Published in final edited form as:
Arterioscler Thromb Vasc Biol. 2008 January ; 28(1): 173–179. doi:10.1161/ATVBAHA.107.153981.

Association of Gene Variants with Incident Myocardial Infarction in the Cardiovascular Health Study

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Abstract

Objective—We asked if single nucleotide polymorphisms (SNPs) that had been nominally associated with cardiovascular disease in antecedent studies were also associated with cardiovascular disease in a population–based prospective study of 4,522 individuals aged 65 or older.

Methods—Based on antecedent studies, we prespecified a risk allele and an inheritance model for each of 74 SNPs. We then tested the association of these SNPs with myocardial infarction (MI) in the Cardiovascular Health Study (CHS).

Results—The prespecified risk alleles of 8 SNPs were nominally associated (1-sided $P<0.05$) with increased risk of MI in white CHS participants. The false discovery rate for these 8 was 0.43, suggesting that about 4 of these 8 are likely to be true positives. The 4 of these 8 SNPs that had the strongest evidence for association with cardiovascular disease prior to testing in CHS (association

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Disclosures: DS, LAB, CMR, JZL, ARA, OI, MML, BAY and JJD have employment and ownership interests. ESO, MJM, JPK, RPT and received research grants, SGE has consulting fees. The remaining authors have no disclosures.

in 3 antecedent studies) were in *KIF6* (CHS HR=1.29; 90%CI 1.1–1.52), *VAMP8* (HR=1.2; 90%CI 1.02–1.41), *TAS2R50* (HR=1.13; 90%CI 1–1.27), and *LPA* (HR=1.62; 90%CI 1.09–2.42).

Conclusions—Although most of the SNPs investigated were not associated with MI in CHS, evidence from this investigation combined with previous studies suggests that 4 of these SNPs are likely associated with MI.

Keywords

coronary disease; myocardial infarction; genetics; polymorphisms

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Cardiovascular disease is a complex disease with a genetic component[1], and many genetic polymorphisms have been reported to be associated with cardiovascular disease[2]. However, to confirm these associations, they should be examined in other populations, ideally in population-based prospective studies that have sufficient power to detect the hypothesized associations. One such population-based prospective study is the Cardiovascular Health Study (CHS), a study of American men and women 65 years and older sponsored by the National Heart, Lung, and Blood Institute.[3, 4] CHS offers several strengths, including a large population-based cohort, collection of baseline data for traditional risk factors, long follow-up, and central adjudication of cardiovascular events.

We have been investigating the association between cardiovascular disease and single nucleotide polymorphisms (SNPs) using a panel of ~12,000 mostly nonsynonymous SNPs.[5, 6, 7] The discovery studies for these investigations were conducted in case–control studies that included patients enrolled by investigators at the Cleveland Clinic Foundation (CCF) and the University of California, San Francisco (UCSF).[5, 6, 7] and the association between 9 of these SNPs and cardiovascular disease in multiple discovery studies has been previously described.[5–9] We have used these 9 SNPs to build multiplex assays that are suitable for genotyping thousands of samples even when only a limited quantity of DNA is available for each sample. These multiplex assays also contain assays for 65 additional SNPs that were found to be associated with cardiovascular disease in one or more of the discovery studies (for these 65 SNPs, the results of the antecedent discovery studies are presented in the online supplement of this paper). We investigated whether the risk allele that was identified for each of these 74 SNPs in the antecedent studies would be associated with increased risk of MI in CHS.

Methods

Cardiovascular Health Study

CHS is a prospective observational study of risk factors for cardiovascular disease in older adults. Men and women aged 65 years and older were recruited from random samples of Medicare eligibility lists in four U.S. communities (Sacramento County, California; Washington County, Maryland; Forsyth County, North Carolina; and Pittsburgh, Pennsylvania) and from age-eligible participants in the same household. Potential participants were excluded if they were institutionalized, not ambulatory at home, under hospice care, receiving radiation or chemotherapy for cancer, not expected to remain in the area for at least three years, or unable to be interviewed. CHS enrolled 5201 participants in 1989–90; an additional 687 African American participants entered the cohort in 1992–93. The combined cohort of 5888 was 57.6% female and 15.7% African American. The mean age at enrollment was 72.8 years (standard deviation 5.6). Participants who did not donate DNA or who did not consent to the use of their DNA for studies by private companies (N=514) were excluded from the present study. Participants for whom DNA samples were inadequate (N=130) were also excluded. The institutional review board at each site approved the study methods, and all

participants gave written informed consent. Details of CHS recruitment[3] and design[4] have been reported.

Participants completed a baseline clinic examination[4] that included a medical history interview, physical examination, and blood draw.[10] Baseline self-reports of MI or stroke were confirmed by information from the clinic examination or by review of medical records or physician questionnaires.[11] Genotypes of the CHS participants were determined using a multiplex method that combines PCR, allele-specific oligonucleotide ligation assays, and hybridization to oligonucleotides coupled to Luminex® 100TM xMAP microspheres (Luminex, Austin, TX). See online supplementary text for details.

Diabetes mellitus was defined by fasting serum glucose of at least 126 mg/dL or the use of insulin or oral hypoglycemic medications.[12] Impaired fasting glucose was defined as a fasting glucose of 110–125 mg/dL. Hypertension was defined by systolic blood pressure of at least 140 mmHg, diastolic blood pressure of at least 90 mmHg, or a physician's diagnosis of hypertension plus the use of anti-hypertensive medications. Body mass index (BMI) was defined as body weight in kilograms divided by the square of height in meters.

Cardiovascular events during follow-up were identified at semi-annual contacts, which alternated between clinic visits and telephone calls. Suspected events were adjudicated according to standard criteria by a physician review panel using information from medical records and, in some cases, interviews with the physician, participant, or a proxy informant.[13] Medicare utilization files were searched to ascertain events that may have been missed. In this analysis, MI was defined as definite or probable nonfatal MI or definite fatal MI.

Prespecification of risk alleles and inheritance models for SNPs investigated in CHS

For each of the 74 SNPs that were genotyped in CHS we prespecified a risk allele and an inheritance model based on antecedent data (online Data Supplement Table I). For 9 of the 74 SNPs, genotypic association results have been previously published.[5–9] The remaining 65 SNPs were associated with MI in at least one of two case-control studies described in the online supplementary text (Online Data Supplement text and online Table II). An inheritance model for each SNP was prespecified using the following three rules: (a) for SNPs that had been previously reported to be associated with cardiovascular disease the inheritance model was based on the published data; (b) for SNPs that were nominally associated ($P<0.1$) in the two antecedent MI case-control studies reported in the online supplement (Data Supplement Table I) and had the same inheritance model in both studies, we used that model; (c) for all other SNPs we used an additive inheritance model. For example, if a SNP had the same risk allele in both studies and was nominally associated with MI ($P<0.1$) using an additive model in one study and using a recessive model in the second study, we used an additive model. We also used an additive model for SNPs that were associated with MI in only one of the two antecedent studies of MI.

Statistical analysis

Analyses excluded participants with a baseline history of MI (N=517 of the 5244 participants with genotype data) or stroke (N=222). Participants who were neither white nor African American were also excluded (N=30). Participant characteristics at baseline were described by counts and percents or means and standard deviations (Table 1).

Hardy–Weinberg equilibrium (HWE) tests were run for each SNP using the "genhw" procedure[14] in Stata[15] with corresponding Pearson chi-square tests; if either homozygote count was 5 or less, an exact test was used.

Since genetic risk factors can have different magnitude in whites and in African Americans, we investigated the association of SNPs with incident MI in CHS in each race separately.

We conducted analyses of time to incident MI. Follow-up began at CHS enrollment and ended on the date of incident MI, death, loss to follow-up, or June 30, 2003, whichever occurred first. The median time at risk was 11.3 years for incident MI (12.7 years for the 1989–90 cohort and 10.1 years for the African American cohort).

Cox regression was used to estimate hazard ratios associated with each SNP in each race. Multivariate analyses were adjusted for baseline age and sex. Additional analyses were also adjusted for traditional risk factors: BMI, current smoking, diabetes or impaired fasting glucose, hypertension, LDL cholesterol, and HDL cholesterol. Because the expected direction of the effect (risk allele) was prespecified, we used a 1-sided *P*-value to test the significance of the coefficient associated with each SNP. Correspondingly, we estimated 90% confidence intervals for the hazard ratios (for hazard ratios greater than one, there is 95% confidence that a true risk estimate is greater than the lower bound of a 90% confidence interval). Data were analyzed using Stata statistical software.[15]

The expected influence of multiple testing was evaluated using two approaches. First, we used false discovery rates (FDR) as described by Benjamini and Hochberg[16] to estimate the expected fraction of false positives in a group of SNPs with *P* values below a given threshold. For the 8 pairs of SNPs that are located in the same gene (rs529038 and rs619203 in *ROS1*; rs11016076 and rs10082504 in *MKI67*; rs3129196 and rs3130210 in *LOC651870*; rs7439293 and rs12510359 in *PALLD*; rs3813135 and rs892145 in *PGLYRP2*; rs428785 and rs402007 in *ADAMTS1*; rs2296436 and rs1804689 in *HPS1*; rs3749817 and rs13183672 in *FSTL4*), we included only the SNP with the higher (less significant) *P* value in FDR calculations, which were performed with R statistical software.[17] Second, false positive report probabilities were calculated as described by Wacholder et al.[18] Since assigning a prior probability is subjective, we used a range of prior probabilities to calculate a range of false positive report probabilities for each SNP. The assumptions we used to determine the range of prior probabilities are described in the online supplement. The prior probability is directly proportional to the assumptions: alternative false positive report probability estimates can be calculated by choosing different prior probability assumptions.

Results

During 13 years of follow-up, 539 (12%) of the 4522 CHS participants in this analysis had an incident MI. We tested 74 SNPs separately in whites and in African Americans for deviation from the genotype distribution expected under HWE and we found that 8 SNPs (5 in whites and 3 in African Americans) deviated from HWE expectations ($P<0.05$, online Data Supplement Table III). Had we adjusted the HWE test for multiple testing using a Bonferroni correction, none of the SNPs in African Americans, and only 3 of the SNPs in whites would have deviated from HWE expectations. In whites the 5 SNPs that nominally deviated from HWE expectations were rs3027309 in *ALOX12B*, rs11538264 in *BAT2*, rs11758242 in *LY6G5B*, rs402007 in *ADAMTS1*, and rs35690712 in *SLC39A7*. In African Americans the 3 SNPs were rs220479 in *ITGAE*, rs1804689 in *HPS1*, and rs3813135 in *PGLYRP2*. Since none of these SNPs deviated from HWE expectations in both whites and African Americans this deviation is unlikely to be due to genotyping error. Therefore we included all 74 SNPs in the analysis. Table 2 lists all 74 SNPs and the genes in which they are located.

In whites, 8 SNPs in 7 genes were nominally associated ($P<0.05$) with incident MI after adjustment for age and sex (Table 3). The associations between all 74 SNPs and MI in whites are available in the online Data Supplement Table IV. The 8 nominally associated SNPs were

in *KIF6*, *PGLYRP2* (2 SNPs), *LPA*, *MCM10*, *VAMP8*, *DCC*, and *TAS2R50*. We estimated the FDR for these 8 SNPs to be 0.43, indicating that about 4 of these SNPs are expected to be false positives. When we considered the evidence for association with cardiovascular disease prior to testing in CHS, 4 of these 8 SNPs were among those with the strongest prior evidence (association in 3 studies after adjustment for multiple testing. online data supplement Table I). The false positive report probabilities for these 4 SNPs were all ≤0.01 [*KIF6* (0.0005; range 0.0005–0.08), *VAMP8*, (0.005; range 0.002–0.31) *TAS2R50* (0.005; range 0.003–0.33) and *LPA* (0.01; range (0.01–0.66)], suggesting that they are unlikely to be false positives. In contrast, 2 of the SNPs (in *MCM10* and *DCC*) had high false positive report probability (>0.9) indicating that they are likely to be false positives, and the remaining 2 SNPs (both in *PGLYRP2*) had false positive report probabilities that were intermediate (0.3). Adjustment for traditional risk factors did not appreciably change the risk estimates for these 8 SNPs although the association of the SNP in *LPA* was no longer nominally significant (*P*=0.069). Since we had previously observed that this *LPA* SNP was associated with plasma Lp(a) levels,[7] we investigated the association of the *LPA* SNP with Lp(a) and found that carriers of the risk allele had a higher median level of Lp(a) (63 mg/dL) than non carriers (42 mg/dL, *P*<0.00005). However, for the MI endpoint, adjustment of the risk estimate of the *LPA* SNP to account for Lp(a) levels did not appreciably change the hazard ratio (HR=1.64, 90%CI; 1.10–2.45).

In African Americans, 3 SNPs were nominally associated with incident MI after adjustment for age, sex and traditional risk factors (*P*<0.05, Table 4). The association between all 74 SNPs and MI in African Americans are available in the online Data Supplement V. One of these 3 SNPs (rs2213948) is located in an intergenic region; the other 2 SNPs are located in *AQP10* and *FCAR*. This risk allele of the SNP in *FCAR* had been previously reported to be associated with increased risk of cardiovascular disease in the placebo arms of CARE and WOSCOPS.[8] The estimated FDR for this set of 3 SNPs was 0.67. For the SNPs in *VAMP8* and *KIF6*, which had the lowest false positive report probabilities in white participants of CHS, the risk estimates in African Americans were high [1.71 (CI 0.92–3.19) for *VAMP8* and 4.14 (CI 0.79–21.77) for *KIF6*] but did not reach statistical significance (*P*=0.08 for both).

Discussion

We investigated the association between MI and 74 SNPs in CHS and found that 8 SNPs were nominally associated (*P*<0.05) with MI among white participants of CHS. The false discovery rate for these 8 SNPs was 0.43, suggesting that about 4 of these 8 are truly associated with MI.

Of these 8 SNPs, 4 had strong evidence for association with cardiovascular disease prior to testing in CHS. These 4 SNPs are located in *KIF6*, *TAS2R50*, *VAMP8*, and *LPA*. The strongest prior evidence for association with cardiovascular disease was for the SNPs in *KIF6* and *VAMP8*. The SNP in *KIF6* had been previously found to be associated with cardiovascular disease in the placebo arms of two statin trials, and the association remained significant after a Bonferroni correction for multiple testing.[9] The SNP in *VAMP8* had been found to be associated with MI in 3 case–control studies, with an FDR <0.1 in the third study.[6] The risk alleles of these 2 SNPs have also been found to be associated with increased risk of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) study,19, 20 a large population based prospective study of middle-aged Americans. Thus the SNPs in *KIF6* and *VAMP8* had been found to be consistently associated with cardiovascular disease prior to testing in CHS, and the associations found in CHS further strengthen the evidence for these associations. Furthermore, in African Americans participants of CHS, the risk estimates for the SNPs in *VAMP8* and *KIF6* were high (1.71 for *VAMP8* and 4.14 for *KIF6*), although they did not reach statistical significance (*P*=0.08 for both). However, there was a smaller number of African American participants in this study (673 African American compared with 3849 whites), and consequently, the power to detect association was lower among African

Americans than among whites, which could partially account for the lack of statistical significance of these risk estimates.

The SNPs in TAS2R50 and LPA were not associated with MI among African American participants of CHS. However, there are considerable differences in the LD structure of the *LPA* and *TAS2R50* regions between Yoruba in Ibadan and CEPH (Utah residents with ancestry from northern and western Europe) populations.[21] Thus, different SNPs in these two genes should be explored in African American populations to test if other variants of these genes are associated with MI in this population.

For the SNP in *LPA*, the prior evidence was association with coronary stenosis in three case–control studies, association that remained significant after a Bonferroni correction for multiple testing in the third study.[7] For the SNP in *TAS2R50*, the prior evidence was association with MI in 3 case–control studies, with a false discovery rate of <0.1 in the third study.[5] However, these 2 SNPs (in *LPA* and *TAS2R50*) were not associated with coronary heart disease in ARIC.[19]

Since we tested 74 SNPs in CHS, we were concerned that multiple testing may have resulted in false positive associations. In order to reduce the extent of multiple testing, we prespecified the risk allele and inheritance model for each SNP based on antecedent studies. Thus we tested a single hypothesis for each SNP. We used two different approaches to evaluate the extent to which multiple testing resulted in false positives. The first method, FDR, is a frequentist approach that estimates the expected fraction of false positives in a group of SNPs with *P* values below a certain threshold.[16] The FDR is computed from the nominal *P* values and the number of independent tests. The group of 8 SNPs that were nominally associated ($P<0.05$) with MI in white participants of CHS had an FDR of 0.43, suggesting that about 4 of these SNPs are expected to be false positives. However, none of the SNPs we tested in the white participants of CHS had an FDR lower than 0.1.

The second method we used to account for multiple testing was a Bayesian approach—false positive report probability—that takes into consideration not only the observed *P* value but also the power of the study to detect association and the prior probability of the SNP being associated with disease.[18] We found that the false positive report probabilities for the SNPs in *KIF6*, *VAMP8*, *LPA*, and *TAS2R50* were all ≤0.01, suggesting that these 4 SNPs are unlikely to be false positives. For the SNP in *KIF6*, even the high-end of the false positive report probability range (0.08) suggests a low probability of being a false positive. However, the high-end of the false positive report probability range of the SNPs in *VAMP8* (0.23), *TAS2R50* (0.31) and *LPA* (0.66) indicated an intermediate probability of being false positives when the more conservative end of the prior-probability range was used to estimate the false positive report probability.

We have previously discussed the potential role *LPA*, *VAMP8*, *TAS2R50*, and *KIF6* in cardiovascular disease,[5–7,9] however, the mechanisms by which the variants of these genes influence the pathophysiology of disease is unknown. Briefly, the SNP in *LPA* encodes the apolipoprotein(a) protein portion of the Lp(a) particle, a known risk factor for cardiovascular disease.[22, 23] We had previously reported that this SNP in *LPA* was associated with increased plasma levels of Lp(a).[7] We have now confirmed this finding in CHS whites. We also found that in CHS, the risk associated with this *LPA* SNP remains unchanged after adjustment for Lp(a) levels. The protein encoded by the *VAMP8* gene plays a role in platelet degranulation.[24] The *TAS2R50* gene is a bitter taste receptor, and thus might be involved in food preference and diet.[25] *KIF6* encodes a member of the kinesin superfamily that plays a role in microtubule-mediated intracellular transport; however, its potential role in cardiovascular disease is unknown.

This study has several limitations. The antecedent studies that provided the prior evidence for the 74 SNPs were case–control studies, that might have resulted in selection and survival bias. Furthermore, because DNA limitations required the use of multiplexed assays for genotyping the CHS subjects, not all SNPs that were associated with disease in the antecedent studies were tested in CHS and some of the SNP included in the multiplexed assays had only been associated with cardiovascular disease in a single antecedent study. In this genetic study of CHS, we have not formally tested for population stratification, which could confound genetic association studies. However, since none of the 4 SNPs that are most likely to be true positives deviated from HWE expectations, these associations are unlikely to be confounded by population stratification. Additionally, participants in CHS were older than 65 at baseline (median 72 years); therefore, since cardiovascular disease heritability decreases with age,[1] it may be more difficult to identify genetic associations in this population. Furthermore, in this older population gene variants might be associated with MI because they affect disease pathways that are particularly important in older individuals.

In summary, we found that 4 gene variants that have strong prior- evidence for their association with cardiovascular disease were also associated with incident MI in CHS. This study suggests that even in older adults, genetic variation may affect cardiovascular risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

The authors would like to thank the CHS participants. A full list of participating CHS investigators and institutions can be found at http://www.chs-nhlbi.org.

Funding sources: The research reported in this article was supported by contracts N01-HC-15103, N01-HC-35129, N01-HC-45133, N01-HC-55222, N01-HC-75150, N01-HC-85079 through N01-HC-85086 and U01 HL080295 from the National Heart, Lung, and Blood Institute, with additional contribution from the National Institute of Neurological Disorders and Stroke. RPT was supported by NIH RO1 HL077499, JPK and MJM were supported by the Leducq Foundation.

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Table 1

Baseline characteristics of CHS participants in this study

Characteristic	Whites	African Americans
Number of individuals	3849	673
Male	1575 (41)	243 (36)
Age, mean (SD), y	72.7 (5.6)	72.9 (5.7)
BMI, mean (SD), kg/m^2	26.3 (4.5)	28.5 (5.6)
Smoking, current	423 (11)	113 (17)
Diabetes	511 (13)	151 (23)
Impaired fasting glucose	522 (14)	92 (14)
Hypertension	2110 (55)	490 (73)
LDL cholesterol, mean (SD), mg/dL	130 (36)	129 (36)
HDL cholesterol, mean (SD), mg/dL	54 (16)	58 (15)
Total cholesterol, mean (SD), mg/dL	212 (39)	210 (39)

Data presented as number of participants (%) unless otherwise indicated.

Table 2

SNP2 tested in CHS

Gene Symbol	dbSNP ID	Description
ABCG2	rs2231137	ATP-binding cassette, sub-family G (WHITE), member 2
ADAMTS1	rs428785	ADAM metallopeptidase with thrombospondin type 1 motif, 1
ADAMTS1	rs402007	ADAM metallopeptidase with thrombospondin type 1 motif, 1
ALOX12B	rs3027309	arachidonate 12-lipoxygenase, 12R type
AP3B1	rs6453373	adaptor-related protein complex 3, beta 1 subunit
AQP10	rs6685323	aquaporin 10
BAT2	rs11538264	HLA-B associated transcript 2
CALM1	rs3814843	calmodulin 1 (phosphorylase kinase, delta)
COG2	rs1051038	component of oligomeric golgi complex 2
CYBRD1	rs10455	cytochrome b reductase 1
CYP17A1	rs2486758	cytochrome P450, family 17, subfamily A, polypeptide 1
CYP2C8	rs10509681	cytochrome P450, family 2, subfamily C, polypeptide 8
DCC	rs1675225	deleted in colorectal carcinoma
EDG1	rs2038366	endothelial differentiation, sphingolipid G-protein-coupled receptor, 1
EIF2AK2	rs2307469	eukaryotic translation initiation factor 2-alpha kinase 2
F13A1	rs5985	coagulation factor XIII, A1 polypeptide
FABP2	rs1799883	fatty acid binding protein 2, intestinal
FCAR	rs11666735	Fc fragment of IgA, receptor for
FCRLM2	rs34868416	Fc receptor-like and mucin-like 2 isoform a
FSTL4	rs3749817	follistatin-like 4
FSTL4	rs13183672	follistatin-like 4
GJA4	rs1764391	gap junction protein, alpha 4, 37kDa
GRM8	rs3808117	glutamate receptor, metabotropic 8
HPS1	rs2296436	Hermansky-Pudlak syndrome 1
HPS1	rs1804689	Hermansky-Pudlak syndrome 1
IL1F10	rs6761276	interleukin 1 family, member 10 (theta)
IL1F5	rs2515401	interleukin 1 family, member 5 (delta)
ITGAE	rs220479	integrin, alpha E (antigen CD103)
K6IRS4	rs592720	keratin 74
KIAA1414	chr2:37081301	hypothetical protein LOC54497
KIF6	rs20455	kinesin family member 6
KRT5	rs89962	keratin 5
LGALS14	rs35541195	lectin, galactoside-binding, soluble, 14
LOC391102	rs943133	similar to 60S acidic ribosomal protein P0 (L10E)
LOC651870	rs3130210	similar to HLA class II histocompatibility antigen
LOC651870	rs3129196	similar to HLA class II histocompatibility antigen
LPA	rs3798220	lipoprotein, Lp(a)
LY6G5B	rs11758242	lymphocyte antigen 6 complex, locus G5B
MCM10	rs7905784	minichromosome maintenance complex component 10
MKI67	rs10082504	antigen identified by monoclonal antibody Ki-67
MKI67	rs11016076	antigen identified by monoclonal antibody Ki-67

Gene Symbol	dbSNP ID	Description
MLF1	rs4875	myeloid leukemia factor 1
MYH15	rs3900940	myosin, heavy chain 15
MYOM3	rs12145360	myomesin family, member 3
None	rs2477037	
None	rs2213948	
OR13G1	rs1151640	olfactory receptor, family 13, subfamily G, member 1
OR2A25	rs2961135	olfactory receptor, family 2, subfamily A, member 25
P2RXL1	rs2277838	purinergic receptor P2X-like 1, orphan receptor
PALLD	rs12510359	palladin, cytoskeletal associated protein
PALLD	rs7439293	palladin, cytoskeletal associated protein
PGLYRP2	rs3813135	peptidoglycan recognition protein 2
PGLYRP2	rs892145	peptidoglycan recognition protein 2
PON1	rs662	paraoxonase 1
PRKG1	rs211070	protein kinase, cGMP-dependent, type I
DMXL2	rs12102203	Dmx-like 2
ROS1	rs619203	v-ros UR2 sarcoma virus oncogene homolog 1 (avian)
ROS1	rs529038	v-ros UR2 sarcoma virus oncogene homolog 1 (avian)
SERPINA9	rs17090921	serpin peptidase inhibitor, clade A (antitrypsin), member 9
SERPINB8	rs1944270	serpin peptidase inhibitor, clade B (ovalbumin), member 8
SGIP1	rs1325268	SH3-domain GRB2-like (endophilin) interacting protein 1
SLC26A8	rs2295852	solute carrier family 26, member 8
SLC39A7	rs35690712	solute carrier family 39 (zinc transporter), member 7
SNX19	rs2298566	sorting nexin 19
STRN	rs11685600	striatin, calmodulin binding protein
TAF3	rs4747647	TAF3 RNA polymerase II
TAS2R50	rs1376251	taste receptor, type 2, member 50
TMPRSS11B	rs12331141	transmembrane protease, serine 11B
TOX	rs2290526	thymocyte selection-associated high mobility group box
VAMP8	rs1010	vesicle-associated membrane protein 8 (endobrevin)
VTI1A	rs11814680	vesicle transport through interaction with t-SNAREs homolog 1A
WDR31	rs10817479	WD repeat domain 31
WDR55	rs2286394	WD repeat domain 55
ZNF132	rs1122955	zinc finger protein 132

Table 3

SNPs nominally associated ($P<0.05$) with incident MI in the white participants of CHS.

Gene (SNP)	Prespecifed Model	Adjusted for age and sex				Fully adjusted*	
		HR (90% CI)	*P*	FDR†	FPRP‡ (range)	HR (90% CI)	*P*
KIF6 (rs20455)	Dom	1.29 (1.1–1.52)	0.004	0.20	0.0005 (0.0005–0.08)	1.29 (1.1–1.52)	0.005
PGLYRP2 (rs3813135)	Dom	1.28 (1.09–1.5)	0.006	0.20	0.28 (0.03–0.80)	1.28 (1.09–1.51)	0.006
PGLYRP2 (rs892145)	Dom	1.27 (1.09–1.49)	0.006	NA§	0.27 (0.03–0.80)	1.27 (1.08–1.49)	0.007
LPA (rs3798220)	Add	1.62 (1.09–2.42)	0.022	0.40	0.01 (0.01–0.66)	1.46 (0.96–2.24)	0.069
MCM10 (rs7905784)	Add	1.19 (1.02–1.37)	0.028	0.40	0.92 (0.53–0.99)	1.16 (1–1.35)	0.048
VAMP8 (rs1010)	Dom	1.2 (1.02–1.41)	0.032	0.40	0.005 (0.002–0.31)	1.21 (1.03–1.42)	0.029
DCC (rs1675225)	Add	1.22 (1.02–1.45)	0.036	0.40	0.95 (0.64–0.99)	1.24 (1.03–1.48)	0.026
TAS2R50 (rs1376251)	Add	1.13 (1–1.27)	0.046	0.43	0.005 (0.003–0.33)	1.14 (1.01–1.28)	0.038

Hazard ratios and P values were calculated using an additive inheritance model unless indicated otherwise. 1-sided *P* values for the HR using the prespecified risk allele.

*Adjusted for baseline age (continuous), sex, BMI (continuous), current smoking, diabetes or impaired fasting glucose, hypertension, LDL cholesterol (continuous), and HDL cholesterol (continuous).

†False discovery rate

‡False positive report probability

§For pairs of SNPs in the same gene, false discovery rate was calculated for the SNP with the higher (less significant) *P* value.

Table 4

10 SNPs with lowest *P* values for association with incident MI in the African American participants of CHS.

		Adjusted for age and sex			Fully adjusted*	
Gene (SNP)	**Prespecified model**	**HR (90% CI)**	***P***	**FDR†**	**HR (90% CI)**	***P***
FCAR (rs11666735)	Dom	2.08 (1.23–3.53)	0.01	0.67	2.21 (1.29–3.79)	0.008
None (rs2213948)	Add	2.38 (1.04–5.43)	0.042	0.67	20.51 (1.08–50.82)	0.036
AQP10 (rs6685323)	Add	1.35 (1–1.82)	0.048	0.67	1.4 (1.03–1.91)	0.034
PALLD (rs12510359)	Rec	1.78 (0.98–3.22)	0.055	NA§	1.3 (0.67–20.54)	0.26
GJA4 (rs1764391)	Add	1.29 (0.97–1.71)	0.074	0.67	1.23 (0.91–1.65)	0.13
VAMP8 (rs1010)	Dom	1.71 (0.92–3.19)	0.078	0.67	1.81 (0.93–3.52)	0.07
TMPRSS11B (rs12331141)	Add	1.29 (0.96–1.72)	0.078	0.67	1.31 (0.97–1.77)	0.069
KIF6 (rs20455)	Dom	4.14 (0.79–21.77)	0.08	0.67	NA‡	
VTI1A (rs11814680)	Add	1.29 (0.95–1.73)	0.083	0.67	1.27 (0.93–1.73)	0.10
DCC (rs1675225)	Add	3.82 (0.73–20.1)	0.092	0.67	3.81 (0.72–20.2)	0.09

Hazard ratios and P values were calculated using an additive inheritance model unless indicated otherwise. 1-sided *P* values for the HR using the prespecified risk allele.

*Adjusted for baseline age (continuous), sex, BMI (continuous), current smoking, diabetes or impaired fasting glucose, hypertension, LDL cholesterol (continuous), and HDL cholesterol (continuous).

†False discovery rate

‡HR could not be estimated because there were no incident events in either the risk genotype or nonrisk genotype groups.

§For pairs of SNPs in the same gene, false discovery rate was calculated for the SNP with the higher (less significant) *P* value.