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

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Contents

Online Only Supplementary Text: Genotype Determination

DNA isolation

DNA was isolated from peripheral blood leukocytes collected at baseline and stored as buffy coats at -80°C using a standard salt precipitation method[1]. In addition, some DNA was isolated using the Gentra Puregene DNA purification kit (Gentra Systems 13355 10th Ave North, Suite 120 Minneapolis, Minnesota 55441) from peripheral blood leukocytes collected at follow up examinations and stored as buffy coats at -80°C. DNA stock solutions were stored at -80°C.

Multiplex Genotyping

Genotypes of the CHS participants were determined using a genotyping method that included the following steps: multiplex PCR, allele-specific oligonucleotide ligation assays (OLA), hybridization to conjugated Luminex®100TM xMAP microspheres (Luminex, Austin, TX, USA), labeling with streptavidin-R-phycoerythrin, and detection on the Luminex®100TM flow cytometer instrument (Luminex, Austin, TX, USA).

Multiplex PCR

For each DNA sample, genomic regions (100bp to 150bp long) containing the target SNPs were simultaneously amplified using multiplex PCR[2]. 15µL PCR reactions were assembled using the following reagents: 2.5µL of pooled (1.2µM each) PCR primers (all oligonucleotides were obtained from Integrated DNA Technologies, Coralville, IA, USA), 1.5µL of 10X PCR buffer (150mM Tris-HCl pH 8.25; 500mM KCl; 40mM $MgCl_2$; 1mM dATP, dCTP, and dGTP; 0.5mM dTTP; 3mM dUTP; and 0.2% Triton X-

100), 0.5 units of AmpErase™ UNG (Applied Biosystems, Foster City, CA, USA), 5 units of Amplitaq Gold™ (Applied Biosystems, Foster City, CA, USA), and 3ng of genomic DNA. Thermalcycling was performed in a GeneAmp® PCR System 9700 (Applied Biosystems, Foster City, CA, USA) as follows: first, incubation for 2 min at 50°C; second, incubation for 12 min at 95°C; third, 28 cycles (ramp setting 9600) of 15s at 95°C, 15s at 58°C, and 45s at 72°C; fourth, incubation for 7 min at 72°C; fifth, incubation for 30 min at 99°C and finally storage at 4°C.

Allele-specific oligonucleotide ligation

SNP alleles in each of the amplified regions were detected using multiplex OLA[3]. OLA reactions were assembled as follows: to each 15µl of multiplex PCR reaction from the previous step we added 5µL of OLA reaction mix, which contained 1µL of pooled (0.1µM each) allele-specific oligonucleotides (2 for each SNP), 1µL of pooled (0.2µM-0.8µM each) 3 prime biotinylated oligonucleotides that were to be ligated to the allele-specific oligonucleotides (1 for each SNP), 2µL of 10X OLA buffer (150mM Tris pH 6.7, 100mM $MgCl_2$, 750mM KCl, 100mM DTT, 10mM NAD, 1% Triton X-100), and 20 units of r*Tth* thermostable DNA ligase (Abbott Labs, Abbott Park, IL, USA). Thermalcycling was performed in a GeneAmp® PCR System 9700 as follows: 24 cycles (ramp setting 9600) of 5s at 95.5°C and 2 minutes at 50°C. After thermocycling, the reaction was incubated for 10 min at 99°C and finally stored at 4°C.

Hybridization to conjugated Luminex®100TM xMAP microspheres

The 5 prime end of each allele-specific oligonucleotide was designed to have a unique sequence that was complementary to one of 100 distinct types of capture oligonucleotides. Capture oligonucleotides were conjugated[4] to microspheres, such that each class of 100 spectrally distinct Luminex®100TM xMAP microsphere classes[5] was conjugated to one type of distinct capture oligonucleotides. The ligation products from the OLA step were hybridized with these conjugated Luminex®100TM xMAP microspheres by adding a 40µL of hybridization solution to the 20µL OLA reaction from the previous step. This 40µL of hybridization solution contained 1000 microspheres of each of the 100 different conjugated microsphere classes (a total of 100,000 microspheres) in hybridization buffer (20mM Tris-HCl pH 8, 20mM $MgCl_2$, 300mM NaCl, 0.1% Tween 20 with 0.09% (w/v) NaN_3). The hybridization reaction was carried out by incubation for 30 minutes at 55°C.

Labeling with streptavidin R-phycoerythrin

The ligation products that had been specifically captured in the previous hybridization step were fluorescently labeled by adding to the hybridization reaction from the previous step a 15µL solution containing 1µg PhycoLink® streptavidin-R-phycoerythrin (Prozyme, San Leandro, CA, USA), 10mM Tris-HCl pH 8, 10mM $MgCl_2$, 150mM NaCl, 0.05% Tween 20 with 0.09% (w/v) NaN_3 and incubating for 15 minutes at 45°C. The reaction was then stored at room temperature for up to 8 hours before data collection.

Detection on the Luminex®100TM flow cytometer instrument

Genotyping data was collected using the Luminex®100TM instrument[5] at 45°C. The Luminex®100TM instrument sampled 50µL per reaction well and analyzed a minimum of 100 microspheres of each microsphere class in the sample, and the median fluorescent intensity was reported.

Genotyping Accuracy

Genotyping accuracy of this methodology has been assessed in three previous studies by comparing genotype calls from the multiplex OLA assays to those from real time kinetic PCR assays for the same SNPs, and the overall concordance of the genotype calls from these two methods was >99% in each of these studies[6-8].

References

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3. Barany F. Genetic disease detection and DNA amplification using cloned thermostable ligase. *Proc Natl Acad Sci U S A.* 1991;88:189-193.
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7. Shiffman D, Rowland CM, Louie JZ, Luke MM, Bare LA, Bolonick JI, Young BA, Catanese JJ, Stiggins CF, Pullinger CR, Topol EJ, Malloy MJ, Kane JP, Ellis SG, Devlin JJ. Gene variants of VAMP8 and HNRPUL1 are associated with early-onset myocardial infarction. *Arterioscler Thromb Vasc Biol.* 2006;26:1613-1618.
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Online Only Supplementary Text: Antecedent studies

The patient characteristics of the 2 case–control studies of MI are summarized in online Data Supplement Table II. One study of MI comprised 793 cases and 1000 controls that were enrolled between July 1989 and May 2005 by UCSF Genomic Resource in Arteriosclerosis. Participants included patients who underwent diagnostic or interventional cardiac catheterization, patients of the UCSF Lipid Clinic and healthy individuals. Cases had a history of MI. Controls had no history of MI, diabetes or symptomatic vascular disease. The other study of MI comprised 475 cases and 619 controls that were patients of CCF Heart Center and had undergone diagnostic or interventional cardiac catheterization between July 2001 and March 2003. Cases had a history of MI. Controls had no history of MI, and had less than 50% coronary luminal narrowing based on clinical angiography. This CCF study is similar to a study that was previously described (Study-2 in Shiffman et al.[1]).

All subjects in the antecedent studies were self–described non-Hispanic whites who had completed an Institutional Review Board approved questionnaire and given informed consent to participate in genetic studies.

The 65 SNPs with evidence for association in these 2 case–control studies were selected from a set of 16,339 SNPs that had been tested for association with MI.

1. Shiffman D, Ellis SG, Rowland CM, Malloy MJ, Luke MM, Iakoubova OA, Pullinger CR, Cassano J, Aouizerat BE, Fenwick RG, Reitz RE, Catanese JJ, Leong DU, Zellner C, Sninsky JJ, Topol EJ, Devlin JJ, Kane JP. Identification of four gene variants associated with myocardial infarction. *Am J Hum Genet.* 2005;77:596-605.

Online Only Supplementary Text: Prespecification of prior probabilities for SNPs investigated in CHS

The range of prior probabilities for the SNPs in *VAMP8*, *ROS1* (2 SNPs), TAS2R50, *OR13G1*, and *PALLD* (rs12510359) was based on previously published false discovery rates. These SNPs were associated with MI in 3 case–control studies, with a false discovery rate of <0.1 in the third study.[1, 2] Therefore, since the false discovery rate is <0.1, we used prior probabilities that ranged from 0.09 to 0.9. The *KIF6* SNP (rs20455) was associated with CHD in the placebo arms of two CHD prevention trials and the association remained significant after a Bonferroni correction for multiple testing.[3] Therefore, since the significance threshold was 0.05, we used prior probabilities that ranged from 0.095 to 0.95. Similarly, the SNP in *LPA* gene (rs3798220) was assigned a prior probability range of 0.095 to 0.95 because it was associated with CHD in three case–control studies and remained significant after a Bonferroni correction for multiple testing in the third study.[4] The remaining 65 SNPs fall into 3 categories corresponding to the number of studies in which they were found to be associated with CHD. For the SNPs in these 3 categories we assigned a range of prior probabilities based on point estimates of 0.003, 0.03 and 0.3 for SNPs that were found to be associated in 1, 2 or 3 studies respectively (counting the 2 antecedent MI case–control studies described here, and ARIC,[5] provided the same risk allele was found in all studies; none of these studies adjusted for multiple hypothesis testing). We arrived at this point estimate by assuming that 1 out of 3,000 functional SNPs (mainly non-synonymous in these studies) confers a measurable risk of CHD and that each of the studies resulted in a 10 fold enrichment of true positive SNPs. We then assigned a range that extended ten fold higher and ten fold lower from this point estimate.

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4. Luke MM, Kane JP, Liu DM, Rowland CM, Shiffman D, Cassano J, Catanese JJ, Pullinger CR, Leong DU, Arellano AR, Tong CH, Movsesyan I, Naya-Vigne J, Noordhof C, Feric NT, Malloy MJ, Topol EJ, Koschinsky ML, Devlin JJ, Stephen G. Ellis SG. A Polymorphism in the Protease-like Domain of Apolipoprotein(a) is

Associated with Severe Coronary Artery Disease. *Arterioscler Thromb Vasc Biol.* 2007; online prior to publication.

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Online Supplement Table I. Prior evidence for 74 SNPs tested in CHS

Gene	SNP	Prior evidence*	Prior model	Risk allele	Reference
Previously published Data					
KIF6	rs20455	A	dom	G	*J Amer Coll Cardiol.* 2007; in press.
LPA	rs3798220	A	add	C	*Arterioscler Thromb Vasc Biol.* 2007; online prior to publication.
OR13G1	rs1151640	A	dom	C	*Am J Hum Genet.* 2005;77:596-605
PALLD	rs12510359	A	rec	G	*Am J Hum Genet.* 2005;77:596-605
ROS1	rs619203	A	add	C	*Am J Hum Genet.* 2005;77:596-605
ROS1	rs529038	A	add	T	*Am J Hum Genet.* 2005;77:596-605
TAS2R50	rs1376251	A	add	C	*Am J Hum Genet.* 2005;77:596-605
VAMP8	rs1010	A	dom	C	*Arterioscler Thromb Vasc Biol.* 2006;26:1613-1618
FCAR	rs11666735	C	dom	A	*Arterioscler Thromb Vasc Biol.* 2006;26:2763-2768

					CCF				**UCSF**			
Gene	**SNP**	**Prior evidence***	**Prior model**	**Risk allele**	**OR**	***P***	**Strata**	**Model**	**OR**	***P***	**Strata**	**Model**
MYH15	rs3900940	B	rec	C	2.08	0.029	F	rec	1.71	0.03	F	rec
PALLD	rs7439293	B	add	A	1.21	0.042	ALL	add	1.22	0.006	ALL	add
SNX19	rs2298566	B	rec	C	1.24	0.093	ALL	rec	1.21	0.05	ALL	rec
ALOX12B	rs3027309	C	add	T	1.27	0.035	ALL	add	1.18	0.068	ALL	add
AP3B1	rs6453373	C	add	T	1.54	0.029	ALL	add	1.26	0.094	ALL	add
AQP10	rs6685323	C	add	T	1.33	0.003	ALL	add	1.19	0.02	ALL	add
BAT2	rs11538264	C	rec	G	2.92	0.061	F	rec	1.87	0.055	F	rec
CALM1	rs3814843	C	add	G	1.65	0.018	ALL	add	1.97	0.01	M	add
COG2	rs1051038	C	add	A	1.23	0.063	ALL	add	1.19	0.088	ALL	rec
CYBRD1	rs10455	C	add	A	1.18	0.086	ALL	add	1.13	0.079	ALL	add
CYP17A1	rs2486758	C	add	C	1.37	0.02	M	add	1.25	0.067	M	add
CYP2C8	rs10509681	C	rec	T	1.31	0.091	ALL	rec	1.37	0.09	F	rec

DMXL2	rs12102203	C	add	G	1.38	<0.001	ALL	add	1.18	0.014	ALL	add
EDG1	rs2038366	C	add	G	1.19	0.061	ALL	add	1.44	0.061	M	dom
EIF2AK2	rs2307469	C	add	C	1.48	0.086	ALL	add	1.71	0.006	ALL	add
F13A1	rs5985	C	add	A	1.23	0.04	ALL	add	1.21	0.013	ALL	add
FCRLM2	rs34868416	C	add	A	1.37	0.043	ALL	add	1.32	0.024	ALL	add
GRM8	rs3808117	C	add	T	1.58	<0.001	ALL	add	1.21	0.026	ALL	add
HPS1	rs2296436	C	add	T	1.36	0.054	ALL	add	1.32	0.095	M	add
HPS1	rs1804689	C	dom	T	1.26	0.065	ALL	dom	1.25	0.02	ALL	dom
IL1F10	rs6761276	C	add	T	1.25	0.021	ALL	add	1.23	0.004	ALL	add
IL1F5	rs2515401	C	add	T	1.26	0.012	ALL	add	1.13	0.077	ALL	add
ITGAE	rs220479	C	add	C	1.36	0.036	M	add	1.56	0.092	ALL	dom
KIAA1414	chr2:37081301	C	add	G	1.54	0.019	ALL	add	1.59	0.002	ALL	add
LGALS14	rs35541195	C	add	T	1.7	0.018	F	add	1.78	<0.001	F	add
LOC391102	rs943133	C	add	A	1.24	0.03	ALL	add	1.19	0.023	ALL	add
LOC651870	rs3130210	C	add	T	1.24	0.037	ALL	add	1.29	0.002	ALL	add
LOC651870	rs3129196	C	add	A	1.25	0.035	ALL	add	1.29	0.002	ALL	add
LY6G5B	rs11758242	C	rec	C	1.69	0.083	ALL	rec	1.51	0.034	ALL	rec
MKI67	rs10082504	C	add	C	1.38	0.034	ALL	add	1.26	0.043	ALL	add
MYOM3	rs12145360	C	add	A	1.36	0.069	M	add	1.59	0.001	M	add
None	rs2477037	C	add	G	1.31	0.021	M	add	1.31	0.006	M	add
None	rs2213948	C	add	G	1.61	0.019	F	add	1.43	0.013	F	add
P2RXL1	rs2277838	C	add	A	1.27	0.032	ALL	add	1.21	0.032	ALL	add
PGLYRP2	rs3813135	C	dom	C	1.25	0.095	ALL	dom	1.27	0.02	ALL	dom
PGLYRP2	rs892145	C	dom	T	1.29	0.048	ALL	dom	1.27	0.016	ALL	dom
PRKG1	rs211070	C	add	G	1.71	0.029	ALL	add	1.42	0.034	ALL	add
SERPINA9	rs17090921	C	rec	A	2.31	0.02	F	rec	1.5	0.087	F	rec
SLC39A7	rs35690712	C	add	G	1.55	0.06	ALL	add	1.42	0.024	ALL	add
STRN	rs11685600	C	add	C	1.78	0.014	ALL	add	1.39	0.061	ALL	add
TAF3	rs4747647	C	add	A	1.22	0.033	ALL	add	1.15	0.056	ALL	add
VTI1A	rs11814680	C	add	A	1.37	0.043	M	add	1.26	0.018	ALL	add
WDR31	rs10817479	C	add	G	1.44	0.068	ALL	add	1.39	0.016	ALL	add

WDR55	rs2286394	C	add	T	1.24	0.037	ALL	add	1.18	0.044	ALL	add
ABCG2	rs2231137	D	add	C	1.6	0.041	ALL	add	1.23	0.205	ALL	Add
ADAMTS1	rs428785	D	add	C	0.96	0.623	M	dom	1.28	0.096	M	Dom
ADAMTS1	rs402007	D	add	C	1.59	0.499	M	dom	1.29	0.083	M	Dom
DCC	rs1675225	D	add	C	0.78	0.763	ALL	dom	2.54	0.07	ALL	dom
FABP2	rs1799883	D	add	T	1.23	0.041	ALL	add	1.08	0.318	ALL	add
FSTL4	rs3749817	D	add	G	2.71	0.084	F	dom	1.1	0.68	ALL	dom
FSTL4	rs13183672	D	add	A	1.19	0.088	ALL	add	1.1	0.24	ALL	add
GJA4	rs1764391	D	add	C	1.21	0.056	ALL	add	1.05	0.499	ALL	add
K6IRS4	rs592720	D	add	G	0.65	0.953	ALL	dom	1.42	0.074	ALL	dom
KRT5	rs89962	D	add	T	1.2	0.04	ALL	add	1.03	0.629	ALL	add
MCM10	rs7905784	D	add	T	1.25	0.079	ALL	add	1.03	0.746	ALL	add
MKI67	rs11016076	D	add	C	1.2	0.111	ALL	add	1.17	0.087	ALL	add
MLF1	rs4875	D	add	C	1.19	0.051	ALL	add	1.07	0.291	ALL	add
OR2A25	rs2961135	D	add	G	1.37	0.03	ALL	dom	1.14	0.238	ALL	dom
PON1	rs662	D	add	C	1.33	0.078	F	add	0.83	0.96	F	add
SERPINB8	rs1944270	D	add	A	1.24	0.355	ALL	rec	1.59	0.009	ALL	rec
SGIP1	rs1325268	D	add	T	1.08	0.425	ALL	add	1.15	0.056	ALL	add
SLC26A8	rs2295852	D	add	C	1.1	0.284	ALL	add	1.15	0.051	ALL	add
TMPRSS11B	rs12331141	D	add	T	0.97	0.598	ALL	add	1.23	0.019	ALL	add
TOX	rs2290526	D	add	G	1.15	0.294	ALL	add	1.23	0.069	ALL	add
ZNF132	rs1122955	D	add	C	1.17	0.148	ALL	add	1.21	0.026	ALL	add

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[*] A – published data in a manuscript that corrected for multiple testing; B – evidence from 2 MI studies reported in this table and from ARIC (Morrison et al. *Am J Epidemiol.* 2007;166:28-35); C – evidence from 2 studies; D – evidence from only one of two studies reported in this table.

Online Data Supplement Table II. Distribution of Traditional Risk Factors in Two Antecedent Case–Control Studies of MI

Data presented as percent of participants unless otherwise indicated.

	UCSF		**CCF**	
	Cases (n=793)	**Controls (n=1000)**	**Cases (n=475)**	**Controls (n=619)**
Male	61	43	61	62
Age at enrollment, median (range) ,y	62 (29–86)	70 (24–100)	60 (32–86)	58 (37–88)
Age at MI, median (range) ,y	52 (27–76)	NA	53 (29–77)*	NA
Smoking	64	45	73	54
Diabetes	20	0†	38	10
Dyslipidemia‡	84	53	95	56
Hypertension§	60	34	96	78
BMI mean ±SD, kg/m^2	28±5	26±4	31±6	30±7

Study participants were recruited at the University of California at San Francisco (UCSF) or the Cleveland Clinic Foundation (CCF).

NA indicates not applicable.

*Data available for 254 cases.

†Individuals with diabetes were excluded from control group.

‡Dyslipidemia was defined in CCF by the use of lipid lowering prescription drug(s), LDL cholesterol >129mg/dL, triglyceride >149 mg/dL or HDL cholesterol <45mg/dL and defined in UCSF by a self-reported history of a physician diagnosis of dyslipidemia or the use of lipid lowering prescription drugs.

§Hypertension was defined in CCF as the use of antihypertensive prescription drug(s), systolic blood pressure >160 mmHg, or diastolic blood pressure >90 mmHg and was defined in UCSF by a self–reported history of a physician diagnosis of hypertension or use of antihypertensive prescription drugs.

Online Data Supplement: Table III. 74 SNPs Tested in CHS

		African Americans		Whites	
Gene	**SNP[*]**	**Allele freq.**	**HWE *P*-Value§**	**Allele freq.**	**HWE *P*-Value§**
ABCG2	rs2231137	0.95	1	0.95	0.15
ADAMTS1	rs428785	0.10	0.99	0.23	0.26
ADAMTS1	rs402007	0.10	0.51	0.23	0.01
ALOX12B	rs3027309	0.08	1	0.19	0.02
AP3B1	rs6453373	0.95	1	0.93	0.55
AQP10	rs6685323	0.30	0.46	0.29	0.36
BAT2	rs11538264	0.91	0.16	0.97	<0.0001
CALM1	rs3814843	0.02	0.18	0.04	0.19
COG2	rs1051038	0.79	0.56	0.79	0.15
CYBRD1	rs10455	0.88	0.27	0.67	0.11
CYP17A1	rs2486758	0.08	0.79	0.21	0.7
CYP2C8	rs10509681	0.98	1	0.89	0.5
DCC	rs1675225	0.97	1	0.89	0.05
DMXL2	rs12102203	0.47	0.47	0.51	0.49
EDG1	rs2038366	0.74	0.28	0.66	0.38
EIF2AK2	rs2307469	0.02	1	0.03	1
F13A1	rs5985	0.20	0.25	0.25	0.65

		African Americans		Whites	
Gene	**SNP**[*]	**Allele freq.**	**HWE *P*-Value§**	**Allele freq.**	**HWE *P*-Value§**
FABP2	rs1799883	0.23	0.48	0.26	0.86
FCAR	rs11666735	0.05	1	0.08	0.54
FCRLM2	rs34868416	0.03	0.4	0.09	0.15
FSTL4	rs13183672	0.77	0.99	0.76	0.82
FSTL4	rs3749817	0.90	0.2	0.78	0.93
GJA4	rs1764391	0.47	0.04	0.69	0.92
GRM8	rs3808117	0.86	0.15	0.79	0.19
HPS1	rs2296436	0.87	0.36	0.91	0.74
HPS1	rs1804689	0.16	0.02	0.30	0.75
IL1F10	rs6761276	0.42	0.33	0.42	0.15
IL1F5	rs2515401	0.31	0.4	0.38	0.98
ITGAE	rs220479	0.95	0.04	0.82	0.17
K6IRS4	rs592720	0.95	0.7	0.74	0.72
KIAA1414	2:37139448	0.20	0.68	0.06	0.23
KIF6	rs20455	0.79	0.17	0.36	0.81
KRT5	rs89962	0.11	0.22	0.43	0.57
LGALS14	rs35541195	0.06	0.72	0.12	0.74
LOC391102	rs943133	0.09	0.05	0.27	0.22
LOC651870	rs3130210	0.39	0.46	0.22	0.79

		African Americans		**Whites**	
Gene	**SNP**[*]	**Allele freq.**	**HWE *P*-Value§**	**Allele freq.**	**HWE *P*-Value§**
LOC651870	rs3129196	0.39	0.46	0.22	0.86
LPA	rs3798220	0.01	1	0.01	0.46
LY6G5B	rs11758242	0.89	0.38	0.96	<0.0001
MCM10	rs7905784	0.11	0.31	0.15	0.84
MKI67	rs11016076	0.67	0.59	0.81	0.76
MKI67	rs10082504	0.92	0.57	0.89	0.96
MLF1	rs4875	0.70	0.68	0.54	0.33
MYH15	rs3900940	0.17	0.54	0.29	0.46
MYOM3	rs12145360	0.84	0.17	0.85	0.32
OR13G1	rs1151640	0.18	0.61	0.45	0.8
OR2A25	rs2961135	0.33	0.12	0.51	0.26
P2RXL1	rs2277838	0.04	0.26	0.18	0.91
PALLD	rs12510359	0.28	0.54	0.63	0.29
PALLD	rs7439293	0.19	0.39	0.60	0.58
PGLYRP2	rs892145	0.42	0.21	0.36	0.63
PGLYRP2	rs3813135	0.37	0.005	0.37	0.29
PON1	rs662	0.67	0.34	0.30	0.91
PRKG1	rs211070	0.86	0.93	0.95	0.35
ROS1	rs529038	0.09	0.72	0.26	0.78

		African Americans		Whites	
Gene	**SNP**[*]	**Allele freq.**	**HWE *P*-Value§**	**Allele freq.**	**HWE *P*-Value§**
ROS1	rs619203	0.10	0.72	0.26	0.74
SERPINA9	rs17090921	0.18	0.73	0.30	0.26
SERPINB8	rs1944270	0.57	0.3	0.29	0.51
SGIP1	rs1325268	0.26	0.81	0.29	0.48
SLC26A8	rs2295852	0.63	0.99	0.35	0.1
SLC39A7	rs35690712	0.99	1	0.95	0.0003
SNX19	rs2298566	0.92	0.59	0.74	0.79
STRN	rs11685600	0.15	0.5	0.03	1
TAF3	rs4747647	0.67	0.09	0.40	0.1
TAS2R50	rs1376251	0.88	0.49	0.67	0.88
TMPRSS11B	rs12331141	0.48	0.76	0.24	0.43
TOX	rs2290526	0.03	1	0.11	0.37
VAMP8	rs1010	0.55	0.57	0.41	0.27
VTI1A	rs11814680	0.52	0.92	0.15	0.16
WDR31	rs10817479	0.98	1	0.94	0.23
WDR55	rs2286394	0.08	0.78	0.22	0.98
ZNF132	rs1122955	0.88	0.28	0.79	0.35
None	rs2213948	0.93	0.22	0.84	0.26
None	rs2477037	0.76	0.14	0.61	0.16

*rs number or chromosome location (Build36)

§Hardy-Weinberg equilibrium: P-values from Pearson chi-square tests are shown. If either homozygote frequency was 5 or fewer, an exact test was used. Number of participants: African Americans, 673; whites, 3849.

Online Data Supplement: Table IV. Association of 74 SNPs with MI in the white participants of CHS.

Gene	Prespecified model	Adjusted for age and sex		Fully adjusted	
		HR (90% CI)	*P*	HR (90% CI)	*P*
KIF6 (rs20455)	dom	1.29 (1.1-1.52)	0.004	1.29 (1.1-1.52)	0.005
PGLYRP2 (rs3813135)	dom	1.28 (1.09-1.5)	0.006	1.28 (1.09-1.51)	0.006
PGLYRP2 (rs892145)	dom	1.27 (1.09-1.49)	0.006	1.27 (1.08-1.49)	0.007
LPA (rs3798220)	add	1.62 (1.09-2.42)	0.022	1.46 (0.96-2.24)	0.069
MCM10 (rs7905784)	add	1.19 (1.02-1.37)	0.028	1.16 (1-1.35)	0.048
VAMP8 (rs1010)	dom	1.2 (1.02-1.41)	0.032	1.21 (1.03-1.42)	0.029
DCC (rs1675225)	add	1.22 (1.02-1.45)	0.036	1.24 (1.03-1.48)	0.026
TAS2R50 (rs1376251)	add	1.13 (1-1.27)	0.046	1.14 (1.01-1.28)	0.038
GRM8 (rs3808117)	add	1.13 (0.99-1.3)	0.061	1.16 (1.01-1.33)	0.036
ROS1 (rs619203)	add	1.11 (0.99-1.25)	0.071	1.1 (0.98-1.25)	0.086
ROS1 (rs529038)	add	1.1 (0.98-1.24)	0.092	1.09 (0.97-1.23)	0.11
ALOX12B (rs3027309)	add	1.1 (0.97-1.26)	0.11	1.12 (0.99-1.28)	0.071
FABP2 (rs1799883)	add	1.09 (0.97-1.23)	0.12	1.12 (0.99-1.27)	0.061
MLF1 (rs4875)	add	1.07 (0.96-1.19)	0.15	1.07 (0.96-1.19)	0.17
IL1F5 (rs2515401)	add	1.07 (0.96-1.19)	0.17	1.06 (0.95-1.18)	0.21
EDG1 (rs2038366)	add	1.07 (0.95-1.2)	0.17	1.06 (0.94-1.19)	0.21
FCRLM2 (rs34868416)	add	1.11 (0.92-1.32)	0.18	1.1 (0.92-1.33)	0.19
STRN (rs11685600)	add	1.14 (0.86-1.52)	0.22	1.2 (0.9-1.59)	0.15
OR13G1	dom	1.08 (0.91-1.28)	0.22	1.11 (0.94-1.32)	0.16

Gene	Prespecified model	Adjusted for age and sex		Fully adjusted	
		HR (90% CI)	*P*	HR (90% CI)	*P*
(rs1151640)					
LOC391102 (rs943133)	add	1.05 (0.93-1.18)	0.25	1.04 (0.92-1.17)	0.29
P2RXL1 (rs2277838)	add	1.06 (0.92-1.21)	0.25	1.02 (0.89-1.18)	0.39
CYP17A1 (rs2486758)	add	1.05 (0.92-1.2)	0.26	1.09 (0.95-1.25)	0.14
BAT2 (rs11538264)	rec	1.13 (0.82-1.56)	0.26	1.18 (0.85-1.63)	0.20
WDR55 (rs2286394)	add	1.05 (0.92-1.19)	0.27	1.06 (0.93-1.2)	0.24
LY6G5B (rs11758242)	rec	1.12 (0.82-1.52)	0.28	1.17 (0.85-1.61)	0.21
KIAA1414 (chr2:37081301)	add	1.08 (0.86-1.36)	0.28	1.12 (0.89-1.41)	0.21
TAF3 (rs4747647)	add	1.03 (0.93-1.15)	0.30	1.02 (0.92-1.14)	0.36
ABCG2 (rs2231137)	add	1.08 (0.84-1.4)	0.31	1.07 (0.83-1.38)	0.34
PRKG1 (rs211070)	add	1.06 (0.82-1.38)	0.35	1.11 (0.85-1.45)	0.26
GJA4 (rs1764391)	add	1.03 (0.92-1.16)	0.35	1.03 (0.92-1.16)	0.33
MYOM3 (rs12145360)	add	1.04 (0.89-1.21)	0.35	1.04 (0.89-1.21)	0.35
HPS1 (rs2296436)	add	1.05 (0.86-1.27)	0.35	1.01 (0.83-1.23)	0.46
LGALS14 (rs35541195)	add	1.04 (0.88-1.22)	0.36	1.04 (0.88-1.23)	0.35
EIF2AK2 (rs2307469)	add	1.06 (0.79-1.43)	0.37	1.1 (0.82-1.49)	0.29
AQP10 (rs6685323)	add	1.02 (0.91-1.15)	0.38	1.03 (0.91-1.16)	0.35
ADAMTS1 (rs428785)	add	1.02 (0.9-1.16)	0.38	1.01 (0.89-1.15)	0.43
CYP2C8 (rs10509681)	rec	1.03 (0.85-1.25)	0.40	1 (0.82-1.21)	0.51
ZNF132 (rs1122955)	add	1.02 (0.89-1.16)	0.41	1.01 (0.89-1.16)	0.44
MKI67 (rs10082504)	add	1.02 (0.86-1.21)	0.43	1.03 (0.87-1.23)	0.38
DMXL2 (rs12102203)	add	1.01 (0.91-1.12)	0.44	1.03 (0.92-1.14)	0.34

Gene	**Prespecified model**	**Adjusted for age and sex**		**Fully adjusted**	
		HR (90% CI)	***P***	**HR (90% CI)**	***P***
PON1 (rs662)	add	1.01 (0.9-1.14)	0.45	1 (0.89-1.12)	0.52
SERPINB8 (rs1944270)	add	1 (0.89-1.13)	0.48	1.02 (0.9-1.15)	0.39
ADAMTS1 (rs402007)	add	1 (0.89-1.14)	0.48	0.99 (0.87-1.12)	0.55
KRT5 (rs89962)	add	1 (0.89-1.11)	0.51	0.99 (0.89-1.11)	0.56
TOX (rs2290526)	add	0.99 (0.83-1.18)	0.54	0.97 (0.81-1.16)	0.61
AP3B1 (rs6453373)	add	0.98 (0.79-1.21)	0.56	0.99 (0.8-1.22)	0.54
K6IRS4 (rs592720)	add	0.98 (0.86-1.1)	0.63	0.96 (0.85-1.09)	0.69
MYH15 (rs3900940)	rec	0.94 (0.71-1.25)	0.64	0.98 (0.74-1.29)	0.56
SNX19 (rs2298566)	rec	0.97 (0.83-1.13)	0.64	0.97 (0.83-1.13)	0.62
FCAR (rs11666735)	dom	0.95 (0.77-1.17)	0.67	0.92 (0.75-1.14)	0.74
None (rs2477037)	add	0.97 (0.87-1.08)	0.68	0.98 (0.88-1.1)	0.59
FSTL4 (rs3749817)	add	0.96 (0.84-1.09)	0.70	0.99 (0.87-1.13)	0.55
MKI67 (rs11016076)	add	0.96 (0.84-1.09)	0.71	0.96 (0.83-1.1)	0.71
ITGAE (rs220479)	add	0.95 (0.83-1.09)	0.73	0.97 (0.85-1.11)	0.64
COG2 (rs1051038)	add	0.95 (0.83-1.09)	0.73	0.93 (0.82-1.07)	0.81
OR2A25 (rs2961135)	add	0.95 (0.85-1.06)	0.78	0.95 (0.86-1.06)	0.77
VTI1A (rs11814680)	add	0.93 (0.79-1.08)	0.79	0.95 (0.81-1.11)	0.72
TMPRSS11B (rs12331141)	add	0.93 (0.82-1.06)	0.83	0.94 (0.83-1.07)	0.79
SGIP1 (rs1325268)	add	0.93 (0.83-1.05)	0.83	0.93 (0.82-1.05)	0.85
FSTL4 (rs13183672)	add	0.93 (0.82-1.05)	0.84	0.95 (0.84-1.08)	0.73
SLC39A7 (rs35690712)	add	0.86 (0.68-1.08)	0.86	0.89 (0.71-1.12)	0.80
WDR31	add	0.86 (0.7-1.07)	0.87	0.89 (0.71-1.1)	0.82

		Adjusted for age and sex		Fully adjusted	
Gene	**Prespecified model**	**HR (90% CI)**	***P***	**HR (90% CI)**	***P***
(rs10817479)					
SERPINA9 (rs17090921)	rec	0.83 (0.62-1.1)	0.87	0.8 (0.6-1.06)	0.90
None (rs2213948)	add	0.9 (0.78-1.03)	0.90	0.9 (0.78-1.04)	0.88
LOC651870 (rs3130210)	add	0.9 (0.79-1.03)	0.90	0.91 (0.79-1.04)	0.89
IL1F10 (rs6761276)	add	0.92 (0.83-1.03)	0.90	0.92 (0.83-1.03)	0.89
LOC651870 (rs3129196)	add	0.9 (0.79-1.03)	0.91	0.9 (0.79-1.03)	0.89
HPS1 (rs1804689)	dom	0.87 (0.75-1.02)	0.93	0.87 (0.75-1.02)	0.93
F13A1 (rs5985)	add	0.89 (0.78-1.01)	0.93	0.85 (0.75-0.97)	0.98
CALM1 (rs3814843)	add	0.77 (0.58-1.02)	0.94	0.8 (0.61-1.06)	0.91
PALLD (rs7439293)	add	0.9 (0.81-1.01)	0.94	0.91 (0.81-1.01)	0.93
PALLD (rs12510359)	rec	0.86 (0.74-1.01)	0.94	0.86 (0.74-1.01)	0.94
SLC26A8 (rs2295852)	add	0.89 (0.79-1)	0.95	0.89 (0.79-1)	0.95
CYBRD1 (rs10455)	add	0.88 (0.79-0.98)	0.97	0.88 (0.78-0.98)	0.98

Online supplement Table V. Association of 74 SNPs with MI in the African American participants of CHS.

	Adjusted for age and sex		Fully adjusted	
Gene (SNP)	**HR (90% CI)**	***P***	**HR (90% CI)**	***P***
FCAR (rs11666735)	2.08 (1.23-3.53)	0.01	2.21 (1.29-3.79)	0.008
None (rs2213948)	2.38 (1.04-5.43)	0.042	20.51 (1.08-50.82)	0.036
AQP10 (rs6685323)	1.35 (1-1.82)	0.048	1.4 (1.03-1.91)	0.034
PALLD (rs12510359)	1.78 (0.98-3.22)	0.055	1.3 (0.67-20.54)	0.26
GJA4 (rs1764391)	1.29 (0.97-1.71)	0.074	1.23 (0.91-1.65)	0.13
VAMP8 (rs1010)	1.71 (0.92-3.19)	0.078	1.81 (0.93-3.52)	0.07
TMPRSS11B (rs12331141)	1.29 (0.96-1.72)	0.078	1.31 (0.97-1.77)	0.069
KIF6 (rs20455)	4.14 (0.79-21.77)	0.08	NA*	
VTI1A (rs11814680)	1.29 (0.95-1.73)	0.083	1.27 (0.93-1.73)	0.10
DCC (rs1675225)	3.82 (0.73-20.1)	0.092	3.81 (0.72-20.2)	0.09
CALM1 (rs3814843)	1.77 (0.77-4.05)	0.13	1.55 (0.66-3.64)	0.20
COG2 (rs1051038)	1.28 (0.88-1.87)	0.14	1.31 (0.89-1.93)	0.13
TAF3 (rs4747647)	1.24 (0.89-1.73)	0.14	1.33 (0.94-1.87)	0.087
MYH15 (rs3900940)	1.87 (0.7-5.01)	0.15	2.24 (0.83-6.06)	0.091
SERPINB8 (rs1944270)	1.22 (0.89-1.65)	0.15	1.24 (0.91-1.7)	0.13
F13A1 (rs5985)	1.23 (0.87-1.74)	0.16	1.32 (0.92-1.88)	0.10
IL1F10 (rs6761276)	1.18 (0.89-1.57)	0.16	1.15 (0.86-1.53)	0.22
EDG1 (rs2038366)	1.2 (0.85-1.7)	0.19	1.23 (0.86-1.76)	0.18
ZNF132 (rs1122955)	1.24 (0.78-1.99)	0.22	1.25 (0.78-2)	0.22
GRM8 (rs3808117)	1.22 (0.78-1.9)	0.23	1.17 (0.72-1.88)	0.30

	Adjusted for age and sex		**Fully adjusted**	
Gene (SNP)	**HR (90% CI)**	***P***	**HR (90% CI)**	***P***
CYBRD1 (rs10455)	1.25 (0.76-2.05)	0.23	1.19 (0.72-1.97)	0.29
LOC391102 (rs943133)	1.22 (0.75-1.98)	0.25	1.28 (0.79-2.08)	0.20
FSTL4 (rs3749817)	1.24 (0.73-2.13)	0.25	1.43 (0.81-20.53)	0.15
MLF1 (rs4875)	1.14 (0.82-1.59)	0.26	1.11 (0.79-1.56)	0.30
PGLYRP2 (rs3813135)	1.18 (0.76-1.83)	0.27	1.4 (0.88-2.22)	0.12
FABP2 (rs1799883)	1.12 (0.81-1.55)	0.28	1.17 (0.84-1.63)	0.22
P2RXL1 (rs2277838)	1.24 (0.63-2.43)	0.30	1.21 (0.61-2.38)	0.33
FSTL4 (rs13183672)	1.12 (0.78-1.6)	0.31	1.13 (0.78-1.63)	0.30
LPA (rs3798220)	1.55 (0.29-8.21)	0.33	1.75 (0.33-9.36)	0.29
HPS1 (rs2296436)	1.11 (0.71-1.74)	0.35	1.03 (0.66-1.62)	0.46
K6IRS4 (rs592720)	1.16 (0.58-2.32)	0.36	1.17 (0.58-2.37)	0.36
SNX19 (rs2298566)	1.1 (0.63-1.94)	0.39	1.09 (0.62-1.93)	0.40
TAS2R50 (rs1376251)	1.04 (0.66-1.62)	0.45	0.99 (0.63-1.54)	0.52
MKI67 (rs11016076)	1.02 (0.74-1.4)	0.46	1.05 (0.76-1.46)	0.41
PRKG1 (rs211070)	1.02 (0.67-1.56)	0.47	0.92 (0.6-1.41)	0.62
IL1F5 (rs2515401)	1.01 (0.74-1.39)	0.47	0.98 (0.71-1.37)	0.53
CYP17A1 (rs2486758)	1.02 (0.59-1.76)	0.48	1.05 (0.61-1.82)	0.44
CYP2C8 (rs10509681)	NA*		NA*	
ITGAE (rs220479)	NA*		NA*	
SLC39A7 (rs35690712)	0.96 (0.18-5.04)	0.52	1.13 (0.21-6.07)	0.45
PON1 (rs662)	0.97 (0.72-1.31)	0.56	0.98 (0.72-1.34)	0.54
SGIP1 (rs1325268)	0.96 (0.69-1.35)	0.58	0.92 (0.65-1.31)	0.65

	Adjusted for age and sex		**Fully adjusted**	
Gene (SNP)	**HR (90% CI)**	***P***	**HR (90% CI)**	***P***
PGLYRP2 (rs892145)	0.95 (0.62-1.46)	0.58	1.14 (0.73-1.8)	0.31
WDR31 (rs10817479)	0.89 (0.34-2.35)	0.58	1.29 (0.39-4.26)	0.36
OR13G1 (rs1151640)	0.94 (0.6-1.46)	0.60	1.07 (0.68-1.68)	0.41
ABCG2 (rs2231137)	0.88 (0.46-1.67)	0.63	0.83 (0.43-1.58)	0.69
EIF2AK2 (rs2307469)	0.81 (0.31-2.14)	0.64	0.94 (0.35-20.5)	0.54
HPS1 (rs1804689)	0.9 (0.57-1.42)	0.65	0.92 (0.57-1.48)	0.61
AP3B1 (rs6453373)	0.84 (0.44-1.6)	0.68	0.76 (0.4-1.46)	0.75
FCRLM2 (rs34868416)	0.76 (0.29-1.96)	0.68	0.69 (0.26-1.8)	0.74
KRT5 (rs89962)	0.83 (0.52-1.33)	0.74	0.79 (0.49-1.29)	0.79
DMXL2 (rs12102203)	0.88 (0.66-1.19)	0.76	0.88 (0.65-1.2)	0.75
LGALS14 (rs35541195)	0.72 (0.34-1.54)	0.76	0.74 (0.35-1.59)	0.74
LOC651870 (rs3130210)	0.87 (0.64-1.19)	0.76	0.92 (0.67-1.27)	0.66
LOC651870 (rs3129196)	0.87 (0.64-1.19)	0.76	0.92 (0.67-1.27)	0.66
TOX (rs2290526)	0.59 (0.18-1.94)	0.77	0.63 (0.19-2.09)	0.74
ALOX12B (rs3027309)	0.76 (0.41-1.39)	0.77	0.77 (0.42-1.41)	0.76
WDR55 (rs2286394)	0.76 (0.42-1.37)	0.78	0.83 (0.45-1.51)	0.70
KIAA1414 (chr2:37081301)	0.83 (0.57-1.22)	0.78	0.85 (0.57-1.27)	0.74
SLC26A8 (rs2295852)	0.87 (0.64-1.16)	0.79	0.85 (0.62-1.15)	0.81
SERPINA9 (rs17090921)	0.44 (0.08-2.3)	0.79	0.47 (0.09-20.5)	0.77
LY6G5B (rs11758242)	0.78 (0.49-1.26)	0.80	0.81 (0.5-1.31)	0.77
MCM10 (rs7905784)	0.75 (0.45-1.24)	0.83	0.68 (0.4-1.16)	0.88
OR2A25 (rs2961135)	0.82 (0.59-1.14)	0.83	0.79 (0.56-1.11)	0.88

	Adjusted for age and sex		**Fully adjusted**	
Gene (SNP)	**HR (90% CI)**	***P***	**HR (90% CI)**	***P***
MYOM3 (rs12145360)	0.78 (0.53-1.15)	0.85	0.75 (0.51-1.1)	0.89
PALLD (rs7439293)	0.75 (0.51-1.12)	0.88	0.64 (0.41-0.98)	0.96
BAT2 (rs11538264)	0.68 (0.42-1.1)	0.91	0.69 (0.42-1.12)	0.90
ADAMTS1 (rs402007)	0.61 (0.34-1.12)	0.91	0.66 (0.36-1.22)	0.87
MKI67 (rs10082504)	0.66 (0.4-1.08)	0.92	0.64 (0.39-1.06)	0.93
STRN (rs11685600)	0.65 (0.4-1.06)	0.93	0.72 (0.44-1.18)	0.86
ROS1 (rs619203)	0.58 (0.32-1.05)	0.94	0.53 (0.28-1)	0.95
ROS1 (rs529038)	0.54 (0.28-1.02)	0.94	0.49 (0.25-0.98)	0.96
ADAMTS1 (rs428785)	0.51 (0.27-0.96)	0.96	0.55 (0.29-1.05)	0.94
None (rs2477037)	0.63 (0.46-0.88)	0.99	0.6 (0.43-0.84)	0.99

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