Genetic risk for myocardial infarction in Japanese individuals with or without chronic kidney disease

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Abstract. Although chronic kidney disease (CKD) is recognized as an important risk factor for myocardial infarction (MI), genetic factors underlying predisposition to MI in individuals with or without CKD remain largely unknown. The aim of the present study was to identify genetic variants that confer susceptibility to MI in individuals with or without CKD in order to allow prediction of genetic risk for such individuals separately. The study population comprised a total of 4344 individuals, including 1247 individuals with CKD (506 subjects with MI and 741 controls) and 3097 individuals without CKD (833 subjects with MI and 2264 controls). The 150 polymorphisms examined in this study were selected by genome-wide association studies of ischemic stroke and MI with the use of the GeneChip Human Mapping 500K Array Set (Affymetrix) and determined by a method that combines the polymerase chain reaction and sequence-specific oligonucleotide probes with suspension array technology. In individuals with CKD, no polymorphism was significantly related to MI. In individuals without CKD, an initial screen by the Chi-square test revealed that the C→T polymorphism of *CLEC16A* (rs9925481) and the A→G polymorphism of *LAMA3* (rs12373237) were significantly (false discovery rate for allele frequencies of <0.05) associated with MI. Subsequent multivariable logistic regression analysis with adjustment for covariates revealed that the C→T polymorphism of *CLEC16A* (dominant model; P=0.0003; odds ratio, 0.66) and the A→G polymorphism of *LAMA3* (recessive model; P=0.0087; odds ratio, 0.75) were significantly (P<0.05) associated with MI. A stepwise forward selection procedure also revealed that these polymorphisms were significant and independent determinants of MI. *CLEC16A* and *LAMA3* may be susceptibility loci for MI in Japanese individuals without CKD. Determination of genotypes for *CLEC16A* and *LAMA3* may prove informative for assessment of the genetic risk for MI in such individuals.

Introduction

Myocardial infarction (MI) is a multifactorial and polygenic disease, and is strongly influenced by a genetic component (1). Although recent genome-wide association studies (GWAS) have implicated various candidate genes underlying predisposition to MI (2-7), the genes that confer susceptibility to this condition remain to be identified definitively.

It is increasingly recognized that chronic kidney disease (CKD) is an independent risk factor not only for end-stage renal disease but also for atherosclerotic cardiovascular diseases including MI (8,9). Individuals with CKD have a 1.9 to 2.9 times higher risk for the development of MI compared to the general population without CKD (10). Although epidemiological studies have suggested that genetic factors and gene-environment interactions may contribute to the development of MI (11,12), genetic variants underlying predisposition to MI in individuals with or without CKD remain largely unknown.

We previously showed that a polymorphism of *F7* was significantly associated with MI among individuals with CKD (13). To further examine whether the association of polymorphisms with MI is influenced by CKD, we

performed an association study for 150 polymorphisms of 144 candidate genes and MI in a total of 4344 Japanese individuals, including 1247 subjects with CKD and 3097 subjects without this condition. The purpose of the present study was to identify genetic variants that confer susceptibility to MI in Japanese individuals with or without CKD in order to allow prediction of genetic risk for such individuals separately.

Materials and methods

Study population. The study population comprised a total of 4344 unrelated Japanese individuals who either visited outpatient clinics of or were admitted to one of the participating hospitals (Gifu Prefectural General Medical Center and Gifu Prefectural Tajimi Hospital in Gifu Prefecture, Japan; Hirosaki University Hospital, Reimeikyo Rehabilitation Hospital, and Hirosaki Stroke Center in Aomori Prefecture, Japan) between October 2002 and March 2008 with various symptoms or for an annual health check-up, or who were recruited to a population-based prospective cohort study of aging and age-related diseases in Nakanojo, Gunma Prefecture, Japan. Estimated glomerular filtration rate (eGFR) was calculated with the use of the simplified prediction equation proposed by the Japanese Society of Nephrology and based on that described in the Modification of Diet in Renal Disease Study (14): eGFR (ml min^{-1} 1.73 m^{-2}) = 194 x [age (years)]$^{-0.287}$ x [serum creatinine (mg/dl)]$^{-1.094}$ (x 0.739 if female). The National Kidney Foundation - Kidney Disease Outcome Quality Initiative guidelines recommend a dianosis of CKD if eGFR is <60 ml min^{-1} 1.73 m^{-2} (15), on the basis of which 1247 individuals were diagnosed with CKD and 3097 individuals whose eGFR of ≥60 ml min^{-1} 1.73 m^{-2} were diagnosed without CKD in the present study.

The 1247 individuals with CKD comprised 506 subjects with MI and 741 controls. The 3097 individuals without CKD comprised 833 subjects with MI and 2264 controls. The 1339 subjects with MI (1048 men, 291 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 activity of creatine kinase (MB isozyme) and in the serum concentration of cardiac troponin T. The diagnosis of MI was confirmed by the presence of wall motion abnormality on left ventriculography and by 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 3005 individuals (1354 men, 1651 women) who had no history of coronary heart disease, aortic aneurysm, or peripheral arterial occlusive disease; of ischemic or hemorrhagic stroke or other cerebral diseases; or of other atherosclerotic, thrombotic, embolic or hemorrhagic disorders.

The study protocol complied with the Declaration of Helsinki and was approved by the committees on the Ethics of Human Research of Mie University Graduate School of Medicine, Hirosaki University Graduate School of Medicine, Gifu International Institute of Biotechnology, Tokyo Metropolitan Institute of Gerontology, and participating hospitals. Written informed consent was obtained from each participant.

Table I. Primers, probes, and other conditions for genotyping of polymorphisms related (P-value for allele frequency of <0.005) to myocardial infarction by the Chi-square test.

Gene	SNP	Sense primer (5'→3')	Antisense primer (5'→3')	Probe 1 (5'→3')	Probe 2 (5'→3')	Annealing (°C)	Cycles
Individuals with CKD							
LLGL2	A→G (rs1671021)	GCTCCTGGCCTCACCTTGCG	GCTGCTCTACAAACTCAGCACTG	CTGGGCACTGAAGTTCTCGTT	CCAACGAGAACCTCAGTGCC	60	50
Individuals without CKD							
CLEC16A	C→T (rs9925481)	GTACCTACTTTGTAGTGTTCATACA	CCAGGCACTGTTTGGAGCACA	AATTAAATGAGCGAATATGTGCAA	AATTAAATGAGTGAATATGTGCAAT	60	50
LAMA3	A→G (rs12373237)	GAATGATAGCGATTCTCCTCCTCA	TATAGCTCAATAAAGTGGTTACCAA	TTATACACATAGGTCAACTTTTTTG	ATTATACACATAGGTCGACTTTTTT	60	50
COL13A1	A→G (rs942576)	TGGCCCAGGTTGTGTTTCAGAG	GGCTATTCATCCCCATCACACTC	ACACTCACCACCTTTTGCACT	ACACTCACCACCTGTTGCAC	60	50
SEMA3F	A→G (rs12632110)	GGTGCTGCACCGTGGATGTGA	CTCCAGATCACTCCTCTACTACA	TGTGAGTCCTTGCACAGTGGT	CATTTCACCACTGCGCAAGGA	60	50

Baseline characteristics of the subjects with myocardial infarction (MI) and controls in the presence or absence of kidney disease (CKD).

Characteristic	Individuals with CKD			Individuals without CKD		
	MI (n=506)	Controls (n=741)	P-value	MI (n=833)	Controls (n=2264)	P-value
Age (years)	70.5±8.9	70.5±9.4	0.9917	63.8±9.9	65.0±10.8	0.0045
Gender (male/female)	395/111	357/384	<0.0001	653/180	997/1267	<0.0001
Body mass index (kg/m^2)	23.5±3.2	23.6±3.5	0.6191	23.9±3.3	23.3±3.3	<0.0001
Current or former smoker (%)	18.6	20.9	0.3100	29.2	22.4	<0.0001
Serum creatinine (μmol/l)	130.5±144.1	94.4±70.3	<0.0001	66.3±12.3	60.3±12.0	<0.0001
Estimated glomerular filtration rate (ml min^{-1} 1.73 m^{-2})	45.9±12.5	50.8±8.9	<0.0001	78.7±15.9	78.5±15.9	0.6677
Hypertension (%)	78.9	49.0	<0.0001	66.5	39.3	<0.0001
Systolic blood pressure (mmHg)	146.7±27.9	138.5±22.9	<0.0001	139.7±24.9	136.7±20.0	0.0014
Diastolic blood pressure (mmHg)	74.5±14.6	78.3±13.5	<0.0001	74.5±14.5	78.8±11.6	<0.0001
Diabetes mellitus (%)	50.8	19.7	<0.0001	46.6	13.7	<0.0001
Fasting plasma glucose level (mmol/l)	7.59±3.46	6.62±2.98	<0.0001	7.72±3.51	6.43±2.71	<0.0001
Blood glycosylated hemoglobin (%)	6.53±1.77	5.60±1.27	<0.0001	6.68±1.87	5.59±1.35	<0.0001
Hypercholesterolemia (%)	29.8	29.6	0.9132	29.1	27.0	0.2498
Serum total cholesterol (mmol/l)	5.16±0.98	5.15±0.98	0.9347	5.18±1.09	5.13±0.89	0.2665
High density lipoprotein-cholesterol (mmol/l)	1.21±0.39	1.45±0.40	<0.0001	1.20±0.33	1.50±0.39	<0.0001
Serum triglycerides (mmol/l)	1.70±0.90	1.65±1.02	0.3175	1.78±1.29	1.51±0.97	<0.0001

Quantitative data are means ± SD. Hypertension: systolic blood pressure of ≥140 mmHg, diastolic blood pressure of ≥90 mmHg, or taking of antihypertensive medication. Diabetes mellitus: fasting plasma glucose level of ≥6.93 mmol/l (126 mg/dl), blood glycosylated hemoglobin (hemoglobin A$_{1c}$) content of ≥6.5%, or taking of antidiabetes medication. Hypercholesterolemia: serum total cholesterol concentration of ≥5.72 mmol/l (220 mg/dl) or taking of lipid-lowering medication.

Selection of polymorphisms. Our aim was to identify genetic variants associated with MI in the Japanese population in a case-control association study. A total of 150 polymorphisms examined in the present study (data not shown) were selected by GWAS of ischemic stroke (16) and MI (P-value for allele frequency $<1.0\times10^{-7}$) with the use of the GeneChip Human Mapping 500K Array Set (Affymetrix, Santa Clara, CA). We have not examined the relation of these polymorphisms to MI among individuals with or without CKD in our previous studies (17-23).

Genotyping of polymorphisms. Venous blood (7 ml) was collected into tubes containing ethylenediaminetetraacetic acid at a final concentration of 50 mM, and genomic DNA was isolated with a kit (Genomix; Talent, Trieste, Italy). Genotypes of 150 polymorphisms were determined at G&G Science (Fukushima, Japan) by a method that combines the polymerase chain reaction and sequence-specific oligo-nucleotide probes with suspension array technology (Luminex, Austin, TX, USA). Primers, probes, and other conditions for genotyping of polymorphisms related (P-value for allele frequency <0.005) to MI as determined by the initial Chi-square test are shown in Table I. The detailed genotyping method was described previously (24).

Statistical analysis. Quantitative data were compared between subjects with MI and controls by the unpaired Student's t-test. Categorical 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 geno-type distribution (3x2) and the allele frequencies (2x2) of each polymorphim were compared between subjects with MI and controls by the Chi-square test. Given the multiple comparisons of genotypes with MI, the false discovery rate (FDR) was calculated from the distributions of P-values of the 150 polymorphisms (25). Polymorphisms with a P-value for allele frequency of <0.005 were further examined by multivariable logistic regression analysis with adjustment for covariates. Such analysis was thus performed with MI as a dependent variable and independent variables including age, gender (0, woman; 1, man), body mass index (BMI), smoking status (0, nonsmoker; 1, smoker), the serum concentration of creatinine, the history of hypertension, diabetes mellitus, and hypercholesterolemia (0, no history; 1, positive history), and genotype of each polymorphism; and the P-value, odds ratio, and 95% confidence interval were calculated. Each genotype was assessed according to dominant, recessive, and additive genetic models. Additive models included the additive 1 (heterozygotes versus wild-type homozygotes) and the additive 2 (variant homozygotes versus wild-type homo-zygote) models, which were analyzed simultaneously with a single statistical model. We also performed a stepwise forward selection procedure to examine the effects of geno-types as well as of other covariates on MI. In this analysis, each genotype was examined according to a dominant or

Table III. Polymorphisms related (P-value for allele frequency <0.005) to myocardial infarction (MI) in individuals with or without chronic kidney disease (CKD) as determined by the Chi-square test.

Gene	Polymorphisms	dbSNP	MI[a]	Controls[a]	P-value (genotype)	P-value (allele)	FDR
Individuals with CKD							
LLGL2	A→G	rs1671021			0.0135	0.0044	0.2532
	AA		393 (77.7)	526 (71.2)			
	AG		108 (21.3)	194 (26.2)			
	GG		5 (1.0)	19 (2.6)			
Individuals without CKD							
CLEC16A	C→T	rs9925481			0.0005	0.0001	0.0148
	CC		674 (81.2)	1659 (74.5)			
	CT		145 (17.5)	524 (23.6)			
	TT		11 (1.3)	43 (1.9)			
LAMA3	A→G	rs12373237			0.0003	0.0001	0.0148
	AA		14 (1.7)	33 (1.5)			
	AG		204 (24.6)	404 (18.1)			
	GG		612 (73.7)	1788 (80.4)			
COL13A1	A→C	rs942576			0.0077	0.0015	0.0735
	AA		25 (3.0)	47 (2.1)			
	AC		215 (26.0)	479 (21.5)			
	CC		590 (71.0)	1707 (76.4)			
SEMA3F	A→G	rs12632110			0.0017	0.0019	0.0735
	AA		216 (26.0)	449 (20.1)			
	AG		387 (46.7)	1108 (49.7)			
	GG		226 (27.3)	674 (30.2)			

[a]Numbers in parentheses are percentages.

recessive model on the basis of statistical significance in the multivariable logistic regression analysis. The P-levels for inclusion in and exclusion from the model were 0.25 and 0.1, respectively. With the exception of the initial screen by the Chi-square test (FDR <0.05), a P-value of <0.05 was considered statistically significant. Statistical significance was examined by two-sided tests performed with JMP version 6.0 and JMP Genomics version 3.2 softwares (SAS Institute, Cary, NC).

Results

Baseline characteristics of the subjects with MI and controls in the presence or absence of CKD are shown in Table II. Among individuals with CKD, the frequency of male subjects, serum concentration of creatinine, systolic blood pressure, fasting plasma glucose level, blood glycosylated hemoglobin content, and the prevalence of hypertension and diabetes mellitus were greater, whereas eGFR, diastolic blood pressure, and serum concentration of high density lipoprotein (HDL)-cholesterol were lower in subjects with MI than in controls. Among individuals without CKD, the frequency of male subjects, BMI, the percentage of smokers, serum concentrations of creatinine and triglycerides, systolic blood pressure, fasting plasma glucose level, blood glycosylated hemoglobin

Table IV. Hardy-Weinberg P-values in subjects with myocardial infarction (MI) and controls.

Gene	SNP	dbSNP	MI	Controls
Individuals with CKD				
LLGL2	A→G	rs1671021	0.4173	0.8258
Individuals without CKD				
CLEC16A	C→T	rs9925481	0.3186	0.8283
LAMA3	A→G	rs12373237	0.5231	0.0664
COL13A1	A→C	rs942576	0.3195	0.0526
SEMA3F	A→G	rs12632110	0.0566	0.8693

content, and the prevalence of hypertension and diabetes mellitus were greater, whereas age, diastolic blood pressure, and serum concentration of HDL-cholesterol were lower in subjects with MI than in controls.

The genotype distributions and allele frequencies of polymorphisms were compared between subjects with MI and controls by the Chi-square test (Table III). For individuals with CKD, although one polymorphism was related (P-value for allele frequency of <0.005) to the prevalence of

Table V. Multivariable logistic regression analysis of polymorphisms related (P-value for allele frequency <0.005 by the Chi-square test) to myocardial infarction with adjust for age, gender, body mass index, smoking status, serum concentration of creatinine, and the prevalence of hypertension, diabetes mellitus, and hypercholesterolemia.

Gene	Polymorphism	Dominant		Recessive		Additive 1		Additive 2	
		P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)
Individuals with CKD									
LLGL2	A→G	**0.0125**	0.68 (0.50-0.92)	**0.0207**	0.27 (0.08-0.77)	**0.0487**	0.73(0.53-0.99)	**0.0144**	0.24 (0.07-0.71)
Individuals without CKD									
CLEC16A	C→T	**0.0003**	0.66 (0.53-0.83)	0.4877		**0.0004**	0.66 (0.52-0.83)	0.3604	
LAMA3	A→G	0.7944		**0.0087**	0.75 (0.61-0.93)	0.3929		0.9322	
COL13A1	A→C	0.4416		**0.0331**	0.80 (0.65-0.98)	0.8572		0.3407	
SEMA3F	A→G	**0.0015**	0.71 (0.57-0.88)	0.3007		**0.0028**	0.71 (0.56-0.89)	**0.0083**	0.71 (0.55-0.92)

OR, odds ratio; CI, confidence interval. P-values <0.05 are shown in bold.

Table VI. Effects of genotypes and other characteristics on the prevalence of myocardial infarction as determined by a stepwise forward selection procedure.

Characteristics	P-value	R^2
Individuals with CKD		
Diabetes mellitus	<0.0001	0.0784
Male gender	<0.0001	0.0607
Hypertension	<0.0001	0.0521
Smoking	<0.0001	0.0100
LLGL2 (dominant model, AG + GG versus AA)	0.0130	0.0037
Serum creatinine concentration	0.0133	0.0036
Individuals without CKD		
Diabetes mellitus	<0.0001	0.0981
Male gender	<0.0001	0.0634
Hypertension	<0.0001	0.0243
Age	0.0003	0.0038
CLEC16A (dominant model, CT + TT versus CC)	0.0003	0.0036
SEMA3F (dominant model, AG + GG versus AA)	0.0022	0.0027
LAMA3 (recessive model, GG versus AA + AG)	0.0094	0.0019
Smoking	0.0163	0.0016
COL13A1 (recessive model, CC versus AA + AC)	0.0221	0.0015

R^2, contribution rate.

MI, it was not significantly associated with this condition. For individuals without CKD, four polymorphisms were related to the prevalence of MI. Among these polymorphisms, the C→T polymorphism of *CLEC16A* (rs9925481) and the A→G polymorphism of *LAMA3* (rs12373237) were significantly (FDR for allele frequency of <0.05) associated with MI. The genotype distributions for the five polymorphisms related to MI are also shown in Table III. Genotype distributions of these polymorphisms related to MI were in Hardy-Weinberg equilibrium for the subjects with MI and controls (Table IV).

Multivariable logistic regression analysis with adjustment for age, gender, BMI, smoking status, serum concentration of creatinine, and the prevalence of hypertension, diabetes mellitus, and hypercholesterolemia revealed that the A→G polymorphism of *LLGL2* (all genetic models) was significantly (P<0.05) associated with MI among individuals with CKD and that the C→T polymorphism of *CLEC16A* (dominant and additive 1 models), the A→G polymorphism of *LAMA3* (recessive model), the A→C polymorphism of *COL13A1* (recessive model), and the A→G polymorphism of *SEMA3F* (dominant and additive 1 and 2 models) were significantly associated with MI among individuals without CKD (Table V). The G allele of *LLGL2*, the T allele of *CLEC16A*, the G allele of *LAMA3*, the C allele of *COL13A1*, and the G allele of *SEMA3F* were all protective against MI.

A stepwise forward selection procedure was performed to examine the effects of genotypes for the polymorphisms related to MI by the Chi-square test as well as of age, gender, BMI, smoking status, serum concentration of creatinine, and

the prevalence of hypertension, diabetes mellitus, and hyper-cholesterolemia on MI (Table VI). For individuals with CKD, diabetes mellitus, male gender, hypertension, smoking, *LLGL2* (dominant model), serum creatinine concentration, in descending order of statistical significance, were significant ($P<0.05$) and independent determinants of MI. For individuals without CKD, diabetes mellitus, male gender, hypertension, age, *CLEC16A* (dominant model), *SEMA3F* (dominant model), *LAMA3* (recessive model), smoking, and *COL13A1* (recessive model), in descending order of statistical significance, were significant and independent determinants of MI (Table VI).

Discussion

We examined the possible relations of 150 polymorphisms to the prevalence of MI in a total of 4344 Japanese individuals with or without CKD. Our association study with three steps of analysis (Chi-square test, multivariable logistic regression analysis with adjustment for covariates, and a stepwise forward selection procedure) revealed that the C→T poly-morphism of *CLEC16A* (rs9925481) and the A→G polymorphism of *LAMA3* (rs12373237) were significantly associated with MI in Japanese individuals without CKD.

C-type lectin domain family 16, member A (CLEC16A) has been detected mainly in immune cells including B lymphocytes and natural killer cells (26). Two independent GWAS in Northern European (27) and American (28) populations showed that several variants of *CLEC16A* were significantly associated with type 1 diabetes mellitus. It was hypothesized that the altered protein structure could elicit an autoimmune response, resulting in the destruction of islet cells of the pancreas as noted in type 1 diabetes mellitus. We now showed that the C→T polymorphism in intron 11 of *CLEC16A* (rs9925481) was significantly associated with the prevalence of MI in Japanese individuals without CKD, with the *T* allele protecting against this condition. The effect of *CLEC16A* on glucose metabolism might account for its association with MI, although the underlying mechanism remains unclear.

Laminins are members of the glycoprotein family that are the main components of the multifunctional extracellular matrix proteins regulating adhesion, motility, gene expression, and apoptosis (29). Targeted disruption of the laminin, α3 gene (*LAMA3*) in mice caused the formation of a lethal epidermal blistering condition similar to human junctional epidermolysis bullosa (29). *LAMA3* was also shown to play an important role in the regulation of endothelial wound healing (30). We now showed that the A→G polymorphism in intron 30 of *LAMA3* (rs12373237) was significantly associated with the prevalence of MI in Japanese individuals without CKD, with the *G* allele protecting against this condition. The altered endothelial function by means of adhesion and cell migration might be implicated in the pathogenesis of MI, although the functional relevance of this polymorphism with the pathogenesis of MI remains to be elucidated.

Our results suggest that *LLGL2* in individuals with CKD, and *COL13A1* and *SEMA3F* in individuals without CKD are also candidate genes for MI in Japanese individuals. Lethal giant larvae homolog 2 (LLGL2) is involved in epithelial cell polarity, asymmetric cell division, and hemidesmosome formation through the association with submembranous actin cytoskeleton of the basolateral cell domain (31,32). Collagen, type XIII, α1 (COL13A1) is a constituent of type XIII collagen. It is a transmembrane protein which belongs to a non-fibrillar collagen group (33), and is expressed in various tissues including the bone, muscle, and heart, being implicated in cellular adhesion and migration (34,35). Sema domain, immunoglobulin domain, short basic domain, secreted, 3F (SEMA3F) is a member of the class 3 semaphorins and plays an important role in endothelial cell functions in vasculature (36). Inhibition of *SEMA3F* expression by small interfering RNA affected the intracellular localization and function of gap junction protein, α1, 43 kDa which is expressed in medial smooth muscle cells of the normal vascular wall (37,38), being increased at early stages of atherosclerosis and reduced in advanced lesion (39).

There are several limitations to the present study. (i) It is possible that one or more of the polymorphisms associated with MI in the present study are in linkage disequilibrium with other polymorphisms in the same gene or in other nearby genes that are actually responsible for the development of this condition. (ii) The functional relevance of identified polymorphisms to gene transcription or to protein structure or function was not determined in the present study. (iii) Although we adopted the criterion of FDR <0.05 for association to compensate for the multiple comparisons of genotypes with MI, it is not possible to exclude completely potential statistical errors such as false-positives. (iv) Given that the results of the present study were not replicated, validation of our findings will require their replication with other independent subject panels.

In conclusion, our present results suggest that *CLEC16A* and *LAMA3* may be susceptibility loci for MI in Japanese individuals without CKD. Determination of genotypes for *CLEC16A* and *LAMA3* may prove informative for assessment of the genetic risk for MI in such individuals. Given that genetic variants that confer susceptibility to MI differed between individuals with CKD and those without this condition, stratification of subjects according to CKD may thus be important for personalized prevention of MI based on genetic information.

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