data; vertical dashed lines demarcate a linkage-disequilibrium block in which $r^2 > 0.8$, and horizontal dashed line shows $r^2 > 0.2$.

eTable 1. Characteristics of the PennCath and MedStar angiographic coronary artery disease (AngCAD) case-control GWAS samples

	PennCath		MedStar	
	AngCAD	**Control**	**AngCAD**	**Control**
Number of subjects	933	468	875	447
Study Criteria				
Ascertainment	Hospital – Cardiac Catheterization		Hospital – Cardiac Catheterization	
Ethnicity	Caucasian		Caucasian	
Country	U.S.A.		U.S.A.	
Case-Control Definition	AngCAD: individuals aged <66y who had one or more coronary vessels with ≥ 50% stenosis equally selected among stable CAD cases without history of MI and CAD cases with a history of MI. Controls: men aged >40y and women aged >45y showing no evidence of CAD (Angiography normal or <10% stenosis in all vessels).		AngCAD: individuals aged <61y who had one or more coronary vessels with ≥ 50% stenosis equally selected among stable CAD cases without history of MI and CAD cases with a history of MI. Controls: individuals aged >45y with no evidence of CAD (Angiography normal or <10% stenosis in all vessels).	
*Mean Age (y)	52.7±7.6*	61.7±9.6*	48.9±6.4*	59.7±8.9*
Female, N (%)	221 (24)	243 (52)	289 (33)	244
MI, N (%)	469 (50)	0	421 (48)	0
CABG, N (%)	209 (22)	0	169 (19)	0
PCI, N (%)	293 (31)	0	506 (58)	0
Cardiovascular risk factors				
Diabetes, N (%)	228 (24)	52 (11)	273 (31)	85 (19)
Hypercholesterolemia, N(%)	748 (80)	292 (62)	698 (80)	261 (58)
Family history of MI, N (%)	454 (49)	137 (29)	364 (42)	95 (21)
HTN, N (%)	572 (61)	230 (49)	668 (76)	271 (61)
Obesity, N (%)	397 43)	170 (36)	458 (52)	224 (50)
Smoking, N (%)	427 (46)	163 35)	465 (53)	223 (50)
BMI (kg/m^2)	29.8±5.6	28.9±6.4	31.7±6.8	31.3±7.9
LDL-Cholesterol (mmol/L)	2.78±0.94	2.80±0.84	2.62±1.06	2.74±0.85
HDL-Cholesterol (mmol/L)	1.11±0.31	1.26±0.39	1.11±0.36	1.29±0.41
Coronary Angiography				
One Vessel Disease, N (%)	259 (28)	0	340 (39)	0
Two Vessel Disease, N (%)	266 (29)	0	200 (23)	0
Three Vessel Disease, N(%)	353 (38)	0	287 (33)	0

CAD = coronary artery disease; MI = myocardial infarction; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; HTN = hypertension; BMI = body mass index; LDL = low-density lipoprotein; HDL = high-density lipoprotein. Cath lab: Hospital-based, cardiac catheterization laboratory. *Age (y = years) at first CAD diagnosis (cases) or recruitment (controls). Smoking was dichotomized into never smokers and ever smokers (ex-smoker and current smokers).

eTable 2. Study A replication samples: Angiographic CAD vs. Controls Free of Angiographic CAD (AngCAD vs. control)

	WTCCC		OHGS		Emory GB		Utah-IHC		VHS		Cleveland GB	
	AngCAD	**Control**	**AngCAD**	**Control**	**AngCAD**	**Control**	**AngCAD**	**Control**	**AngCAD**	**Control**	**AngCAD**	**Control**
Number of subjects	1318	2938	1542	886	1358	438	2707	1519	1013	354	2660	334
Study Criteria												
Ascertainment	Community based	UK National Blood Service & 1958 Birth Cohort	Cath lab Angiographic	Community based	Cath lab Angiographic		Cath lab Angiographic		Cath lab Angiographic		Cath lab Angiographic	
Ethnicity	Caucasian		Caucasian		Caucasian		Caucasian		Caucasian		Caucasian	
Country	U.K.		Canada		U.S.A.		U.S.A.		Italy		U.S.A.	
Case-control Definition	Cases: Age <66y, Coronary revascularization (PCI or CABG) & a strong family history of CAD Controls: Age <66y, from 1958 British birth cohort and UK Blood Services.		Cases: Age <55y (M) and < 65y(F). CAD > 50% stenosis in at least one artery. Controls: Age 65-75y (M), 70-75 (F) asymptomatic individuals.		Cases: Age <66y, CAD >50% stenosis in at least one artery. Controls: Age ≥45y, normal arteries or <10% disease in any artery.		Cases: Age <66y CAD ≥ 70% in at least one artery Controls: Age ≥ 45y, normal arteries or <10% disease in any artery.		Cases: CAD >50% in at least one artery. Controls: normal coronary arteries		Cases: CAD ≥50% stenosis in at least one artery. Controls: Age >50y (M), >60y (F), normal arteries or minimal disease.	
*Mean Age (y)	49.7±7.7	44.7±9.3	48.7±7.3	71.8±2.2	53.85±8.27	60.89±9.3	53.4±7.1	68.3±7.2	61.2±10.0	59.0±12.1	61.7±11.1	73.0±5.7
Female (%)	20	51	24	45	22	53	26	52	20	35	26	45
MI (%)	59	NA	62	0	50	0	47	0	63	0	55	0
CABG (%)	75	NA	32	0	39	0	16	0	72	0	38	0
PCI (%)	38	NA	43	0	62	0	60	0	21	0	46	0
Diabetes(%)	12	NA	0	7	33	19	27	10	18	7	17	0
Hyperchol.(%)	81	NA	46	32	78	54	67	30	79	65	92	62
HTN (%)	43	NA	47	34	71	56	59	45	65	39	73	62
Smoking(%)	75	NA	72	48	66.9	49	27	11	68	43	72	54
BMI (kg/m^2)	27.6±4.2	NA	28.5±4.9	26.4±4.2	29.76±5.79	29.57±6.87	30.3±6.3	29.0±6.4	26.7±3.4	25.3±3.4	29.5±5.6	27.6±5.5
One Vessel Disease	†NA	†NA	36	†NA	28	0	50	0	17	0	35	0
Two Vessel Disease	†NA	†NA	25	†NA	32	0	27	0	21	0	27	0
Three Vessel Disease	†NA	†NA	31	†NA	40	0	23	0	60	0	39	0

WTCCC = Wellcome Trust Case Control Consortium; OHGS = Ottawa Heart Genomics Study; Emory GB = Emory GeneBank Study; Utah Intermountain Heart Collaborative Study (IHCS); VHS = Verona Heart Study; Cleveland GB = Cleveland Clinic GeneBank. CAD = coronary artery disease; MI = myocardial infarction; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; HTN = hypertension; BMI = body mass index. *Age in years (y=years) at first diagnosis of CAD (case) or age at enrollment (control). †In WTCCC coronary angiographic data was not available. However, for the current analysis, WTCCC cases were restricted to those with a history of surgical (CABG) or percutaneous (PCI) revascularization and thus fulfilled criteria for angiographic CAD (AngCAD). In OHGS the controls did not undergo coronary angiography. Smoking was dichotomized into never-smokers and ever-smokers (ex-smoker and current smokers).

eTable 3. Study B Samples: Myocardial infarction (MI) in patients with angiographic coronary artery disease (AngCADMI+ vs. AngCADMI-)

	PennCath		MedStar		WTCCC		OHGS		CADomics		ADVANCE		Cleveland GB #1		Cleveland GB #2	
	MI+	**MI-**	**MI+**	**MI-**	**MI+**	**MI-**	**MI+**	**MI-**	**MI+**	**MI-**	**MI+**	**MI-**	**MI+**	**MI-**	**MI+**	**MI-**
No. of subjects	470	463	421	454	1377	533	950	590	1214	592	140	107	272	337	939	568
Ascertainment	Cath lab		Cath lab		Community-based		Cath lab		Cath lab and community-based		Community-based		Cath lab		Cath lab	
Ethnicity	Caucasian		Caucasian		Caucasian		Caucasian		Caucasian		Caucasian		Caucasian		Caucasian	
Country	USA		USA		UK		Canada		Germany		USA		USA		USA	
Definitions	All: Age <66y; at least one coronary artery with ≥ 50% stenosis. MI defined as validated MI		All: Age <61y; at least one coronary artery with ≥ 50% stenosis. MI defined as validated MI		All: Age <66y; confirmed coronary disease, & family history of CAD. MI defined as validated MI		All: Age ≤55y (M) or ≤ 65y (F); at least one coronary artery with ≥ 50% Diabetics excluded. MI defined as history of MI.		All: Age > 20y; stenosis >30% (MI) or ≥ 50% (no MI) in at least one coronary artery. MI defined as history of MI.		All: Age ≤45y (M) ≤55y (F); CAD ≥50% stenosis in at least one artery, or revascularization, or angina and +non-invasive study. MI defined as validated MI.		All: CAD ≥50% stenosis in at least one artery or history of revascularization at enrollment. MI defined as having a history of MI at enrollment or prospective MI within 3 years of enrollment.			
*Mean Age (y)	53.2±7.5	55.3±9.6	46.8±6.8	50.8±5.3	48.9±7.8	51.8±7.0	47.7±7.3	50.3±7.0	59.3±10.8	63.2±8.2	45.6±6.4	47.0±5.8	68.7±9.6	68.5±9.6	59.4±10.1	57.5±9.9
Female (%)	25	25	24	32	20	22	21	29	21	23	55	57	28	30	21	30
MI (%)	100	0	100	0	100	0	100	0	100	0	100	0	100	0	100	0
CABG %	22	23	24	15	42	74	33	30	NA		NA		31	17	54	33
PCI %	41	21	55	61	22	36	48	34	NA		NA		49	30	57	41
Cardiovascular risk factors																
Diabetes mellitus (%)	26	23	30	31	12	12	0	0	19	23	19	23	62	48	0	0
Hyperchol(%)	79	80	88	84	78	78	44	49	60	56	23	38	91	89	94	91
HTN (%)	58	64	77	76	41	46	46	48	70	76	29	41	81	78	73	69
Smoking (%)	44	47	58	48	78	71	74	68	70	58	59	61	70	69	79	66
BMI (kg/m^2)	30.1±5.3	29.8±6.4	31.4±6.4	32.0±7.1	27.6±4.3	27.5±4.0	28.6±5.1	28.5±4.6	28±4.1	27.5±3.9	30.3±6.9	31.9±7.4	30.0±5.8	30.3±5.9	29.3±5.7	29.1±5.3
Coronary Angiography																
One Vessel Disease	24	31	31	46	NA	NA	36	36	24	29	NA	NA	24	37	22	32
Two Vessel Disease	28	28	36	30	NA	NA	23	28	30	32	NA	NA	32	28	22	26
Three Vessel Disease	39	36	27	19	NA	NA	32	30	46	39	NA	NA	37	27	39	29

WTCCC = Wellcome Trust Case Control Consortium; OHGS = Ottawa Heart Genomics Study; CADomics = Coronary Artery Disease and genomics; ADVANCE = Atherosclerotic Disease, VAscular functioN, and genetiC Epidemiology; Cleveland GB = Cleveland Clinic GeneBank. Cleveland Clinic GB Study #1 was derived from a GWAS of CAD cases with in-stent restenosis. Cleveland Clinic GB Study #2 was derived from a GWAS study of angiographic CAD cases without diabetes mellitus. Cath lab = cardiac catherization laboratory. CAD = coronary artery disease; MI = myocardial infarction; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; hyperchol = hypercholesterolemia; HTN = hypertension; BMI = body mass index. NA = not available. *Age in years (y=years) at first diagnosis of CAD (case) or age at enrollment (control).

eTable 4A. Study A: Genotyping, imputation and analysis criteria for genome wide studies of angiographic CAD vs. control

	Study acronym	**PennCath**	**MedStar**	**WTCCC**	**OHGS**	**Cleveland GB (#1 and #2)**
Genotyping	**Platform**	Affymetrix 6.0	Affymetrix 6.0	Affymetrix 500K Array Set	Affymetrix 500K & 6.0 Array set	Affymetrix 6.0
	Calling algorithm	Birdseed	Birdseed	CHIAMO	BRLMM & Birdseed	Birdseed
QC filters before imputation	**Sample Call Rate**	95%	95%	≥ 97%	>98%	≥ 97%
	SNP Call Rate	95%	95%	≥ 98%	≥ 95%	≥ 97%
	HWE P-value	$>10^{-6}$ in controls	$>10^{-6}$ in controls	$>10^{-4}$ in controls	10^{-3} in controls	$>10^{-7}$
	MAF	> 0.01	> 0.01	≥ 0.01%	> 0.05	>0.01
Imputation	**NCBI Build, HapMap CEU**	36	36	36	36	36
	Software for imputation	MACH 1.0	MACH 1.0	IMPUTE	IMPUTE	*NA
Statistical analysis	**SNP filter**	See above	See above	See above	See above	See above
	Model	Log-Additive	Log-Additive	Log-Additive	Additive	Log-Additive
	Software	PLINK (genotyped); SNPTest (imputed)	PLINK (genotyped); SNPTest (imputed)	PLINK (genotyped); SNPTest (imputed)	SNPTEST	PLINK
	Adjustments	Age, gender	Age, gender	Age, gender	Gender, PC	Age, gender
	QC filters [imputed data]	IC ≥ 0.50 R^2 >0.3	IC ≥ 0.50 R^2 > 0.3	Proper_info>0.5	Proper_info > 0.5	*NA
	Genomic control lambda	0.99	0.99	1.05	1.06	1.01

eTable 4B. Study B: Genotyping, imputation and analysis criteria for genome wide studies of myocardial infarction in patients with angiographic CAD

	Study acronym	**PennCath**	**MedStar**	**WTCCC**	**OHGS**	**CADomics**	**ADVANCE**	**Cleveland GB (#1 and #2)**
Genotyping	**Platform**	Affymetrix 6.0	Affymetrix 6.0	Affymetrix 500K	Affymetrix 500K and 6.0	Affymetrix 6.0	Illumina 550K	Affymetrix 6.0
	Calling algorithm	Birdseed	Birdseed	CHIAMO	BRLMM & Birdseed	Birdseed	BeadStudio	Birdseed
QC filters before Imputation	**Sample Call Rate**	>95%	>95%	≥97%	>98%	>97%	>98.5%	≥ 97%
	SNP Call Rate	>95%	>95%	>98%	>95%	>98%	>95%	≥ 97%
	HWE P-value	$>10^{-6}$ in all samples	$>10^{-6}$ in all samples	$>10^{-7}$ in controls	$>10^{-7}$ in controls	$>10^{-4}$ in controls	>0.001 in all samples	$>10^{-7}$
	MAF	> 0.01	>0.01	>0.01	>0.01	> 0.01	>0.01	>0.01
Imputation	**NCBI Build, HapMap CEU**	36	36	36	36	36	36	36
	Software for imputation	MACH 1.0	MACH 1.0	IMPUTE	IMPUTE	IMPUTE	BimBam	MACH 1.0
Statistical analysis	**SNP filter**	See above	See above	See above	See above	See above	See above	See above
	Model	Log-Additive	Log-Additive	Log-Additive	Log-Additive	Log-Additive	Log-Additive	Log-Additive
	Software	PLINK (genotyped); SNPTest (imputed)	PLINK (genotyped); SNPTest (imputed)	PLINK (genotyped); SNPTest (imputed)	PLINK (genotyped); SNPTest (imputed)	PLINK (genotyped); SNPTest (imputed)	PLINK (genotyped); SNPTest (imputed)	ProbABEL (imputed)
	Adjustments	Age, gender	Age, gender	Age, gender	Gender	Age, gender	Age, gender	Age, gender
	QC filters [imputed data]	R^2 >0.3	R^2 >0.3	Proper_info>0.5	Proper_info>0.5	- -	Proper_info>0.5	Proper_info>0.5
	Genomic control lambda	0.99	1.01	1.01	1.00	1.01	1.01	#1: 1.01 #2: 1.02

WTCCC = Wellcome Trust Case Control Consortium; OHGS = Ottawa Heart Genomics Study; CADomics = Coronary Artery Disease and genomics; ADVANCE = Atherosclerotic Disease, VAscular functioN, and genetiC Epidemiology; Cleveland GB = Cleveland Clinic GeneBank. Cleveland Clinic GB Study #1 was derived from a GWAS of angiographic CAD cases with in-stent restenosis. Cleveland Clinic GB Study #2 was derived from a GWAS study of angiographic CAD cases without diabetes mellitus. Cath lab = cardiac catherization laboratory. HWE = Hardy-Weinberg equilibrium; MAF = minor allele frequency; PC = principal components; *No imputed data for this analysis. Genomic control lambda: The estimated genomic control (GC) inflation factor lambda (λ) (51), an indicator of potential population stratification, was calculated as the median of the test statistics divided by the median of chi-squared distribution with one degree of freedom

Population structure was also investigated by using principal components (PCs) obtained from multidimensional scaling analysis in which samples with similar genetic background will cluster together whereas samples with different genetic backgrounds will appear in different clusters (11). In Study A, the OHGS analysis was adjusted for 10 PCs.

eTable 5. Study A: Association in stages 1-3 combined of the top 35 SNPs tested in stage-3 of angiographic CAD vs. control†.

SNP	Chr	Position (NCBI 36)	Effect allele	Effect allele frequency	Effective N‡	Gene(s) ¶	AngCAD vs. Control OR (95% CI)	*P*
rs11206510*	1	55268627A	A	0.82	7900	PCSK9	1.05 (0.95, 1.16)	0.681
rs646776*	1	109620053	T	0.82	7900	CELSR2,PSRC1,SORT1	1.27 (1.15, 1.40)	$2.41x10^{-6}$
rs17465637*	1	220890152	G	0.73	7900	MIA3	1.08 (0.99, 1.18)	0.123
rs599839	1	109623689	A	0.81	6766	SORT1, PSRC1	1.21 (1.09, 1.36)	$2.82x10^{-4}$
rs2925757	2	160809415	T	0.82	11590	ITGB6(dist=44579), RBMS1(dist=27494)	1.08 (0.99, 1.16)	0.044
rs2943634	2	226776324	C	0.61	5430	KIAA1486(dist=549346), IRS1(dist=527953)	1.10 (0.99, 1.23)	0.038
rs7424620	2	235081722	G	0.90	7900	ARL4C(dist=11290), SH3BP4(dist=443645)	1.13 (0.99, 1.28)	0.060
rs6725887*	2	203454130	C	0.15	6564	WDR12	1.34 (1.17, 1.53)	$3.36x10^{-5}$
rs9818870*	3	139604812	T	0.16	6766	MRAS	1.12 (0.99, 1.26)	0.0835
rs6772643	3	150102818	G	0.67	7900	CPA3(dist=5258), GYG1(dist=89247)	1.10 (1.02, 1.20)	0.025
rs6779672	3	150708572	T	0.16	7900	TM4SF4(dist=4814), WWTR1(dist=9140)	1.10 (0.99, 1.23)	0.050
rs16880108	6	65330216	T	0.75	7900	EYS	1.10 (1.00, 1.20)	0.077
rs12526453*	6	13035530	C	0.69	13810	PHACTR1	1.14 (1.08, 1.21)	$8.06x10^{-6}$
rs3843995	6	131992491	C	0.16	12182	MED23(dist=1435), ENPP3(dist=7644)	1.09 (1.00, 1.18)	0.068
rs7815938	8	92178849	A	0.56	7900	OTUD6B(dist=10350), LRRC69(dist=5174)	1.12 (1.02, 1.22)	0.037
rs10781354	9	78065202	G	0.42	11590	PCSK5(dist=67044), RFK(dist=125051)	1.07 (1.01, 1.14)	0.041
rs1333049	9	22115503	C	0.55	12676	CDKN2A, CDKN2B,ANRIL	1.32 (1.25, 1.40)	$2.20x10^{-25}$
rs4977574*	9	22088574	G	0.55	14402	CDKN2A,CDKN2B,ANRIL	1.35 (1.28,1.43)	$2.98x10^{-27}$
rs1746048*	10	44095830	G	0.87	7900	CXCL12	1.12 (1.00, 1.26)	0.053
rs7948970	11	11686710	T	0.28	11590	GALNTL4(dist=86573), USP47(dist=132836)	1.11 (1.04, 1.19)	0.0031
rs11211864	11	106069196	G	0.14	8492	GUCY1A2	1.09 (0.98, 1.23)	0.057
rs527646	11	132455569	A	0.44	7900	OPCML	1.08 (0.99, 1.17)	0.010
rs2259816	12	119919970	A	0.37	6766	HNF1A	1.14 (1.02, 1.27)	0.028
rs12898340	15	67811800	T	0.91	7900	LOC145837, C15orf50	1.14 (0.99, 1.30)	0.10
rs1994016	15	76867289	C	0.61	14640	ADAMTS7	1.19 (1.13, 1.25)	$2.41x10^{-12}$
rs2277545	15	76870646	T	0.61	10254	ADAMTS7	1.22 (1.13, 1.31)	$1.05x10^{-5}$
rs1051730	15	78894339	G	0.68	3716	CHRNA3	1.20 (1.07, 1.34)	$1.35x10^{-3}$
rs11857537	15	98245852	T	0.40	6564	C15orf51(dist=81197),ADAMTS17(dist=83314)	1.10 (1.00, 1.20)	0.035
rs2307227	16	54412862	G	0.93	4386	CES1	1.38 (0.98, 1.94)	0.072
rs7211029	17	74652903	T	0.35	8492	HRNBP3	1.06 (0.98, 1.15)	0.061
rs7244908	18	73226082	A	0.39	6022	GALR1(dist=114998), SALL3(dist=1615181)	1.11 (1.00, 1.23)	0.047
rs1867185	18	26350648	A	0.12	11590	MIR302F(dist=217725), DSC3(dist=473402)	1.18 (1.07, 1.31)	$8.77x10^{-4}$
rs1529729	19	11024562	G	0.48	13066	LDLR, SMARCA4	1.13 (1.07, 1.20)	$3.06x10^{-6}$
rs1122608*	19	11024601	G	0.77	6564	LDLR/SMARCA4	1.25 (1.13, 1.38)	$3.18x10^{-5}$
rs9982601*	21	34520998	T	0.14	7900	SLC5A3,MRPS6,KCNE2	1.16 (1.03, 1.30)	0.0159

Stage 1: PennCath, MedStar
Stage 2: Wellcome Trust Case Control Consortium, Ottawa Heart Genomics Study, Atherosclerotic Disease, VAscular functioN, and genetiC EpidemiologyStage 3: Emory GeneBank, Utah Intermountain Heart Collaborative Study, Verona Heart Study
Chr = chromosome; OR = Odds ratio; CI = confidence interval.

† Effective N and data differs from Table 1A because Table 1A analysis focused on a subset studies that defined cases and controls exclusively through coronary angiography (i.e., PennCath, MedStar, Emory GeneBank, Utah Intermountain Heart Collaborative Study, Verona Heart Study).
* Denotes published GWAS SNPs.
‡ Differences in effective N for each SNP reflect differential missing data for studies and samples within studies.
¶ Listed are genes or nearest genes to the SNPs. Distance (dist) is measured in bp.

eTable 6. Study B: Association in stages 1&2 combined of the top 49 SNPs from stage-1 with myocardial infarction in patients with angiographic CAD (AngCADMI+ vs. AngCADMI-).

SNP*	Chr	Position (NCBI 36)	Effect allele	Effect allele frequency	Effective N†	Gene(s)¶	Study B: AngCADMI+ vs. AngCADMI- OR (95% CI)	*P*
rs360290*	2	126796531	C	0.19	8436	CNTNAP5(dist=1407198), GYPC(dist=333623)	1.16 (1.07, 1.26)	$1.65x10^{-4}$
rs360292*	2	126796737	G	0.19	8436	CNTNAP5(dist=1407404), GYPC(dist=333417)	1.17 (1.07, 1.26)	$1.50x10^{-4}$
rs360293*	2	126796979	A	0.19	8436	CNTNAP5(dist=1407646), GYPC(dist=333175)	1.17 (1.08, 1.26)	$1.42x10^{-4}$
rs360295*	2	126797119	C	0.19	8436	CNTNAP5(dist=1407786), GYPC(dist=333035)	1.15 (1.07, 1.24)	$1.42x10^{-4}$
rs360296*	2	126797163	G	0.19	8196	CNTNAP5(dist=1407830), GYPC(dist=332991)	1.17 (1.08, 1.27)	$1.87x10^{-4}$
rs360297*	2	126797238	G	0.19	8196	CNTNAP5(dist=1407905), GYPC(dist=332916)	1.17 (1.08, 1.27)	$1.87x10^{-4}$
rs360299*	2	126797630	A	0.19	8196	CNTNAP5(dist=1408297), GYPC(dist=332524)	1.17 (1.08, 1.27)	$1.87x10^{-4}$
rs360300*	2	126797705	G	0.19	8196	CNTNAP5(dist=1408372), GYPC(dist=332449)	1.17 (1.08, 1.27)	$1.87x10^{-4}$
rs360301*	2	126797773	A	0.19	8196	CNTNAP5(dist=1408440), GYPC(dist=332381)	1.17 (1.08, 1.27)	$1.87x10^{-4}$
rs360302	2	126797809	A	0.19	8196	CNTNAP5(dist=1408476), GYPC(dist=332345)	1.17 (1.08, 1.27)	$1.92x10^{-4}$
rs360303*	2	126797950	G	0.19	8196	CNTNAP5(dist=1408617), GYPC(dist=332204)	1.17 (1.08, 1.27)	$1.87x10^{-4}$
rs360307*	2	126798678	T	0.19	8196	CNTNAP5(dist=1409345), GYPC(dist=331476)	1.17 (1.08, 1.27)	$1.86x10^{-4}$
rs360308*	2	126798780	G	0.19	8196	CNTNAP5(dist=1409447), GYPC(dist=331374)	1.17 (1.08, 1.27)	$1.86x10^{-4}$
rs360309*	2	126799286	A	0.19	8196	CNTNAP5(dist=1409953), GYPC(dist=330868)	1.17 (1.08, 1.27)	$1.86x10^{-4}$
rs360312*	2	126799534	G	0.19	8196	CNTNAP5(dist=1410201), GYPC(dist=330620)	1.17 (1.08, 1.27)	$1.86x10^{-4}$
rs360313*	2	126799561	G	0.19	8196	CNTNAP5(dist=1410228), GYPC(dist=330593)	1.17 (1.08, 1.27)	$1.86x10^{-4}$
rs360316*	2	126800343	A	0.19	8196	CNTNAP5(dist=1411010), GYPC(dist=329811)	1.17 (1.08, 1.27)	$1.86x10^{-4}$
rs360317*	2	126800430	C	0.19	8196	CNTNAP5(dist=1411097), GYPC(dist=329724)	1.17 (1.08, 1.27)	$1.86x10^{-4}$
rs360318*	2	126800452	C	0.19	8196	CNTNAP5(dist=1411119), GYPC(dist=329702)	1.17 (1.08, 1.27)	$1.86x10^{-4}$
rs360319*	2	126800717	C	0.19	8196	CNTNAP5(dist=1411384), GYPC(dist=329437)	1.17 (1.08, 1.27)	$1.86x10^{-4}$
rs360320	2	126800940	G	0.19	8196	CNTNAP5(dist=1411607), GYPC(dist=329214)	1.17 (1.08, 1.27)	$1.88x10^{-4}$
rs360321*	2	126801602	T	0.19	8196	CNTNAP5(dist=1412269), GYPC(dist=328552)	1.17 (1.08, 1.27)	$1.71x10^{-4}$
rs360322	2	126801998	T	0.19	8196	CNTNAP5(dist=1412665), GYPC(dist=328156)	1.17 (1.08, 1.27)	$1.88x10^{-4}$
rs11684492	2	126806776	T	0.16	8196	CNTNAP5(dist=1417443), GYPC(dist=323378)	1.18 (1.09, 1.29)	$1.80x10^{-4}$
rs11684427*	2	126839026	A	0.16	8196	CNTNAP5(dist=1449693), GYPC(dist=291128)	1.19 (1.09, 1.30)	$1.01x10^{-4}$
rs11690602	2	126840341	T	0.16	8196	CNTNAP5(dist=1451008), GYPC(dist=289813)	1.19 (1.09 1.29)	$9.45x10^{-5}$
rs11695746*	2	126841043	C	0.16	8196	CNTNAP5(dist=1451710), GYPC(dist=289111)	1.19 (1.10, 1.30)	$8.15x10^{-5}$
rs12999792*	2	126841508	A	0.16	8196	CNTNAP5(dist=1452175), GYPC(dist=288646)	1.19 (1.09, 1.30)	$8.16x10^{-5}$
rs359708*	2	126844404	A	0.17	8436	CNTNAP5(dist=1455071), GYPC(dist=285750)	1.17 (1.08, 1.27)	$4.29x10^{-5}$
rs13034238*	2	126846852	C	0.17	8436	CNTNAP5(dist=1457519), GYPC(dist=283302)	1.16 (1.08, 1.27)	$4.30x10^{-5}$
rs359706	2	126847551	T	0.17	8436	CNTNAP5(dist=1458218), GYPC(dist=282603)	1.18 (1.09, 1.27)	$3.63x10^{-5}$
rs359688	2	126853475	C	0.17	8436	CNTNAP5(dist=1464142), GYPC(dist=276679)	1.19 (1.10, 1.30)	$4.16x10^{-5}$
rs13002032*	2	126864230	A	0.16	8196	CNTNAP5(dist=1474897), GYPC(dist=265924)	1.19 (1.10, 1.30)	$5.14x10^{-5}$
rs13001771*	2	126865450	G	0.16	8196	CNTNAP5(dist=1476117), GYPC(dist=264704)	1.19 (1.10, 1.31)	$4.72x10^{-5}$
rs11709686*	3	20340262	A	0.84	6916	SGOL1(dist=137575), VENTXP7(dist=1081960)	1.16 (1.06, 1.26)	$1.34x10^{-3}$
rs3749494	4	169518762	A	0.07	8436	DDX60L	1.23 (1.08, 1.39)	$1.06x10^{-3}$
rs1860759*	7	28364985	G	0.48	8436	CREB5	1.14 (1.07, 1.21)	$5.09x10^{-5}$
rs4498447	7	28370297	C	0.48	8436	CREB5	1.14 (1.07, 1.21)	$3.05x10^{-5}$
rs687621*	9	135126886	G	0.37	8436	ABO	1.20 (1.13, 1.28)	$7.81x10^{-9}$
rs687289*	9	135126927	A	0.37	8436	ABO	1.19 (1.11, 1.26)	$7.75x10^{-9}$
rs505922*	9	135139050	C	0.37	8436	ABO	1.20 (1.13, 1.28)	$1.03x10^{-8}$

rs657152*	9	135129086	A	0.40	8436	ABO	1.19 (1.12, 1.27)	$4.11x10^{-8}$
rs514659*	9	135132024	C	0.37	8436	ABO	1.21 (1.13, 1.28)	$7.62x10^{-9}$
rs644234*	9	135132038	G	0.39	8436	ABO	1.20 (1.13, 1.28)	$1.57x10^{-8}$
rs643434*	9	135132176	A	0.39	8436	ABO	1.18 (1.11, 1.26)	$1.64x10^{-8}$
rs545971*	9	135133193	T	0.37	8436	ABO	1.20 (1.13, 1.28)	$8.96x10^{-9}$
rs612169	9	135133263	G	0.37	8436	ABO	1.20 (1.12, 1.28)	$3.66x10^{-8}$
rs529565*	9	135139321	C	0.37	8436	ABO	1.20 (1.13, 1.28)	$1.08x10^{-8}$
rs674302*	9	135136485	A	0.37	8436	ABO	1.20 (1.13, 1.28)	$9.59x10^{-9}$

Chr = chromosome; OR = Odds ratio; CI = confidence interval.
Stage 1: PennCath, MedStar, Wellcome Trust Case Control Consortium; Ottawa Heart Genomics Study; Coronary Artery Disease and genomics; Atherosclerotic Disease, VAscular functioN, and genetiC Epidemiology.
Stage 2: Cleveland Clinic GeneBank Studies. Study #1 was derived from a GWAS of CAD cases with in-stent restenosis. Study #2 was derived from a GWAS study of angiographic CAD cases without diabetes mellitus.
*denotes imputed SNPs
† Differences in effective N reflect differential missing data for studies and samples within studies.
¶ Listed are genes or nearest genes to the SNPs. Distance (dist) is measured in bp.

eTable 7. Inference of ABO blood groups in PennCath and their association with myocardial infarction in patients with angiographic CAD (AngCADMI+ vs. AngCADMI-).

(A) Inference of ABO blood groups using three tag-SNPs(41). Haplotype frequencies were estimated in PennCath using PHASE software(42).

	Genotype			
Allele	rs8176672	rs612169	rs8176704	Frequency
A1	G	G	G	0.19
A2	G	G	A	0.06
B	A	G	G	0.09
O	G	A	G	0.66

(B) Association of genetically-inferred ABO blood groups with myocardial infarction in patients with angiographic CAD (AngCADMI+ vs. AngCADMI-).

Test group	**Reference group (frequency) Odds Ratio (Confidence Interval), *P* value**			
	A(41.4%)	**B (11.75%)**	**AB (4.93%)**	**O (41.92%)**
A	1.0	0.69 (0.44, 1.09) *P* = 0.11	0.90 (0.46, 1.76) *P* = 0.76	1.49 (1.11, 2.00) *P* = 0.0072
B	1.44 (0.92, 2.28) *P* = 0.11	1.0	1.30 (0.61, 2.77) *P* = 0.48	2.15 (1.37, 3.40) *P* = 0.00055
AB	1.11 (0.57, 2.17) *P* = 0.76	0.77 (0.36, 1.64) *P* = 0.48	1.0	1.65 (0.85, 3.25) *P* = 0.12
O	0.69 (0.5, 0.9) *P* = 0.0072	0.47 (0.29, 0.73) *P* = 0.00055	0.61 (0.31, 1.18) *P* = 0.12	1.0

(C) Haplotype frequencies based on rs514659, other published ABO SNPs for cardiovascular risk factors, and ABO blood group tagging SNPs. Haplotype frequencies were estimated based on 60 CEU samples from the 1000 Genomes Project using PHASE software(42).

	Genotype							
Allele	**rs8176704**	**rs8176672**	**rs514659**	**rs612169**	**rs507666**	**rs651007**	**rs579459**	**Frequency**
A1	G	G	C	G	A	T	C	0.21
A2	A	G	C	G	G	C	T	0.06
B	G	A	C	G	G	C	T	0.07
O	G	G	A	A	G	C	T	0.63
O	G	G	C	G	A	C	C	0.02
O	G	G	C	G	A	C	T	0.01

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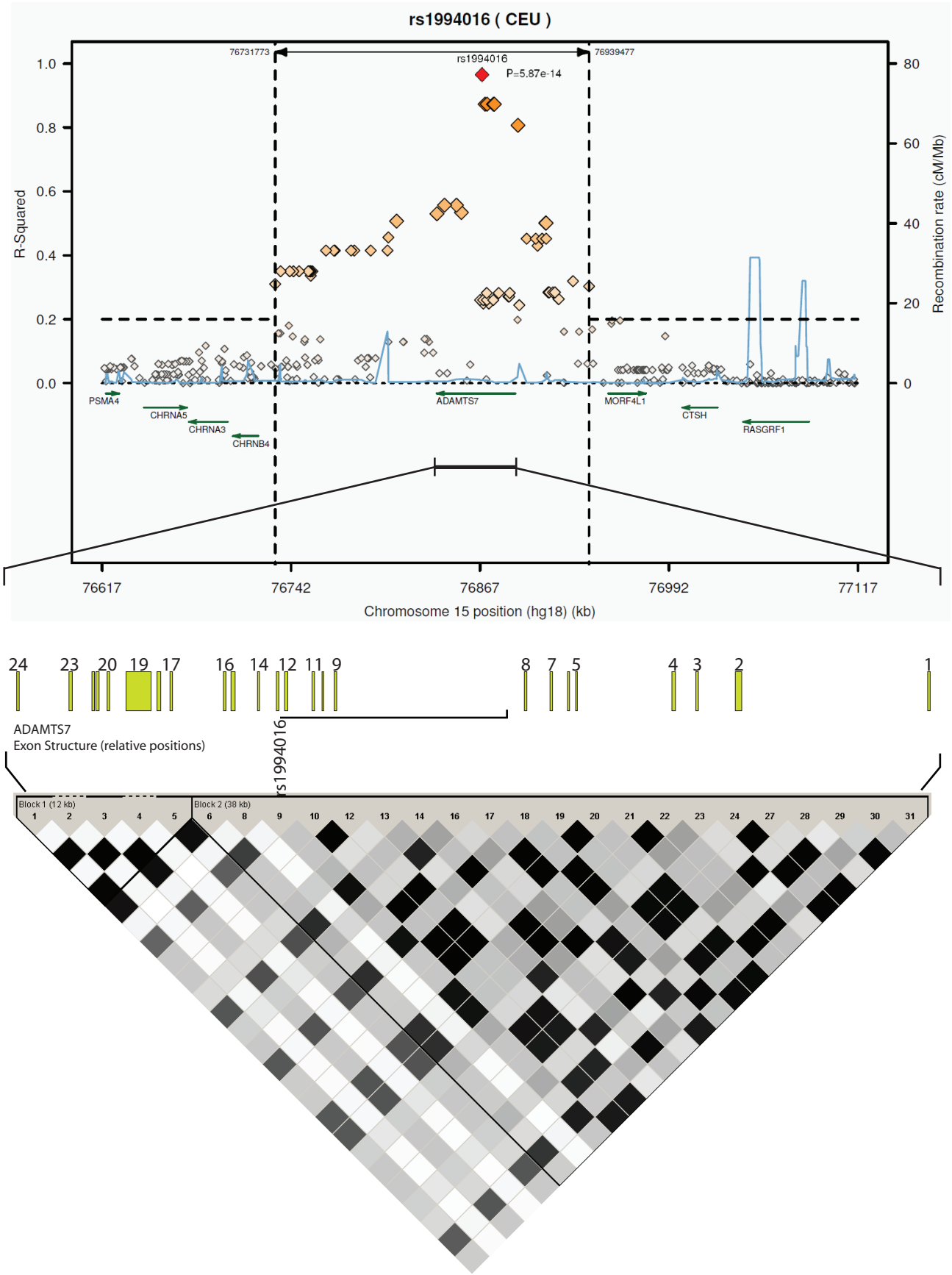
eFigure 1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ADAMTS7
MORF4L1
CTSH
RASGRF1
76617
76742
76867
76992
77117
Chromosome 15 position (hg18) (kb)
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Exon Structure (relative positions)
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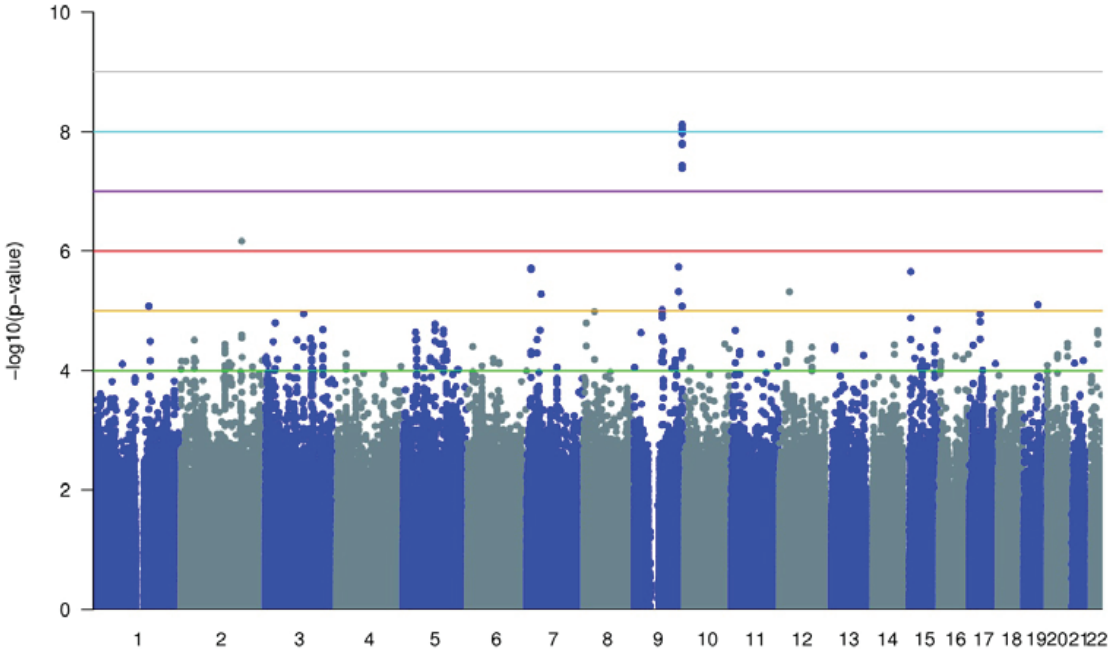
Block 2 (38 kb)

eFigure 2

[A]


−log10(p−value)
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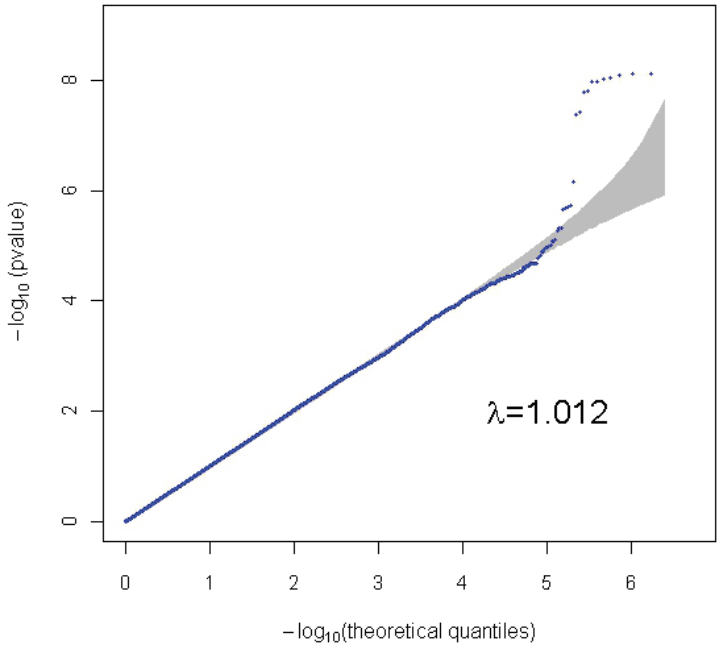
2
4
6
8
10
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22

[B]


$-\log_{10}$ (pvalue)
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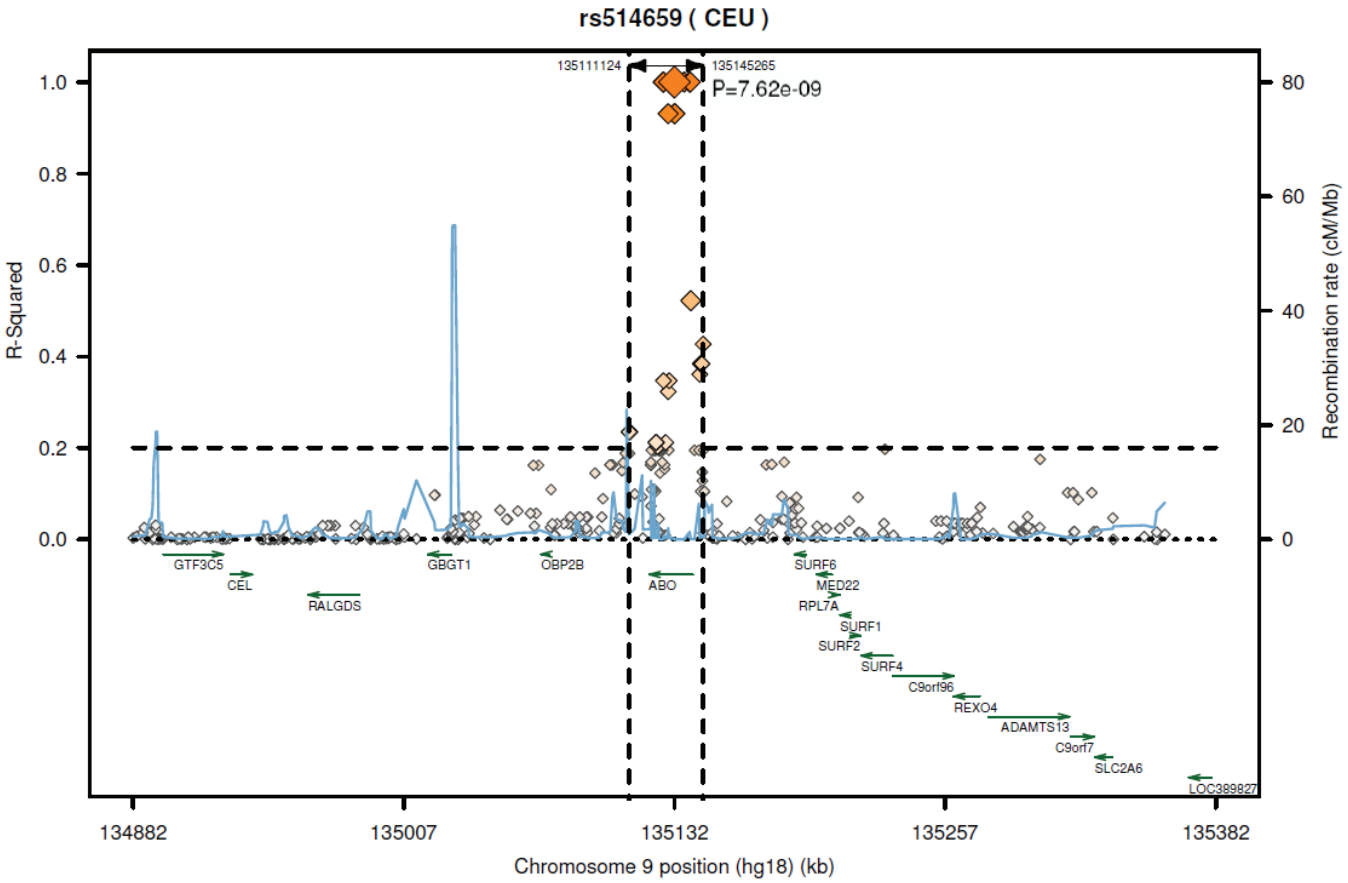
2
4
6
8
λ=1.012
0 1 2 3 4 5 6
$-\log_{10}$(theoretical quantiles)

eFigure 3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0.4
0.2
0.0
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60
40
20
0
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CEL
RALGDS
GBGT1
OBP2B
ABO
SURF6
MED22
RPL7A
SURF1
SURF2
SURF4
C9orf96
REXO4
ADAMTS13
C9orf7
SLC2A6
LOC389827
134882
135007
135132
135257
135382
Chromosome 9 position (hg18) (kb)