Association of gene polymorphisms with myocardial infarction in individuals with or without conventional coronary risk factors

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Abstract. The purpose of the present study was to assess the genetic risk for myocardial infarction (MI) in individuals with or without conventional coronary risk factors and thereby to contribute to the personalized prevention of MI in such individuals. The study population comprised 3483 unrelated Japanese individuals (1913 men, 1570 women). The 1192 subjects with MI (926 men, 266 women) and 2291 controls (987 men, 1304 women) either had or did not have conventional coronary risk factors, including hypertension, hypercholesterolemia, and diabetes mellitus. The genotypes for 164 polymorphisms of 137 candidate genes were determined by a method that combines the polymerase chain reaction and sequence-specific oligonucleotide probes with suspension array technology. Multivariable logistic regression analysis and a stepwise forward selection procedure revealed that nine different polymorphisms were significantly ($P<0.005$) associated with MI among individuals with or without hypertension, hypercholesterolemia, or diabetes mellitus: 1018C→T of *GP1BA*, -108/3G→4G of *IPF1*, 677C→T of *MTHFR*, and G→A of *UTS2* in hypertensive individuals; 2445G→A of *FABP2*, -108/3G→4G of *IPF1*, 677C→T of *MTHFR*, -11,377C→G of *ACDC*, A→G of *AKAP10*, 11,496G→A of *F7*, and 46C→T of *F12* in individuals without hypercholesterolemia; 2445G→A of *FABP2* in diabetic individuals; and -108/3G→4G of *IPF1* in nondiabetic individuals. Polymorphisms associated with MI may thus differ among individuals with different conventional coronary risk factors. Stratification of subjects on the basis of such risk factors may thus be important in order to achieve personalized prevention of MI with the use of genetic information.

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Introduction

Myocardial infarction (MI) is an important clinical problem because of its large contribution to mortality. The total number of individuals affected by MI in the United States is 7.2 million, with nearly 170,000 patients dying annually from this condition (1). In Japan, approximately 50,000 people die annually from MI (Ministry of Health, Labor, and Welfare of Japan). The main causal and treatable risk factors for MI include hypertension, hypercholesterolemia, diabetes mellitus, and smoking. In addition to these risk factors, studies have shown the importance of genetic factors and interactions between multiple genes and environmental factors in this condition (2).

Although various association studies (3-8) have attempted to identify genetic variants that contribute to coronary heart disease (CHD) or MI, the genetic components of these conditions have not been determined definitively. In addition, we previously showed that gene polymorphisms that confer susceptibility to MI differ between men and women (5,9). We hypothesized further that the association of polymorphisms with MI might be influenced by the absence or presence of conventional major risk factors for CHD. We have thus examined the relations of polymorphisms to MI in individuals with or without hypertension, hypercholesterolemia, or diabetes mellitus independently in order to provide a basis for the personalized prevention of this condition.

Materials and methods

Study population. The study population comprised 3483 unrelated Japanese individuals (1913 men, 1570 women) who either visited outpatient clinics of or were admitted to one of the six participating hospitals (Gifu Prefectural Gifu, Tajimi, and Gero Hot Spring Hospitals; Hirosaki University

Table I. Characteristics of subjects with or without hypertension.

Characteristic	Hypertension (+)			Hypertension (-)		
	Myocardial infarction	Controls	P	Myocardial infarction	Controls	P
No. of subjects	870	1015		322	1276	
Age (years)	64.4±10.8	65.5±10.7	0.0200	61.9±11.6	60.2±12.1	0.0190
Sex (female/male, %)	24.5/75.5	51.2/48.8	<0.0001	16.5/83.5	61.5/38.5	<0.0001
Body mass index (kg/m^2)	23.7±3.3	23.5±3.4	0.2450	23.5±3.0	23.2±2.8	0.1500
Smoker (%)	22.6	16.3	0.0005	22.4	16.0	0.0083
Hypercholesterolemia (%)	60.0	38.0	<0.0001	48.5	22.8	<0.0001
Diabetes mellitus (%)	51.7	31.2	<0.0001	40.7	11.2	<0.0001

Data for age and body mass index are means ± SD.

Hospital; Reimeikyo Rehabilitation Hospital; and Yokohama General Hospital) between October 2002 and March 2005. The 1192 subjects with MI (926 men, 266 women) all underwent coronary angiography and left ventriculography. The diagnosis of MI was based on typical electrocardiographic changes and increases both in the serum activities of enzymes such as creatinine kinase, aspartate aminotransferase, and lactate dehydrogenase and in the serum concentration of troponin T. The diagnosis was confirmed by the presence of a wall motion abnormality on left ventriculography and identification of the responsible stenosis in any of the major coronary arteries or in the left main trunk by coronary angiography.

The control subjects comprised 2291 individuals (987 men, 1304 women) who visited the outpatient clinics of participating hospitals for an annual health checkup. They had no history of CHD, peripheral arterial occlusive disease, or other atherosclerotic diseases; of ischemic or hemorrhagic stroke or other cerebral diseases; or of other thrombotic, embolic, or hemorrhagic disorders.

Subjects with MI and controls either had or did not have conventional risk factors for CHD, including hypertension (systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg, or both, or taking antihypertensive medication), hypercholesterolemia (serum total cholesterol of ≥5.72 mmol/l or taking lipid-lowering medication), diabetes mellitus (fasting blood glucose of ≥6.93 mmol/l or hemoglobin A1c of ≥6.5%, or both, or taking antidiabetes medication), obesity (body mass index of ≥25 kg/m^2), or cigarette smoking (≥10 cigarettes daily). The study protocol complied with the Declaration of Helsinki and was approved by the Committees on the Ethics of Human Research of Mie University School of Medicine, Hirosaki University School of Medicine, Gifu International Institute of Biotechnology, and participating hospitals, and written informed consent was obtained from each participant.

Selection of polymorphisms. With the use of public databases, we selected 137 candidate genes that have been characterized and were suggested to be associated with MI on the basis of a comprehensive overview of hypertension; atherosclerosis; arterial spasm; arterial aneurysm; platelet function; leukocyte, lymphocyte, and monocyte-macrophage biology; coagulation and fibrinolysis cascades; neurological factors; as well as lipid, glucose, and homocysteine metabolism and other metabolic factors. We further selected 164 polymorphisms of these genes, most located in the promoter region, exons, or splice donor or acceptor sites of introns, that might be expected to result in changes in the function or expression of the encoded protein (9).

Genotyping of polymorphisms. Venous blood (7 ml) was collected into tubes containing 50 mmol/l EDTA (disodium salt), and genomic DNA was isolated with a kit (Genomix; Talent, Trieste, Italy). Genotypes of the 164 polymorphisms were determined (G&G Science, Fukushima, Japan) by a method that combines the polymerase chain reaction and sequence-specific oligonucleotide probes with analysis by suspension array technology (Luminex 100 flow cytometer; Luminex, Austin, TX, USA). Detailed methodology for genotyping was described previously (10).

Statistical analysis. Clinical data were compared between subjects with MI and controls by the unpaired Student's t-test. Qualitative data were compared by the chi-square test. Allele frequencies were estimated by the gene counting method, and the chi-square test was used to identify departures from Hardy-Weinberg equilibrium. In the initial screen, the genotype distribution of each autosomal polymorphism was compared between subjects with MI and controls by the chi-square test (3x2); for polymorphisms on the X chromosome, allele frequencies were compared by the chi-square test (2x2). Polymorphisms related ($P<0.05$) to MI were further examined by multivariable logistic regression analysis with adjustment for covariates (with the exception of that used for stratification of subjects), with MI as a dependent variable and independent variables including age, sex (0, woman; 1, man), body mass index (BMI), smoking status (0, nonsmoker; 1, smoker), metabolic variables (0, no history of hypertension, hypercholesterolemia, or diabetes mellitus; 1, positive history), and genotype of each polymorphism. Each genotype was assessed according to dominant, recessive, and additive (additive 1 and 2) genetic models, and the P value, odds ratio, and 95% confidence interval were calculated. Each genetic model

Table II. Multivariable logistic regression analysis of polymorphisms associated with myocardial infarction in hypertensive individuals.

Gene	Polymorphism	Dominant model		Recessive model		Additive 1 model		Additive 2 model	
		P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)
IPF1	-108/3G→4G	**0.0005**	0.66 (0.52-0.83)	0.1265		**0.0016**	0.67 (0.52-0.86)	**0.0018**	0.64 (0.48-0.85)
MTHFR	677C→T (Ala222Val)	0.1460		**0.0004**	1.59 (1.23-2.05)	0.8025		**0.0010**	1.61 (1.21-2.15)
LPL	C→G (Ser447Stop)	0.0682		0.0144	0.29 (0.10-0.74)	0.1922		0.0120	0.28 (0.10-0.72)
ACDC	-11,377C→G	0.0213	1.26 (1.04-1.54)	0.5943		0.0107	1.31 (1.06-1.61)	0.9851	
MMP2	-1306C→T	0.3216		0.0190	3.61 (1.31-11.7)	0.0985		0.0227	3.49 (1.26-11.3)
GP1BA	1018C→T (Thr145Met)	**0.0044**	1.41 (1.11-1.79)	0.6002		**0.0025**	1.45 (1.14-1.85)	0.7359	
CAPN10	4852G→A (SNP-43)	0.5116		0.6010		0.7971		0.6008	
UTS2	G→A (Ser89Asn)	0.4323		**0.0009**	2.26 (1.40-3.68)	0.8664		**0.0011**	2.24 (1.38-3.67)
PON1	584G→A (Gln192Arg)	0.0792		0.1011		0.0167	1.29 (1.05-1.59)	0.3999	
PLAT	-7351C→T	0.0087	0.77 (0.63-0.94)	0.1437		0.0224	0.78 (0.64-0.97)	0.0506	
PCK1	-232C→G	0.4300		0.0261	1.44 (1.04-1.98)	0.9167		0.0320	1.44 (1.03-2.02)
F7	11,496G→A (Arg353Gln)	0.0212	0.69 (0.50-0.94)	0.6213		0.0244	0.69 (0.50-0.95)	0.5861	

OR, odds ratio; CI, confidence interval. Multivariable logistic regression analysis was performed with adjustment for age, sex, body mass index, and the prevalence of smoking, hypercholesterolemia, and diabetes mellitus. P values of <0.005 are shown in bold.

comprised two groups: the combined group of variant homozygotes and heterozygotes versus wild-type homozygotes for the dominant model; variant homozygotes versus the combined group of wild-type homozygotes and heterozygotes for the recessive model; heterozygotes versus wild-type homozygotes for the additive 1 model; and variant homozygotes versus wild-type homozygotes for the additive 2 model. We also performed a stepwise forward selection procedure to examine the effects of genotypes as well as of other covariates on MI. Given the multiple comparisons of genotypes with MI, we adopted the criterion of P<0.005 for significant association. For other clinical background data, a P value of <0.05 was considered statistically significant. Statistical significance was examined by two-sided tests, and statistical analyses were performed with JMP version 5.1 software (SAS Institute, Cary, NC, USA).

Results

Association of polymorphisms with MI in the absence or presence of hypertension. Characteristics of subjects with MI and controls in the absence or presence of hypertension are shown in Table I. For hypertensive individuals, the incidence among men and the prevalence of smoking, hypercholesterolemia, and diabetes mellitus were greater, whereas age was younger, in subjects with MI than in controls. For normotensive individuals, age, incidence among men, and the prevalence of smoking, hypercholesterolemia, and diabetes mellitus were greater in subjects with MI than in controls.

The chi-square test revealed that 12 and 13 polymorphisms were related to MI in hypertensive and normotensive individuals, respectively (Supplementary Table I). Multivariable logistic regression analysis with adjustment for age, sex, BMI, and the prevalence of smoking, hypercholesterolemia, and diabetes mellitus revealed that the -108/3G→4G polymorphism of *IPF1* (dominant and additive 1 and 2 models), the 677C→T (Ala222Val) polymorphism of *MTHFR* (recessive and additive 2 models), the 1018C→T (Thr145Met) polymorphism of

Table III. Effects of genotypes and other characteristics on the prevalence of myocardial infarction as determined by a stepwise forward selection procedure in hypertensive or normotensive individuals.

Parameter	P	R^2
	Hypertension (+)	
Sex	<0.0001	0.0555
Hypercholesterolemia	<0.0001	0.0450
Diabetes mellitus	<0.0001	0.0200
MTHFR (*TT* versus *CC* + *CT*)	0.0003	0.0049
IPF1 (*4G4G* + *3G4G* versus *3G3G*)	0.0006	0.0045
UTS2 (*AA* versus *GG* + *GA*)	0.0010	0.0042
GP1BA (*TT* + *CT* versus *CC*)	0.0036	0.0033
PLAT (*TT* + *CT* versus *CC*)	0.0119	0.0024
LPL (*GG* versus *CC* + CG)	0.0196	0.0021
MMP2 (*TT* versus *CC* + *CT*)	0.0203	0.0021
F7 (*AA* + *GA* versus *GG*)	0.0247	0.0019
ACDC (*GG* + *CG* versus *CC*)	0.0296	0.0018
	Hypertension (-)	
Sex	<0.0001	0.1385
Diabetes mellitus	<0.0001	0.0641
Hypercholesterolemia	<0.0001	0.0448
Age	0.0026	0.0056
Smoking	0.0157	0.0036
AKAP10 (*GG* versus *AA* + *AG*)	0.0182	0.0035
TNFSF4 (*GG* + *AG* versus *AA*)	0.0202	0.0034
CETP (*AA* versus *CC* + *CA*)	0.0278	0.0030

Table IV. Characteristics of subjects with or without hypercholesterolemia.

Characteristic	Hypercholesterolemia (+)			Hypercholesterolemia (-)		
	Myocardial infarction	Controls	P	Myocardial infarction	Controls	P
No. of subjects	678	677		514	1614	
Age (years)	62.4±10.3	62.8±11.0	0.5310	65.4±10.7	62.4±12.1	<0.0001
Sex (female/male, %)	27.0/73.0	64.0/36.0	<0.0001	16.2/83.8	54.0/46.0	<0.0001
Body mass index (kg/m^2)	24.0±3.2	23.7±3.2	0.1880	23.2±3.1	23.2±3.0	0.7650
Smoker (%)	21.7	13.2	<0.0001	23.7	17.3	0.0016
Hypertension (%)	77.0	57.0	<0.0001	67.7	39.0	<0.0001
Diabetes mellitus (%)	50.2	27.9	<0.0001	46.9	16.8	<0.0001

Data for age and body mass index are means ± SD.

Table V. Multivariable logistic regression analysis of polymorphisms associated with myocardial infarction in individuals without hypercholesterolemia.

Gene	Polymorphism	Dominant model		Recessive model		Additive 1 model		Additive 2 model	
		P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)
MTHFR	677C→T (Ala222Val)	0.1141		**0.0001**	1.74 (1.32-2.30)	0.7650		**0.0004**	1.78 (1.30-2.45)
AGER	G→A (Gly82Ser)	0.4782		0.0065	0.18 (0.04-0.53)	0.1464		0.0084	0.19 (0.04-0.56)
ACDC	-11,377C→G	**0.0018**	1.43 (1.14-1.79)	0.3036		**0.0004**	1.52 (1.21-1.92)	0.7174	
AACT	G→A (Ala15Thr)	0.6688		0.0113	0.73 (0.57-0.93)	0.2090		0.3770	
LPL	C→G (Ser447Stop)	0.0143	0.71 (0.54-0.93)	0.8105		0.0139	0.70 (0.53-0.93)	0.6804	
FABP2	2445G→A (Ala54Thr)	**0.0020**	1.44 (1.14-1.81)	0.1131		0.0064	1.41 (1.10-1.80)	0.0118	1.53 (1.10-2.14)
IPF1	-108/3G→4G	**0.0017**	0.67 (0.52-0.86)	0.3183		**0.0031**	0.67 (0.51-0.87)	0.0118	0.67 (0.49-0.92)
F7	11,496G→A (Arg353Gln)	0.0072	0.60 (0.41-0.86)	0.3079		**0.0044**	0.57 (0.39-0.83)	0.3377	
AKAP10	A→G (Ile646Val)	0.9564		**0.0026**	2.12 (1.29-3.44)	0.3854		**0.0046**	2.04 (1.24-3.34)
APOE	4070C→T (Arg158Cys)	0.0833		0.7404		0.0992		0.7390	
TGFB1	-509C→T	0.0325	0.76 (0.59-0.98)	0.8384		0.0286	0.74 (0.57-0.97)	0.1621	
FLJ23476	C→A (Pro55Gln)	0.0389	0.64 (0.43-0.98)	0.7590		0.0389	0.63 (0.41-0.98)	0.0528	
CETP	-629C→A	0.1022		0.0183	1.34 (1.05-1.71)	0.3647		0.0167	1.47 (1.07-2.02)
F12	46C→T	0.9975		**0.0032**	1.40 (1.12-1.76)	0.3037		0.2915	
TNFSF4	A→G	0.0530		0.0454	2.54 (1.00-6.28)	0.1233		0.0361	2.66 (1.04-6.59)
PPARG	-681C→G	0.0559		0.3085		0.0193	1.32 (1.05-1.67)	0.6365	
IRS1	3494G→A (Gly972Arg)	0.3787		0.6658		0.5440		0.6654	

OR, odds ratio; CI, confidence interval. Multivariable logistic regression analysis was performed with adjustment for age, sex, body mass index, and the prevalence of smoking, hypertension, and diabetes mellitus. P values of <0.005 are shown in bold.

GP1BA (dominant and additive 1 models), and the G→A (Ser89Asn) polymorphism of *UTS2* (recessive and additive 2 models) were significantly associated with MI in hypertensive individuals (Table II), whereas no polymorphism was significantly associated with MI in normotensive individuals (Supplementary Table II). We also performed a stepwise forward selection procedure to examine the effects of genotypes for the polymorphisms identified by the chi-square test as well as of age, sex, BMI, smoking, hypercholesterolemia, and diabetes mellitus on MI (Table III). For hypertensive individuals, sex, hypercholesterolemia, diabetes mellitus, *MTHFR* genotype (recessive model), *IPF1* genotype (dominant model), *UTS2* genotype (recessive model), and *GP1BA* genotype (dominant model) were significant and independent determinants of the prevalence of MI. For normotensive individuals, sex, diabetes mellitus, hypercholesterolemia, and age significantly and independently influenced MI.

Association of polymorphisms with MI in the absence or presence of hypercholesterolemia. Characteristics of subjects with MI and controls in the absence or presence of hypercholesterolemia are shown in Table IV. For individuals with hypercholesterolemia, incidence among men and the prevalence of smoking, hypertension, and diabetes mellitus were greater

Table VI. Effects of genotypes and other characteristics on the prevalence of myocardial infarction as determined by a stepwise forward selection procedure in individuals with or without hypercholesterolemia.

Parameter	P	R^2
	Hypercholesterolemia (+)	
Sex	<0.0001	0.1016
Diabetes mellitus	<0.0001	0.0288
Hypertension	<0.0001	0.0181
UCP3 (*TT* + *CT* versus *CC*)	0.0069	0.0039
ENG (*GG* versus *CC* + *CG*)	0.0293	0.0025
EDNRA (*GG* + *AG* versus *AA*)	0.0400	0.0022
	Hypercholesterolemia (-)	
Sex	<0.0001	0.1045
Diabetes mellitus	<0.0001	0.0541
Hypertension	<0.0001	0.0218
MTHFR (*TT* versus *CC* + *CT*)	0.0002	0.0061
FABP2 (*AA* + *GA* versus *GG*)	0.0013	0.0044
Age	0.0018	0.0041
IPF1 (*4G4G* + *3G4G* versus *3G3G*)	0.0020	0.0041
AGER (*AA* versus *GG* + *GA*)	0.0020	0.0041
AKAP10 (*GG* versus *AA* + *AG*)	0.0024	0.0039
F7 (*AA* + *GA* versus *GG*)	0.0025	0.0039
ACDC (*GG* + *CG* versus *CC*)	0.0037	0.0036
F12 (*TT* versus *CC* + CT)	0.0039	0.0035
AACT (*AA* versus *GG* + *GA*)	0.0089	0.0029
LPL (*GG* + *CG* versus *CC*)	0.0348	0.0019
TNFSF4 (*GG* versus *AA* + *AG*)	0.0451	0.0017

in subjects with MI than in controls. For individuals without hypercholesterolemia, age, incidence among men, and the prevalence of smoking, hypertension, and diabetes mellitus were greater in subjects with MI than in controls. The chi-square test revealed that 8 and 17 polymorphisms were related to the prevalence of MI in individuals with or without hypercholesterolemia, respectively (Supplementary Table III). Multivariable logistic regression analysis with adjustment for age, sex, BMI, and the prevalence of smoking, hypertension, and diabetes mellitus revealed that no polymorphism was significantly associated with MI in individuals with hypercholesterolemia (Supplementary Table IV), whereas the 677C→T (Ala222Val) polymorphism of *MTHFR* (recessive and additive 2 models), the -11,377C→G polymorphism of *ACDC* (dominant and additive 1 models), the 2445G→A (Ala54Thr) polymorphism of *FABP2* (dominant model), the -108/3G→4G polymorphism of *IPF1* (dominant and additive 1 models), the 11,496G→A (Arg353Gln) polymorphism of *F7* (additive 1 model), the A→G (Ile646Val) polymorphism of *AKAP10* (recessive and additive 2 models), and the 46C→T polymorphism of *F12* (recessive model) were significantly associated with MI in individuals without hypercholesterolemia (Table V). We performed a stepwise forward selection procedure to examine the effects of genotypes for the polymorphisms identified by the chi-square test as well as of age, sex, BMI, smoking, hypertension, and diabetes mellitus on MI. Whereas sex, diabetes mellitus, and hypertension significantly and independently affected MI in individuals with hypercholesterolemia, sex, diabetes mellitus, hypertension, *MTHFR* genotype (recessive model), *FABP2* genotype (dominant model), age, *IPF1* genotype (dominant model), *AGER* genotype (recessive model), *AKAP10* genotype (recessive model), *F7* genotype (dominant model), *ACDC* genotype (dominant model), and *F12* genotype (recessive model) were significant and independent determinants of the prevalence of MI in individuals without hypercholesterolemia (Table VI).

Association of polymorphisms with MI in the absence or presence of diabetes mellitus. Characteristics of subjects with MI and controls in the absence or presence of diabetes mellitus are shown in Table VII. For diabetic individuals, incidence among men, BMI, and the prevalence of smoking, hypertension, and hypercholesterolemia were greater, and age was younger, in subjects with MI than in controls. For nondiabetic individuals, age, incidence among men, and the prevalence of smoking, hypertension, and hypercholesterolemia were greater in subjects with MI than in controls. The chi-square test revealed that 10 and 11 polymorphisms were related to the

Table VII. Characteristics of subjects with or without diabetes mellitus.

Characteristic	Diabetes mellitus (+)			Diabetes mellitus (-)		
	Myocardial infarction	Controls	P	Myocardial infarction	Controls	P
No. of subjects	581	460		611	1831	
Age (years)	63.9±9.9	65.4±10.8	0.0200	63.5±11.2	61.8±11.9	0.0020
Sex (female/male, %)	21.9/78.1	48.9/51.1	<0.0001	22.7/77.3	59.0/41.0	<0.0001
Body mass index (kg/m^2)	23.9±3.3	23.5±3.6	0.0280	23.3±2.9	23.4±3.1	0.7120
Smoker (%)	25.0	19.1	0.0244	20.3	15.3	0.0051
Hypertension (%)	77.5	68.9	0.0019	68.7	38.1	<0.0001
Hypercholesterolemia (%)	58.5	41.1	<0.0001	55.3	26.6	<0.0001

Data for age and body mass index are means ± SD.

Table VIII. Multivariable logistic regression analysis of polymorphisms associated with myocardial infarction in diabetic individuals.

Gene	Polymorphism	Dominant model		Recessive model		Additive 1 model		Additive 2 model	
		P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)
APOE	4070C→T (Arg158Cys)	0.0225	0.56 (0.34-0.92)	0.7869		0.0132	0.53 (0.32-0.87)	0.7881	
AKAP10	A→G (Ile646Val)	0.5092		0.1022		0.8273		0.0993	
RECQL2	T→C (Cys1367Arg)	0.1191		0.1434		0.0634		0.1562	
APOE	3932T→C (Cys112Arg)	0.0174	1.53 (1.08-2.18)	0.3247		0.0091	1.61 (1.13-2.31)	0.3734	
FABP2	2445G→A (Ala54Thr)	**0.0041**	1.47 (1.13-1.92)	0.1675		0.0109	1.44 (1.09-1.92)	0.0318	1.58 (1.04-2.40)
MTHFR	677C→T (Ala222Val)	0.7322		0.0053	1.64 (1.16-2.32)	0.5199		0.0280	1.55 (1.05-2.29)
PAI1	A→G (Tyr243Cys)	0.4896				0.4896			
PON1	A→G (Arg160Gly)	0.1186		0.7860		0.0928		0.7875	
IPF1	-108/3G→4G	0.0220	0.70 (0.52-0.95)	0.0740		0.0721		0.0128	0.62 (0.43-0.90)
AGER	G→A (Gly82Ser)	0.4354		0.0961		0.2451		0.1131	

OR, odds ratio; CI, confidence interval. Multivariable logistic regression analysis was performed with adjustment for age, sex, body mass index, and the prevalence of smoking, hypertension, and hypercholesterolemia. P values of <0.005 are shown in bold.

Table IX. Multivariable logistic regression analysis of polymorphisms associated with myocardial infarction in nondiabetic individuals.

Gene	Polymorphism	Dominant model		Recessive model		Additive 1 model		Additive 2 model	
		P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)
CETP	-629C→A	0.7201		0.1782		0.3779		0.6257	
LPL	C→G (Ser447Stop)	0.1133		0.2413		0.1699		0.2145	
COMT	G→A (Val158Met)	0.7775		0.8069		0.8262		0.7640	
MTHFR	677C→T (Ala222Val)	0.0250	1.29 (1.03-1.62)	0.0416	1.32 (1.01-1.72)	0.0929		0.0099	1.49 (1.10-2.02)
TNF	-863C→A	0.0508		0.0858		0.1187		0.0669	
GP1BA	1018C→T	0.0102	1.37 (1.08-1.74)	0.6771		0.0064	1.41 (1.10-1.80)	0.8077	
PON1	584G→A (Gln192Arg)	0.2056		0.0797		0.0590		0.2689	
FABP2	2445G→A (Ala54Thr)	0.0279	1.27 (1.03-1.58)	0.4923		0.0362		0.1491	
IPF1	-108/3G→4G	**0.0044**	0.70 (0.55-0.90)	0.6682		**0.0015**	0.66 (0.51-0.85)	0.1073	
PTGS2	G→C	0.2099		0.1993		0.1149		0.2068	
F7	11,496G→A (Arg353Gln)	0.0072	0.63 (0.45-0.88)	0.3122		0.0108	0.64 (0.45-0.90)	0.2845	

OR, odds ratio; CI, confidence interval. Multivariable logistic regression analysis was performed with adjustment for age, sex, body mass index, and the prevalence of smoking, hypertension, and hypercholesterolemia. P values of <0.005 are shown in bold.

prevalence of MI in diabetic and nondiabetic individuals, respectively (Supplementary Table V). Multivariable logistic regression analysis with adjustment for age, sex, BMI, and the prevalence of smoking, hypertension, and hypercholesterolemia revealed that the 2445G→A (Ala54Thr) polymorphism of *FABP2* (dominant model) was significantly associated with MI in diabetic individuals (Table VIII), and that the -108/3G→4G polymorphism of *IPF1* (dominant and additive 1 models) was significantly associated with MI in nondiabetic individuals (Table IX). A stepwise forward selection procedure was performed to examine the effects of genotypes for the polymorphisms identified by the chi-square test as well as of age, sex, BMI, smoking, hypertension, and hypercholesterolemia on MI (Table X). For diabetic individuals, sex, hypercholesterolemia, *FABP2* genotype (dominant model), and *MTHFR* genotype (recessive model) were significant and independent determinants of the prevalence of MI. For nondiabetic individuals, sex, hypercholesterolemia, hypertension, and *IPF1* genotype (dominant model) significantly and independently affected the prevalence of MI.

Polymorphisms significantly associated with MI in both multivariable logistic regression analysis and the stepwise forward selection procedure for individuals with or without hypertension, hypercholesterolemia, or diabetes mellitus are summarized in Table XI.

Discussion

We have examined the association of 164 polymorphisms in 137 candidate genes with MI in individuals with or without

Table X. Effects of genotypes and other characteristics on the prevalence of myocardial infarction as determined by a stepwise forward selection procedure in diabetic or nondiabetic individuals.

Parameter	P	R^2
	Diabetes mellitus (+)	
Sex	<0.0001	0.0586
Hypercholesterolemia	<0.0001	0.0323
FABP2 (*AA* + *GA* versus *GG*)	0.0033	0.0061
MTHFR (*TT* versus *CT* + *CC*)	0.0034	0.0060
APOE (*CC* + *TC* versus *TT*)	0.0154	0.0041
IPF1 (*4G4G* + *3G4G* versus *3G3G*)	0.0182	0.0039
APOE (*TT* + *CT* versus *CC*)	0.0476	0.0027
Hypertension	0.0483	0.0027
	Diabetes mellitus (-)	
Sex	<0.0001	0.0912
Hypercholesterolemia	<0.0001	0.0670
Hypertension	<0.0001	0.0345
IPF1 (*4G4G* + *3G4G* versus *3G3G*)	0.0043	0.0030
F7 (*GG* versus *AG* + *AA*)	0.0055	0.0028
Age	0.0085	0.0025
GP1BA (*TT* + *CT* versus *CC*)	0.0169	0.0021
MTHFR (*TT* + *CT* versus *CC*)	0.0201	0.0020
FABP2 (*AA* + *GA* versus *GG*)	0.0392	0.0015

hypertension, hypercholesterolemia, or diabetes mellitus separately. Our data suggest that polymorphisms associated with MI may differ among individuals with different conventional risk factors for CHD. The major cause of MI is coronary atherosclerosis, which contributes to hemodynamically significant narrowing of the artery lumen and impairment of the control of vasomotor tone, with affected individuals having a propensity for plaque disruption and thrombus formation. We thus selected 137 candidate genes on the basis of a comprehensive overview of vascular biology; platelet, lymphocyte, and leukocyte function; coagulation and fibrinolysis cascades; as well as lipid, glucose, and homocysteine metabolism and other metabolic factors. Indeed, the genes found to be associated with MI may have roles in diverse aspects of the etiology of this condition, including intracellular signaling (*AKAP10*); vascular constriction (*UTS2*); platelet function (*GP1BA*); the coagulation cascade (*F7* and *F12*); lipid (*FABP2*), glucose (*ACDC*), and homocysteine (*MTHFR*) metabolism; and insulin production (*IPF1*).

Among the nine polymorphisms associated with MI in the present study, five (677C→T of *MTHFR*, -108/3G→4G of *IPF1*, 1018C→T of *GP1BA*, 11,496G→A of *F7*, 46C→T of *F12*) have previously been shown to be associated with MI or CHD (9,11-14). The -11,377C→G polymorphism of *ACDC* has not previously been shown to be associated with MI or CHD, but another polymorphism of this gene was associated with CHD (15). The remaining three polymorphisms (G→A

Table XI. Summary of polymorphisms significantly (P<0.005) associated with myocardial infarction as determined by multivariable logistic regression analysis and a stepwise forward selection procedure.

Risk factor	Gene	Polymorphism	Risk allele	Function
Hypertension (+)	*MTHFR*	677C→T (Ala222Val)	T	Enzyme that regulates methylation of homocysteine
	IPF1	-108/3G→4G	3G	Protein that regulates the insulin gene in ß cells and development of the pancreas
	UTS2	G→A (Ser89Asn)	A	Peptide that has potent vasoconstrictive and cardiac inotropic and hypertropic effects
	GP1BA	1018C→T (Thr145Met)	T	Platelet surface receptor for von Willebrand factor
Hypertension (-)				
Hypercholesterolemia (+)				
Hypercholesterolemia (-)	*MTHFR*	677C→T (Ala222Val)	T	See above
	FABP2	2445G→A (Ala54Thr)	A	Intracellular protein that contributes to absorption and transport of long-chain fatty acids
	IPF1	-108/3G→4G	3G	See above
	AKAP10	A→G (Ile646Val)	G	A-kinase anchor protein that directs subcellular localization of protein kinase A
	F7	11,496G→A (Arg353Gln)	G	Factor that, with tissue factor, accelerates conversion of prothrombin to thrombin
	ACDC	-11,377C→G	G	Adipokine that regulates glucose and lipid metabolism
	F12	46C→T	T	Serine protease that activates factor XI and prekallikrein
Diabetes mellitus (+)	*FABP2*	2445G→A (Ala54Thr)	A	See above
Diabetes mellitus (-)	*IPF1*	-108/3G→4G	3G	See above

of *UTS2*, 2445G→A of *FABP2*, A→G of *AKAP10*) have not previously been associated with MI or CHD.

Interactions between gene polymorphisms and conventional coronary risk factors may be important in the development of MI. Our observations suggest that polymorphisms associated with MI may differ among individuals with or without hypertension, hypercholesterolemia, or diabetes mellitus, although the underlying mechanisms responsible for these differences remain to be elucidated. Given that the effects of single polymorphisms on the development of MI are likely to be small, the association between a given polymorphism and the prevalence of MI might be influenced by the absence or presence of conventional coronary risk factors. Furthermore, conventional risk factors, such as hypertension, hypercholesterolemia, and diabetes mellitus, may themselves have genetic components and these components may interact with gene polymorphisms associated with MI.

The 677C→T (Ala222Val) polymorphism of the 5,10-methylenetetrahydrofolate reductase gene (MTHFR). Homocysteine is a sulfur-containing amino acid that plays a pivotal role in methionine metabolism. 5,10-Methylenetetrahydrofolate reductase (MTHFR) catalyzes the reduction of 5,10-methylenetetrahydrofolate to 5-methylenetetrahydrofolate, a reaction that provides a substrate for the methylation of homocysteine to methionine catalyzed by methionine synthase. Individuals with the T variant of the 677C→T (Ala222Val) polymorphism of *MTHFR* manifest reduced enzyme activity and higher homocysteine levels compared with those without it (16-18). Association of this polymorphism with CHD or MI has been described (11,19,20). Other studies, however, did not support such an association (18,21,22). These apparently contradictory results are attributable, at least in part, to differences in intake of folate and other B vitamins (23). A meta-analysis of the association of the 677C→T polymorphism of *MTHFR* with the risk of CHD in 11,162 cases and 12,758 controls from 40 studies revealed that individuals with the *TT* genotype had an odds ratio of 1.16 for CHD compared with those with the *CC* genotype (24). Another meta-analysis of the association of the 677C→T polymorphism of *MTHFR* with CHD in 26,000 cases and 31,183 controls from 80 studies yielded an overall odds ratio of 1.14 for the *TT* genotype versus the *CC* genotype; odds ratios for Europe, Australia, and North America were approximately 1.0, whereas those for the Middle East and Asia were 2.61 and 1.23, respectively (25). These results indicate that the 677C→T polymorphism of *MTHFR* is associated with CHD in the Middle East and Asia, but not in Europe, North America, or Australia, with this geographic variability possibly reflecting higher folate intake in the latter regions (25). These previous observations are consistent with our present results showing that the 677C→T (Ala222Val) polymorphism of *MTHFR* was associated with the prevalence of MI in Japanese individuals with hypertension and in those without hypercholesterolemia, with the *TT* genotype being a risk factor for this condition.

The -108/3G→4G polymorphism of the insulin promoter factor 1 gene (IPF1). Insulin promoter factor 1 (IPF1) is a homeodomain-containing protein that is a key regulator of the insulin gene in pancreatic ß cells (26,27) and plays an important role in development of the pancreas (28,29). IPF1-deficient mice thus selectively lack the pancreas at birth (28), and a patient with pancreatic agenesis and insulin-deficient diabetes was found to have a single nucleotide deletion in codon 63 of IPF1 that caused a frameshift in the transactivation domain (29). A 3G→4G polymorphism of *IPF1* was identified 108 bp upstream of the translation start site in the Japanese population but was found not to be related to the prevalence of type 2 diabetes mellitus (30). Our present results indicate that the -108/3G→4G polymorphism of IPF1 was associated with MI in hypertensive individuals, in individuals without hypercholesterolemia, and in those without diabetes mellitus, with the 4G allele protecting against this condition. Although the underlying molecular mechanism remains to be determined, this association might be attributable to an alteration in insulin metabolism.

The G→A (Ser89Asn) polymorphism of the urotensin II gene (UTS2). The cyclic undecapeptide urotensin II and its high-affinity G protein-coupled receptor, GPR14, are both expressed within the cardiovascular system, including vascular smooth muscle as well as the endothelium and myocardium, and they are thought to contribute to the physiological regulation of cardiovascular homeostasis (31). *In vitro* studies have suggested that urotensin II participates in the control of vascular remodeling by stimulating smooth muscle proliferation and fibroblast-mediated collagen deposition (32,33). These observations thus further suggest that urotensin II may play a role in the etiology of atherosclerosis. Whereas little expression of urotensin II was apparent in any cell type in normal human coronary arteries, endothelial expression of this peptide was increased in coronary atherosclerotic lesions (34). The peptide was especially abundant in endothelial cells of lesions with subendothelial inflammation or fibro-fatty lesions, and it was also detected in myointimal cells and foam cells of such lesions, consistent with a role for urotensin II in the pathogenesis of coronary atherosclerosis (34). We have now shown that the G→A (Ser89Asn) polymorphism of *UTS2* was associated with the prevalence of MI in hypertensive individuals, with the *A* (Asn) allele representing a risk factor for this condition. Whereas the *A* (Asn) allele has been associated with an increased risk of type 2 diabetes mellitus (35), the relation of this polymorphism to MI has not previously been described.

The 1018C→T (Thr145Met) polymorphism of the glycoprotein Ib, platelet, α polypeptide gene (GP1BA). The glycoprotein Ib-IX-V complex is the major platelet surface receptor for von Willebrand factor (36). This complex plays a key role in the adhesion of platelets to injured vascular subendothelium and mediates shear stress-induced platelet activation, suggesting that it might also contribute to the development of thrombosis (37). The 1018C→T (Thr145Met) polymorphism of *GP1BA* was previously shown to be associated with CHD (12) or with acute MI or sudden cardiac death (38), with the *T* allele being a risk factor for these conditions. These previous observations are consistent with our present results showing that the 1018C→T (Thr145Met) polymorphism was associated with MI in hypertensive individuals, with the *T* allele representing a risk factor for this condition.

The 2445G→A (Ala54Thr) polymorphism of the fatty acid-binding protein 2 gene (FABP2). Fatty acid-binding protein 2 (FABP2) is an intracellular protein that is expressed only in the columnar absorptive epithelial cells of the small intestine. It contains a single ligand binding site that has a high affinity for saturated or unsaturated fatty acids, and it contributes to the absorption and intracellular transport of long-chain fatty acids (39). The product of the *A* (Thr) allele of the 2445G→A (Ala54Thr) polymorphism of *FABP2* exhibits a greater affinity for long-chain fatty acids *in vitro* than does that of the *G* (Ala) allele (40). In addition, individuals with the *A* allele were shown to be more insulin resistant and more obese than were those with the *G* allele (40,41). The *A* allele was also found to be associated with higher plasma levels of low density lipoprotein-cholesterol (42) or with metabolic syndrome and dyslipidemia (43). The 2445G→A polymorphism was previously associated with a parental history of stroke, but not with that of MI, in a population in Sweden (44). It was not associated with CHD in a Finnish study (45) or in the Framingham Offspring Study (42). However, the population size of these studies was small. Our results indicate that the 2445G→A (Ala54Thr) polymorphism of *FABP2* was associated with MI in individuals without hypercholesterolemia and in diabetic individuals, with the *A* (Thr) allele representing a risk factor for this condition. The effects of this polymorphism on both insulin resistance and lipid metabolism may account for its association with MI.

The A→G (Ile646Val) polymorphism of the A-kinase anchor protein 10 gene (AKAP10). The A→G (Ile646Val) polymorphism of *AKAP10* has been shown to be related to age, with the frequency of the *G* (Val) allele being lower in older (>60 years) than younger (18 to 39 years) individuals (46). Analysis of an independent cohort indicated that the *G* variant was associated with a decrease in the P-R interval of the electrocardiogram. The Ile646Val polymorphism is located in the A-kinase binding domain of AKAP10, and an *in vitro* binding assay revealed that the extent of binding to the RIα isoform of protein kinase A was approximately three-fold greater for the Val variant than for the Ile variant (46). This change in affinity affected the subcellular distribution of an ectopically expressed RIα isoform. These observations suggest that a change in the subcellular localization of the RIα isoform of protein kinase A caused by variation in *AKAP10* may be related to cardiac dysfunction (46). Our present results show that the A→G (Ile646Val) polymorphism of *AKAP10* was associated with the prevalence of MI in individuals without hypercholesterolemia, with the *G* (Val) allele being a risk factor for this condition. The underlying molecular mechanism of this association remains to be elucidated.

The 11,496G→A (Arg353Gln) polymorphism of the coagulation factor VII gene (F7). Factor VII initiates coagulation in conjunction with tissue factor (TF). Whereas, under normal conditions, TF is not exposed to the bloodstream, vessel injury results in the exposure of this protein to circulating factor VII. The binding of TF to factor VII triggers the conversion of the latter to the active factor VIIa by various proteases including thrombin (factor IIa), factor Xa, and the factor VIIa-TF complex itself (http://www.answers.com/topic/factor-vii). The 11,496G→A (Arg353Gln) polymorphism of *F7* was shown to be related to the plasma level of factor VII (13,47), with individuals with the *AA* genotype having lower levels of both factor VII antigen and factor VII clotting activity compared with those with the *GG* genotype. This polymorphism was also previously associated with MI, with subjects with the *AA* genotype having a reduced risk for this condition (13). The *A* allele of this polymorphism was also found to be protective against acute MI in patients with CHD (48). Our results now show that the 11,496G→A (Arg353Gln) polymorphism of *F7* was associated with the prevalence of MI in individuals without hypercholesterolemia, with the *A* allele protecting against this condition, consistent with the previous observations (13,48). However, other studies have failed to detect a relation between this polymorphism and MI (49,50). A meta-analysis of 1258 cases and 1316 controls showed that the combined group of *GA* and *AA* genotypes had a reduced risk for CHD (odds ratio, 0.78), with the *AA* genotype being even more protective (odds ratio, 0.53) against this condition (51). Another recent meta-analysis, however, showed no significant overall association of this polymorphism with CHD (52). The relation of this *F7* polymorphism to CHD or MI thus requires further evaluation with large populations of various ethnic groups.

The -11,377C→G polymorphism of the adipocyte, C1Q, and collagen domain containing gene (ACDC). Adiponectin is an important modulator of insulin sensitivity and resistance. Plasma levels of adiponectin were found to be lower in individuals with type 2 diabetes mellitus or CHD than in control subjects (53,54). Experimental studies have suggested that adiponectin might play a role in atherosclerosis. Neointimal thickening and proliferation of vascular smooth cells in injured arteries were thus found to be more pronounced in adiponectin-deficient mice than in control animals (55). Genetic epidemiological studies have also implicated the adiponectin gene (*ACDC*) in susceptibility to insulin resistance and type 2 diabetes mellitus (56,57). Furthermore, the Ile164Thr polymorphism of *ACDC* was shown to be associated with metabolic syndrome and with CHD in a Japanese population (15). These observations implicate ACDC as a candidate susceptibility gene for CHD and MI. We have now shown that the -11,377C→G polymorphism of *ACDC*, which was previously found to be associated with type 2 diabetes mellitus (57), was associated with the prevalence of MI in individuals without hypercholesterolemia, with the *G* allele representing a risk factor for this condition. The effects of this polymorphism on both insulin resistance and predisposition to diabetes mellitus may account for its association with MI.

The 46C→T polymorphism of the coagulation factor XII gene (F12). The serine protease factor XII is the first coagulation factor in the intrinsic pathway of the coagulation cascade. It is activated during the contact phase of coagulation in a system consisting of factor XII, prekallikrein, factor XI, and high-molecular-weight kininogen. This system is initiated by the conversion of factor XII to its activated form, factor XIIa, which then activates factor XI and prekallikrein, thereby generating the potential for dissemination of reactions along several pathways concerned with coagulation and fibrinolysis

as well as with tissue defense and repair (58). The 46C→T polymorphism of *F12* was shown to be related to the plasma concentration and coagulation activity of factor XII, with the *T* allele being associated with a reduced concentration and activity (14,58,59). The *TT* genotype of this polymorphism was also found to be protective against acute coronary syndrome in patients with CHD (60). In contrast, other studies showed that the *TT* genotype of this *F12* polymorphism was associated with an increased risk of CHD (58) or MI (14). We have now shown that the 46C→T polymorphism of *F12* was associated with the prevalence of MI in individuals without hypercholesterolemia, with the *T* allele representing a risk factor for this condition, consistent with the latter two studies (14,58). Reduced fibrinolysis as a consequence of a lower plasma concentration of factor XII (58) and an increased pro-inflammatory state related to a higher level of C-reactive protein (14) in individuals with the *T* allele might underlie a higher risk of CHD or MI conferred by this polymorphism.

There are several limitations to the present study. Given the multiple comparisons of genotypes with MI, we adopted a strict criterion of $P<0.005$ for statistical significance of association. However, we are not able to exclude completely the possible occurrence of false positives. It is also possible that one or more of the polymorphisms associated with MI in our study are in linkage disequilibrium with polymorphisms of other nearby genes that are actually responsible for the development of this condition. Finally, the functional relevance of the identified polymorphisms to gene transcription or to protein structure or function was not determined in the present study.

In conclusion, the present observations suggest that nine different polymorphisms are associated with MI in individuals with or without hypertension, hypercholesterolemia, or diabetes mellitus. Given that the absence or presence of conventional coronary risk factors may affect the association of gene polymorphisms with MI, stratification of subjects on the basis of such risk factors may be important in order to achieve personalized prevention of MI with the use of genetic information. Given that multiple variants, each having a small effect, will ultimately be found to be responsible for a large fraction of the genetic component of MI, further identification of MI susceptibility genes will allow more accurate assessment of the genetic component of this condition.

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Supplementary Table I. Polymorphisms related to myocardial infarction in individuals with or without hypertension as determined by the chi-square test.

Hypertension (+)			Hypertension (-)		
Gene	Polymorphism	P	Gene	Polymorphism	P
IPF1	-108/3G→4G	0.0006	*GPX1*	C→T (Pro198Leu)	0.0034
MTHFR	677C→T (Ala222Val)	0.0048	*PTGS2*	G→C	0.0048
LPL	C→G (Ser447Stop)	0.0065	*TNF*	-850C→T	0.0059
ACDC	-11,377C→G	0.0143	*AKAP10*	A→G (Ile646Val)	0.0070
MMP2	-1306C→T	0.0157	*APOE*	4070C→T (Arg158Cys)	0.0220
GP1BA	1018C→T (Thr145Met)	0.0184	*CETP*	-629C→A	0.0252
CAPN10	4852G→A (SNP-43)	0.0242	*APOA5*	1131T→C	0.0288
UTS2	G→A (Ser89Asn)	0.0269	*AGER*	G→A (Gly82Ser)	0.0308
PON1	584G→A (Gln192Arg)	0.0339	*ESR1*	-1989T→G	0.0349
PLAT	-7351C→T	0.0437	*TNF*	-238G→A	0.0372
PCK1	-232C→G	0.0477	*LPL*	C→G (Ser447Stop)	0.0406
F7	11,496G→A (Arg353Gln)	0.0488	*TNFSF4*	A→G	0.0440
			TNF	-863C→A	0.0443

Supplementary Table II. Multivariable logistic regression analysis of polymorphisms associated with myocardial infarction in normotensive individuals.

Gene	Polymorphism	Dominant model		Recessive model		Additive 1 model		Additive 2 model	
		P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)
GPX1	C→T (Pro198Leu)	0.0364	0.60 (0.37-0.96)	0.7152		0.0692		0.7135	
PTGS2	G→C	0.2047		0.7279		0.4130		0.7273	
TNF	-850C→T	0.3513		0.0434	2.01 (1.01-3.94)	0.1003		0.0737	
AKAP10	A→G (Ile646Val)	0.1983		0.0142	2.12 (1.15-3.83)	0.0302	0.69 (0.50-0.96)	0.0389	1.90 (1.02-3.46)
APOE	4070C→T (Arg158Cys)	0.1018		0.8742		0.1045		0.8727	
CETP	-629C→A	0.5340		0.0312	1.40 (1.03-1.90)	0.1356		0.4790	
APOA5	1131T→C	0.3465		0.0644		0.6921		0.0624	
AGER	G→A (Gly82Ser)	0.6520		0.0570		0.3466		0.0646	
ESR1	-1989T→G	0.7613		0.1011		0.8401		0.1306	
TNF	-238G→A	0.6481		0.7787		0.4568		0.7790	
LPL	C→G (Ser447Stop)	0.1040		0.4127		0.0629		0.4975	
TNFSF4	A→G	0.0196	1.49 (1.06-2.07)	0.1743		0.0360	1.44 (1.02-2.03)	0.1349	
TNF	-863C→A	0.0682		0.2459		0.1156		0.1987	

OR, odds ratio; CI, confidence interval. Multivariable logistic regression analysis was performed with adjustment for age, sex, body mass index, and the prevalence of smoking, hypercholesterolemia, and diabetes mellitus.

Supplementary Table III. Polymorphisms related to myocardial infarction in individuals with or without hypercholesterolemia as determined by the chi-square test.

Hypercholesterolemia (+)			Hypercholesterolemia (-)		
Gene	Polymorphism	P	Gene	Polymorphism	P
ENG	C→G (Asp366His)	0.0082	*MTHFR*	677C→T (Ala222Val)	0.0002
EDNRA	-231A→G	0.0156	*AGER*	G→A (Gly82Ser)	0.0006
ACE	-240A→T	0.0168	*ACDC*	-11,377C→G	0.0033
UCP3	-55C→T	0.0193	*AACT*	G→A (Ala15Thr)	0.0037
APOC3	-482C→T	0.0200	*LPL*	C→G (Ser447Stop)	0.0042
F7	11,496G→A (Arg353Gln)	0.0303	*FABP2*	2445G→A (Ala54Thr)	0.0052
IPF1	-108/3G→4G	0.0425	*IPF1*	-108/3G→4G	0.0053
TGFBR2	1167C→T (Asn389Asn)	0.0462	*F7*	11,496G→A (Arg353Gln)	0.0078
			AKAP10	A→G (Ile646Val)	0.0194
			APOE	4070C→T (Arg158Cys)	0.0213
			TGFB1	-509C→T	0.0269
			FLJ23476	C→A (Pro55Gln)	0.0273
			CETP	-629C→A	0.0308
			F12	46C→T	0.0331
			TNFSF4	A→G	0.0340
			PPARG	-681C→G	0.0435
			IRS1	3494G→A (Gly972Arg)	0.0480

Supplementary Table IV. Multivariable logistic regression analysis of polymorphisms associated with myocardial infarction in individuals with hypercholesterolemia.

Gene	Polymorphism	Dominant model		Recessive model		Additive 1 model		Additive 2 model	
		P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)
ENG	C→G (Asp366His)	0.1533		0.0288	0.68 (0.48-0.96)	0.0340	3.46 (1.13-11.5)	0.1895	
EDNRA	-231A→G	0.0285	0.72 (0.53-0.96)	0.0940		0.0835		0.0166	0.66 (0.47-0.93)
ACE	-240A→T	0.1941		0.0547		0.4791		0.0408	0.68 (0.47-0.98)
UCP3	-55C→T	0.0065	1.39 (1.10-1.77)	0.3447		0.0107	1.39 (1.08-1.79)	0.1060	
APOC3	-482C→T	0.1082		0.2062		0.2038		0.0788	
F7	11,496G→A (Arg353Gln)	0.3270		0.0704		0.5853		0.0689	
IPF1	-108/3G→4G	0.0554		0.9525		0.0444	0.73 (0.54-0.99)	0.1942	
TGFBR2	1167C→T (Asn389Asn)	0.0617		0.0596		0.1701		0.0336	0.58 (0.35-0.95)

OR, odds ratio; CI, confidence interval. Multivariable logistic regression analysis was performed with adjustment for age, sex, body mass index, and the prevalence of smoking, hypertension, and diabetes mellitus.

Supplementary Table V. Polymorphisms related to myocardial infarction in individuals with or without diabetes mellitus as determined by the chi-square test.

Diabetes mellitus (+)			Diabetes mellitus (-)		
Gene	Polymorphism	P	Gene	Polymorphism	P
APOE	4070C→T (Arg158Cys)	0.0040	*CETP*	-629C→A	0.0031
AKAP10	A→G (Ile646Val)	0.0090	*LPL*	C→G (Ser447Stop)	0.0059
RECQL2	T→C (Cys1367Arg)	0.0155	*COMT*	G→A (Val158Met)	0.0126
APOE	3932T→C (Cys112Arg)	0.0236	*MTHFR*	677C→T (Ala222Val)	0.0127
FABP2	2445G→A (Ala54Thr)	0.0295	*TNF*	-863C→A	0.0141
MTHFR	677C→T (Ala222Val)	0.0310	*GP1BA*	1018C→T	0.0141
PAI1	A→G (Tyr243Cys)	0.0317	*PON1*	584G→A (Gln192Arg)	0.0179
PON1	A→G (Arg160Gly)	0.0337	*FABP2*	2445G→A (Ala54Thr)	0.0181
IPF1	-108/3G→4G	0.0366	*IPF1*	-108/3G→4G	0.0194
AGER	G→A (Gly82Ser)	0.0392	*PTGS2*	G→C	0.0201
			F7	11,496G→A (Arg353Gln)	0.0237