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Association of a Polymorphism of *BTN2A1* With Hypertension in Japanese Individuals

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BACKGROUND

We previously showed that the C→T polymorphism (rs6929846) in butyrophilin, subfamily 2, member A1 gene (*BTN2A1*) was associated with myocardial infarction in Japanese individuals. Given that hypertension is a major risk factor for myocardial infarction, the association of rs6929846 of *BTN2A1* with myocardial infarction might be attributable, at least in part, to its effect on susceptibility to hypertension. We have thus examined the relation of rs6929846 of *BTN2A1* to hypertension in Japanese individuals.

METHODS

A total of 8,567 Japanese individuals from two independent subject panels were examined: Subject panels A and B comprised 2,317 hypertensive individuals and 1,933 controls, and 2,911 hypertensive individuals and 1,406 controls, respectively. The genotype of rs6929846 was determined by a method that combines the PCR and sequence-specific oligonucleotide probes with suspension array technology.

RESULTS

Multivariable logistic regression analysis with adjustment for covariates revealed that rs6929846 of *BTN2A1* was significantly associated with hypertension in subject panel A ($P = 2.6 \times 10^{-6}$; odds ratio, 1.69) and in subject panel B ($P = 0.0284$; odds ratio, 1.24), with the *T* allele representing a risk factor for hypertension. The rs6929846 was associated with systolic blood pressure (BP) in subject panels A ($P = 0.0063$) and B ($P = 0.0115$) and with diastolic BP in subject panel B ($P = 0.0323$), with the *T* allele being related to high BP.

CONCLUSIONS

BTN2A1 may be a susceptibility gene for hypertension in Japanese individuals. Determination of genotype for this polymorphism may prove informative for assessment of the genetic risk for hypertension.

Keywords: *blood pressure; BTN2A1; genetics; hypertension; polymorphism*

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Hypertension is a complex multifactorial and polygenic disorder that is thought to result from an interaction between an individual's genetic background and various environmental factors.[1] The genetic influence on blood pressure (BP) variability has been suggested to be between 30 and 50% among each individual.[2] Given that hypertension is a major risk factor for coronary heart disease, stroke, and chronic kidney disease, personalized prevention of hypertension is an important public health goal.[3,4] Recent genome-wide association studies have implicated various loci and genes in predisposition to hypertension in Caucasian populations or African Americans.[5–9] Kato *et al.* showed a polymorphism (rs3755351) in the adducin 2 gene as a susceptibility locus for hypertension in Japanese individuals.[10] The genes that confer susceptibility to this condition in Asian populations, however, remain to be identified definitively.

We previously showed that the C→T polymorphism (rs6929846) in the 5′ untranslated region of the butyrophilin, subfamily 2, member A1 gene (*BTN2A1*) was significantly associated with myocardial infarction in Japanese individuals by a genome-wide association study.[11] Given that hypertension is a major risk factor for myocardial infarction, we hypothesized that the association of rs6929846 of *BTN2A1* with myocardial infarction might be attributable, at least in part, to its effects on susceptibility to hypertension. We have thus examined the relation of rs6929846 in *BTN2A1* to hypertension in Japanese individuals.

METHODS

Study population. A total of 8,567 Japanese individuals from two independent subject panels were examined. Subject panel A comprised 4,250 individuals (2,317 hypertensive individuals

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and 1,933 controls) who either visited outpatient clinics of or were admitted to the participating hospitals (Gifu Prefectural General Medical Center, Gifu; and Hirosaki University Hospital and Hirosaki Stroke Center, Hirosaki, Japan) between October 2002 and March 2009 because of various symptoms or for an annual health checkup. Subject panel B comprised 4,317 individuals (2,911 hypertensive individuals and 1406 controls) who either visited outpatient clinics or were admitted to participating hospitals (Gifu Prefectural Tajimi Hospital, Tajimi; Japanese Red Cross Nagoya First Hospital, Nagoya; and Inabe General Hospital, Inabe, Japan) between October 2002 and March 2009, or who were recruited to a population-based cohort study of aging and age-related diseases in Nakanojo, Kusatsu, and Tokyo, Japan.

The hypertensive individuals either had a systolic BP of ≥140 mm Hg or diastolic BP of ≥90 mm Hg (or both) or had taken antihypertensive medication. Individuals with valvular heart disease, congenital malformations of the heart or vessels, renal and endocrinologic diseases that cause secondary hypertension, or drug-induced hypertension (alcohol, corticosteroids, and estrogens) were excluded from the study. The control subjects had normal BP (systolic BP of <140 mm Hg and diastolic BP of <90 mm Hg) and no history of hypertension or of taking antihypertensive medication. The hypertensive and control individuals either had or did not have diabetes mellitus, dyslipidemia, or obesity. BP was measured at least twice with subjects having rested in the sitting position for >5 min; the measurements were taken by a skilled physician according to the guidelines of the American Heart Association.[12]

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.

Genotyping of a polymorphism. Venous blood (7 ml) was collected into tubes containing 50 mmol/l ethylenediaminetetraacetic acid (disodium salt), the peripheral blood leukocytes were isolated, and genomic DNA was extracted from these cells with a DNA extraction kit (Genomix; Talent, Trieste, Italy). Genotypes of rs6929846 of *BTN2A1* were determined at G&G Science (Fukushima, Japan) by a method that combines the PCR and sequence-specific oligonucleotide probes with suspension array technology (Luminex, Austin, TX) as described previously.[11] Detailed genotyping methodology was also described previously.[13]

Statistical analysis. Quantitative data were compared between hypertensive individuals and controls by the unpaired Student's *t*-test. Categorical data were compared by the χ^2 test. Allele frequencies were estimated by the gene counting method. Multivariable logistic regression analysis was performed with hypertension as a dependent variable and independent variables including age, sex (0, woman; 1, man), body mass index (BMI), smoking status (0, nonsmoker; 1, current or former smoker), the serum concentration of creatinine, and the prevalence of diabetes mellitus and hypercholesterolemia (0, no history of these conditions; 1, positive history), and *BTN2A1* genotype; and the *P* value, odds ratio, and 95% confidence interval were calculated. *BTN2A1* genotype was assessed according to dominant, recessive, and additive genetic models. Additive models included the additive 1 (heterozygotes vs. wild-type homozygotes) and additive 2 (variant homozygotes vs. wild-type homozygotes) models, which were analyzed simultaneously with a single statistical model. We also performed a stepwise forward selection procedure to examine the effects of *BTN2A1* genotype as well as other covariates on hypertension. The *P* levels for inclusion in and exclusion from the model were 0.25 and 0.1, respectively. In this procedure, *BTN2A1* genotype was examined according to a dominant model on the basis of statistical significance in the multivariable logistic regression analysis. We also examined the relation of rs6929846 of *BTN2A1* to the prevalence of low serum concentration of high density lipoprotein (HDL)-cholesterol (<1.04 mmol/l), high serum concentration of low density lipoprotein-cholesterol (≥3.64 mmol/l), obesity (BMI ≥25 kg/m^2),[14] or diabetes mellitus (fasting plasma glucose level of ≥6.93 mmol/l, blood glycosylated hemoglobin content of ≥6.5%, or taking of antidiabetes medication). Genotype distributions were compared between individuals with or without each factor by the χ^2 test. Multivariable logistic regression analysis was performed with adjustment for age, sex, and BMI in the case of low serum HDL-cholesterol, high serum low density lipoprotein-cholesterol, and diabetes mellitus; or for age and sex in the case of obesity. A *P* value of <0.05 was considered statistically significant. Statistical tests were performed with JMP 5.1 software (SAS Institute, Cary, NC).

RESULTS

Characteristics of study subjects were shown in **Table 1**. In subject panel A, age, the frequency of men, BMI, the prevalence of smoking, hypercholesterolemia, diabetes mellitus, coronary heart disease, and stroke as well as serum concentrations of triglycerides and creatinine and fasting plasma glucose level were greater, whereas the serum concentration of HDL-cholesterol was lower, in hypertensive individuals than in controls. In subject panel B, the frequency of men, BMI, the prevalence of hypercholesterolemia, diabetes mellitus, coronary heart disease, and stroke as well as serum concentrations of triglycerides and creatinine, fasting plasma glucose level, and blood glycosylated hemoglobin content were greater, whereas the serum concentration of HDL-cholesterol was lower, in hypertensive individuals than in controls.

Comparison of genotype distributions and allele frequencies between hypertensive individuals and controls by the χ^2 test revealed that rs6929846 of *BTN2A1* was significantly related to the prevalence of hypertension in subject panels A and B (**Table 2**). We examined the relation of rs6929846 of *BTN2A1* to hypertension excluding subjects with coronary heart disease and stroke. Comparison of genotype distributions by the χ^2 test revealed that rs6929846 of *BTN2A1* was significantly

Table 1 | Characteristics of 8,567 study subjects

	Subject panel A ($n = 4,250$)			Subject panel B ($n = 4,317$)		
Characteristic	Hypertension	Controls	*P*	Hypertension	Controls	*P*
Number of subjects (*n*)	2,317	1,933		2,911	1,406	
Age (years)	67.5 ± 10.4	62.1 ± 12.7	<0.0001	68.8 ± 9.0	68.6 ± 8.8	0.5103
Sex (men, %)	59.3	48.5	<0.0001	60.1	55.3	0.0010
Body mass index (kg/m^2)	23.7 ± 3.3	23.3 ± 3.2	0.0009	23.8 ± 3.5	22.8 ± 3.2	<0.0001
Current or former smoker (%)	17.7	11.4	<0.0001	36.2	37.1	0.5724
Hypercholesterolemia (%)	45.7	23.8	<0.0001	46.8	42.7	0.0103
Diabetes mellitus (%)	37.4	13.6	<0.0001	41.9	31.2	<0.0001
Coronary heart disease	46.7	20.0	<0.0001	22.1	14.7	<0.0001
Stroke (ischemic and hemorrhagic)	22.4	17.7	0.0001	21.2	5.6	<0.0001
Systolic blood pressure (mm Hg)	150 ± 25	122 ± 11	<0.0001	149 ± 23	122 ± 12	<0.0001
Diastolic blood pressure (mm Hg)	77 ± 15	69 ± 10	<0.0001	85 ± 14	72 ± 9	<0.0001
Serum total cholesterol (mmol/l)	5.66 ± 1.15	5.72 ± 1.04	0.1240	5.69 ± 1.08	5.74 ± 1.09	0.1853
Serum triglycerides (mmol/l)	1.61 ± 1.04	1.46 ± 1.16	0.0002	1.70 ± 1.16	1.56 ± 0.98	<0.0001
Serum HDL-cholesterol (mmol/l)	1.29 ± 0.39	1.44 ± 0.41	<0.0001	1.38 ± 0.39	1.45 ± 0.40	<0.0001
Serum LDL-cholesterol (mmol/l)	3.12 ± 0.90	3.09 ± 0.84	0.4127	3.00 ± 0.86	3.04 ± 0.89	0.2323
Fasting plasma glucose (mmol/l)	7.11 ± 3.22	5.90 ± 2.41	<0.0001	7.01 ± 2.95	6.54 ± 2.91	<0.0001
Blood glycosylated hemoglobin (%)	6.48 ± 1.71	6.52 ± 1.81	0.7895	5.80 ± 1.31	5.62 ± 1.23	<0.0001
Serum creatinine (μmol/l)	74.3 ± 87.7	58.7 ± 18.6	<0.0001	67.6 ± 55.4	59.2 ± 15.9	<0.0001

Quantitative data are means ± s.d. Hypercholesterolemia: serum total cholesterol of ≥5.72 mmol/l or taking lipid-lowering medication. Diabetes mellitus: fasting plasma glucose level of ≥6.93 mmol/l, blood glycosylated hemoglobin (hemoglobin A_{1c}) content of ≥6.5%, or taking antidiabetes medication.
HDL, high density lipoprotein; LDL, low density lipoprotein.

Table 2 | Relation of rs6929846 of butyrophilin, subfamily 2, member A1 gene (*BTN2A1*) to hypertension in subject panels A and B determined by the χ^2 test

Subject	rs6929846 (C→T)	Hypertension[a]	Controls[a]	*P* (genotype)	*P* (allele frequency)
Subject panel A				1.7×10^{-10}	3.3×10^{-10}
	CC	1,887 (81.4)	1,716 (88.8)		
	CT	411 (17.7)	203 (10.5)		
	TT	19 (0.8)	14 (0.7)		
Subject panel B				0.0208	0.0051
	CC	2,445 (84.0)	1,225 (87.1)		
	CT	442 (15.2)	174 (12.4)		
	TT	24 (0.8)	7 (0.5)		
All individuals				3.8×10^{-10}	1.6×10^{-10}
	CC	4,332 (82.9)	2,941 (88.1)		
	CT	853 (16.3)	377 (11.3)		
	TT	43 (0.8)	21 (0.6)		

[a]Numbers in parentheses are percentages.

associated with hypertension in subject panels A ($P = 0.0002$) and B ($P = 0.0177$) or in all individuals ($P = 1.4 \times 10^{-5}$).

Multivariable logistic regression analysis with adjustment for age, sex, BMI, smoking status, the serum concentration of creatinine, and the prevalence of diabetes mellitus and hypercholesterolemia revealed that rs6929846 of *BTN2A1* was significantly associated with hypertension in subject panels A and B (dominant and additive 1 models), with the *T* allele representing a risk factor for this condition (**Table 3**). We examined the relation of rs6929846 of *BTN2A1* to hypertension for men (3,124 hypertensive individuals and 1,709 controls) and women (2,104 hypertensive individuals and 1,630 controls) separately (see **Supplementary Table S1** online). Allele frequencies of rs6929846 were significantly

Table 3 | Multivariable logistic regression analysis of rs6929846 of butyrophilin, subfamily 2, member A1 gene (*BTN2A1*) and hypertension

	Dominant		Recessive		Additive 1		Additive 2	
Subject	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)
Subject panel A	**2.6×10^{-6}**	1.69 (1.36–2.11)	0.5171		**3.1×10^{-6}**	1.70 (1.36–2.14)	0.4052	
Subject panel B	**0.0284**	1.24 (1.02–1.51)	0.3216		**0.0420**	1.23 (1.01–1.49)	0.2917	
All individuals	**7.0×10^{-7}**	1.44 (1.25–1.66)	0.1977		**1.6×10^{-6}**	1.43 (1.24–1.66)	0.1465	

Multivariable logistic regression analysis was performed with adjustment for age, sex, body mass index, smoking status, the serum concentration of creatinine, and the prevalence of diabetes mellitus and hypercholesterolemia. *P* values of <0.05 are shown in bold.
CI, confidence interval; OR, odds ratio.

Table 4 | Relation of rs6929846 butyrophilin, subfamily 2, member A1 gene (*BTN2A1*) to systolic and diastolic blood pressure

	BTN2A1 genotype			*P*	*P*
	CC	CT	TT	Dominant	Recessive
Subject panel A					
Systolic blood pressure (mm Hg)	141 ± 25	145 ± 26	147 ± 27	**0.0063**	0.3777
Diastolic blood pressure (mm Hg)	75 ± 14	75 ± 13	75 ± 10	0.3902	0.9368
Subject panel B					
Systolic blood pressure (mm Hg)	140 ± 24	142 ± 25	148 ± 30	**0.0115**	0.0714
Diastolic blood pressure (mm Hg)	80 ± 14	82 ± 14	82 ± 15	**0.0323**	0.4928
All individuals					
Systolic blood pressure (mm Hg)	141 ± 24	143 ± 26	147 ± 29	**0.0001**	0.0504
Diastolic blood pressure (mm Hg)	78 ± 14	79 ± 14	79 ± 13	0.1768	0.7244

Data are means ± s.d. *P* values of <0.05 are shown in bold.

associated with hypertension both for men and for women. Multivariable logistic regression analysis with adjustment for covariates also revealed that rs6929846 of *BTN2A1* was significantly associated with hypertension both for men and for women, with the *T* allele representing a risk factor for this condition.

A stepwise forward selection procedure was performed to examine the effects of *BTN2A1* genotype as well as age, sex, BMI, smoking status, the serum concentration of creatinine, and the prevalence of diabetes mellitus and hypercholesterolemia on hypertension. Analysis revealed that *BTN2A1* genotype (dominant model) was a significant and independent determinant of hypertension in both subject panels A and B (see **Supplementary Table S2** online).

We examined the relation of rs6929846 of *BTN2A1* to systolic and diastolic BP. The rs6929846 of *BTN2A1* was significantly associated with systolic BP in subject panels A and B and with diastolic BP in subject panel B, with the *T* allele being related to high BP (**Table 4**).

Finally, we examined the relation of rs6929846 of *BTN2A1* to the prevalence of low serum concentration of HDL-cholesterol, high serum concentration of low density lipoprotein-cholesterol, obesity, or diabetes mellitus. Comparison of genotype distributions between individuals with or without each cardiovascular risk factor by the χ^2 test revealed that rs6929846 of *BTN2A1* was significantly related to the prevalence of low serum HDL-cholesterol and diabetes mellitus. Multivariable logistic regression analysis with adjustment for age, sex, and BMI also revealed that rs6929846 of *BTN2A1* was significantly associated with the prevalence of low serum HDL-cholesterol and diabetes mellitus, with the *T* allele representing a risk factor for these conditions (see **Supplementary Table S3** online).

DISCUSSION

The regulation of BP involves the integration of a variety of biological systems that control the structure and tone of the vasculature as well as the volume and composition of body fluid. It also involves the adaptation of these systems to constantly changing physiological needs.[15] Given that genetic factors and interactions between multiple genes and environmental factors are important in the development of hypertension,[1] prediction of the risk for hypertension on the basis of genetic variants would be beneficial for personalized prevention of this condition. We have now shown that the C→T polymorphism (rs6929846) in *BTN2A1* was significantly associated with hypertension in Japanese individuals, with the *T* allele representing a risk factor for this condition. The association of rs6929846 of *BTN2A1* with hypertension was observed in a dominant model (*CT* + *TT* vs. *CC*). The percentages of individuals with the *CT* or *TT* genotype among hypertensive subjects and controls were 17.1 and 11.9%, respectively, in all individuals. Our results suggested that individuals with the *T* allele (15.1% of all individuals) have a 1.4-fold increased risk for hypertension.

BTN2A1 is a member of the BTN2 subfamily of genes, which encode proteins belonging to the butyrophilin protein family. *BTN2A1* is located in a cluster of genes on chromosome 6 that includes seven genes belonging to the expanding B7/butyrophilin-like group, a subset of the immunoglobulin gene superfamily. BTN2A1 is an integral plasma membrane B-box protein that contributes to lipid, fatty acid, and sterol metabolism (Entrez Gene, NCBI). *BTN2A1* mRNA is present in most human tissues, including circulating immune cells[16,17] and vascular smooth muscle cells and endothelial cells.[11] While the butyrophilin family was originally identified by ability to aid production of milk fat globules,[18] many butyrophilin and butyrophilin-like family of proteins were shown to regulate immune function, and polymorphisms in the coding sequences were related to predisposition to inflammatory diseases.[17] Our previous study[11] showed that the *T* allele of rs6929846 increased the transcription activity of *BTN2A1*, and the over expression of *BTN2A1* decreased the expression of elastin mRNA and increased the mRNA expression of matrix metallopeptidase 3 and interleukin 5. In our preliminary experiment, the serum concentrations of high sensitivity C-reactive protein were significantly ($P = 0.0343$) greater in individuals in the combined group of *CT* and *TT* genotypes (3.83 ± 1.45 mg/l (mean ± s.e.), $n = 91$) for rs6929846 of *BTN2A1* than in those with the *CC* genotype (2.12 ± 0.23 mg/l, $n = 664$) in 755 healthy individuals without neoplastic, infectious, or inflammatory disease. These observations suggest that the *T* allele of rs6929846 of *BTN2A1* may accelerate inflammatory processes.

The relation of inflammation to BP has been shown. Plasma levels of high sensitivity C-reactive protein were greater in hypertensive individuals than in normotensive individuals.[19] Oxidative stress and vascular inflammation were shown to affect BP and chronic inflammation may play a key role in the pathogenesis of hypertension.[20,21] We have now shown that rs6929846 of *BTN2A1* was significantly associated with hypertension, with the minor *T* allele representing a risk factor for this condition. The enhancement of chronic inflammation by the *T* allele of rs6929846 may account for its association with hypertension, although the molecular mechanism of the effect of rs6929846 of *BTN2A1* on the development of hypertension remains elucidated.

We have shown that rs6929846 of *BTN2A1* was also significantly associated with the prevalence of low serum HDL-cholesterol and diabetes mellitus, with the *T* allele representing a risk factor for these conditions. Previous studies showed that the inflammation plays an important role in the regulation of lipid metabolism[22] and increases insulin resistance.[23] Our results suggested that acceleration of inflammatory process by the *T* allele of rs6929846 might affect lipid and glucose metabolism as well as hypertension.

Our results showed that rs6929846 of *BTN2A1* was significantly associated with systolic BP in subject panels A and B and with diastolic BP in subject panel B. Although the reason for this discrepancy remains unclear, differences in age (subject panel A, 65.0 ± 11.8 years (mean ± s.d.); subject panel B, 68.8 ± 8.9 years; $P < 0.0001$, unpaired Student's *t*-test) and in diastolic BP (subject panel A, 75 ± 14 mm Hg; subject panel B, 81 ± 14 mm Hg; $P < 0.0001$) of study subjects might be attributable to the different effects of rs6929846 on BP between subject panels A and B.

There were several limitations in the present study: (i) Given that the study subjects comprised only Japanese individuals, further study will be required in other ethnic groups. (ii) Given that subjects were recruited by different methods, our study population was heterogeneous, resulting in differences in basal characteristics between cases and controls. (iii) Data for ambulatory BP monitoring were not available in the present study. (iv) 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 hypertension. (v) The functional relevance of rs6929846 of *BTN2A1* to pathogenesis of hypertension remains unclear.

In conclusion, our present results suggest that *BTN2A1* may be a susceptibility gene for hypertension in Japanese individuals. Determination of genotype of this polymorphism may prove informative for assessment of the genetic risk for hypertension. Given that multiple variants, each having a small effect, will ultimately be found to be responsible for a large fraction of the genetic component of essential hypertension, further identification of hypertension susceptibility genes will allow more accurate assessment of the genetic component of this condition.

Supplementary material is linked to the online version of the paper at http://www.nature.com/ajh

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