Association of a polymorphism of *BTN2A1* with dyslipidemia in community-dwelling individuals

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Abstract. We have previously shown that the C→T polymorphism (rs6929846) of the butyrophilin, subfamily 2, member A1 gene (*BTN2A1*) was significantly associated with myocardial infarction. Considering that dyslipidemia is a significant risk factor for coronary heart disease, it was hypothesized that the association between rs6929846 of *BTN2A1* and myocardial infarction may be attributable, at least in part, to its effect on the susceptibility to dyslipidemia. The purpose of the present study was to examine a possible association of rs6929846 of *BTN2A1* with dyslipidemia in community-dwelling individuals. The study subjects were comprised of 5,958 community-dwelling individuals (2,909 subjects with dyslipidemia and 3,049 controls) who were recruited into a population-based cohort study in Inabe, Japan. Dyslipidemia was defined by a serum concentration of triglycerides of ≥1.65 mmol/l, a serum high-density lipoprotein-cholesterol concentration of <1.04 mmol/l or a serum low-density lipoprotein (LDL)-cholesterol concentration of ≥3.64 mmol/l. A comparison of the allele frequencies or genotype distributions by the χ^2 test revealed that rs6929846 of *BTN2A1* was significantly associated with dyslipidemia (P<0.05). A multivariable logistic regression analysis adjusted for age, gender, body mass index, smoking status and the prevalence of diabetes mellitus revealed that rs6929846 of *BTN2A1* was significantly (dominant model; P=2.4x10^{-4}; odds ratio, 1.29) associated with dyslipidemia, with the minor T allele representing a risk for this condition. Among all the individuals, the serum concentrations of total cholesterol, triglycerides and LDL-cholesterol were significantly greater for individuals in the combined CT and TT genotype groups than for those with the CC genotype. *BTN2A1* may thus be a susceptibility gene for dyslipidemia in community-dwelling individuals.

Introduction

The interaction between genetic and environmental factors, the latter including a high-fat and high-calorie diet and physical inactivity, causes the multifactorial disorder, dyslipidemia (1,2). Considering that dyslipidemia is a major risk factor of coronary heart disease (3,4), the personalized prevention of dyslipidemia is important in order to reduce the chance of future cardiovascular events.

Although genome-wide association studies (GWASs) have implicated various loci and genes in the predisposition to dyslipidemia in Caucasians (5-7), the genes that confer susceptibility to this condition in Japanese individuals remain to be definitively identified. We previously showed that the C→T polymorphism (rs6929846) of the *BTN2A1* gene was significantly associated with myocardial infarction in Japanese individuals by a GWAS (8). Considering that dyslipidemia is a significant risk factor for coronary heart disease, it was hypothesized that the association between rs6929846 of *BTN2A1* and myocardial infarction may be attributable, at least in part, to its effect on the genetic susceptibility to dyslipidemia. In the present study, the correlation of rs6929846 of *BTN2A1* and dyslipidemia in Japanese individuals was examined.

Materials and methods

Study population. The study subjects were comprised of 5,958 community-dwelling individuals (2,909 subjects with dyslipidemia and 3,049 controls) who were recruited to a population-based cohort study (Inabe Health and Longevity Study) in Inabe, Japan, from 2010 to 2012. The individuals with dyslipidemia either had a serum concentration of triglycerides of ≥1.65 mmol/l, a serum high-density lipoprotein (HDL)-cholesterol concentration of <1.04 mmol/l, a serum

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Table I. Characteristics of the 5,958 study subjects.

Characteristic	Dyslipidemia	Controls	P-value
No. of subjects	2909	3049	
Age, years	55.5±11.5	49.8±13.4	<0.0001
Gender, % (male/female)	59.9/40.1	51.1/48.9	<0.0001
Body mass index, kg/m^2	23.9±3.4	22.0±3.1	<0.0001
Current or former smoker, %	41.7	37.1	0.0003
Hypertension, %	35.7	20.8	<0.0001
Diabetes mellitus, %	11.8	5.0	<0.0001
Serum total cholesterol, mmol/l	5.59±0.87	4.78±0.60	<0.0001
Serum triglycerides, mmol/l	1.67±1.06	0.88±0.32	<0.0001
Serum HDL-cholesterol, mmol/l	1.51±0.41	1.79±0.43	<0.0001
Serum LDL-cholesterol, mmol/l	3.66±0.83	2.80±0.52	<0.0001
Fasting plasma glucose, mmol/l	5.75±1.30	5.36±0.79	<0.0001
Blood glycosylated hemoglobin, %	5.84±0.72	5.57±0.50	<0.0001
Serum creatinine, μmol/l	67.1±16.6	63.5±14.6	<0.0001

Quantitative data are means ± standard deviation. Hypertension: Systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or taking antihypertensive medication. Diabetes mellitus: Fasting plasma glucose level of ≥6.93 mmol/l, blood glycosylated hemoglobin content of ≥6.9% or taking antidiabetes medication. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

low-density lipoprotein (LDL)-cholesterol concentration of ≥3.64 mmol/l or had been administered antidyslipidemic drugs. The control subjects had normal lipid profiles (a serum triglyceride concentration of <1.65 mmol/l, a serum HDL-cholesterol concentration of ≥1.04 mmol/l and a serum LDL-cholesterol concentration of <3.64 mmol/l) and no history of dyslipidemia or of taking antidyslipidemic drugs. Diabetes mellitus cases were defined as individuals who either had fasting plasma glucose levels of ≥6.93 mmol/l or a blood glycosylated hemoglobin content of ≥6.9% or as patients who had taken antidiabetes medication. Hypertension cases were defined as individuals who either had a systolic blood pressure of ≥140 mmHg or a diastolic blood pressure of ≥90 mmHg, or as those who had taken antihypertensive medication.

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 and Inabe General Hospital (Inabe, Japan). Written informed consent was obtained from all subjects.

Measurement of serum lipid profiles. Venous blood was collected in the early morning following overnight fasting by the subjects. The blood samples were centrifuged at 1,600 x g for 15 min at 4˚C, and the serum was separated and stored at -30˚C until further analysis. The serum concentrations of total cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol were measured as previously described (9).

Genotyping of rs6929846 of BTN2A1. Venous blood (5 ml) was collected into tubes containing 50 mmol/l ethylenediaminetetraacetic acid (disodium salt), then the peripheral blood leukocytes were isolated and the genomic DNA was extracted from these cells with a DNA extraction kit (SMITEST EX-R&D; Medical & Biological Laboratories, Nagoya, Japan). The genotypes of rs6929846 of *BTN2A1*

were determined at G&G Science (Fukushima, Japan) by the multiplex bead-based Luminex assay, a method that combines polymerase chain reaction (PCR) and sequence-specific oligo-nucleotide probes with suspension array technology (Luminex, Austin, TX, USA). The detailed genotyping methodology has been described previously (8,10).

Statistical analysis. The quantitative data were compared between two groups by unpaired Student's t-test. The categorical data were compared by the χ^2 test. The allele frequencies were estimated by the gene counting method, and the χ^2 test was used to identify departure from the Hardy-Weinberg equilibrium. Multivariable logistic regression analysis was performed with dyslipidemia, hypertriglycedemia, hypo-HDL-cholesterolemia or hyper-LDL-cholesterolemia as a dependent variable, and with independent variables, including age, gender (0, female; 1, male), BMI, smoking status (0, non-smoker; 1, current or former smoker) and the prevalence of diabetes mellitus (0, no history of this condition; 1, positive history) and the *BTN2A1* genotype. The P-value, odds ratio and 95% confidence interval were calculated. The *BTN2A1* genotype was assessed according to dominant, recessive and additive genetic models. Additive models included the additive 1 (heterozygotes versus wild-type homozygotes) and additive 2 (variant homozygotes versus wild-type homozygotes) models, which were analyzed simultaneously with a single statistical model. P<0.05 was considered to indicate a statistically significant difference. Statistical tests were performed with JMP 5.1 software (SAS Institute, Cary, NC, USA).

Results

Patient characteristics. The characteristics of the study subjects are shown in Table I. The age, frequency of males,

Table II. Correlation of rs6929846 of *BTN2A1* to dyslipidemia, hypertriglycedemia, hypo-HDL-cholesterolemia or hyper-LDL-cholesterolemia, as determined by the χ^2 test.

Clinical phenotype	BTN2A1 genotype, n (%)			P-value (genotype)	P-value (allele frequency)
	CC	CT	TT		
Dyslipidemia	2265 (77.9)	599 (20.6)	45 (1.5)	**0.0020**	**0.0004**
Controls	2479 (81.3)	540 (17.7)	30 (1.0)		
Hypertriglycedemia	861 (76.5)	253 (22.5)	12 (1.1)	**0.0058**	**0.0119**
No hypertriglycedemia	3883 (80.4)	886 (18.3)	63 (1.3)		
Hypo-HDL-cholesterolemia	236 (77.9)	65 (21.5)	2 (0.7)	0.3790	0.6439
No hypo-HDL-cholesterolemia	4508 (79.7)	1074 (19.0)	73 (1.3)		
Hyper-LDL-cholesterolemia	1365 (77.9)	360 (20.5)	27 (1.5)	0.0764	**0.0236**
No hyper-LDL-cholesterolemia	3379 (80.3)	779 (18.5)	48 (1.1)		

Bold denotes values P<0.05. Hypertriglycedemia: A serum triglyceride concentration of ≥1.65 mmol/l. Hypo-HDL-cholesterolemia: A serum HDL-cholesterol concentration of <1.04 mmol/l. Hyper-LDL-cholesterolemia: A serum LDL-cholesterol concentration of ≥3.64 mmol/l. *BTN2A1*, butyrophilin, subfamily 2, member A1 gene; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table III. Multivariable logistic regression analysis of rs6929846 of *BTN2A1* and dyslipidemia, hypertriglycedemia, hypo-HDL-cholesterolemia or hyper-LDL-cholesterolemia.

	Dominant model	Recessive model	Additive 1 model	Additive 2 model
Dyslipidemia				
P-value	**0.00024**	**0.0280**	**0.0011**	**0.0177**
OR (95% CI)	1.29 (1.13-1.48)	1.74 (1.07-2.87)	1.26 (1.10-1.45)	1.82 (1.11-3.00)
Hypertriglycedemia				
P-value	**0.0035**	0.7683	**0.0022**	0.8968
OR (95% CI)	1.28 (1.08-1.51)	0.91 (0.49-1.67)	1.30 (1.10-1.54)	0.96 (0.48-1.76)
Hypo-HDL-cholesterolemia				
P-value	0.5678	0.4723	0.4617	0.4920
OR (95% CI)	1.09 (0.81-1.44)	0.59 (0.10-1.94)	1.12 (0.83-1.49)	0.61 (0.10-1.98)
Hyper-LDL-cholesterolemia				
P-value	**0.0254**	0.1910	**0.0462**	0.1553
OR (95% CI)	1.17 (1.02-1.35)	1.38 (0.84-2.21)	1.16 (1.00-1.33)	1.42 (0.87-2.28)

Multivariable logistic regression analysis was performed adjusted for age, gender, body mass index, smoking status and the prevalence of diabetes mellitus. Bold denotes values P<0.05. Hypertriglycedemia: A serum triglyceride concentration of ≥1.65 mmol/l. Hypo-HDL-cholesterolemia: A serum HDL-cholesterol of <1.04 mmol/l. Hyper-LDL-cholesterlemia: A serum LDL-cholesterol of ≥3.64 mmol/l. OR, odds ratio; CI, confidence interval; *BTN2A1*, butyrophilin, subfamily 2, member A1 gene; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

BMI, prevalence of smoking, presence of hypertension and diabetes mellitus, serum concentrations of total cholesterol, triglycerides, LDL-cholesterol and creatinine, fasting plasma glucose levels and blood glycosylated hemoglobin content were higher, whereas the serum concentration of HDL-cholesterol was lower, in the individuals with dyslipidemia compared with the controls. Among the dyslipidemic individuals, 760 subjects (26.1%) had taken antidyslipidemic drugs.

Genotype distributions and allele frequencies. A comparison of genotype distributions and allele frequencies between individuals with dyslipidemia and the controls using the χ^2 test

revealed that rs6929846 of *BTN2A1* was significantly (P<0.05) associated with the prevalence of dyslipidemia (Table II). This polymorphism was also significantly correlated with the prevalence of hypertriglycedemia and hyper-LDL-cholesterolemia, but not to hypo-HDL-cholesterolemia (Table II). The genotype distributions of rs6929846 were in Hardy-Weinberg equilibrium among the subjects with dyslipidemia, hypertriglyceridemia, hypo-HDL-cholesterolemia, hyper-LDL-cholesterolemia and all the corresponding controls (Table II).

A multivariable logistic regression analysis adjusted for age, gender, BMI, smoking status and the prevalence of diabetes mellitus revealed that rs6929846 of *BTN2A1* was significantly

Table IV. Correlation of rs6929846 of *BTN2A1* with serum lipid profiles.

	BTN2A1 genotype			P-value	
				Dominant	Recessive
Profile	CC	CT	TT	(CT + TT vs. CC)	(TT vs. CC + CT)
All individuals					
Number of subjects	4744	1139	75		
Serum total cholesterol, mmol/l	5.15±0.85	5.26±0.85	5.38±0.98	**0.0007**	0.0724
Serum triglycerides, mmol/l	1.25±0.87	1.32±0.88	1.23±0.54	**0.0244**	0.7456
Serum HDL-cholesterol, mmol/l	1.66±0.44	1.63±0.46	1.70±0.45	0.1604	0.2924
Serum LDL-cholesterol, mmol/l	3.21±0.82	3.28±0.81	3.49±0.86	**0.0017**	**0.0054**
Individuals not taking antidyslipidemic drugs					
Number of subjects	4164	976	58		
Serum total cholesterol, mmol/l	5.16±0.85	5.26±0.86	5.50±1.03	**0.0012**	**0.0131**
Serum triglycerides, mmol/l	1.22±0.87	1.30±0.89	1.20±0.52	**0.0181**	0.7376
Serum HDL-cholesterol, mmol/l	1.67±0.44	1.64±0.46	1.73±0.49	0.2458	0.2676
Serum LDL-cholesterol, mmol/l	3.22±0.82	3.31±0.81	3.54±0.88	**0.0009**	**0.0055**

Bold denotes values P<0.05. *BTN2A1*, butyrophilin, subfamily 2, member A1 gene; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

associated with dyslipidemia (dominant, reccesive and additive 1 and 2 models), hypertriglycedemia (dominant and additive 1 models) and hyper-LDL-cholesterolemia (dominant and additive 1 models), with the minor T allele representing a risk for these conditions (Table III). The *BTN2A1* genotype was not correlated with hypo-HDL-cholesterolemia.

Among all the individuals, the *BTN2A1* genotype was significantly associated with the serum concentrations of total cholesterol (dominant model), triglycerides (dominant model) and LDL-cholesterol (dominant and recessive models) (Table IV). Among the 5,198 individuals who were not taking antidyslipidemic drugs, the *BTN2A1* genotype was also significantly associated with the serum concentrations of total cholesterol (dominant and recessive models), triglycerides (dominant model) and LDL-cholesterol (dominant and recessive models).

Discussion

Previous research over the past four decades has consistently demonstrated the burden of dyslipidemia to be extremely high in terms of morbidity, mortality and medical costs (11), and the World Health Organization estimates that dyslipidemia is associated with more than half of the global cases of coronary heart disease and more than four million mortalities per year (12). Considering that dyslipidemia is a major risk factor of atherosclerotic cardiovascular disease (3,4,12), the prediction of the risk for dyslipidemia on the basis of genetic variants would be beneficial for the personalized prevention of this condition.

In the present study it has been revealed that the C→T polymorphism (rs6929846) of *BTN2A1* was significantly associated with dyslipidemia in Japanese individuals, with the T allele representing a risk factor for this condition. The

results demonstrated that individuals with the TT genotype or those with the CT genotype had a 1.82-fold or 1.26-fold increased risk for dyslipidemia, respectively, compared with those with the CC genotype. In addition, individuals with the T allele had a 1.28-fold or 1.17-fold increased risk of hypertriglycedemia or hyper-LDL-cholesterolemia, respectively, compared with those with the CC genotype. The *BTN2A1* genotype was associated with the serum concentrations of total cholesterol, triglycerides and LDL-cholesterol for all individuals, including those who did not take antidyslipidemic drugs, with the T allele being correlated with increased serum concentrations.

It was previously revealed that the T allele of rs6929846 of *BTN2A1* was associated with an increased serum concentration of triglycerides and a decreased concentration of HDL-cholesterol in individuals who had visited the studied hospitals (13). Although this polymorphism was associated with the serum concentrations of triglycerides in a previous study (13) and the present study, there were discrepancies between the two. In the present study, the *BTN2A1* genotype was correlated with the serum concentration of LDL-cholesterol, but not with the serum HDL-cholesterol concentration. This may be attributable to the variation in study populations between the previous (hospital-visiting individuals) (13) and present (community-dwelling individuals) study. The age (65.1±11.4 and 68.8±8.9 years in panels A and B, respectively) and the prevalence of diabetes mellitus (31.3 and 38.0% in panels A and B, respectively) and hypertension (61.5 and 67.3% in panels A and B, respectively) were increased among the subjects in the previous study (13) compared with those in the present study.

The *BTN2A1* gene is a member of the BTN2 subfamily, which encode proteins belonging to the butyrophilin protein family. While the butyrophilin family was originally

identified by its ability to aid the production of milk fat globules (14), numerous butyrophilin and butyrophilin-like families of proteins were demonstrated to regulate immune function, and polymorphisms in the coding sequences were correlated with the predisposition to inflammatory diseases (15). Our previous study (8) revealed that the T allele of rs6929846 increased the transcription activity of *BTN2A1*, and the serum concentrations of high-sensitivity C-reactive protein were significantly greater in individuals in the combined group of CT and TT genotypes than in those with the CC genotype in healthy individuals without neoplastic, infectious or inflammatory disease (16). These observations indicate that the T allele of rs6929846 of *BTN2A1* may accelerate inflammatory processes.

Inflammation is a key component of regulating lipid metabolism, and it leads to changes in lipid metabolism aimed at decreasing the toxicity of a variety of harmful agents and tissue repair by redistributing nutrients to cells involved in the host defense (17,18). An inflammatory condition under bacterial or viral infection has been shown to result in an increase in the serum concentration of triglycerides and a decrease in the serum HDL-cholesterol (19,20). Multiple cytokines are likely to affect the metabolism of cholesterol or triglycerides through several pathways, including the increased production and decreased clearance of extremely low density lipoproteins, impaired reverse cholesterol transport and decreased excretion of bile acids (17,21-23). Furthermore, the acceleration of the inflammatory process by the T allele of rs6929846 may result in alterations in lipid metabolism, although the underlying mechanism remains to be elucidated.

There were several limitations to the current study: i) Considering that the study subjects comprised only Japanese individuals, further studies are likely to be required that include other ethnic groups; ii) it is possible that rs6929846 of *BTN2A1* is in linkage disequilibrium with other polymorphisms in *BTN2A1* or in other nearby genes that are actually responsible for the development of dyslipidemia; iii) the functional relevance of rs6929846 of *BTN2A1* to the pathogenesis of dyslipidemia remains unclear; and iv) environmental factors, including dietary habits, which affect lipid metabolism were not evaluated in the present study.

In conclusion, the current results indicate that *BTN2A1* may be a susceptibility gene for dyslipidemia in Japanese individuals. The determination of genotype of this polymorphism may prove to be informative for the assessment of the genetic risk for dyslipidemia. Considering that multiple variants, each having a small effect, are likely to ultimately be found to be responsible for a large fraction of the genetic component of dyslipidemia, further identification of dyslipidemia susceptibility genes is likely to allow a more accurate assessment of the genetic components of this condition.

Acknowledgements

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