Supplemental Material

Genome-wide Analysis Identifies Novel Susceptibility Loci for Myocardial Infarction

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Supplemental References

Members of The GENIUS-CHD Consortium

Members of The CHARGE Consortium Hemostasis Working Group

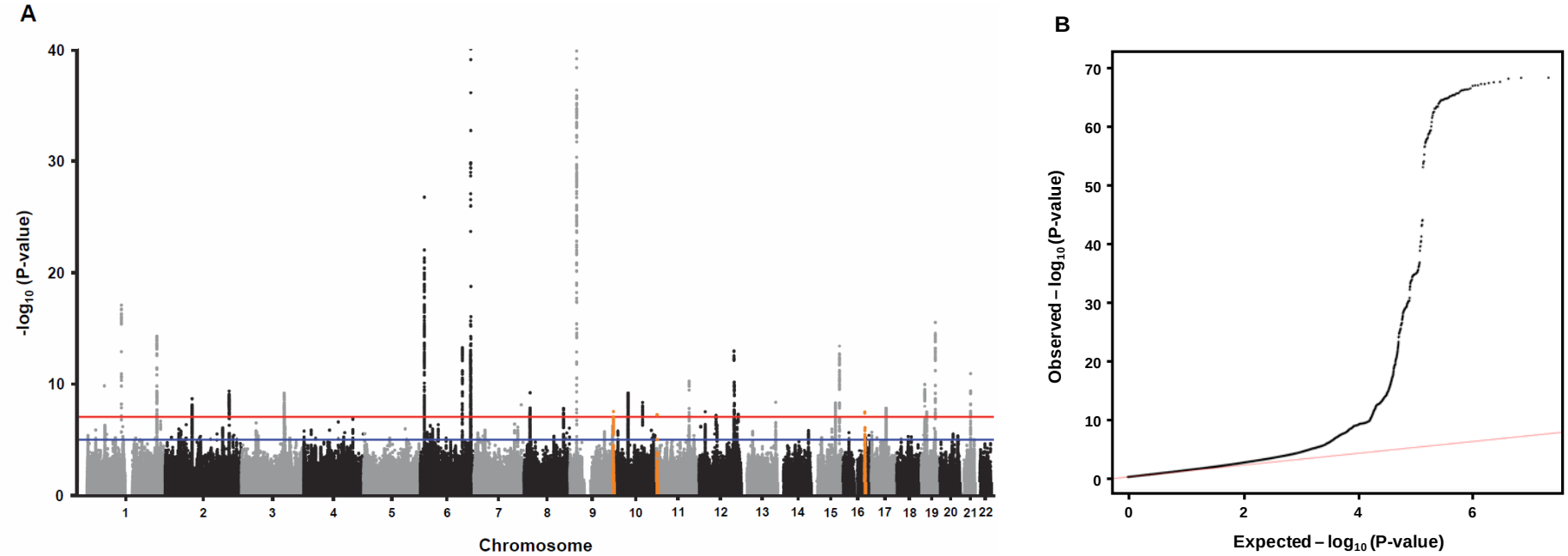

Figure S1. Results of GWAS analysis for MI in UK Biobank. (A) A Manhattan plot shows 1,966 significantly associated SNPs distributed among 31 loci that were significantly associated with MI in UK Biobank, of which three were not previously reported (orange dots). Logistic regression was carried out with 10,903,881 in 454,212 controls and 17,505 MI cases, defined as positive for International Classification of Diseases version-10 (ICD10) codes: I21, I22, I23, I25.2, which include MI, and complications following acute MI. Doctor-diagnosed and self-reported MI were also included in the definition. Genome-wide thresholds for significant ($P=5.0x10^{-8}$) and suggestive ($P=5.0x10^{-6}$) association are indicated by the horizontal red and dark blue lines, respectively. P-values are truncated at -log10(P)=40. **(B)** A quantile-quantile plot shows the observed versus expected P-values from the association analyses for MI. The genomic control factor (λ) in GWAS results using all subjects from the UK Biobank was 1.19 and the LD Score intercept from BOLT-LMM was 1.008 (SE=0.0074). The LD Score intercept was virtually identified when the analysis in the UK Biobank was restricted to only subjects of European ancestry (1.008; SE=0.0073), suggesting that any inflation of test statistics was more likely due to many small genetic effects rather than population structure.

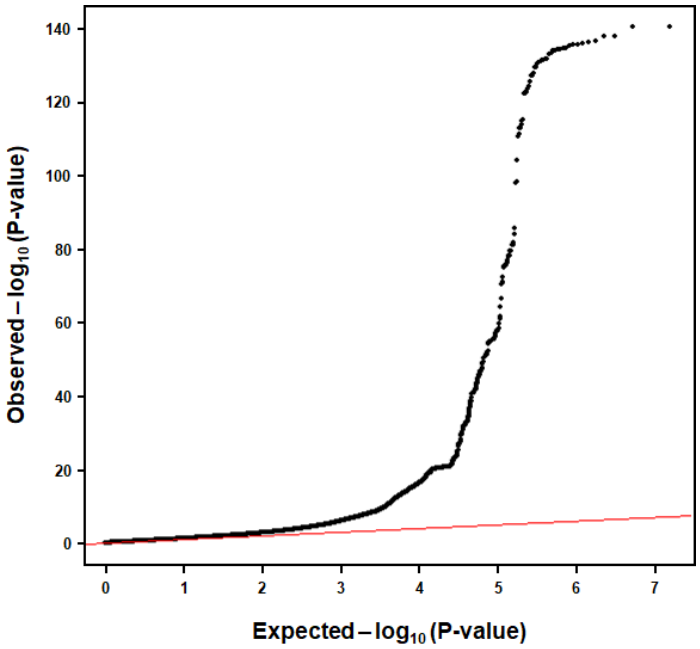

Figure S2. Quantile-quantile plot for results of GWAS meta-analysis for MI with UK Biobank and CARDIoGRAM+C4D. The observed versus expected P-values from the fixed-effects meta-analysis for MI are shown in the quantile-quantile plot. The genomic control factor (λ) in the meta-analysis was 1.24 and the LD Score intercept was 0.969 (SE=0.0093). An LD Score intercept <1 may be due to a genomic control correction or the existence of low frequency SNPs. However, we used a linear mixed-model to control for population stratification in the UK Biobank and did not carry out a genomic control correction in the meta-analysis since subjects in the cohorts in the CARDIoGRAM+C4D Consortium were mostly of European ancestry. Therefore, the LD Score intercept we obtained is likely a consequence of including SNPs with MAFs as low as 0.5% in the meta-analysis. A total of ~61,000 cases and ~577,000 controls from UK Biobank (17,505 cases and 454,241 controls) and CARDIoGRAM+C4D (~44,000 cases and 123,504 controls) and 8,126,035 SNPs common to both datasets were included in the meta-analysis.

Methods

Study Populations. The UK Biobank recruited participants between 40-69 years of age who were registered with a general practitioner of the UK National Health Service (NHS)[1]. From 2006-2010, a total of 503,325 individuals were included. All study participants provided informed consent and the study was approved by the North West Multi-centre Research Ethics Committee. Individual cohorts in the CARDIoGRAMplusC4D Consortium 1000 Genomes GWAS studies have been previously described in detail[2]. All subjects gave written consent for participation in genetic studies, and the protocol of each study was approved by the corresponding local research ethics committee or institutional review board. The present study was approved by the Institutional Review Boards of the Cleveland Clinic and USC Keck School of Medicine.

Clinical Definitions in the UK Biobank. MI cases were defined as positive for International Classification of Diseases version-10 (ICD10) codes I21, I22, I23, I25.2, which included myocardial infarction (MI), and complications following acute MI. Doctor-diagnosed and self-reported MI were also included in the definition of MI. CAD cases were defined in two ways. The first was an all-inclusive definition that included subjects positive for MI according to the criteria described above, as well as positive for other ICD-10 codes I24.0, I24.8, I24.9, I25.0, I25.1, I25.4, I25.8, and I25.9, which included ischemic heart diseases. Additional criteria to define CAD included Office of Population Censuses and Surveys Classification of Interventions and Procedures, version 4 (OPCS-4) codes K40-K46, K49, K50 and K75, covering replacement, transluminal balloon angioplasty, other therapeutic transluminal operations on coronary artery and percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery.

The second definition of CAD was more restricted (CAD only) and included subjects who were only positive for CAD and negative for MI. To avoid any misclassification of cases, we also excluded samples who were only positive for ICD10 codes I24.1 (Dressler's syndrome), I25.3 (aneurysm of heart), I25.5 (ischaemic cardiomyopathy), or I25.6 (silent myocardial ischaemia). This overall strategy in the UK Biobank led to the definition of 17,505 MI cases, 15,580 CAD only cases, 33,085 all-inclusive CAD cases, and 454,212 controls who were negative for all of the clinical designations used to define CAD and MI. Clinical definitions in the UK Biobank were based on follow-up data up to October 2018.

GWAS Analyses in the UK Biobank. Quality control of samples and DNA variants and imputation were performed by the Wellcome Trust Centre for Human Genetics[1]. Briefly, ~90 million single nucleotide polymorphisms (SNPs) imputed from the Haplotype Reference Consortium, UK10K, and 1000 Genomes imputation were available in the UK Biobank. Of these, 10,903,881 variants were used for GWAS analysis after filtering on autosomal SNPs with INFO scores >0.8 and with minor allele frequencies (MAF) >0.5% in the 487,379 individuals with imputed genotypes. A GWAS analysis for MI was performed with BOLT-LMM V2.3.2 using a standard (infinitesimal) mixed model to correct for structure due to relatedness or ancestral heterogeneity, with adjustment for age, sex, the first 20 principal components, and genotyping array[3]. The genome-wide significance threshold was set at $P=5.0x10^{-8}$. Since BOLT-LMM relies on linear models even for qualitative traits, SNP effect size estimates on the quantitative scale were transformed to obtain odds ratios (ORs) and standard errors (SEs) using the following formula: β or $SE/(\mu * (1 - \mu))$, where μ = case fraction[3]. In addition to the genomic control factor (λ), we also used LD Score regression to evaluate stratification in the UK

Biobank GWAS results. This approach can provide a more accurate correction factor than genomic control in GWAS with large sample sizes and help distinguish between inflation that is due to true genetic signals from inflation that is due to population stratification[4]. Although LD Score regression assumes a homogenous population, it could still be applicable to the UK Biobank since most subjects are of European ancestry. Manhattan and quantile-quantile plots were constructed using 'qqman' package (v0.1.4) in R[5].

Meta-analysis for MI. Publicly available summary statistics for MI with 9,289,491 SNPs from the CARDIoGRAMplusC4D Consortium[2] were combined with our GWAS results for MI in the UK Biobank. We carried out a fixed-effects meta-analysis with 8,126,035 SNPs common to both datasets assuming an additive model, as implemented in GWAMA[6]. Similar to the GWAS analysis in the UK Biobank alone, the genomic control factor (λ) and LD Score intercept were used to evaluate population stratification/structure in the meta-analysis results. The genome-wide threshold for significant association was set at $P=5.0x10^{-8}$. A locus was defined as novel if our lead SNP was >1Mb away or in weak or no ($r^2 \leq 0.1$) linkage disequilibrium (LD) with the lead variants at the 205 previously reported loci for CAD (which also included MI as a criteria for case status)[7,11]. Replication of the 162 known CAD loci was considered significant at a Bonferroni-corrected threshold of $P=3.0x10^{-4}$ (0.05/162). Manhattan and quantile-quantile plots were constructed using 'qqman' package (v0.1.4) in R[5].

Colocalization Analyses. We used a Bayesian method[8] to evaluate whether the loci identified for MI and colocalizing expression quantitative trait loci (eQTL) best fit a model in which the associations were due to a single shared variant (summarized by the posterior probability). For

each of the 8 novel MI loci, SNP summary statistics from our meta-analysis were selected for a 2Mb window centered on the lead variant. Summary eQTL data in the same 2Mb intervals were obtained from the Stockholm-Tartu Atherosclerosis Reverse Networks Engineering Task (STARNET) cohort[9] (details provided below) in blood, atherosclerotic aortic artery, internal mammary artery, visceral and subcutaneous adipose, liver, and skeletal muscle. For each locus, the genes with the highest probability of being responsible for the MI meta-analysis signal are reported for each tissue analyzed. A posterior probability of colocalization ≥75% was considered strong evidence of a GWAS-eQTL SNP pair influencing both risk of MI and expression of the causal positional candidate gene at a locus. Colocalization analyses were performed with the 'coloc' (v3.2-1) in R (http://dx.doi.org/10.1093/hmg/dds098).

Comparison of Association Signals at Novel Loci in the UK Biobank. Several different analyses were carried out to compare the association signals at the eight novel loci. First, we determined the association of the lead SNPs at each of the eight MI loci with the all-inclusive definition of CAD in the UK Biobank. These analyses were carried out with BOLT-LMM V2.3.2 using a standard (infinitesimal) mixed model to correct for structure due to relatedness or ancestral heterogeneity, with adjustment for age, sex, the first 20 principal components, and genotyping array[3]. A fixed-effects meta-analysis was then carried out for the eight novel loci with the all-inclusive CAD association results from the UK Biobank and those from the CARDIoGRAMplusC4D Consortium under an additive model, as implemented in GWAMA[6]. As another approach, we also used primary level data in the UK Biobank alone to carry out additional case-control analyses. The first compared individuals without MI or CAD (controls, n=454,212) to CAD only cases (CAD^+/MI^-; n=15,580). The second case-control analysis tested

the eight novel loci for association in subjects with both MI and CAD (CAD^+/MI^+ cases, n=17,505) compared to subjects who only had CAD (CAD^+/MI^- "controls"; n=15,580).

Sensitivity Analyses in the UK Biobank. Sensitivity analyses were carried out in the UK Biobank to compare the association signals at the eight MI loci for various other CAD phenotypes, including "soft" endpoints such as angina or death from CAD. Angina cases were defined as positive for ICD10 codes I20.0, I20.1, I20.8 and I20.9, which included angina pectoris. Doctor-diagnosed and self-reported angina were also included in the definition of angina. This strategy led to the definition of 9,546 angina cases, with controls defined as subjects negative for angina, CAD, or MI (n=444,666). CAD death cases (n=1,856) were defined as subjects negative for angina and whose cause of death was due to CAD ICD10 codes I24.0, I24.8, I24.9, I25.0, I25.1, I25.4, I25.8, or I25.9, with controls defined as negative for CAD death, CAD, or MI (n=454,212). Logistic regression with these phenotypes was conducted with adjustment for age, sex, PC1-20, and genotyping array. We also carried out logistic regression for MI separately in subjects of non-European ancestry (n=2,680 cases and 73,242 controls) and European ancestry (n= 14,825 cases and 380,970 controls), followed by a meta-analysis with CARDIoGRAMplusC4D Consortium to assess whether there was any potential confounding due to population structure.

Association of Novel Loci with CAD Risk Factors in the UK Biobank. The lead variants at the newly identified MI loci were evaluated for association with various CAD risk factors in the UK Biobank, including blood pressure (systolic and diastolic), plasma lipids (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides), body

mass index (BMI), and type 2 diabetes. Quantitative and qualitative traits were tested by linear and logistic regression, respectively, with adjustment for age, sex, PC1-20, and genotyping array. Analyses for lipid levels were adjusted further by the inclusion of cholesterol lowering medication as a covariate. For subjects on hypertension medication, 10mmHg and 5mmHg were added to systolic and diastolic blood pressure values, respectively[10]. Type 2 diabetes status was defined based on ICD10 code E11.

Replication Analyses in Biobank Japan. Replication of MI- and CAD-specific associations in Biobank Japan was carried out using the same analytical approach described above for the UK Biobank. A detailed description of the Biobank Japan study is provided in the **Supplementary Material**. Following a recently published GWAS analysis[11], MI cases (n=10,745) were defined based a physician's diagnosis of general medical practices according to relevant guidelines, clinical symptoms, and diagnostic tests. Subjects with stable angina pectoris but no evidence of MI were classified as CAD only cases (n=11,830). Due to uncertainty with respect to a definitive diagnosis of MI, individuals with unstable angina were excluded from these analyses. Controls were defined as subjects negative for MI and stable angina (n=142,336). After exclusion of related individuals with PIHAT scores >0.20, association of lead SNPs at the identified loci with MI or CAD only, and with MI among CAD cases was tested by logistic regression with adjustment for age, sex, and PC1-10.

Replication Analyses in Angiography-based Cohorts. To replicate the association of the novel MI loci and determine their phenotypic specificity, we carried out a case-control analysis in an initial set of six independent cohorts with angiographically-documented CAD patients of

northern European ancestry with (CAD^+/MI^+ cases) and without (CAD^+/MI^- controls) prior diagnoses of MI. This was followed by similar case-control association analyses in a separate set of 10 independent angiography-based replication datasets. Detailed descriptions of these 16 cohorts are provided in the **Supplementary Material**. Association of lead SNPs at the identified loci with MI in the presence of coronary atherosclerosis was carried out in each cohort individually using logistic regression with adjustment for age and sex. Analyses in the ANGES/FINCAVAS cohort additionally adjusted for smoking status, hyperlipidemia, statin use, hypertension, and diabetes status. This was followed by a fixed-effects meta-analysis with all angiography-based cohorts using the 'meta' package[12] (v4.12.-0) in R.

Metabolomics Analyses with the *SLC44A3* Locus. Association of the *SLC44A3* locus with plasma levels of proatherogenic choline-derived metabolites was evaluated in the GeneBank cohort[13-19]. Briefly, metabolites were quantified using stable isotope dilution high performance liquid chromatography (HPLC) with online electrospray ionization tandem mass spectrometry. Stable isotope labeled internal standards for each monitored analyte were added to plasma samples prior to protein precipitation and monitored at the appropriate transitions in in multiple reaction monitoring mode using characteristic parent-daughter ion transitions at m/z ratios for each metabolite. Genotypes for rs12743267 were obtained in subjects profiled on either the Affymetrix 6.0 GeneChip or Illumina Infinium Global Screening Array. Linear regression analysis for each metabolite was carried out using log-transformed values, with adjustment for age, sex, and genotyping array (SAS 9.4 (SAS Institute, Inc, Cary, NC).

Expression Analyses of *SLC44A3* in the STARNET Cohort. STARNET recruited 600 patients with CAD who were eligible for open-thorax surgery at the Department of Cardiac Surgery, Tartu University Hospital in Estonia[9]. After providing written informed consent, venous blood (n=559) and tissue biopsies were obtained from atherosclerotic aortic artery (n=515), internal mammary artery (n=520), visceral (n=247) and subcutaneous (n=237) adipose, liver (n=257), and skeletal muscle (n=294) at the time of surgery. RNA sequencing was performed on the Illumina TruSeq platform and genotyping was performed using the Illumina Infinium assay with the human OmniExpressExome-8v1 bead chip[9]. Expression data were adjusted for age, sex, library protocols, sequencing laboratory, and four genotyping multidimensional scaling components using linear regression. Association of the lead SNP (rs12743267) at the chromosome 1p21.3 locus with adjusted *SLC44A3* expression levels in aorta and mammary artery was computed by one-way ANOVA in R (v3.6.0) among all subjects and separately in subjects with and without MI.

Expression Analyses of *SLC44A3* in Human Coronary Artery and Aortic Endothelial Cells. De-identified coronary artery tissue samples were obtained from heart transplant donors with CAD or from non-diseased donor hearts rejected for orthotopic heart transplantation at the Stanford University School of Medicine. All subjects provided consent for participation in research studies under an IRB-approved protocol. Proximal coronary artery segments from main branches of the left anterior descending, circumflex or right coronary arteries were dissected from all donor hearts. Clinical and histopathology information from diseased hearts was used to classify ischemic and non-ischemic arteries. All normal arteries originated from non-diseased hearts with left ventricular ejection fraction >50%. Total RNA was extracted from frozen

coronary artery segments using the miRNeasy Mini RNA Extraction kit (Qiagen, catalog # 217004). Libraries were prepared using TruSeq Stranded Total RNA Library Prep Gold kits (Illumina, catalog # 20020599) and subjected to 150bp paired-end sequencing on an Illumina NovaSeq S4 Flowcell to achieve a minimum of 100 million fragments per library. Expression levels of *SLC44A3* were compared between ischemic (n=36) and normal (n=24) coronary arteries using DEseq2 (v3.1)[20], after correcting for age, sex, RIN (RNA integrity number) score, ethnicity, and hidden confounding variables.

Human aortic endothelial cells (HAECs) were isolated from aortic explants of anonymous donors (n=149) through the UCLA heart transplant program[21, 22]. Cells were grown to 90% confluence and incubated for 4hrs in M-199 medium (catalog # MT10–060-CV, ThermoFisher Scientific, Waltham, MA) supplemented with 1.2% sodium pyruvate (catalog # 11360070, ThermoFisher Scientific, Waltham, MA), 1% 100X pen strep glutamine (catalog # 10378016, ThermoFisher Scientific, Waltham, MA), 20% fetal bovine serum (FBS, GE Healthcare, Hyclone, Pittsburgh, PA), 1.6% endothelial cell growth serum (Product #356006, Corning, Corning, NY), 1.6% heparin, and 10µl/50ml amphotericin B (catalog #15290018, ThermoFisher Scientific, Waltham, MA). Donor HAECs from up to 53 individuals were expanded at 5% CO_2 at 37ºC and subsequently treated for 4 hours in media containing 1% FBS with and without 10ng/ml human recombinant interleukin (IL)-1β protein (catalog # 201-LB-005/CF, R&D Systems, Minneapolis, MN). RNA was extracted from approximately $5x10^6$ cells using the Quick-RNA MicroPrep kit (catalog # R1051, Zymo Research, Irvine, CA) for preparation of libraries, as described previously[23], and subjected to sequencing on an Illumina HiSeq 4000 according to the manufacturer's specifications. Expression levels of *SLC44A3* in HAECs with and without IL-1β treatment were compared using DEseq[20].

***In Vitro* Smooth Muscle Cell Migration Assay:** Vascular smooth muscle cells (SMCs) were isolated from aortic explants of anonymous donors (n=151) through the UCLA heart transplant program and characterized for atherosclerosis-relevant phenotypes, as described recently[24]. A portion of these donors overlapped with those from whom HAECs were isolated. The cells were grown in Smooth Muscle Cell Basal Medium (catalog # CC-3181, Lonza, Basel, Switzerland) supplemented with the Smooth Muscle Growth Medium-2 SingleQuots Kit (SmGM-2, catalog # CC-4149, Lonza, Basel, Switzerland). Migration of SMCs was monitored continuously for 24 hours using electronically integrated 16-well Boyden chamber plates (CIM-plate 16, catalog # 5665817001, ACEA Biosciences, San Diego, CA) with 8μm pores in an xCelligence Real-Time Cell Analysis Instrument (ACEA Biosciences, San Diego, CA) placed in a 5% CO_2 humidified incubator and maintained at 37°C. The upper chamber of each well was seeded with $3x10^5$ cells in serum-free media whereas the lower chamber contained either serum-free media (control) or serum-free media supplemented with 100ng/mL PDGF-BB as the chemoattractant. Changes in electrical impedance as the cells migrated to the lower chamber was monitored and translated to an index that was proportional to the number of migrating cells. All experiments were performed in quadruplicate. For each donor, the response to PDGF-BB was calculated by estimating the difference in the area-under-the-curve (AUC) between PDGF-BB and control media (migration response difference). The difference in migration rate was also determined by calculating the difference in the slopes between PDGF-BB and control media before the cells reached maximum migration.

Description of Biobank Japan and 16 Angiography-Based Cohorts

The Biobank Japan: Biobank Japan is a hospital-based Japanese national biobank project including data from approximately 200,000 patients enrolled between 2003-2007[25, 26]. Participants were recruited at 12 medical institutes throughout Japan (Osaka Medical Center for Cancer and Cardiovascular Diseases, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Juntendo University, Tokyo Metropolitan Geriatric Hospital, Nippon Medical School, Nihon University School of Medicine, Iwate Medical University, Tokushukai Hospitals, Shiga University of Medical Science, Fukujuji Hospital, National Hospital Organization Osaka National Hospital and Iizuka Hospital). Subjects were genotyped using the HumanOmniExpressExome v.1.0/v.1.2 platform (Illumina) or a combination of the HumanOmniExpress v.1.0 and Human Exome BeadChip v.1.0/v.1.1 (Illumina). Variants with call rates <99%, Hardy–Weinberg equilibrium P-values<1.0×10^{-6}, and heterozygous counts <5 were excluded. Pre-phasing was performed using Eagle[27] and phased haplotypes were imputed to reference panels by minimac3[28]. Individuals <18 years of age (n=830), without clinical information (n=384), with excess heterozygosity (n=114), excess missing genotypes (n=30), non-Japanese ancestry as determined by principal component analysis (n=501), and who were closely related based on identity by state PIHAT scores >0.2 (n=9,330) were excluded. Written informed consent was obtained from all participants in each study and the protocol was approved by the relevant ethical committees at each facility.

Cleveland Clinic GeneBank: The Cleveland Clinic GeneBank cohort is a single site sample repository generated from ~10,000 consecutive patients who underwent elective diagnostic coronary angiography or elective cardiac computed tomographic angiography with extensive

clinical and laboratory characterization and longitudinal observation. Written informed consent was obtained from all participants prior to enrollment. The GeneBank study has been approved by the Institutional Review Board of the Cleveland Clinic. The present analysis included 3,484 subjects of northern European ancestry from the GeneBank cohort, all of whom had coronary artery disease (CAD) has defined by angiographic evidence of ≥50% stenosis in one or more major epicardial vessel and/or a documented history of known CAD. Among these 3,395 subjects, 1,827 had an adjudicated prior diagnosis of myocardial infarction (MI) based on defined electrocardiographic changes or elevated cardiac enzymes, with the remaining 1,568 subjects having CAD but no history of MI. Subject recruitment occurred between 2001 and 2007. Ethnicity was self-reported and information regarding demographics, medical history, and medication use was obtained by patient interviews and confirmed by chart reviews. All clinical outcome data were verified by source documentation. The GeneBank cohort has been used previously for discovery and replication of novel genes and risk factors for atherosclerotic disease[13, 15, 17, 29, 30].

Emory Cardiovascular Biobank: The Emory Cardiovascular Biobank is a prospective cohort of 5,876 patients undergoing elective or emergent heart catheterization for suspected or confirmed CAD at three Emory healthcare sites in Atlanta, GA. Subjects with congenital heart disease and heart transplantation cancer were excluded. Replication analyses were carried out using genotypes or imputed genotypes obtained from the Illumina Infinium Multi-Ethnic Global Array. The study was approved by the Institutional Review Board of Emory University, Atlanta, GA. All subjects provided written informed consent at the time of enrollment.

ANGES/FINCAVAS: The Angiography and Genes Study (ANGES) cohort consists of 1,000 Finnish individuals who underwent coronary angiography at Tampere University Hospital to detect CAD between September 2002 and July 2005. Data were collected on age, sex, body mass index, alcohol consumption, smoking, medication as well as traditional risk factors of atherosclerosis. A clinical diagnosis of MI was based on symptoms, electrocardiographic findings and biochemical marker tests measuring troponin I and creatine kinase. Previous cardiovascular diseases, therapeutic procedures and data on CAD and MI were retrieved from patient records at Tampere University Hospital. Follow-up data were derived from the national health care registers maintained by the National Institute for Welfare and Health. Replication analyses in ANGES/FINCAVAS were carried out using genotypes or imputed genotypes for obtained from the Metabochip and Core Exome array. The local ethical committee has approved the study and a written informed consent was obtained from all participants[31]. The Finnish Cardiovascular Study (FINCAVAS) cohort includes 4,567 patients who underwent exercise stress tests at Tampere University Hospital. Study participants were followed up for major cardiovascular events, coronary procedures and cause of death with follow-up data gathered at 2, 5 and 10 years post-recruitment[32].

LIFE-HEART: The Leipzig Heart Study (LIFE-Heart) is an observational cohort of patients recruited at the Leipzig Heart Center, Germany. Patients with suspected CAD (CAD), stable CAD or MI were recruited. Patients received a comprehensive assessment of vessel status and cardiologic function including coronary angiography, carotid ultrasound, ankle-brachial index, echo-cardiography and electrocardiography. Details of the study can be found in Beutner et al[33]. Replication analyses in LIFE-Heart was carried out using genotypes or imputed genotypes

obtained from the Affymetrix Axiom CEU1 or Affymetrix Axiom CADLIFE arrays, as described previously by Pott et al[34]. The study was approved by the ethics committee of the Faculty of Medicine of Leipzig University, Germany (Reg. No 276-2005) and is registered at ClinicalTrials.gov (NCT00497887). Written informed consent was obtained from all participants included in the study.

LURIC: The LUdwigshafen RIsk and Cardiovascular Health Study (LURIC) is a monocentric hospital-based prospective cohort including 3316 individuals referred for coronary angiography recruited in the Ludwigshafen Cardiac Center, southwestern Germany from 1997 – 2000[35]. Clinical indications for angiography were chest pain or a positive non-invasive stress test suggestive of myocardial ischemia. To limit clinical heterogeneity, individuals suffering from acute illnesses other than acute coronary syndrome, chronic non-cardiac diseases and a history of malignancy within the five past years were excluded. All participants completed a detailed questionnaire, which gathered information on medical history, clinical, and lifestyle factors. Fasting blood samples were obtained by venipuncture in the early morning and stored for later analyses. Information on vital status during follow-up was obtained from local registries. Death certificates, medical records of local hospitals, and autopsy data were reviewed independently by two experienced clinicians who were blinded to patient characteristics and who classified the causes of death. CAD at baseline was defined as the presence of a visible luminal narrowing (>50% stenosis) in at least one of 15 coronary segments according to the classification of the American Heart Association. Replication analyses in LURIC was carried out using genotypes or imputed genotypes obtained from the Affymetrix 6.0 GeneChip. Study protocols were approved by the ethics committee of the "Landesärztekammer Rheinland-Pfalz" and the study was

conducted in accordance with the "Declaration of Helsinki". Informed written consent was obtained from all participants.

UCORBIO: The Utrecht Coronary Biobank Study (UCORBIO) enrolled 2,591 patients who underwent coronary angiography for any indication at the University Medical Center Utrecht (UMCU). Baseline assessment and blood sampling took place between 2011 and 2014. Patients were followed up (maximum: 3 years) for the occurrence of major adverse cardiovascular events (stroke, MI, coronary revascularization, death). The study was approved by the Ethics Committee of the UMCU and was conducted according to the Declaration of Helsinki. UCORBIO is registered with clinicaltrials.gov (ID: NCT02304744).

SMART: The Second Manifestations of ARTerial disease (SMART) study is an ongoing prospective cohort study at the University Medical Center Utrecht (UMCU) in the Netherlands[36]. Since September 1996, more than 12,000 patients have been referred to the UMCU with clinically manifested vascular disease (coronary heart disease, cerebrovascular disease, peripheral arterial disease or abdominal aortic aneurysm) or vascular risk factors (dyslipidemia, hypertension or diabetes mellitus) and were asked to participate in the study. Patients underwent a standardized vascular screening protocol consisting of a health questionnaire including medical history and risk factors, physical examination and laboratory testing. All patients were biannually asked to fill in a short questionnaire regarding hospitalization and outpatient clinical visits. If a patient reported a possible event, all available relevant data were collected and an outcome committee of three staff members assesses whether study outcomes (primary events: myocardial infarction, stroke and vascular death) occurred. The study was approved by the

ethics committee of the University Medical Center at Utrecht, and written informed consent was obtained from all participants.

SCADGENS: Singapore Coronary Artery Disease Genetics Study (SCADGENS) is an ongoing multi-ethnic study from June 2011 that is designed to assess the genetic determinants of CAD in Singapore and has been previously used in genetic studies[37]. The cohort has enrolled patients undergoing diagnostic coronary angiography at National University Heart Centre, Singapore, with angiographically-proven coronary artery stenosis of at least 50% in one or more epicardial coronary arteries or their branches. The diagnosis of MI was ascertained through review of medical records in accordance with the Universal Definition of Myocardial Infarction[38]. A total of 1,035 Chinese subjects (561 CAD^+/MI^+ cases and 474 CAD^+/MI^- controls), and 380 Malay subjects (262 CAD^+/MI^+ cases and 118 CAD^+/MI^- controls) met these inclusion criteria and were available for the present analysis. At recruitment, a face-to-face interview was performed by a research nurse based on a standardized questionnaire that asked for information related to demographics, alcohol consumption, smoking status, physical activity, and medical history (hypertension, diabetes mellitus and hyperlipidemia). Written informed consent was obtained from all participants, and the National Health Group Domain Specific Review Boards (NHG DSRB) approved the study. All methods were performed in accordance with the relevant guidelines and regulations.

PennCATH: PennCATH is a coronary angiographic study based at the University of Pennsylvania Medical Center and has been used previously for genetic and clinical studies of atherosclerotic cardiovascular disease and type-2 diabetes[39]. A total of 3,850 subjects were

recruited between 1998-2003 and provided informed consent through a protocol approved by the Institutional Review Board of the University of Pennsylvania. 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, sex, 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). 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 with 933 subjects with angiographic evidence of CAD based on one or more coronary vessels having ≥50% stenosis. Of these subjects, 470 had a history or presentation of MI and were defined as CAD^+/MI^+ cases, with the remaining 463 subjects defined as CAD^+/MI^- controls. Subjects were genotyped on the Affymetrix 6.0 array at the University of Pennsylvania Medical Center.

MedStar: MedStar is a cross-sectional study of 1,500 patients undergoing cardiac catheterization that was conducted by the Cardiovascular Research Institute of the MedStar Health Research Institute at the Washington Hospital Center between 2004-2007[39]. Enrollment criteria included any clinical indication for cardiac catheterization and ability to give informed consent. Data on age, sex, self-reported 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 were extracted from the medical record. 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. A nested case-control GWAS was with 875 CAD cases with one or more coronary vessels having ≥50% stenosis. Cases were selected to be young with age at diagnosis of CAD ≤55 for males and ≤60 for females. Of these subjects, 421 had a history or presentation of MI and were defined as CAD^+/MI^+ cases, with the remaining 454 subjects defined as CAD^+/MI^- controls. Subjects were genotyped on the Affymetrix 6.0 array at the University of Pennsylvania Medical Center. The Institutional Review Board of the MedStar Health Research Institute approved the protocol and all subjects provided written informed consent.

OHGS: The Ottawa Heart Genomic Study (OHGS) is a GWAS using the Affymetrix 500K and 6.0 arrays designed to detect genes associated with CAD[40]. 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. Subjects with a history of diabetes were excluded. CAD was defined as angiography-based stenosis >50% of a coronary artery. Among 1540 CAD cases, 950 were defined as CAD^+/MI^+ based on a positive history of myocardial infarction and 590 subjects were defined as CAD^+/MI^- controls. OHGS was approved by the Institutional Review Board at the University of Ottawa Heart Institute and all participants provided written informed consent.

CADomics: Coronary Artery Disease and Genomics (CADomics) is a pooled study from the population-based Gutenberg-Heart Study (GHS) and the hospital (cath-lab)-based Atherogene Registry[41-43]. The GHS is a population-based, prospective, observational single-center cohort

study in the Rhein-Main-Region in western Mid-Germany. Individuals between ages 35 and 74 were enrolled and stratified for sex, 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 first 3,500 GHS participants recruited from 2007-2008 were included in the present analysis. The Atherogene Registry enrolled patients with documented CAD who were 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 between 1999-2004. All participants underwent coronary angiography and information on cardiovascular risk factors were extracted from medical records. Angiograms were scored at the time of procedure by an interventional cardiologist. Individuals from the GHS and Atherogene Registry with a history of MI and with angiography documented stenosis of >30% in one or more coronary vessels were defined categorized as $CAD^{+}MI^{+}$ cases (n=1,214). Individuals without a history of MI, but angiographically documented stenosis of >50% in one or more coronary vessels were categorized as $CAD^{+}MI^{-}$ controls (n=592).

ADVANCE: The Atherosclerotic Disease VAscular functioN and genetiC Epidemiology (ADVANCE) cohort is a multi-ethnic study that enrolled 3,179 members of the Kaiser Permanente of Northern California health maintenance organization between 2001-2003[44]. Early

onset CAD (as defined by a CAD qualifying event captured by the electronic databases at any time after January 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. Among the 247 subjects meeting these criteria, 140 were defined as CAD^+/MI^+ cases and 107 were defined as CAD^+/MI^- controls.

WTCCC: The Wellcome Trust Case Control Consortium Study (WTCCC) design and findings for CAD have been described in detail in prior publications[45]. The WTCCC cases were recruited as part of the British Heart Foundation Family Heart Study and comprised subjects of European ancestry with a validated history of myocardial infarction or coronary revascularisation (PTCA or CABG) before their 66th birthday as well as a strong familial basis of CAD. Verification of the history of CAD was required either from hospital or primary care records. The present analysis included 1,377 CAD^+/MI^+ cases and 533 CAD^+/MI^- controls. Genotyping was performed on the Affymetrix 500K GeneChip array as part of the WTCCC Study. Subjects provided written informed consent, and the study was performed under the principles of the Declaration of Helsinki and complied with UK legislation for data protection.

CATHGEN: The Duke CATHGEN study recruited individuals through the cardiac catheterization laboratories at Duke University Medical Centre (Durham, NC)[46]. Clinical data were provided by the Duke Database for Cardiovascular Disease (DDCD). Subjects with CAD had at least 50% blockage in at least one epicardial coronary vessel. Among these subjects, MI was defined based on adjudicated clinical data. Subjects were excluded if they had severe

pulmonary hypertension or congenital heart disease or were diabetic. The Duke Institutional Review Board approved the protocols for CATHGEN and informed consent was obtained from each subject.

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