Association of gene polymorphisms with myocardial infarction in individuals with different lipid profiles

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Abstract. Hyperlipidemia or dyslipidemia is one of the most important risk factors for coronary heart disease. The purpose of the present study was to identify gene polymorphisms for assessment of the genetic risk for myocardial infarction (MI) in individuals with low or high serum concentrations of high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, or triglyceride (TG), thereby contributing to the personalized prevention of MI in such individuals. The study population comprised 2682 unrelated Japanese individuals (1796 men, 886 women), including 1113 subjects (869 men, 244 women) with MI and 1569 controls (927 men, 642 women). 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 analyses and stepwise forward selection procedures revealed that seven different polymorphisms were significantly ($P<0.005$) associated with MI in individuals with low or high serum concentrations of HDL- or LDL-cholesterol or of TG: the 190T→C (Trp64Arg) polymorphism of *ADRB3* in individuals with low HDL-cholesterol; the 1018C→T (Thr145Met) polymorphism of *GP1BA*, the A→G (Ile646Val) polymorphism of *AKAP10*, and the -55C→T polymorphism of *UCP3* in individuals with high HDL-cholesterol; the -603A→G polymorphism of *F3* and the -11377C→G polymorphism of *ADIPOQ* in individuals with low LDL-cholesterol; the 1018C→T polymorphism of *GP1BA* in individuals with low TG; and the 4G→5G polymorphism of *PAI1* in individuals with high TG. No polymorphism was associated with MI in individuals with high LDL-cholesterol. These results suggest that polymorphisms associated with MI may differ among individuals with different lipid profiles. Stratification of subjects according to lipid profiles may thus be important for personalized prevention of MI based on genetic information.

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Introduction

Myocardial infarction (MI) is a multifactorial disorder that is thought to result from an interaction between genetic background and environmental factors. Disease prevention is an important strategy for reducing the overall burden of MI, and the identification of markers for disease risk is the key both for risk prediction and for potential intervention to reduce the chance of future events.

Although various association studies have attempted to identify genetic variants that contribute to coronary heart disease (CHD) or MI (1-3), the genetic components of these conditions have not been determined definitively. We previously showed that gene polymorphisms that confer susceptibility to MI differ between men and women (1,4) as well as between individuals with or without major risk factors for atherosclerosis (5). We further hypothesized that the association of polymorphisms with MI might be influenced by baseline lipid profiles. Therefore, we have now performed a large-scale association study for 164 polymorphisms of 137 candidate genes and MI in 2682 Japanese individuals with low or high serum concentrations of high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, or triglyceride (TG). The purpose of the present study was to identify gene polymorphisms that confer susceptibility to MI in individuals with different lipid profiles and thereby to provide a basis for the personalized prevention of this condition.

Materials and methods

Study population. The study population comprised 2682 unrelated Japanese individuals (1796 men, 886 women) who either visited outpatient clinics or who were admitted to participating hospitals (Gifu Prefectural General Medical Center and Gifu Prefectural Tajimi Hospital) between October 2002 and March 2005. The 1113 subjects with a first MI (869 men, 244 women) all underwent coronary angiography and left ventriculography. The diagnosis of MI was based on typical electrocardiographic changes and on increases both in the serum activities of enzymes such as creatine 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 by 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 1569 individuals (927 men, 642 women) who visited the outpatient clinics of the participating hospitals. They had no history of MI or CHD, peripheral arterial occlusive disease, other atherosclerotic diseases or other thrombotic, embolic, or hemorrhagic disorders.

The subjects with MI and the 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), 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 (BMI) of ≥25 kg/m^2], or cigarette smoking (≥10 cigarettes daily). Among the total study population, 1664 and 1018 individuals had low (<1.70 mmol/l) or high (≥1.70 mmol/l) serum concentrations of TG, respectively, and 748 and 1934 individuals had low (<1.03 mmol/l) or high (≥1.03 mmol/l) serum concentrations of HDL-cholesterol, respectively. The values for LDL-cholesterol were calculated by the Friedewald formula: serum concentration of LDL-cholesterol = (serum concentration of total cholesterol) - (serum concentration of HDL-cholesterol) - [0.2 x (serum concentration of TG)]. Among the total study population, 1920 and 762 individuals had low (<3.63 mmol/l) or high (≥3.63 mmol/l) serum concentrations of LDL-cholesterol, respectively. 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, Gifu International Institute of Biotechnology, and participating hospitals, and written informed consent was obtained from each participant.

Selection and genotyping of polymorphisms. With the use of public databases, we selected 164 polymorphisms from 137 candidate genes (4). Genotypes of the 164 polymorphisms were determined at 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 (6).

Statistical analysis. Clinical data were compared between the subjects with MI and the 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 screening, the genotype distribution of each autosomal polymorphism was compared between the subjects with MI and the 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 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), serum concentrations of HDL- or LDL-cholesterol or of TG, history of hypertension or diabetes mellitus (0 = no history; 1 = positive history), and genotype of each polymorphism. Each genotype was assessed according to dominant, recessive, additive 1 (heterozygotes versus wild-type homozygotes), and additive 2 (variant homozygotes versus wild-type homozygotes) genetic models, and the P value, odds ratio (OR), and 95% confidence interval (CI) were calculated. We also performed a stepwise forward

Table I. Characteristics of the subjects with low or high serum concentrations of HDL-cholesterol.

Characteristic	Low serum HDL-cholesterol			High serum HDL-cholesterol		
	MI	Controls	P	MI	Controls	P
No. of subjects	382	366		731	1203	
Age (years)	61.9±10.6	66.0±10.2	<0.0001	64.5±10.4	65.3±11.1	0.0944
Sex (male/female, %)	89.5/10.5	77.6/22.4	<0.0001	72.1/27.9	53.4/46.6	<0.0001
BMI (kg/m^2)	24.4±3.1	23.8±3.4	0.0337	23.3±3.2	23.1±3.4	0.2189
Smoker (%)	28.3	23.0	0.0954	18.6	14.7	0.0252
Hypertension (%)	72.0	81.7	0.0016	73.9	78.0	0.0403
Diabetes mellitus (%)	52.6	52.2	0.9059	46.5	37.8	0.0002
Serum LDL-cholesterol (mmol/l)	3.19±3.55	3.05±0.89	0.0407	3.22±0.85	3.18±0.97	0.3097
Serum TG (mmol/l)	2.00±1.13	2.14±1.58	0.1540	1.59±0.91	1.54±0.92	0.2822

Data for age, BMI, and serum LDL-cholesterol and TG concentrations are the means ± SD.

Table II. Multivariable logistic regression analysis of polymorphisms related to MI in individuals with a low serum concentration of HDL-cholesterol.

Symbol	Polymorphism	Dominant		Recessive		Additive 1		Additive 2	
		P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)
APOC3	-482C→T	0.0106	1.56 (1.11-2.20)	0.9294		0.0074	1.64 (1.14-2.37)	0.1162	
ADRB3	190T→C (Trp64Arg)	**0.0026**	1.64 (1.19-2.27)	0.3817		**0.0010**	1.75 (1.26-2.45)	0.6086	
CAPN10	4852G→A (SNP-43)	0.7140		0.7492		0.8478		0.7493	
ESR1	-1989T→G	0.2430		0.0086	1.85 (1.18-2.95)	0.7480		0.0099	1.90 (1.17-3.12)
PPARG	34C→G (Pro12Ala)	0.0241	2.26 (1.13-4.71)			0.0241	2.26 (1.13-4.71)		
UCP2	-866G→A	0.0239	0.68 (0.48-0.95)	0.2764		0.0057	0.60 (0.42-0.86)	0.5570	
PPARG	-681C→G	0.0282	1.40 (1.04-1.89)	0.6854		0.0293	1.42 (1.04-1.96)	0.3538	
AGER	G→A (Gly82Ser)	0.4548		0.0183	0.15 (0.02-0.61)	0.1902		0.0233	0.17 (0.02-0.65)
UTS2	G→A (Ser89Asn)	0.0312	1.40 (1.03-1.91)	0.0251	2.19 (1.12-4.46)	0.1194		0.0133	2.41 (1.22-4.96)
MMP3	A→G (Lys45Glu)	0.8184		0.0058	1.53 (1.13-2.07)	0.5139		0.3216	

OR, odds ratio; CI, confidence interval. Multivariable logistic regression analysis was performed with adjustment for age, sex, BMI, smoking status, serum LDL-cholesterol and TG concentrations, and the prevalence of hypertension and diabetes mellitus. P values <0.005 are shown in bold.

Table III. Multivariable logistic regression analysis of polymorphisms related to MI in individuals with a high serum concentration of HDL-cholesterol.

Symbol	Polymorphism	Dominant		Recessive		Additive 1		Additive 2	
		P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)
APOE	4070C→T (Arg158Cys)	0.0263	0.65 (0.45-0.94)	0.4091		0.0180	0.63 (0.43-0.92)	0.4389	
ADRB2	46A→G (Arg16Gly)	0.0255	1.29 (1.03-1.62)	0.0262	1.28 (1.03-1.58)	0.1080		0.0062	1.46 (1.11-1.91)
GJA4	1019C→T (Pro319Ser)	0.0801		0.3084		0.0341	1.25 (1.02-1.54)	0.4554	
FABP2	2445G→A (Ala54Thr)	0.0258	1.25 (1.03-1.51)	0.7516		0.0134	1.30 (1.06-1.59)	0.5185	
GP1BA	1018C→T (Thr145Met)	**<0.0001**	1.57 (1.26-1.96)	0.1697		**0.0002**	1.55 (1.23-1.94)	0.1107	
MMP1	1G→2G	0.1097		0.1093		0.0270	1.44 (1.05-2.01)	0.3973	
PECAM1	1454C→G (Leu125Val)	0.0605		0.0339	0.79 (0.64-0.98)	0.2179		0.0147	0.72 (0.55-0.94)
TNF	-238G→A	0.2267		0.7005		0.4231		0.7003	
UCP3	-55C→T	**0.0020**	1.35 (1.12-1.63)	0.3931		**0.0029**	1.30 (1.11-1.66)	0.0923	
AGER	G→A (Gly82Ser)	0.3407		0.0491	0.49 (0.23-0.96)	0.1270		0.0648	
AKAP10	A→G (Ile646Val)	0.5745		**0.0007**	2.21 (1.40-3.50)	0.6711		**0.0010**	2.17 (1.37-3.46)
LGALS2	3279C→T (intron1)	0.0492	1.21 (1.00-1.47)	0.0324	1.37 (1.03-1.83)	0.1754		0.0137	1.47 (1.08-2.00)
SLC26A8	A→G (lle639Val)	0.1698		0.0096	1.59 (1.12-2.25)	0.0240	0.79 (0.65-0.97)	0.0476	1.44 (1.00-2.06)

OR, odds ratio; CI, confidence interval. Multivariable logistic regression analysis was performed with adjustment for age, sex, BMI, smoking status, serum LDL-cholesterol and TG concentrations, and the prevalence of hypertension and diabetes mellitus. P values of <0.005 are shown in bold.

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 with JMP version 5.1 software (SAS Institute, Cary, NC, USA).

Results

Polymorphisms related to MI in individuals with low or high serum concentrations of HDL-cholesterol. Characteristics of the subjects with MI and the controls who had low or high serum concentrations of HDL-cholesterol are shown in Table I. For individuals with low HDL-cholesterol, the frequency of men, BMI, and the serum concentration of LDL-cholesterol were greater, whereas age and the prevalence of hypertension were lower in the subjects with MI than in the controls. For individuals with high HDL-cholesterol, the frequency of men and the prevalence of smoking and diabetes mellitus were greater, whereas the prevalence of hypertension was lower in the subjects with MI than in the controls.

The Chi-square test revealed that 10 and 13 polymorphisms were related (P<0.05) to MI in individuals with low (Table II) or high (Table III) serum concentrations of HDL-cholesterol,

Table IV. Effects of genotypes and other characteristics on the prevalence of MI as determined by a stepwise forward selection procedure in individuals with low or high serum concentrations of HDL-cholesterol.

Variable	P	R^2
Low serum HDL-cholesterol		
Age	<0.0001	0.0275
Sex	0.0005	0.0118
ADRB3 (*CC* + *CT* vs. *TT*)	0.0043	0.0079
High serum HDL-cholesterol		
Sex	<0.0001	0.0262
GP1BA (*TT* + *CT* vs. *CC*)	<0.0001	0.0065
Diabetes mellitus	0.0005	0.0048
AKAP10 (*GG* vs. *AA* + *AG*)	0.0008	0.0043
UCP3 (*TT*+*CT* vs. *CC*)	0.0027	0.0035

respectively. Multivariable logistic regression analysis with adjustment for age, sex, BMI, smoking status, serum concentrations of LDL-cholesterol and TG, and the prevalence of hypertension and diabetes mellitus revealed that the 190T→C (Trp64Arg) polymorphism of *ADRB3* (dominant and additive 1 models) was significantly (P<0.005) associated with MI in individuals with low HDL-cholesterol (Table II), and that the 1018C→T (Thr145Met) polymorphism of *GP1BA* (dominant and additive 1 models), the -55C→T polymorphism of *UCP3* (dominant and additive 1 models), and the A→G (Ile646Val) polymorphism of *AKAP10* (recessive and additive 2 models) were significantly associated with MI in individuals with high HDL-cholesterol (Table III).

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 the effects of age, sex, BMI, smoking status, serum concentrations of LDL-cholesterol and TG, and the prevalence of hypertension and diabetes mellitus on MI (Table IV). For individuals with low HDL-cholesterol, age, sex, and the *ADRB3* genotype (dominant model) were significant and were independent determinants of the prevalence of MI. For individuals with high HDL-cholesterol, sex, the *GP1BA* genotype (dominant model), diabetes mellitus, the *AKAP10* genotype (recessive model), and *UCP3* genotype (dominant model) significantly and independently influenced MI.

Polymorphisms related to MI in individuals with low or high serum concentrations of LDL-cholesterol. Characteristics of the subjects with MI and the controls who had low or high serum concentrations of LDL-cholesterol are shown in Table V. For individuals with low or high LDL-cholesterol, the frequency of men, BMI, and the prevalence of smoking and diabetes mellitus were greater, whereas age, serum HDL-cholesterol level, and the prevalence of hypertension were lower, in the subjects with MI than in the controls.

The Chi-square test revealed that 14 (Table VI) and 6 (data not shown) polymorphisms were related (P<0.05) to MI in individuals with low or high serum concentrations of LDL-cholesterol, respectively. Multivariable logistic regression analysis with adjustment for age, sex, BMI, smoking status, serum HDL-cholesterol and TG concentrations, and the prevalence of hypertension and diabetes mellitus revealed that the 1018C→T (Thr145Met) polymorphism of *GP1BA* (dominant and additive 1 models), the 677C→T (Ala222Val) polymorphism of *MTHFR* (additive 2 model), the -11377C→G polymorphism of *ADIPOQ* (additive 1 model), and the -603A→G polymorphism of *F3* (dominant and additive 1 models) were significantly (P<0.005) associated with MI in individuals with low LDL-cholesterol (Table VI), and that the 1454C→G (Leu125Val) polymorphism of *PECAM1* (additive 2 model) was significantly associated with MI in individuals with high LDL-cholesterol (data not shown).

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 the effects of age, sex, BMI, smoking status, serum HDL-cholesterol and TG levels, and the prevalence of hypertension and diabetes mellitus on MI (Table VII). Sex, serum HDL-cholesterol concentration, the *F3* genotype (dominant model), *AGER* genotype (recessive model), *ADIPOQ* genotype (dominant model), and the *UTS2* genotype (recessive model) were

Table V. Characteristics of the subjects with low or high serum concentrations of LDL-cholesterol.

Characteristic	Low serum LDL-cholesterol			High serum LDL-cholesterol		
	MI	Controls	P	MI	Controls	P
No. of subjects	779	1141		334	428	
Age (years)	64.0±10.6	65.6±11.2	0.0014	62.6±10.5	65.1±10.1	0.0008
Sex (male/female, %)	81.4/18.6	61.9/38.1	<0.0001	70.0/30.0	51.6/48.4	<0.0001
BMI (kg/m^2)	23.6±3.1	23.3±3.5	0.0478	23.9±3.2	23.4±3.1	0.0264
Smoker (%)	22.1	17.5	0.0140	21.6	14.3	0.0089
Hypertension (%)	73.2	78.6	0.0062	73.3	79.6	0.0417
Diabetes mellitus (%)	49.0	42.3	0.0035	47.8	38.3	0.0087
Serum HDL-cholesterol (mmol/l)	1.20±0.36	1.32±0.39	<0.0001	1.20±0.33	1.30±0.35	<0.0001
Serum TG (mmol/l)	1.77±1.08	1.71±1.23	0.2871	1.63±0.82	1.59±0.84	0.5903

Data for age, BMI, and serum HDL-cholesterol and TG concentrations are the means ± SD.

Table VI. Multivariable logistic regression analysis of polymorphisms related to MI in individuals with a low serum concentration of LDL-cholesterol.

Symbol	Polymorphism	Dominant		Recessive		Additive 1		Additive 2	
		P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)
APOC3	-482C→T	0.0767		0.5894		0.0367	1.27 (1.02-1.60)	0.4832	
NPPA	664G→A (Val7Met)	0.0247	0.75 (0.58-0.96)	0.3239		0.0364	0.76 (0.58-0.98)	0.2887	
ADRB3	190T→C (Trp64Arg)	0.1504		0.1222		0.0548		0.1900	
ITGB2	1323C→T	0.1168		0.1395		0.0356	0.81 (0.66-0.99)	0.3034	
GP1BA	1018C→T (Thr145Met)	**0.0049**	1.37 (1.10-1.71)	0.7403		**0.0032**	1.40 (1.12-1.76)	0.8872	
MTHFR	677C→T (Ala222Val)	0.0121	1.30 (1.06-1.59)	0.0101	1.37 (1.08-1.74)	0.0800		**0.0020**	1.54 (1.17-2.02)
PON1	584G→A (Gln192Arg)	0.7084		0.1259		0.3737		0.2299	
RECQL2	T→C (Cys1367Arg)	0.0090	1.41 (1.09-1.84)	0.9505		0.0074	1.44 (1.10-1.88)	0.9748	
ADIPOQ	-11377C→G	0.0052	1.31 (1.08-1.59)	0.8451		**0.0046**	1.33 (1.09-1.62)	0.4588	
AGER	G→A (Gly82Ser)	0.2950		0.0054	0.31 (0.12-0.67)	0.0677		0.0080	0.32 (0.13-0.70)
UTS2	G→A (Ser89Asn)	0.2186		0.0071	1.86 (1.19-2.94)	0.6056		0.0061	1.90 (1.20-3.02)
COLIA2	G→C (Ala459Pro)	0.0389	0.71 (0.51-0.98)	0.6750		0.0687		0.6736	
SLC26A8	A→G (lle639Val)	0.6028		0.0531		0.2457		0.1048	
F3	-603A→G	**0.0007**	0.71 (0.58-0.86)	0.9155		**0.0003**	0.68 (0.58-1.40)	0.6558	

OR, odds ratio; CI, confidence interval. Multivariable logistic regression analysis was performed with adjustment for age, sex, BMI, smoking status, serum HDL-cholesterol and TG concentrations, and the prevalence of hypertension and diabetes mellitus. P values of <0.005 are shown in bold.

Table VII. Effects of genotypes and other characteristics on the prevalence of MI as determined by a stepwise forward selection procedure in individuals with low or high serum concentrations of LDL-cholesterol.

Variable	P	R^2
Low serum LDL-cholesterol		
Sex	<0.0001	0.0332
Serum HDL-cholesterol	<0.0001	0.0092
F3 (*GG* + *AG* vs. *AA*)	0.0006	0.0045
AGER (*AA* vs. *GG* + *AG*)	0.0015	0.0039
ADIPOQ (*GG* + *CG* vs. *CC*)	0.0032	0.0034
UTS2 (*AA* vs. *GG* + *AG*)	0.0040	0.0032
High serum LDL-cholesterol		
Sex	<0.0001	0.0244
Serum HDL-cholesterol	0.0029	0.0086

significant and were independent determinants of the prevalence of MI in individuals with low LDL-cholesterol, whereas sex and serum HDL-cholesterol concentration significantly and independently influenced MI in individuals with high LDL-cholesterol.

Polymorphisms related to MI in individuals with low or high serum concentrations of TG. Characteristics of the subjects with MI and the controls who had low or high serum concentrations of TG are shown in Table VIII. For individuals with low serum TG, the frequency of men, BMI, and the prevalence of smoking and diabetes mellitus were greater, whereas age, the prevalence of hypertension, and serum HDL-cholesterol level were lower in the subjects with MI than in the controls. For individuals with high serum TG, the frequency of men and the prevalence of diabetes mellitus were greater, whereas age and serum HDL-cholesterol were lower in the subjects with MI than in the controls.

The Chi-square test revealed that 11 (Table IX) and 8 (Table X) polymorphisms were related (P<0.05) to MI in individuals with low or high serum TG concentrations, respectively. Multivariable logistic regression analysis with adjustment for age, sex, BMI, serum HDL- and LDL-cholesterol concentrations, and the prevalence of smoking, hypertension, and diabetes mellitus revealed that the 1018C→T (Thr145Met) polymorphism of *GP1BA* (dominant and additive 1 models) was significantly (P<0.005) associated with MI in individuals with low serum TG (Table IX), and that the 4G→5G polymorphism of *PAI1* (recessive and additive 2 models) was significantly associated with MI in individuals with high serum TG (Table X).

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 the effects of age, sex, BMI, smoking status, serum concentrations of HDL- and LDL-cholesterol, and the prevalence of hypertension and diabetes mellitus on MI (Table XI). For individuals with low serum TG, sex, serum HDL-cholesterol level, the *GP1BA* genotype (dominant model), and hypertension were significant and independent determinants of the prevalence of MI. For individuals with high serum TG, sex, serum HDL-cholesterol concentration, age, and the *PAI1* genotype (recessive model) significantly and independently affected the prevalence of MI.

Polymorphisms significantly related to MI in both multivariable logistic regression analysis and the stepwise forward selection procedure for individuals with low or high serum concentrations of HDL- or LDL-cholesterol or of TG are summarized in Table XII.

Table VIII. Characteristics of the subjects with low or high serum concentrations of TG.

Characteristic	Low serum TG			High serum TG		
	MI	Controls	P	MI	Controls	P
No. of subjects	651	1013		462	556	
Age (years)	61.8±10.6	66.0±11.1	0.0225	61.9±10.2	64.5±10.4	<0.0001
Sex (male/female, %)	76.2/23.8	55.5/44.5	0.0001	80.7/19.3	64.7/34.3	<0.0001
BMI (kg/m^2)	23.2±3.1	22.8±3.4	0.0081	24.3±3.2	24.2±3.3	0.6197
Smoker (%)	20.3	14.5	0.0023	24.2	20.5	0.1536
Hypertension (%)	70.7	77.5	0.0018	76.8	81.3	0.0813
Diabetes mellitus (%)	45.6	39.5	0.0134	52.8	44.2	0.0064
Serum HDL-cholesterol (mmol/l)	1.27±0.39	1.39±0.39	<0.0001	1.09±0.30	1.19±0.33	<0.0001
Serum LDL-cholesterol (mmol/l)	3.23±0.86	3.16±0.89	0.0965	3.18±0.94	3.13±1.07	0.4150

Data for age, BMI, and serum HDL- and LDL-cholesterol concentrations are the means ± SD.

Table IX. Multivariable logistic regression analysis of polymorphisms related to MI in individuals with low serum concentrations of TG.

Symbol	Polymorphism	Dominant		Recessive		Additive 1		Additive 2	
		P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)
ANXA5	-1C→T	0.1267		0.3514		0.0788		0.3866	
APOC3	-482C→T	0.0363	1.27 (1.02-1.60)	0.2776		0.0084	1.38 (1.09-1.76)	0.6492	
APOE	4070C→T (Arg158Cys)	0.0843		0.4034		0.0685		0.4285	
GP1BA	1018C→T (Thr145Met)	**0.0010**	1.49 (1.18-1.90)	0.3914		**0.0015**	1.49 (1.16-1.90)	0.2897	
AGER	G→A (Gly82Ser)	0.2505		0.0742		0.0921		0.1001	
UTS2	G→A (Ser89Asn)	0.7325		0.0094	1.98 (1.18-3.33)	0.7278		0.0119	1.95 (1.16-3.30)
IPF1	-108/3G→4G	0.0679		0.2608		0.1263		0.0718	
OLR1	501G→C (Lys167Asn)	0.0072	0.74 (0.60-0.92)	0.9227		0.0052	0.73 (0.58-0.91)	0.8004	
AKAP10	A→G (Ile646Val)	0.8958		0.0081	1.89 (1.18-3.04)	0.4609		0.0122	1.84 (1.14-2.97)
CCL11	G→A (Ala23Thr)	0.0450	1.28 (1.01-1.64)	0.0188	2.86 (1.21-7.10)	0.1334		0.0149	2.97 (1.25-7.41)
SLC26A8	A→G (lle639Val)	0.9730		0.0109	1.66 (1.12-2.46)	0.4467		0.0210	1.60 (1.07-2.40)

OR, odds ratio; CI, confidence interval. Multivariable logistic regression analysis was performed with adjustment for age, sex, BMI, smoking status, serum HDL- and LDL-cholesterol concentrations, and the prevalence of hypertension and diabetes mellitus. P values of <0.005 are shown in bold.

Table X. Multivariable logistic regression analysis of polymorphisms related to MI in individuals with high serum concentrations of TG.

Symbol	Polymorphism	Dominant		Recessive		Additive 1		Additive 2	
		P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)
LPL	C→G (Ser447Stop)	0.6703		0.0521		0.9657		0.0524	
PON1	584G→A (Gln192Arg)	0.7146		0.0109	0.58 (0.38-0.88)	0.5929		0.0229	0.60 (0.39-0.93)
PAI1	4G→5G	0.1353		**0.0024**	0.57 (0.39-0.82)	0.6518		**0.0029**	0.55 (0.37-0.81)
TNF	-850C→T	0.7732		0.0130	2.54 (1.24-5.47)	0.2914		0.0188	2.43 (1.18-5.26)
AGTR1	1166A→C	0.2462		0.0203	12.8 (2.11-247.30)	0.5551		0.0196	13.0 (2.15-251.70)
AGER	G→A (Gly82Ser)	0.6031		0.0268	0.19 (0.03-0.67)	0.2763		0.0309	0.19 (0.03-0.70)
CETP	-629C→A	0.5346		0.0084	1.45 (1.10-1.92)	0.1056		0.3396	
CCL5	-28C→G	0.0159	0.70 (0.52-0.93)	0.6846		0.0172	0.69 (0.51-0.94)	0.5550	

OR, odds ratio; CI, confidence interval. Multivariable logistic regression analysis was performed with adjustment for age, sex, BMI, smoking status, serum HDL- and LDL-cholesterol concentrations, and the prevalence of hypertension and diabetes mellitus. P values of <0.005 are shown in bold.

Table XI. Effects of genotypes and other characteristics on the prevalence of MI as determined by a stepwise forward selection procedure in individuals with low or high serum concentrations of TG.

Variable	P	R^2
Low serum TG		
Sex	<0.0001	0.0333
Serum HDL-cholesterol	0.0002	0.0061
GP1BA (*TT* + *CT* vs. *CC*)	0.0006	0.0053
Hypertension	0.0036	0.0038
High serum TG		
Sex	<0.0001	0.0210
Serum HDL-cholesterol	0.0001	0.0109
Age	0.0011	0.0076
PAI1 (*5G5G* vs. *4G4G* + *4G5G*)	0.0034	0.0061

Discussion

We examined the relation of 164 polymorphisms in 137 candidate genes to MI in individuals with low or high serum concentrations of HDL- or LDL-cholesterol or of TG, given that interactions between gene polymorphisms and lipid profiles may be important in the development of MI. Our results suggest that polymorphisms associated with MI may differ among individuals with different lipid profiles, although the underlying mechanisms responsible for these differences remain to be elucidated. Given that lipid profiles may themselves have genetic components, these components might interact with gene polymorphisms associated directly with MI.

The 190T→C (Trp64Arg) polymorphism of ADRB3. The ß$_3$-adrenergic receptor (ADRB3) is expressed predominantly in adipose tissue and plays an important role in lipid metabolism and the control of metabolic rate (7,8). The receptor mediates cathecholamine-induced lipolysis and thermogenesis in adipose tissue, both of which are important processes for the control of energy expenditure and body weight (9). The 190T→C (Trp64Arg) polymorphism of *ADRB3* was previously shown to be associated with obesity and insulin resistance (10), the capacity to gain weight (11), and the age of onset of type 2 diabetes mellitus (12). It has also been associated with obesity and type 2 diabetes mellitus (13) as well as with CHD (14) in Japanese. These observations have thus implicated *ADRB3* as a candidate susceptibility gene for CHD and MI. We have now shown that the 190T→C polymorphism of *ADRB3* was significantly associated with the prevalence of MI in individuals with a low serum concentration of HDL-cholesterol, with the *C* allele representing a risk factor for this condition. The effects of this polymorphism on both insulin resistance and the development of diabetes mellitus may account for its association with MI.

The 1018C→T (Thr145Met) polymorphism of GP1BA. The glycoprotein Ib-IX-V complex is the major platelet surface receptor for von Willebrand factor (15). 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 (16). The 1018C→T polymorphism of the glycoprotein Ibα gene (*GP1BA*) results in a Thr145Met substitution within the binding domain for von Willebrand factor. This polymorphism was previously shown to be associated with CHD (17) or with MI or sudden cardiac death (18), with the *T* allele representing a risk factor for these conditions. We also previously showed that this polymorphism was associated with MI in hypertensive individuals (5). These previous observations are consistent with our present results showing that the 1018C→T (Thr145Met) polymorphism of *GP1BA* was associated with the prevalence of MI in individuals with a high serum concentration of HDL-cholesterol or in those with a low serum TG level, with the *T* allele representing a risk factor for this condition.

The A→G (Ile646Val) polymorphism of AKAP10. The A→G (Ile646Val) polymorphism of the A kinase anchor protein 10

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

Lipid profile	Gene symbol	Polymorphism	Risk allele
Low serum HDL-cholesterol	*ADRB3*	190T→C (Trp64Arg)	C
High serum HDL-cholesterol	*GP1BA*	1018C→T (Thr145Met)	T
	AKAP10	A→G (Ile646Val)	G
	UCP3	-55C→T	T
Low serum LDL-cholesterol	*F3*	-603A→G	A
	ADIPOQ	-11377C→G	G
High serum LDL-cholesterol	None	None	None
Low serum TG	*GP1BA*	1018C→T (Thr145Met)	T
High serum TG	*PAI1*	4G→5G	4G

gene (*AKAP10*) has previously been associated with age, with the frequency of the *G* allele being lower in older (>60 years) than in younger (18-39 years) individuals (19). Analysis of an independent sample indicated that the Val variant of *AKAP10* was associated with a decrease in the length of the P-R interval on the electrocardiogram. The Ile646Val polymorphism of *AKAP10* is located in the binding domain for protein kinase A (PKA), and an *in vitro* binding assay revealed that the extent of binding to the RIα isoform of PKA was ~3-fold greater for the Val variant of *AKAP10* than for the Ile variant (19). This change in the affinity of AKAP10 for the RIα isoform of PKA resulted in a shift in the subcellular distribution of recombinantly expressed PKA-RIα. These observations suggest that changes in the subcellular distribution of PKA-RIα caused by variation in *AKAP10* may be related to cardiac dysfunction (19). We previously showed that the A→G (Ile646Val) polymorphism of *AKAP10* was associated with the prevalence of MI in Japanese individuals without hypercholesterolemia (5), and we have now shown that this polymorphism was significantly associated with MI in individuals with a high serum concentration of HDL-cholesterol, with the *G* allele being a risk factor for this condition. The underlying molecular mechanism of these associations remains to be elucidated.

The -55C→T polymorphism of UCP3. Uncoupling protein 3 (UCP3) is a mitochondrial transmembrane carrier protein that is predominantly expressed in skeletal muscle and has been proposed to regulate energy metabolism (20). The -55C→T polymorphism of *UCP3*, which is located in the promoter region of the gene, has been associated with the risk of obesity (21). The *T* allele of this polymorphism has also been associated with an atherogenic lipid profile and a lower risk for the development of type 2 diabetes mellitus (22). We have now shown that the -55C→T polymorphism of *UCP3* was significantly associated with the prevalence of MI in individuals with a high serum concentration of HDL-cholesterol, with the *T* allele representing a risk factor for this condition. This is the first demonstration of an association of this polymorphism of *UCP3* with MI, although the underlying molecular mechanism remains to be elucidated.

The -603A→G polymorphism of F3. F3 (tissue factor or tissue thromboplastin) is a 47-kDa transmembrane glycoprotein that plays a key role in the atherothrombotic process, with the F3 content of plaques appearing to predict their thrombogenicity (23). F3 is not normally expressed by circulating blood cells or vascular endothelial cells, but its expression is induced in monocytes and endothelial cells by a variety of stimuli including proinflammatory cytokines (24). The *G* allele of the -603A→G polymorphism of *F3* was previously associated with an increased abundance of *F3* mRNA in monocytes (25). We previously showed that the *G* allele of this polymorphism might affect the prevalence of type 2 diabetes mellitus in the Japanese population (26). We have now shown that the -603A→G polymorphism of *F3* was significantly associated with the prevalence of MI in individuals with a low serum concentration of LDL-cholesterol, with the *G* allele representing a protective factor for this condition. In contrast to our results, a previous case-control study suggested that the *G* allele of this polymorphism was associated with an increased risk for MI in Caucasians (27), possibly because the higher plaque levels of F3 associated with this allele lead to an increased risk of thrombosis (28). The discordant results might be attributed to the stratification of subjects by lipid profiles in the present study. The relation of this *F3* polymorphism to MI thus requires further evaluation with large populations of individuals with various coronary risk factors.

The -11377C→G polymorphism of ADIPOQ. Adiponectin (adipocyte, C1Q) is an adipocyte-derived plasma protein that accumulates in injured arteries (29) and inhibits growth factor-induced proliferation of vascular smooth muscle cells (30). The plasma level of adiponectin has also been found to be lower in individuals with type 2 diabetes mellitus or CHD than in control subjects (31,32), consistent with the notion that this protein is an important modulator of insulin sensitivity and resistance (33) as well as of atherosclerosis (34). The -11377C→G polymorphism of *ADIPOQ*, which is located in the proximal promoter region of the gene, was found to be associated with type 2 diabetes mellitus in Swedish Caucasians (35). An Ile64Thr polymorphism of *ADIPOQ* was also shown to be associated with metabolic syndrome and CHD in a Japanese population (36). In addition, we previously demonstrated that the -11377C→G polymorphism of *ADIPOQ* was associated with the prevalence of MI in Japanese without hypercholesterolemia (5). These various observations implicate *ADIPOQ* as a candidate susceptibility gene for CHD and MI. We have now shown that the -11377C→G polymorphism of *ADIPOQ* was significantly associated with MI in individuals with a low serum concentration of LDL-cholesterol, with the *G* allele representing a risk factor for this condition. Effects of this polymorphism on both insulin resistance and the development of atherosclerosis may account for its association with MI.

The 4G→5G polymorphism of PAI1. Plasminogen activator inhibitor 1 (PAI1) is the primary inhibitor of both tissue-type and urokinase-type plasminogen activators (37). The plasma concentration of PAI1 is correlated with variables associated with insulin resistance syndrome including obesity, hyperinsulinemia, and hypertriglyceridemia, and PAI1 is also an acute-phase reactant (38). The 4G→5G polymorphism of *PAI1*, which is located in the promoter region of the gene, is a common single-nucleotide insertion/deletion polymorphism that affects gene transcription (39). The plasma concentration of PAI1 has thus been shown to decrease according to the rank order of genotypes *4G/4G>4G/5G>5G/5G* (40). The plasma PAI1 level was also previously shown to be increased in patients with CHD (41) and to predict future coronary events in individuals with angina pectoris (42) or with a history of MI (43,44). A meta-analysis of nine studies (mostly case-control studies) revealed a moderately increased risk for MI in individuals with the *4G/4G* genotype (45). We have now shown that the 4G→5G polymorphism of *PAI1* was significantly associated with the prevalence of MI in individuals with a high serum concentration of TG, with the *5G* allele being a protective factor for this condition. Given that TG is stored in adipose tissue, which secretes PAI1, the

interaction of this *PAI1* polymorphism with adipose tissue metabolism may account for its association with MI.

Study limitations. Given the multiple comparisons of genotypes with MI in the present study, we adopted the strict criterion of P<0.005 for significant association in statistical analysis. It is not possible, however, to completely exclude potential statistical errors such as false positives. Validation of our findings will require their replication with independent subject panels. 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. Furthermore, the relevance of the identified polymorphisms to gene transcription or to protein structure or function was not determined in the present study.

To conclude, our present results implicate seven different polymorphisms as being associated with MI in individuals with low or high serum concentrations of HDL- or LDL-cholesterol or of TG. Determination of combined genotypes for these polymorphisms may prove informative for assessment of the genetic risk for MI and may contribute to the primary, personalized prevention of this condition.

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