Association of polymorphisms of *BTN2A1* and *ILF3* with myocardial infarction in Japanese individuals with or without hypertension, diabetes mellitus or chronic kidney disease

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Abstract. Recent evidence suggests that genetic variants that confer susceptibility to myocardial infarction (MI) may differ between men and women or between individuals with or without conventional risk factors for MI. We previously showed that rs6929846 of *BTN2A1* and rs2569512 of *ILF3* were significantly associated with MI in Japanese individuals. In the present study, we examined the associations of rs6929846 of *BTN2A1* or rs2569512 of *ILF3* to MI among individuals stratified by the absence or presence of hypertension, diabetes mellitus (DM) and chronic kidney disease (CKD). The study population was comprised of 5689 unrelated Japanese individuals, including 1626 subjects with MI and 4063 controls with or without hypertension, DM or CKD. Multivariable logistic regression analyses with adjustment for covariates revealed that rs6929846 of *BTN2A1* was significantly associated with MI in individuals with (P=0.0001; odds ratio, 1.49) or without ($P=1.6x10^{-7}$; odds ratio, 2.32) hypertension; in individuals with (P=0.0002; odds ratio, 1.65) or without ($P=8.1x10^{-7}$; odds ratio, 1.76) DM; and in individuals without CKD ($P=6.0x10^{-11}$; odds ratio, 2.03), but not in those with CKD. Similar analyses revealed that rs2569512 of *ILF3* was significantly associated with MI in individuals with (P=0.0041; odds ratio, 1.26) or without (P=0.0051; odds ratio, 1.78) hypertension; in individuals with (P=0.0200; odds ratio, 1.46) or without (P=0.0174; odds ratio, 1.43) DM; and in individuals with (P=0.0011, odds ratio, 1.47) or without (P=0.0237; odds ratio, 1.34) CKD. Results suggested that the association of rs6929846 in *BTN2A1* with MI was more apparent in low-risk individuals than in high-risk individuals, whereas the association of rs2569512 in *ILF3* with MI was not influenced by the absence or presence of hypertension, DM or CKD. Stratification of subjects based on hypertension, DM or CKD may thus be informative in order to achieve personalized prevention of MI with the use of genetic information.

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Introduction

Myocardial infarction (MI) is a complex disease resulting from an interaction between genetic and environmental factors. Disease prevention is an important strategy for reducing the overall burden of coronary heart disease (CHD) and MI, and the identification of biomarkers for disease risk is essential both for risk prediction and for potential intervention to reduce the chance of future events.

Recent studies have shown the importance of genetic factors and of interactions between multiple genes and environmental factors in CHD and MI in addition to conventional risk factors, including hypertension, diabetes mellitus (DM), dyslipidemia, chronic kidney disease (CKD), and smoking (1,2). The common forms of CHD and MI are thus thought to

Table I. Baseline characteristics of the subjects with myocardial infarction (MI) and controls in the absence or presence of hypertension.

	Individuals with hypertension (n=3326)			Individuals without hypertension (n=2363)		
Characteristic	MI	Controls	P-value	MI	Controls	P-value
No. of subjects	1178	2148		448	1915	
Age (years)	66.0±9.8	70.0±8.8	<0.0001	63.4±11.1	65.6±10.9	<0.0001
Gender (male/female, %)	77.3/22.7	51.5/48.5	<0.0001	85.0/14.5	43.2/56.8	<0.0001
Body mass index (kg/m^2)	24.0±3.5	23.8±3.4	0.0903	23.6±3.1	23.0±3.2	0.0002
Current or former smoker (%)	31.5	30.2	0.4279	35.5	26.4	0.0002
Systolic blood pressure (mmHg)	151±26	146±19	<0.0001	119±13	122±12	<0.0001
Diastolic blood pressure (mmHg)	79±16	82±12	<0.0001	67±10	72±9	<0.0001
Diabetes mellitus (%)	52.2	47.8	<0.0001	44.0	20.1	<0.0001
Chronic kidney disease (%)	40.8	29.1	<0.0001	26.6	23.3	0.1474
Hypercholesterolemia (%)	59.6	42.1	<0.0001	49.8	36.5	<0.0001

Quantitative data are means ± SD.

Table II. Comparisons of genotype distributions of two SNPs between subjects with myocardial infarction (MI) and controls in the absence or presence of hypertension by the Chi-square test.

Gene symbol	SNP	dbSNP	MI (%)	Controls (%)	P-value
Individuals with hypertension					
BTN2A1	C→T	rs6929846			1.2×10^{-7}
	CC		921 (78.2)	1846 (85.9)	
	CT		246 (20.9)	288 (13.4)	
	TT		11 (0.9)	14 (0.7)	
ILF3	A→G	rs2569512			0.0013
	AA		126 (10.7)	287 (13.4)	
	AG		494 (41.9)	977 (45.5)	
	GG		558 (47.4)	884 (41.1)	
Individuals without hypertension					
BTN2A1	C→T	rs6929846			6.0×10^{-11}
	CC		351 (78.4)	1735 (90.6)	
	CT		91 (20.3)	174 (9.1)	
	TT		6 (1.3)	6 (0.3)	
ILF3	A→G	rs2569512			0.0492
	AA		39 (8.7)	244 (12.7)	
	AG		214 (47.8)	880 (46.0)	
	GG		195 (43.5)	791 (41.3)	

be multifactorial and to be determined by many genes, each with a relatively small effect, working alone or in combination with modifier genes or environmental factors (or both). Although recent genome-wide association studies (3-7) have implicated several loci and candidate genes in predisposition to MI in the Caucasian population, the genes that contribute to genetic susceptibility to MI in Asian populations remain to be identified. We previously showed that genetic variants that confer susceptibility to MI differ between men and women (8,9), between individuals with or without conventional risk factors for CHD, including hypertension, DM, hypercholesterolemia, or CKD (10-12), or between individuals with different lipid profiles (13,14). We also showed that the C→T polymorphism (rs6929846) of *BTN2A1* and the A→G polymorphism (rs2569512) of *ILF3* were significantly associated with MI in Japanese individuals by a genome-wide association study (15).

To further examine whether the association of polymorphisms with MI is influenced by the absence or presence of conventional risk factors, we have now examined an association of rs6929846 of *BTN2A1* or rs2569512 of *ILF3* with MI in 5689 Japanese individuals with or without hypertension, DM, or CKD, separately.

Subjects and methods

Study population. The study population was comprised of 5689 unrelated Japanese individuals (3227 men, 2462 women) who either visited outpatient clinics of or were admitted to participating hospitals (Gifu Prefectural General Medical Center, Gifu; Gifu Prefectural Tajimi Hospital, Tajimi; Hirosaki University Hospital and Hirosaki Stroke Center, Hirosaki; Japanese Red Cross Nagoya First Hospital, Nagoya; and Inabe General Hospital, Inabe, Japan) between October 2002 and March 2009 because of various symptoms or for an annual health checkup, or who were recruited to a population-based prospective cohort study of aging and age-related diseases in Nakanojo, Kusatsu and Tokyo, Japan.

The 1626 subjects with MI (1292 men, 334 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 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 4063 control individuals (1935 men, 2128 women) were recruited from individuals who visited outpatient clinics of the participating hospitals for an annual health checkup or who were community-dwelling individuals enrolled in the cohort studies. They had no history of MI or CHD, ischemic or hemorrhagic stroke, peripheral arterial occlusive disease, or other atherosclerotic, 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 ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or drug treatment for hypertension), DM [fasting plasma glucose level ≥6.93 mmol/l or blood glycosylated hemoglobin (hemoglobin A1c) content ≥6.5%, or drug treatment for diabetes], and CKD [estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2], where eGFR (ml/min/1.73 m^2) = 194 x (age in years)$^{-0.287}$ x [serum creatinine (mg/dl)]$^{-1.094}$ (x 0.739 if female) (16,17). On the basis of these criteria, 3326 or 2363 individuals were diagnosed with or without hypertension, respectively, 1901 or 3788 individuals were diagnosed with or without DM, respectively, and 1671 or 4018 individuals were diagnosed with or without CKD, respectively.

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

Table III. Multivariable logistic regression analysis of polymorphisms associated with myocardial infarction in individuals with or without hypertension.

		Dominant		Recessive		Additive 1		Additive 2	
Gene symbol	SNP	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)
Individuals with hypertension									
BTN2A1	C→T	0.0001	1.49 (1.21-1.82)	0.7962		0.0001	1.50 (1.22-1.85)	0.6691	
ILF3	A→G	0.0445	1.28 (1.01-1.64)	0.0041	1.26 (1.08-1.47)	0.2561		0.0080	1.41 (1.10-1.83)
Individuals without hypertension									
BTN2A1	C→T	$1.6x10^{-7}$	2.32 (1.69-3.17)	0.1989		$3.6x10^{-7}$	2.30 (1.67-3.17)	0.1339	
ILF3	A→G	0.0079	1.69 (1.16-2.51)	0.9923		0.0051	1.78 (1.20-2.69)	0.0249	1.59 (1.07-2.41)

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

Table IV. Baseline characteristics of the subjects with myocardial infarction (MI) and controls in the absence or presence of diabetes mellitus.

	Individuals with diabetes mellitus (n=1901)			Individuals without diabetes mellitus (n=3788)		
Characteristic	MI	Controls	P-value	MI	Controls	P-value
No. of subjects	812	1089		813	2975	
Age (years)	65.4±9.6	69.5±9.1	<0.0001	65.2±10.9	67.1±10.3	<0.0001
Gender (male/female, %)	79.8/20.2	57.0/43.0	<0.0001	79.1/20.9	44.2/55.8	<0.0001
Body mass index (kg/m^2)	24.2±3.5	23.7±3.6	0.0004	23.6±3.3	23.3±3.2	0.0251
Current or former smoker (%)	35.5	32.4	0.1641	29.8	26.9	0.1111
Fasting plasma glucose (mmol/l)	9.41±3.75	9.10±3.75	0.0157	5.52±0.81	5.25±0.86	<0.0001
Blood glycosylated hemoglobin (%)	7.12±1.81	6.36±1.71	<0.0001	5.35±0.38	5.21±0.36	<0.0001
Hypertension (%)	75.7	64.7	<0.0001	69.1	48.5	<0.0001
Chronic kidney disease (%)	39.7	27.6	<0.0001	34.2	25.9	<0.0001
Hypercholesterolemia (%)	58.4	43.3	<0.0001	55.5	38.0	<0.0001

Quantitative data are means ± SD.

Table V. Comparisons of genotype distributions of two SNPs between subjects with myocardial infarction (MI) and controls in the absence or presence of diabetes mellitus by the Chi-square test.

Gene symbol	SNP	dbSNP	MI (%)	Controls (%)	P-value
Individuals with diabetes mellitus					
BTN2A1	C→T	rs6929846			4.0x10^{-6}
	CC		633 (78.0)	943 (86.6)	
	CT		172 (21.2)	138 (12.7)	
	TT		7 (0.8)	8 (0.7)	
ILF3	A→G	rs2569512			0.0014
	AA		85 (10.5)	150 (13.8)	
	AG		335 (41.2)	500 (45.9)	
	GG		392 (48.3)	439 (40.3)	
Individuals without diabetes mellitus					
BTN2A1	C→T	rs6929846			2.7x10^{-12}
	CC		638 (78.5)	2638 (88.7)	
	CT		165 (20.3)	324 (10.9)	
	TT		10 (1.2)	12 (0.4)	
ILF3	A→G	rs2569512			0.0478
	AA		80 (9.8)	381 (12.8)	
	AG		372 (45.8)	1357 (45.6)	
	GG		361 (44.4)	1236 (41.6)	

Genotyping of polymorphisms. Venous blood (7 ml) was collected into tubes containing 50 mmol/l ethylene-diamine-tetraacetic acid (disodium salt), and genomic DNA was isolated with a kit (Genomix, Talent, Trieste, Italy). Genotypes of single nucleotide polymorphisms (SNPs, rs6929846 and rs2569512) were determined at G&G Science (Fukushima, Japan) by a method that combines the polymerase chain reaction (PCR) and sequence-specific oligonucleotide probes with suspension array technology (Luminex, Austin, TX). Primers, probes, and other PCR conditions for genotyping of two SNPs (15) and detailed genotyping methodology (18) were previously described.

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. Initially, genotype distribution of each SNP was compared between subjects with MI and controls by the Chi-square test.

SNPs with a P-value for genotype distribution of <0.05 were further examined by multivariable logistic regression analysis with adjustment for covariates. Multivariable logistic regression 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, non-smoker; 1, smoker), the serum concentration of creatinine, history of hypertension, DM, or hypercholesterolemia (0, no history; 1, positive history), and genotype of each SNP. P-values, odds ratios, and 95% confidence intervals were calculated. Each genotype was assessed according to dominant, recessive, and additive genetic models. Additive models included the additive 1 model (heterozygotes vs. wild-type homozygotes) and the additive 2 model (variant homozygotes vs. wild-type homozygotes), which were analyzed simultaneously with a single statistical model. 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 software (SAS Institute, Cary, NC).

Results

Genetic variants related to MI in individuals with or without hypertension. The characteristics of the subjects with or without hypertension are shown in Table I. For hypertensive individuals, the frequency of male subjects, systolic blood pressure, and the prevalence of DM, CKD, and hypercholesterolemia were greater, whereas age and diastolic blood pressure were smaller, in subjects with MI than in controls. For normotensive individuals, the frequency of male subjects, BMI, and the prevalence of smoking, DM and hypercholesterolemia were greater, whereas age and systolic and diastolic blood pressure were smaller, in subjects with MI than in controls.

Comparison of genotype distributions by the Chi-square test revealed that rs6929846 of *BTN2A1* and rs2569512 of *ILF3* were significantly (P<0.05) associated with MI in individuals with or without hypertension (Table II). Multivariable logistic regression analysis with adjustment for age, gender, BMI, smoking status, the serum concentration of creatinine, and the prevalence of DM and hypercholesterolemia revealed that rs6929846 of *BTN2A1* (dominant and additive 1 models) and rs2569512 of *ILF3* (dominant, recessive, and additive 2 models) were significantly associated with MI in hypertensive individuals, and that rs6929846 of *BTN2A1* (dominant and additive 1 models) and rs2569512 of *ILF3* (dominant and additive 1 and 2 models) were significantly associated with MI in normotensive individuals (Table III).

Genetic variants related to MI in individuals with or without DM. The characteristics of the subjects with or without DM are shown in Table IV. For individuals with or without DM, the frequency of male subjects, BMI, fasting plasma glucose level, blood glycosylated hemoglobin content, and the prevalence of hypertension, CKD and hypercholesterolemia were greater, whereas age was lower, in subjects with MI than in controls.

Comparison of genotype distributions by the Chi-square test revealed that rs6929846 of *BTN2A1* and rs2569512 of *ILF3*

Table VI. Multivariable logistic regression analysis of polymorphisms associated with myocardial infarction in individuals with or without diabetes mellitus.

		Dominant		Recessive		Additive 1		Additive 2	
Gene symbol	SNP	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)
Individuals with diabetes mellitus									
BTN2A1	C→T	0.0004	1.60 (1.24-2.08)	0.7055		0.0002	1.65 (1.26-2.15)	0.8265	
ILF3	A→G	0.0617		0.0233	1.26 (1.03-1.53)	0.2390		0.0200	1.46 (1.06-2.02)
Individuals without diabetes mellitus									
BTN2A1	C→T	8.1×10^{-7}	1.76 (1.40-2.20)	0.1363		2.3×10^{-6}	1.74 (1.38-2.19)	0.0907	
ILF3	A→G	0.0197	1.39 (1.06-1.85)	0.2163		0.0385	1.74 (1.38-2.19)	0.0174	1.43 (1.07-1.92)

OR, odds ratio; CI, confidence interval. Multivariable logistic regression analysis was performed with adjustment for age, gender, body mass index, smoking status, serum concentration of creatinine, and the prevalence of hypertension and hypercholesterolemia.

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

	Individuals with CKD (n=1671)			Individuals without CKD (n=4018)		
Characteristic	MI	Controls	P-value	MI	Controls	P-value
No. of subjects	600	1071		1026	2992	
Age (years)	69.6±9.2	71.3±8.8	<0.0001	62.8±10.1	66.4±10.2	<0.0001
Gender (male/female, %)	78.5/21.5	48.6/51.4	<0.0001	80.0/20.0	47.3/52.7	<0.0001
Body mass index (kg/m^2)	23.6±3.3	23.6±3.5	0.9053	24.1±3.4	22.3±3.3	<0.0001
Current or former smoker (%)	25.0	28.0	0.1816	37.0	28.5	<0.0001
Serum creatinine (μmol/l)	134.2±148.2	93.3±63.5	<0.0001	66.4±12.3	61.2±11.7	<0.0001
eGFR (ml/min/1.73 m^2)	45.4±12.9	50.8±8.6	<0.0001	79.6±16.7	77.3±14.9	0.0009
Hypertension (%)	80.2	58.4	<0.0001	67.9	50.9	<0.0001
Diabetes mellitus (%)	53.7	28.1	<0.0001	47.8	26.3	<0.0001
Hypercholesterolemia (%)	56.3	40.7	<0.0001	26.6	29.2	0.0762

Quantitative data are means ± SD. eGFR, estimated glomerular filtration rate.

Table VIII. Comparisons of genotype distributions of two SNPs between subjects with myocardial infarction (MI) and controls in the absence or presence of chronic kidney disease (CKD) by the Chi-square test.

Gene symbol	SNP	dbSNP	MI (%)	Controls (%)	P-value
Individuals with CKD					
BTN2A1	C→T	rs6929846			0.0006
	CC		475 (79.2)	923 (86.2)	
	CT		115 (19.2)	141 (13.2)	
	TT		10 (1.6)	7 (0.6)	
ILF3	A→G	rs2569512			0.0001
	AA		64 (10.7)	149 (13.9)	
	AG		244 (40.7)	514 (48.0)	
	GG		292 (48.6)	408 (38.1)	
Individuals without CKD					
BTN2A1	C→T	rs6929846			1.4×10^{-16}
	CC		797 (77.7)	2658 (88.8)	
	CT		222 (21.6)	321 (10.7)	
	TT		7 (0.7)	13 (0.5)	
ILF3	A→G	rs2569512			0.0323
	AA		101 (9.8)	382 (12.8)	
	AG		464 (45.2)	1343 (44.9)	
	GG		461 (45.0)	1267 (42.3)	

were significantly associated with MI in individuals with or without DM (Table V). Multivariable logistic regression analysis with adjustment for age, gender, BMI, smoking status, the serum concentration of creatinine, and the prevalence of hypertension and hypercholesterolemia revealed that rs6929846 of *BTN2A1* (dominant and additive 1 models) and rs256951 of *ILF3* (recessive and additive 2 models) were significantly associated with MI in diabetic individuals, and that rs6929846 of *BTN2A1* (dominant and additive 1 models) and rs2569512 of *ILF3* (dominant and additive 1 and 2 models) were significantly associated with MI in non-diabetic individuals (Table VI).

Genetic variants related to MI in individuals with or without CKD. The characteristics of the subjects with or without CKD are shown in Table VII. For individuals with CKD, the frequency of male subjects, the serum concentration of creatinine, and the prevalence of hypertension, DM, and hypercholesterolemia were greater, whereas age and

Table IX. Multivariable logistic regression analysis of polymorphisms associated with myocardial infarction in individuals with or without chronic kidney disease (CKD).

		Dominant		Recessive		Additive 1		Additive 2	
Gene symbol	SNP	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)
Individuals with CKD									
BTN2A1	C→T	0.0945		0.3587		0.1354		0.3211	
ILF3	A→G	0.0138	1.56 (1.10-2.23)	0.0011	1.47 (1.16-1.85)	0.1380		0.0015	1.83 (1.26-2.67)
Individuals without CKD									
BTN2A1	C→T	$1.0x10^{-10}$	1.99 (1.62-2.45)	0.9378		$6.0x10^{-11}$	2.03 (1.64-2.51)	0.7590	
ILF3	A→G	0.0237	1.34 (1.04-1.74)	0.6242		0.0257	1.36 (1.02-1.74)	0.0387	1.33 (1.02-1.74)

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

eGFR were lower, in subjects with MI than in controls. For individuals without CKD, the frequency of male subjects, BMI, the serum concentration of creatinine, eGFR, and the prevalence of smoking, hypertension, and DM were greater, whereas age was lower, in subjects with MI than in controls.

Comparison of genotype distributions by the Chi-square test revealed that rs6929846 of *BTN2A1* and rs2569512 of *ILF3* were significantly associated with MI in individuals with or without CKD (Table VIII). Multivariable logistic regression analysis with adjustment for age, gender, BMI, smoking status, the serum concentration of creatinine, and the prevalence of hypertension, DM, and hypercholesterolemia revealed that rs2569512 of *ILF3* (dominant, recessive, and additive 2 models) was significantly associated with MI in individuals with CKD, and that rs6929846 of *BTN2A1* (dominant and additive 1 models) and rs2569512 of *ILF3* (dominant and additive 1 and 2 models) were significantly associated with MI in individuals without CKD (Table IX).

Discussion

Atherosclerosis is a complex multifactorial process resulting from an excessive inflammatory response to various forms of injurious stimuli to the arterial wall (19). In addition, the transition of a stable coronary atherosclerotic lesion into a ruptured or eroded plaque results in the clinical manifestation of the acute coronary syndrome (20-22). We previously showed that the C→T polymorphism (rs6929846) of *BTN2A1* and the A→G polymorphism (rs2569512) of *ILF3* were significantly associated with MI in Japanese individuals by a genome-wide association study (15). The T allele of rs6929846 increased the transcription activity of *BTN2A1* and the overexpression of *BTN2A1* decreased the expression of elastin mRNA and increased the mRNA expression of matrix metallopeptidase 3 and interleukin 5 in cultured human cells (15).

The butyrophilin, subfamily 2, member A1 gene (*BTN2A1*) is a member of the *BTN2* subfamily of genes, which encode proteins belonging to the butyrophilin protein family. Many butyrophilin and butyrophilin-like family of proteins were shown to regulate the immune function, and polymorphisms in the coding sequences were related to predisposition to inflammatory diseases (23). Genomic mapping of disease loci identified an SNP (rs2076530) in the butyrophilin-like 2 gene (*BTNL2*) that increases the risk for sarcoidosis (24). Polymorphisms in *BTNL2* in linkage disequilibrium with HLA-DRB were related to other inflammatory diseases, all of which can be characterized by inappropriate T cell activation (25-27). We have shown that the rs6929846 of *BTN2A1* was significantly associated with MI in Japanese individuals with or without hypertension or DM and in those without CKD, with the T allele representing a risk factor for MI. Our results suggest that the association of rs6929846 of *BTN2A1* with MI was more apparent in low-risk individuals than in high-risk individuals and that *BTN2A1* may interact with CKD in relation to the development of MI, suggesting a role of the cardio-renal interaction in the pathogenesis of MI.

We have also shown that the A→G polymorphism (rs2569512) of *ILF3* was significantly associated with the MI in Japanese individuals with or without hypertension, DM, or CKD, with the G allele representing a risk factor for

MI. The association of rs2569512 in *ILF3* with MI was not influenced by the absence or presence of hypertension, DM, or CKD. *ILF3* is a subunit of the nuclear factor of activated T-cells, a transcription factor required for the expression of interleukin 2 in T-cells (28). Our previous study demonstrated that *ILF3* is abundantly accumulated in the necrotic core of the coronary plaque, suggesting that *ILF3* may have a role in the development of coronary thrombosis, although functional relevance of rs2569512 located in intron 7 of *ILF3* with the pathogenesis of MI remains unclear.

In conclusion, the association of rs6929846 in *BTN2A1* with MI was more apparent in low-risk individuals than in high-risk individuals, and *BTN2A1* may interact with CKD in the development of MI. The association of rs2569512 in *ILF3* with MI was not influenced by the absence or presence of hypertension, DM or CKD. Prediction of the risk for MI on the basis of genetic variants would be useful for deciding how aggressively to target the clinical risk factors which are currently amenable to treatment. Stratification of subjects based on hypertension, DM, or CKD may thus be informative in order to achieve personalized prevention of MI with the use of genetic information. Validation of our findings will require their replication with independent subject panels of other ethnic groups.

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