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Genetic variations of regulator of G-protein signaling 2 in hypertensive patients and in the general population

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Objectives **Mice deficient in the regulator of G-protein signaling 2 (RGS2) exhibit a strong hypertensive phenotype. We studied whether genetic variations in *RGS2* are implicated in hypertension or other phenotypes in Japanese hypertensive individuals and the general population.**

Methods **We sequenced all exons of *RGS2* and the promoter region in 953 and 48 hypertensive individuals, respectively. Genotyping by the TaqMan polymerase chain reaction method was performed for six missense or frameshift mutations and common single nucleotide polymorphisms in the general population, with a sample size of 1872 individuals (862 men and 1011 women).**

Results **We identified five novel missense mutations (Q2L; $n = 2$, Q2R; $n = 1$, M5V; $n = 1$, R44H; $n = 2$, Q78H; $n = 1$) and one novel frameshift mutation (1925–1926insT; $n = 2$) in a heterozygous state, in addition to 33 variations including five common single nucleotide polymorphisms. Six missense/frameshift mutations and three common single nucleotide polymorphisms (−638A > G, 1026T > A, 1891–1892delTC) were successfully genotyped in the general population. Mutations Q2L ($n = 2$), M5V ($n = 1$), and 1925–1926insT ($n = 2$) were only identified in hypertensive subjects. Six out of seven individuals with the R44H mutation, which occurs in the amphipathic α-helical domain of RGS2, had hypertension. The results showed a significant association of two common single nucleotide polymorphisms, 1026T > A [TT versus TA + AA: odds ratio (OR) 1.33; 95% confidence interval (CI) 1.02–1.74; $P = 0.035$] and 1891–1892delTC (I: insertion allele, D: deletion allele, II versus ID + DD: OR 1.47; 95% CI 1.09–1.97; $P = 0.012$), with hypertension in women by multivariate logistic regression analysis.**

Conclusion **Our results suggest that genetic variations in *RGS2* contribute partly to the hypertensive phenotype.** *J Hypertens* **23:1497–1505 © 2005 Lippincott Williams & Wilkins.**

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Keywords: association study, hypertension, missense mutation, *RGS2*, single nucleotide polymorphism

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Introduction

Signaling by G-protein-coupled neurotransmitter receptors in the autonomic nervous system and vasoregulatory factor receptors in the periphery govern both blood pressure, by controlling the constriction and dilatation of resistance arterioles, and electrolyte and fluid balance by the kidneys [1,2]. Hypertension can arise in rodents after the deletion of genes encoding G-protein-coupled receptors (GPCR) such as the dopamine D3 receptor and the endothelin type B receptor [3,4], which normally decrease blood pressure. It can also be caused by the overproduction of GPCR agonists, such as angiotensin and endothelin, which act together to elevate blood pressure [5,6]. In addition, an increased risk of hypertension has been associated with genetic polymorphisms in genes encoding components of GPCR signaling pathways in certain human populations [7–10].

The recently identified regulator of G-protein signaling (RGS) proteins are important in regulating signaling cascades initiated by GPCR activation [11]. RGS proteins facilitate the intrinsic inactivating guanosine triphosphatase reaction of G-protein α-subunits, and thereby serve as effecter antagonists. Of the approximately 30 RGS proteins encoded in the human or mouse genome, RGS2 may be critical for blood pressure regulation. RGS2 is unique among the RGS proteins in its apparent selectivity towards Gqα, which mediates the action of most physiological vasoconstrictors, including norepinephrine, angiotensin II, endothelin-1, and thrombin. RGS2 can also attenuate Gi and Gs-mediated pathways [12,13],

which can also affect blood pressure via other physiologically important agonists such as serotonin, dopamine, and bradykinin. In addition, human *RGS2* maps to chromosome 1q31 [14], within an interval (1q31–42) linked to one of three allelic forms of the gene for pseudohypoaldosteronism type II, an inherited human hypertension disorder [15]. More importantly, it was recently reported that mice lacking *Rgs2* exhibit a strong hypertensive phenotype and persistent constriction of the resistance vasculature [16,17]. Both heterozygous and homozygous *Rgs2*-null mice exhibited a similar level of profound hypertension [16], suggesting that naturally occurring mutations that affect the level of RGS2 protein may have a significant impact on blood pressure regulation.

So far, there are no reports about the relationship between genetic variations in human *RGS2* and hypertension or other phenotypes. Human *RGS2* consists of five exons that encode 211 amino acid residues. In the present study, we screened the promoter and exon regions of *RGS2* in Japanese hypertensive individuals for genetic variations. By genotyping the rare missense/frameshift mutations and common single nucleotide polymorphisms (SNP) in a Japanese general population, we assessed the role of these genetic variations in hypertension and clarified the contribution of common SNP to hypertension and to other phenotypes.

Methods

Hypertensive patients

A total of 953 hypertensive patients (522 men and 431 women, average age 65.0 ± 10.5 years) were recruited from the Division of Hypertension and Nephrology at the National Cardiovascular Center as reported previously [18,19]. Briefly, 92% of study subjects (880 subjects) were diagnosed with essential hypertension, and the rest had secondary hypertension. Hypertension was defined as systolic blood pressure (SBP) of 140 mmHg or greater, diastolic blood pressure (DBP) of 90 mmHg or greater, or the current use of antihypertensive medication. Hyperlipidemia was defined by total cholesterol 220 mg/dl or greater or the current use of antihyperlipidemia medication. Diabetes mellitus was defined by fasting plasma glucose of 126 mg/dl or greater or non-fasting plasma glucose of 200 mg/dl or greater or haemoglobin A1c of 6.5% or greater or the current use of antidiabetic medication. Study subjects had routine laboratory tests, including electrolytes, renal function, blood glucose, haemoglobin A1c, plasma renin activity and plasma aldosterone concentration.

Screening of genetic variations in RGS2

We sequenced all exons and the promoter region of *RGS2* in 953 Japanese hypertensive patients. Blood samples were obtained from hypertensive patients, and genomic DNA was isolated from peripheral blood leukocyte [20]. All exons with their flanking sequences and approximately 1.6 kb of the upstream region were directly sequenced using an ABI PRISM 3700 DNA analyser (Applied Biosystems, Foster City, California, USA) using seven sets of primers, as described previously [20]. Information on primers and polymerase chain reaction (PCR) conditions is available on request. The obtained sequences were examined for the presence of variations using Sequencher software (Gene Codes Corporation, Ann Arbor, Michigan, USA), followed by visual inspection. The A of the ATG of the initiator Met codon is denoted nucleotide +1. The nucleotide sequence (GenBank accession ID NT-004671) was used as a reference sequence.

General population (the Suita Study)

The sample selection and study design of the Suita Study have been described previously [21–23]. Briefly, the subjects visited the National Cardiovascular Center every 2 years for general health check-ups. In addition to performing a routine blood examination that included lipid profiles, glucose levels, blood pressure, anthropometric measurements, a physician or nurse administered questionnaires covering the personal history of cardiovascular diseases, including angina pectoris, myocardial infarction or stroke. Blood pressure was measured after at least 10 min of rest in a sitting position. SBP and DBP were the means of two measurements by well-trained doctors using a mercury sphygmomanometer (recorded in a 3 min pause). The subjects were classified as current drinkers if they drank at least 30 ml ethanol per day, non-drinkers if they had never drunk, and past drinkers if they previously had drunk above 30 ml ethanol per day.

Genotyping of mutations and single nucleotide polymorphisms in the general population

Six rare missense/frameshift mutations and four common SNP with a minor allele frequency of greater than 10% were tried for genotyping (Table 1). The TaqMan PCR method was used for genotyping [24]. The sequences of PCR primers and probes for the TaqMan PCR method are available on request. Among four common SNP, genotyping for −161G > T failed. Nine genetic variations were thus successfully genotyped in 1873 subjects (862 men and 1011 women) participating in the large cohort of the Suita Study. All the participants for genetic analysis in the present study gave written informed consent. All clinical data and sequencing and genotyping results were anonymous. The study protocol was approved by the Ethical Review Committee of the National Cardiovascular Center.

Statistical analysis

Values are expressed as means ± SD. The distribution of patient characteristics between men and women in the Japanese general population was analysed using Student's *t* test or χ^2 analysis. The correlations of three

Table 1 **Sequence variations in the promoter region and exons in RGS2 identified in 953 Japanese hypertensive patients**

SNP name	LD	Region	Amino acid substitution	Allele 1 freq.	Allele 2 freq.	Flanking sequence	Typing	db SNP ID
(−1502)−(−1501)insA*		Promoter		0.979	0.021	cttaagaaaaaa[−/a]tggcattcctag		
−956C > T*		Promoter		0.979	0.021	aaatctctatgt[c/t]tgcagctttctc		
−638A > G*	a	Promoter		0.617	0.383	gagggtctcccc[a/g]ttgcctcagttc	Taqman	rs2746071
−395G > C*	a	Promoter		0.656	0.344	ggcgcccccgcc[g/c]ggccgccgccaa		
−339G > A*		Promoter		0.979	0.021	cgagcccgcccg[g/a]ccgccacgcttc		
−218C > G	b	Promoter		0.965	0.035	aagccggggccg[c/g]agacgtcagcag		
−204G > T		Promoter		1.000	0.000	gacgtcagcagc[g/t]ccccggcttcga		
−203C > T		Promoter		0.999	0.001	acgtcagcagcg[c/t]cccggcttcgag		
−194C > G	c	Promoter		0.996	0.004	gcgccccggctt[c/g]gagacccttcgg		
−193G > C		Promoter		1.000	0.000	cgccccggcttc[g/c]agacccttcggc		
−183G > A		Promoter		0.995	0.005	tcgagacccttc[g/a]gcagcagccgtg		
−167G > A		Promoter		1.000	0.000	gcagccgtgact[g/a]ccgccggcgggc		
−161G > T		Promoter		0.885	0.115	gtgactgccgcc[g/t]gcgggcgctgac	Failed	rs16834859
−155C > G		Promoter		0.999	0.001	gccgccggcggg[c/g]gctgacccatcc		
−149C > T		Promoter		0.999	0.001	ggcgggcgctga[c/t]ccatccccgtgc		
−43A > T	d	Promoter		0.958	0.042	atgctgcgacgc[a/t]cgcccagccgca	rs12130714	
5A > T**		Exon 1	Q2L	0.998	0.001	gaacgataatgc[a/t]aagtgctatgtt	Taqman	
5A > G**		Exon 1	Q2R		0.001	gaacgataatgc[a/g]aagtgctatgtt	Taqman	
9T > C	c	Exon 1	S3S	0.996	0.004	gataatgcaaag[t/c]gctatgttcttg		
13A > G		Exon 1	M5V	0.999	0.001	atgcaaagtgct[a/g]tgttcttggctg	Taqman	
144C > G		Intron 1		0.992	0.008	ctcccgccaccc[c/g]ctgccccacact		
169C > T		Intron 1		0.999	0.001	gcaagctgcaaa[c/t]gcggtactttcg		
928G > A	e	Intron 1		0.930	0.070	tgctcagtacat[g/a]aggtttaaatgt		
969C > A	b	Intron 1		0.963	0.037	atttgaagagtt[c/a]ttgctttgcctt		
1026T > A	a	Intron 1		0.572	0.428	atttggtaaaaa[t/a]gcgttcagctgc	Taqman	rs2746073
1115G > A		Exon 2	R44H	0.999	0.001	attggaagaccc[g/a]tttgagctactt	Taqman	
1229A > G		Intron 2		0.992	0.008	ttgcaaatatca[a/g]tagttagctgct		
1245C > G		Intron 2		0.998	0.002	ttagctgctgaa[c/g]tgaaaaggggaa		
1255G > A		Intron 2		0.999	0.001	aactgaaaaggg[g/a]aactctgatgtg		
1294T > C		Intron 2		0.999	0.001	cagaacctctct[t/c]gcaggccttctc		
1320G > C		Exon 3	Q78H	0.999	0.001	tgaggaagcaca[g/c]ctgtggtcagaa	Taqman	
1891−1892delTC	a	Intron3		0.594	0.406	ttctgcatgctc[tc/−]ttttctcccccc	Taqman	
1925−1926insT		Exon 4	Frameshift	0.999	0.001	tcttgctgcatt[−/t]cagggcttttt	Taqman	
2067T > C	e	Exon 4	A144A	0.927	0.073	agaaaaggaagc[t/c]ccaaaagaggta		
2297A > G	d	Intron4		0.956	0.044	ctttaactctga[a/g]taccaaataaac	rs17647363	
2456C > T	b	Exon 5	F189F	0.965	0.035	ttatcctcgttt[c/t]ttggagtcagaa		
2474C > T		Exon 5	Y195Y	0.998	0.002	gtcagaattcta[c/t]caggacttgtgt		
2642T > A	e	Exon 5	3′UTR	0.935	0.065	aggaaacatcac[t/a]cagaactattga		
2643C > A	e	Exon 5	3′UTR	0.935	0.065	ggaaacatcact[c/a]agaactattgat		

UTR, Untranslated region. *Sequence variations were screened in 48 hypertensive patients. **Triallelic. The apparent linkage disequilibrium (LD), defined by r-square more than 0.5, was indicated by a–e in the LD column. Taqman, The single nucleotide polymorphism (SNP) was successfully genotyped by the Taqman method. Failed, The typing was failed. The A of the ATG of the initiator Met codon is denoted nucleotide +1, as recommended by the Nomenclature Working Group (*Hum Mut* 1998; **11**:1–3). The nucleotide sequence (GenBank Accession ID: NT-004671) was used as a reference sequence.

common SNP to hypertension or diabetes mellitus were analysed by logistic regression analysis, adjusting for confounding factors, including age, body mass index (BMI), present illness (hyperlipidemia and diabetes mellitus), and lifestyle (smoking and drinking). All analyses were performed using the SAS (release 8.2, SAS Institute Inc., Cary, North Carolina, USA). Statistical significance was established at $P < 0.05$. Linkage disequilibrium was calculated using the SNPAlyze version 2.1 (DYNACOM Co. Ltd., Mobara, Japan).

Results

Identification of genetic variations in RGS2 in a Japanese hypertensive population

We identified five missense mutations and one frameshift mutation in *RGS2* by sequencing 953 hypertensive individuals (Table 1). Two out of 925 individuals successfully genotyped had an A-to-T substitution at nucleotide 5 in exon 1, which led to an amino acid substitution from Q to L at position 2 (Q2L). One individual had an A-to-G substitution at nucleotide 5 in exon 1, resulting in an amino acid substitution from Q to R at position 2 (Q2R). One out of 938 individuals had an A-to-G substitution at nucleotide 13 in exon 1, leading to an amino acid substitution from M to V at position 5 (M5V). Two out of 924 individuals had a G-to-A substitution at nucleotide 1115 in exon 2, leading to an amino acid substitution from R to H at position 44 (R44H). One out of 937 individuals had a G-to-C substitution at nucleotide 1320 in exon 3, resulting in an amino acid substitution from Q to H at position 78 (Q78H). We also found one out of 914 individuals with a frameshift mutation that resulted in a thymine insertion at position 1925–1926 in exon 4 (1925–1926insT). These missense/frameshift mutations were all found in the heterozygous form.

We also identified four synonymous polymorphisms, which encoded for S3 (9T > C in exon 1) with a minor allele frequency of 0.4%, A144 (2067T > C in exon 4) with a minor allele frequency of 7.3%, F189 (2456C > T

in exon 5) with a minor allele frequency of 3.5%, and Y195 (2474C > T in exon 5) with a minor allele frequency of 0.2%. Twenty-nine additional genetic variations in the promoter, intronic, and 3′-untranslated regions were also identified. Among these were five common SNP with a minor allele frequency over 10% (−638A>G, −395G>C, −161G>T, 1026T>A, and 1891–1892delTC), and four of them (−638A>G, −395G>C, 1026T > A, 1891–1892delTC) were in tight linkage disequilibrium with an r-square of more than 0.5 (Table 1).

Characteristics of patients with rare missense/frameshift mutations in the hypertensive population

The characteristics of eight hypertensive patients who had missense/frameshift mutations are shown in Table 2. With the exception of one hypertensive patient with the R44H mutation (case 5), seven other hypertensive patients with mutations had hyperlipidemia. Two patients with the R44H mutation (cases 5 and 6) had non-insulin-dependent diabetes mellitus (NIDDM), one of which (case 6) showed diabetic nephropathy with overt proteinurea, even when treated with insulin and an angiotensin-converting enzyme inhibitor. The patient with the 1925–1926insT frameshift mutation (case 8) was diagnosed with NIDDM and hyperlipidemia. Regarding the antihypertensive medication for this patient (case 8), the angiotensin II type 1 receptor blocker (ARB), losartan, was prescribed for this patient; however, losartan was totally ineffective at lowering blood pressure (pre-treatment blood pressure: 162/97 mmHg, post-treatment blood pressure 185/110 mmHg). He also showed low plasma renin activity (0.3 ng/ml per hour). There were no records regarding which other patients with missense mutations of RGS2 were taking ARB.

Table 3 Basic characteristics of subjects in the Suita Study.

	Women (n = 1011)	Men (n = 862)
Age (years)	63.3 ± 11.0	66.3 ± 11.1*
Systolic blood pressure (mmHg)	128.0 ± 19.8	131.8 ± 19.4*
Diastolic blood pressure (mmHg)	76.5 ± 9.8	79.7 ± 10.7*
Body mass index (kg/m^2)	22.2 ± 3.2	23.3 ± 2.9*
Total cholesterol (mg/dl)	215.6 ± 30.8*	197.9 ± 30.4
HDL-cholesterol (mg/dl)	64.5 ± 15.2*	55.0 ± 14.2
Current smokers (%)	6.2	30.4†
Current drinkers (%)	29.5	67.2†
Present illness (%)		
Hypertension	38.0	47.3†
Hyperlipidemia	54.3†	27.8
Diabetes mellitus	5.2	12.8†

Hypertension indicates systolic blood pressure of 140 mmHg or greater, or diastolic blood pressure of 90 mmHg or greater, or antihypertensive medication. Hyperlipidemia, total cholesterol 220 mg/dl or greater, or antihyperlipidemia medication. Diabetes, fasting plasma glucose 126 mg/dl or greater, or non-fasting plasma glucose level of 200 mg/dl or greater, or haemoglobin A1c 6.5% or greater, or antidiabetic medication. HDL, high-density lipoprotein. Values are mean ± SD or percentage. *P < 0.05 between women and men by Student's t-test; †P < 0.05 between women and men by χ^2 test.

Characteristics of individuals with rare missense/frameshift mutations in the general population

The characteristics of the 1873 subjects comprising the Japanese general population group (862 men, 1011 women) are summarized in Table 3. Age, SBP, DBP, BMI, the percentage of current smokers, the percentage of current drinkers, and the prevalence of hypertension and diabetes mellitus were significantly higher in men than in women. Total cholesterol, high-density

Table 2 Clinical profiles of eight hypertensive patients with missense/frameshift mutation in the hypertensive population

Case	1	2	3	4	5	6	7	8
Mutation	Q2L	Q2L	Q2R	M5V	R44H	R44H	Q78H	1925–1926insT
Age (years)	63	72	74	64	54	68	71	60
Sex	Female	Male	Male	Male	Male	Female	Male	Male
Body mass index (kg/m^2)	24.1	24.7	–	23.2	23.4	17.0	22.3	28.7
Diagnosis	EHT, HL	EHT, HL, HU, VSA	EHT, HL, IGT	EHT, HL	EHT, NIDDM	EHT, NIDDM, HL, HU, DN	EHT, HL, AF, CAS	EHT, NIDDM, HL, VSA
Hypertension duration (years)	5	42	< 1	24	10	26	30	25
Hypertension family history	Mother, brother	Father, mother, brother	None	Mother, brother	Father, mother, brother	Mother	Mother, brother	None
Systolic blood pressure (mmHg)	140	140	122	140	122	126	170	134
Diastolic blood pressure (mmHg)	66	90	86	72	80	68	100	70
Medication	CCB, HLD	CCB, BB, HLD, HUD	CCB, ACEI, AB, DU	CCB, ACEI	CCB	CCB, ACEI, HUD, AP, INS	BB	CCB, ARB, BB AB, DMD
Sodium ion (mEq/l)	141	137	139	139	142	139	140	145
Potassium ion (mEq/l)	4.0	4.1	4.2	4.4	3.7	4.4	4.4	4.0
Chloride ion (mEq/l)	107	105	96	104	107	103	106	107
Creatinine (mg/dl)	0.5	0.6	0.6	0.8	0.4	0.9	0.7	0.6
Overt proteinuria	No	No	No	No	No	Yes	No	N
Plasma renin activity (ng/ml/h)	1.2	3.0	–	–	1.2	–	1.0	0.3
Plasma aldosterone concentration (ng/dl)	15.6	15.3	–	–	14.0	–	15.1	12.0
Fasting blood sugar (mg/dl)	98	77	103	110	136	159	89	115
Haemoglobin A1c (%)	5.2	–	5.4	5.2	6.7	6.0	5.0	5.3

AB, α-adrenergic blocker; ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AP, anti-platelet aggregation drug; ARB, angiotension II receptor blocker; BB, β-adrenergic blocker; CAS, carotid artery stenosis; CCB, calcium antagonist; DMD, diabetes mellitus drug; DN, diabetic nephropathy; DU, diuretics; EHT, essential hypertension; HL, hyperlipidemia; HLD, hyperlipidemia drug; HU, hyperuricemia; HUD, hyperuricemia drug; IGT, impaired glucose tolerance; INS, insulin; NIDDM, non-insulin dependent diabetes mellitus; VSA, vasospastic angina. Normal values in our institute: sodium ion, 136–146 mEq/l; potassium ion, 3.6–4.9 mEq/l; chloride ion, 99–109 mEq/l; creatinine, 0.6–1.1 mg/dl; plasma renin activity, 0.2–2.7 ng/ml per hour; plasma aldosterone concentration, 2–13 ng/dl.