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Association of polymorphisms in platelet and hemostasis system genes with acute myocardial infarction

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Abstract

Background—Genetic polymorphisms may affect the balance between coagulation and fibrinolysis and thereby affect individual vulnerability to acute myocardial infarction (MI) among patients with underlying coronary atherosclerosis.

Methods—We enrolled 1375 patients with an initial clinical presentation of coronary disease. We genotyped 49 single nucleotide polymorphisms (SNPs) in 9 coagulation system genes and compared patients who had an initial acute MI with patients who presented with stable exertional angina.

Results—An SNP in *CD36* (rs3211956) was significantly (*P* = .04) more common among patients who presented with acute MI (minor allele frequency 10.5%) than patients with stable exertional angina (minor allele frequency 8.0%). This association became marginally significant, however, after adjustment for conventional cardiac risk factors in an additive genetic model (odds ratio 1.34, CI 1.00-1.88, *P* = .053). An SNP in *ITGB3* (Leu59Pro, rs5918) was slightly, but not significantly (*P* = .083), more common among patients with acute MI (minor allele frequency 14.5%) than among patients with stable exertional angina (minor allele frequency 12.0%). Two linked SNPs in *THBD* (Ala473Val, rs1042579; and rs3176123) were slightly, but not significantly (*P* = .079 and 0.052, respectively), less common among patients with acute MI (minor allele frequency 16.1%) than among patients with stable exertional angina (18.7% and 19.0%, respectively).

Conclusions—Four SNPs in platelet glycoprotein and hemostatic genes were nominally associated with acute MI rather than stable exertional angina as the initial clinical presentation of coronary artery disease. These findings are suggestive but require independent confirmation in larger studies.

Acute myocardial infarction (MI) is typically precipitated by thrombosis superimposed upon a ruptured coronary plaque and can be effectively treated by timely fibrinolytic therapy. These observations highlight the central role of the coagulation and fibrinolytic systems in

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the pathogenesis of acute MI and suggest that a patient's vulnerability to an MI may be modulated by individual variations in the balance between coagulation and fibrinolysis.

Large numbers of proteins interact within the complex, regulated systems of coagulation and fibrinolysis. Polymorphisms in genes that encode these circulating or cell-bound proteins may affect their structure, concentration, or function, and thereby alter the balance between coagulation and fibrinolysis. Polymorphisms in factor V, factor VII, prothrombin, plasminogen activator inhibitor I, and platelet glycoproteins, have been investigated in several studies for their association with coronary disease.1-3 The potential association of polymorphisms in the genes for tissue plasminogen activator, thrombomodulin, and tissue factor, has been less extensively investigated.4-9

Most prior epidemiological studies have compared patients who had an acute MI with healthy control subjects. This approach does not, however, distinguish factors that predict development of coronary atherosclerosis in general from the more specific factors that define vulnerability to an acute MI among patients with underlying coronary disease. We therefore investigated the specific risk factors for acute MI by comparing carefully selected patients with different initial clinical manifestations of coronary atherosclerosis—either as an acute MI or as stable exertional angina.

Methods

The ADVANCE study is a collaboration between investigators at Stanford University, Stanford, CA, and the Kaiser Permanente of Northern California Division of Research, Oakland, CA which includes several coordinated epidemiological studies. The goal of this project within ADVANCE was to investigate the clinical and genetic predictors of acute MI in patients with underlying atherosclerosis.

Patient recruitment has been described in detail previously.10 Briefly, we identified patients with an initial clinical presentation of acute MI by screening 8184 patients admitted to a Kaiser hospital with an elevated serum troponin I level and a primary discharge diagnosis of acute MI. We excluded patients with prior evidence of coronary disease, with complicating conditions (eg, end-stage renal disease, prior organ or bone marrow transplant, dementia), or who resided outside the San Francisco Bay Area. We interviewed 1252 potentially eligible patients and excluded 161 patients who reported any ischemic symptoms >14 days before the index hospitalization for acute MI. We enrolled 909 eligible patients who agreed to participate in the study and provided an adequate DNA sample for genotyping.

We identified patients with an initial clinical presentation of stable exertional angina by screening 16837 patients with an outpatient clinic visit with a diagnosis of angina and then applying the same exclusions. We interviewed 1284 potentially eligible subjects to confirm that they had typical stable exertional angina and excluded 750 patients who reported episodes of pain at rest, episodes of pain lasting >20 minutes, or more than a 6-month history of chest pain. We enrolled 466 eligible patients who agreed to participate in the study and provided an adequate DNA sample for genotyping.

After obtaining written informed consent, we asked all subjects to complete a baseline health survey and drew blood samples for serum and plasma testing and for extraction of DNA. We obtained confirmatory information on clinical history from Kaiser Permanente databases.11,12 The institutional review boards of the Kaiser Foundation Research Institute and Stanford University approved the study.

Genetic analysis

Of the approximately 100 candidate genes examined in the overall ADVANCE study, 21 were selected a priori to test for association with acute MI rather than stable exertional angina as the initial clinical presentation of coronary disease. In this article, we report the 9 genes within the platelet and coagulation systems chosen a priori: platelet glycoprotein Ia/IIa (*ITGA2*), glycoprotein Ib α (*GP1BA*), glycoprotein IIb (*ITGA2B*), glycoprotein IIIa (*ITGB3*), glycoprotein IIIb/platelet glycoprotein IV (*CD36*), plasminogen activator inhibitor I (*PAI1*), thrombomodulin (*THBD*), coagulation factor III/tissue factor (*F3*), and tissue plasminogen activator (*PLAT*). We sequenced these genes to identify single nucleotide polymorphisms (SNPs) in a sample of 24 diverse patients with prior MI (6 European Americans, 6 African Americans, 6 Asian/Pacific Islanders, and 6 Hispanic Americans) not included in the study sample. We developed genotyping assays for the ABI 7900 TaqMan platform (Applied Biosystems, Foster City, CA) of 49 SNPs (Table I) selected because they were likely to have functional consequences, were relatively common, or both.13 The “no-call” rate was only 0.35%, and the concordance rate was 99.998% in a random sample of SNPs in which genotypes were repeated.

Statistical analyses

We compared patient groups using contingency tables for discrete variables and nonparametric tests for continuous variables. We used logistic regression to test an additive genetic model of the effect of SNPs on the mode of clinical presentation after controlling for potential confounding factors, including age, sex, race/ancestry, conventional cardiac risk factors, and cardiac medications. We also formally tested for interactions between SNPs and race/ancestry and smoking in the association with mode of clinical presentation. We performed analyses using R statistical software, versions 2 through 2.2.0 patched (www.R-project.org).

Results

As previously reported,10 several demographic and clinical variables differed significantly between the 909 patients whose initial clinical manifestation of coronary disease was an acute MI and the 466 patients who presented with stable, exertional angina (Table II). Patients who presented with an acute MI were more likely to be male, current smokers, and hypertensive. Moreover, patients who presented with an acute MI were significantly less likely to be taking statins and β-blockers (Table II). On the other hand, there were no statistically significant differences between the 2 groups in the distribution of ancestry or in the prevalence of diabetes or hyperlipidemia.

The SNP CD36.3 (rs3211956) in the gene for glycoprotein IIIb/platelet glycoprotein IV was associated ($P = .04$) with an initial clinical presentation of acute MI rather than stable exertional angina, with 80.6% of patients with MI homozygous for the major allele versus 84.3% of patients with angina (Table III). Although the odds ratio for each copy of the minor allele of CD36.3 was not attenuated by multivariable adjustment (unadjusted odds ratio 1.34, adjusted odds ratio 1.37), the association became marginally significant ($P = .053$). The minor allele frequency of CD36.3 varied significantly by patient ancestry (Table IV), but the interaction of race/ancestry with CD36.3 was not statistically significant ($P = .22$), and the association of CD36.3 with acute MI was essentially unchanged in the subset of patients with European ancestry (Table V).

The SNP ITGB3.13 (rs5918), which results in the coding change Leu59Pro in glycoprotein IIIa, had a borderline significant association with acute MI (unadjusted odds ratio 1.23, $P = .083$) that was essentially unchanged after multivariable adjustment for potential confounding factors (adjusted odds ratio 1.26, $P = .079$). Although the minor allele frequency of ITGB3.13 varied significantly according to patient ancestry (Table IV), the interaction between this SNP and race/ancestry was not statistically significant ($P = .78$), and association of ITGB3.13 was essentially unchanged in the subset of patients with European ancestry (odds ratio 1.27) (Table V).

The SNP THBD.2 (rs1042579), which results in the coding change Ala473Val in thrombomodulin, was in almost complete linkage disequilibrium with THBD.10 (rs3176123), and consequently, these SNPs had virtually identical strengths of association with acute MI (Table III). The unadjusted odds ratios were not appreciably attenuated by multivariable adjustment for confounding factors (0.83 to 0.87 for THBD.2 and 0.81 to 0.84 for THBD.10) but were of only borderline statistical significance ($P = .079$ and $P = .052$, respectively). Although the minor allele frequencies varied significantly by ancestry (Table IV), the results of the interaction tests between these SNPs and race/ancestry were not statistically significant ($P = .92$ and $P = .69$), and the associations were essentially unchanged in patients of European ancestry (Table V).

We also tested for interactions between these SNPs (Table I) and smoking, but none were significant.

Discussion

Platelets, coagulation, and fibrinolysis are central to the pathophysiology of acute MI in patients with coronary atherosclerosis. We hypothesized that polymorphisms in the genes encoding key proteins in these systems would affect a patient's vulnerability to develop an acute MI. We tested this hypothesis in a prospective study on patients who had an initial clinical presentation of coronary disease in a large representative population. This study was designed to detect associations with odds ratios of ≥1.5; because none of the polymorphisms we studied had a significant association of this magnitude, our results are negative overall. Several polymorphisms had associations with MI in the range of 1.2 to 1.4, however, a level for which this study did not have adequate statistical power to document associations definitively. Polymorphisms in glycoprotein IIIa (ITGB3.13, Leu59Pro, rs5918) and

thrombomodulin (THBD.2, Ala473Val, rs1042579) that had only borderline associations with MI in this study have been previously associated with coronary events in other studies.9,14-17 Our results in an independent population provide some evidence of replication and suggest that these polymorphisms may be worth examining in larger studies. The nominally significant association we found for an SNP in the gene for glycoprotein IIIb/platelet glycoprotein IV (CD36.3, rs3211956) has not been reported previously and must be interpreted cautiously in light of its modest strength of association (odds ratio for MI of 1.36) and the number of statistical tests performed.

CD36 or glycoprotein IIIb/platelet glycoprotein IV is a mediator of platelet adhesion to collagen18 and a receptor for thrombospondin 1 (TSP-1). CD36 has been broadly implicated in atherosclerotic processes18,19 as a receptor for oxidized low-density lipoprotein and its potential role in insulin resistance and binding of long-chain fatty acids.18,20,21 Studies of CD36 deficiency in atherosclerotic mouse models have been equivocal,18,22,23 but individuals with rare null mutations of *CD36* may have a higher rate of coronary disease.19 The polymorphism CD36.3 (rs3211956) is intronic and not known to have functional effects. We did not genotype the relatively rare Pro90Ser polymorphism (rs3765187) that has been found associated with CD36 deficiency in East Asian subjects.24 Although *CD36* is a plausible candidate gene, this modest association of CD36.3 (rs3211956) with acute MI must be confirmed by other studies.

Polymorphisms in glycoprotein IIIa have been investigated fairly extensively for their association with coronary disease. The SNP ITGB3.13, (rs5918) in particular, has been studied by others, although its nomenclature has been changing and is confusing. The SNP rs5918 is now termed Leu59Pro but has been previously referred to in the literature as C1565T, Leu33Pro, Pl^{A2}, and $Pl^{A1/A2}$.1,25,26 In 1996, Weiss et al25 reported that this polymorphism was more common in patients <60 years old with an acute MI than in control subjects without coronary disease. A recent meta-analysis of 43 studies that compared cases with healthy controls reported significant heterogeneity among the study results and no overall effect of the Leu59Pro polymorphism on coronary disease.1 These studies did not, however, test for differences between the more specific phenotypes of acute MI and stable exertional angina without MI. Bray et al14 found Leu59Pro to be associated with a higher rate of subsequent events in a population of patients with established coronary disease. Walter et al15 reported that this polymorphism was associated with stent thrombosis, and Zotz et al16 reported that it was associated with acute MI in younger patients with coronary disease. These studies suggest that the Leu59Pro polymorphism may be prothrombotic among patients with atherosclerosis and thereby increase vulnerability to acute MI. Our finding of a modest association of Leu59Pro (rs5918) with acute MI is consistent with these prior studies in patients with coronary disease but was of only borderline statistical significance, especially in light of the multiple comparisons performed.

Thrombomodulins have been investigated previously for association with acute MI. The SNP THBD.2 (rs1042579) leads to a coding change (Ala473Val) in a region critical to the binding of protein C. The ARIC investigators found Ala473Val to be associated with incident coronary disease,9 and Norlund et al17 found an association with MI. This association was not confirmed, however, in other studies.27-30 Our finding of a borderline

association of Ala473Val with acute MI, in light of prior positive studies, suggests that continued investigation of this polymorphism is warranted.

We found no significant associations with acute MI and polymorphisms in genes for several platelet glycoproteins, despite some prior suggestive studies. None of the 5 SNPs in glycoprotein IIb (part of the platelet receptor for fibrinogen) that we genotyped had a significant association with acute MI, including ITGA2B.4 (rs5911, also called IIe843Ser or HPA-331), which had a positive association with MI in young women in one study32 but no association in other studies.33,34 Nor did we find any significant associations between acute MI and 4 SNPs in glycoprotein Ia/IIa (ITGA2), a major mediator of platelet adhesion to collagen. We did not genotype the C807T SNP (rs1126643), which had a positive association in some studies35-38 but not in others.1,2,28,32,39 We also found no association with acute MI of the so-called Kozak polymorphism in glycoprotein Ib α (GPIBA1.1, rs2243093, also termed T[−5]C), in broad agreement with many other studies. 1,28,32,40,41

We did not confirm an association between acute MI and SNP in the gene for tissue factor (F3.11, also known as –603 A/G). Although Ott et al4 found that the –603G allele was associated with an increased risk of MI, 2 other studies have not.42,43

None of the 4 SNPs in the gene for tissue plasminogen activator (*PLAT*) we studied were associated with MI. In the literature, a polymorphism in the enhancer of *PLAT* referred to as –7315C/T has been associated with MI,44 but not consistently across all studies.45,46 We did not genotype the Alu repeated insertion/deletion polymorphism of *PLAT* that has been associated with MI in some46 but not all studies.6,47,48 Nor did we find an association between any of the 5 SNPs in the gene for plasminogen activator inhibitor (*PAI1*) and acute MI. We did not, however, genotype the 4G/5G polymorphism in *PAI1* (rs1799889) that has occasionally (but not always) been associated with MI,28,41 because it is an insertion/ deletion polymorphism that is not readily genotyped with the methods we used.

ADVANCE is one of the largest candidate gene studies to date and has several strengths, including its population-based approach, high-quality genotyping of multiple SNPs in each candidate gene, and careful phenotyping of subjects. In particular, the ADVANCE study underscores the potential value of using more precisely defined phenotypes, such as initial acute MI and stable exertional angina, to investigate genetic contributions to complex disease. Risk factors for particular manifestations or stages of coronary disease may well differ, so that broad, nonspecific definitions of affected patients may obscure true genetic associations with more specific manifestations of disease. Nevertheless, this study also has several limitations. We could study only a subset of polymorphisms in the candidate genes, so a lack of association for tested SNPs does not exclude the possibility of an association between other polymorphisms in the candidate gene and acute MI. A more comprehensive “tag SNP” approach may be feasible once the complete linkage disequilibrium structure of these genes has been established. Furthermore, we designed this study to examine the association of SNPs specifically with acute MI in subjects with underlying atherosclerosis. This design would not necessarily identify an association between the candidate gene SNPs and atherosclerosis per se because both cases (acute MI) and controls (stable exertional

angina) have underlying coronary disease. The statistical power of this study was >80% to detect odds ratios of ≥1.5 for SNPs with a prevalence of ≥15% but was limited for lesser degrees of association, less common SNPs, or both. Finally, we could not include patients who died as a result of their initial MI, who may comprise as many as a quarter of the patients, which may have blunted genetic associations.

This study found no strong effect of SNPs in either platelet glycoproteins or hemostatic factors and acute MI. The modest associations between polymorphisms in *CD36* (glycoprotein IIIb/platelet glycoprotein IV), thrombomodulin, and glycoprotein IIIa and acute MI, are interesting but require replication in other populations.

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Table I

Polymorphisms genoryped

SNP alias	dbSNP	Minor/major allele	Type	Change
Glycoprotein Ia/IIa				
ITGA2.2	rs41459150	G/A	Intron	6 bp 5′ exon 13
ITGA2.4	rs3212555	C/T	Intron	4 bp 5′ exon 15
ITGA2.12	rs26678	T/G	Intron	21 bp 3′ exon 2
ITGA2.16	rs2287870	G/A	Exon	Asn 927 Ser (exon 23)
ITGA2.25	rs1109527	A/C	Exon	3′ UTR
ITGA2.26	rs1109526	C/T	Exon	3′ UTR
ITGA2.37	rs1062535	A/G	Exon	Thr 275 Thr (exon 8)
ITGA2.39	rs41377544	C/A	Exon	Met 291 Leu (exon 8)
ITGA2.41	rs2303127	C/T	Intron	10 bp 3′ exon 11
Glycoprotein Ib α				
GP1BA.1	rs2243093	C/T	Exon	5′ UTR
GP1BA.4	rs6067	G/A	Exon	Arg 358 Arg (exon 1)
GP1BA.500	rs12948309	A/T	Exon	Leu 453 STOP (exon 2)
GP1BA.501	rs6068	A/G	Exon	Arg 72 His (exon 1)
Glycoprotein IIb				
ITGA2B.1	rs850731	G/A	Intron	107 bp 3′ exon 22
ITGA2B.4	rs5911	G/T	Exon	Ile 874 Ser (exon 26)
ITGA2B.6	rs5910	T/C	Exon	Val 1021 Val (exon 30)
ITGA2B.9	rs41369850	A/G	5′	199 bp 5′ transc start
ITGA2B.12	rs850730	G/C	Intron	2 bp 5′ exon 22
Glycoprotein IIIa				
ITGB3.1	rs4642	G/A	Exon	Glu 511 Glu (exon 10)
ITGB3.5	rs3809863	T/C	Intron	8 bp 3′ exon 14
ITGB3.10	rs3809865	T/A	Exon	3′ UTR
ITGB3.13	rs5918	C/T	Exon	Leu 59 Pro (exon 3)
ITGB3.14	rs36080296	G/T	Exon	Leu 63 Arg (exon 3)
ITGB3.17	rs7208055	A/C	5′	385 5′ transc start
ITGB3.24	rs15908	A/C	Exon	Val 381 Val (exon 9)
Glycoprotein IIIb (IV)				
CD36.1	rs1405747	C/A	Intron	150 5′ exon 11
CD36.3	rs3211956	G/T	3′	26 3′ exon 13
CD36.4	rs3173798	C/T	Intron	4 5′ exon 3
CD36.5	rs3211892	A/G	Intron	8 5′ exon 4
CD36.7	rs1049654	C/A	5′	180 5′ transc start
CD36.10	rs3211938	G/T	Exon	Tyr 325 stop (exon 10)
CD36.11	rs41478146	T/A	Exon	Tyr-Phe
Plasminogen activator inhibitor 1				
PAI1.1	rs6092	A/G	Exon	Ala 15 Thr (exon 1)

SNP alias	dbSNP	Minor/major allele	Type	Change
PAI1.2	rs6090	A/G	Exon	Val 17 Ile (exon 1)
PAI1.12	rs11178	C/T	Exon	3′ UTR
PAI1.15	rs7242	G/T	Exon	3′ UTR
PAI1.16	rs1050813	A/G	Exon	3′ UTR
Thrombomodulin				
THBD.2	rs1042579	T/C	Exon	Ala 473 Val (exon 1)
THBD.3	rs41348347	T/G	Exon	Asp 486 Tyr (exon 1)
THBD.4	rs41328344	A/G	Exon	3′ UTR
THBD.9	rs1042580	G/A	Exon	3′ UTR
THBD.10	rs3176123	C/A	Exon	3′ UTR
Tissue factor				
F3.6	rs41346844	C/T	Intron	124 bp 3′ exon 5
F3.11	rs1361600	A/G	5′	603 bp 5′ start transcript
Tissue plasminogen activator				
PLAT.1	rs2020924	C/T	Exon	Ser 456 Ser (exon 12)
PLAT.7	rs1058720	T/C	Exon	Asp 167 Asp (exon 5)
PLAT.10	rs2020919	C/T	5′	15 bp 5′ transc start
PLAT.13	rs2020922	A/T	Intron	26 bp 5′ exon 11

transc, Transcription; UTR, untranslated region.

Table II

Baseline characteristics in adults with incident acute MI or incident stable exertional angina

Variables	Acute MI (n = 909)	Stable angina (n = 466)	*P*
Mean age (y)	62.0	61.5	.74
Women (%)	23	34	.0001
Ancestry (%)			.84
European	69	69	
African American	4	3	
Asian	7	6	
Hispanic	6	6	
Admixed/other	13	15	
Smoking (%)			.02
Current	10	7	
Former	55	50	
Never	35	42	
Diabetes mellitus (%)	26	23	.30
Hypertension (%)	82	76	.03
Hyperlipidemia (%)	88	87	.48
Medications before event			
Statin	19	48	<.001
β-Blocker	19	48	<.001
Calcium blocker	13	10	.06

Table III

Minor allele frequencies in genes in patients with incident acute MI or incident stable exertional angina

SNP alias	MI minor allele frequency (%)	Angina minor allele frequency (%)	*P*
Glycoprotein Ia/IIa			
ITGA2.2	0.0	0.0	NA
ITGA2.4	1.0	0.5	.22
ITGA2.12	30.6	29.9	.69
ITGA2.16	0.3	0.0	.97
ITGA2.25	11.8	11.2	.63
ITGA2.26	29.0	28.8	.89
ITGA2.37	37.7	39.5	.36
ITGA2.39	0.0	0.0	NA
ITGA2.41	37.7	39.4	.38
Glycoprotein Ib α			
GP1BA.1	14.2	13.3	.54
GP1BA.4	6.3	5.4	.38
GP1BA.500	0.0	0.0	NA
GP1BA.501	0.4	0.1	.23
Glycoprotein IIb			
ITGA2B.1	44.8	43.6	.57
ITGA2B.4	36.8	37.0	.89
ITGA2B.6	36.8	37.0	.91
ITGA2B.9	0.3	0.0	.97
ITGA2B.12	37.0	37.3	.89
Glycoprotein IIIa			
ITGB3.1	29.7	28.4	.50
ITGB3.5	44.9	46.0	.57
ITGB3.10	30.4	28.7	.38
ITGB3.13	14.5	12.0	.083
ITGB3.14	0.3	0.2	.60
ITGB3.17	14.4	13.7	.59
ITGB3.24	60.8	62.5	.40
Glycoprotein IIIb (IV)			
CD36.1	54.8	54.4	.87
CD36.3	10.5	8.0	.04
CD36.4	12.9	11.8	.42
CD36.5	3.3	2.8	.48
CD36.7	51.2	50.8	.82
CD36.10	0.6	0.9	.45
CD36.11	0.3	0.0	.97
Plasminogen activator inhibitor I			
PAI1.1	9.2	9.6	.73

SNP alias	MI minor allele frequency (%)	Angina minor allele frequency (%)	*P*
PAI1.2	1.5	1.7	.66
PAI1.12	42.6	43.7	.60
PAI1.15	42.7	43.9	.57
PAI1.16	17.8	18.7	.56
Thrombomodulin			
THBD.2	16.1	18.7	.079
THBD.3	0.2	0.1	.52
THBD.4	0.0	0.0	NA
THBD.9	36.8	39.0	.29
THBD.10	16.1	19.0	.052
Tissue factor			
F3.6	28.1	30.4	.20
F3.11	53.7	55.7	.33
Tissue plasminogen activator			
PLAT.1	12.1	13.5	.30
PLAT.7	55.6	54.0	.42
PLAT.10	9.1	10.2	.39
PLAT.13	26.5	27.6	.56

P values are based on univariate logistic models linear in the number of minor alleles, using the entire patient sample. *NA*, Not applicable.

Table IV

Minor allele frequencies of CD36.3, ITBG3.13, THBD.2, and THBD.10 by patient ancestry

	Patient ancestry *				
SNP	**European**	**African American**	**Asian**	**Hispanic**	**Admixed/other**
CD36.3	8.2	3.1	30.7	10.1	6.6
ITGB3.13	15.1	7.5	1.7	10.7	15.9
THBD.2	17.5	3.4	28.5	15.1	15.9
THBD.10	17.7	3.4	29.1	15.4	16.1

* $P < .001$ for all.

Table V

Multivariate adjusted odds ratios (95% confidence limits) for presenting with acute MI*

	All patients	European ancestry
CD36.3	1.37 (1.00-1.88)	1.44 (0.96-2.16)
ITGB3.13	1.26 (0.97-1.62)	1.27 (0.94-1.70)
THBD.2	0.87 (0.69-1.10)	0.89 (0.68-1.18)
THBD.10	0.84 (0.67-1.06)	0.86 (0.66-1.14)

*Adjusted for age, sex, smoking, hypertension, hypercholesterolemia, diabetes, and prior use of statins, β-blockers, and calcium blockers, as well as for race/ancestry in the “all patients” analysis.