Supplemental Materials

Genome-wide Analysis Identifies Novel Susceptibility Loci for Myocardial Infarction

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Detailed Description of Cohorts Used for MI Replication Analyses

**Cleveland Clinic GeneBank:** The Cleveland Clinic GeneBank cohort is a single site sample repository generated from ~10,000 consecutive patients undergoing elective diagnostic coronary angiography or elective cardiac computed tomographic angiography with extensive clinical and laboratory characterization and longitudinal observation. 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\(^1\)\(^-\)\(^5\).

**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. 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.

**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.\(^8\). 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.\(^9\). 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\(^{10}\). 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).
Extended Data Figure 1. 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. 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 the UK Biobank GWAS results was 1.19 and the LD Score intercept from BOLT-LMM was 1.008 (SE=0.0074), suggesting that any inflation of test statistics was more likely due to many small genetic effects rather than population structure.
Extended Data Figure 2. 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 ($\lambda$) 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 the cohorts in the CARDIoGRAM+C4D Consortium were of European ancestry. Therefore, the LD Score intercept we obtained is likely as 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.
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