Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 57 (2008) 421–427
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

RGS2 C1114G polymorphism and body weight gain in hypertensive patients

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Received 17 July 2007; accepted 29 October 2007

Abstract

RGS2 is a negative regulator of G_α protein signaling and promotes adipocyte differentiation. Recently, we described a polymorphism at the C1114G locus with the G allele associated with hypertension in a cross-sectional study. The aim of the present study was to assess whether the RGS2 C1114G is predictive of overweight in young subjects with grade I hypertension. We genotyped at the RGS2 C1114G locus 406 (male, n = 294; female, n = 112) white hypertensive subjects (age, 33 ± 9 years) never treated for hypertension and at low cardiovascular risk. Median follow-up was 7.85 years. At baseline, male patients carrying the RGS2 1114G allele had higher body mass index (BMI) than patients with CC genotype (26.1 ± 0.3 vs 25.3 ± 0.3 kg/m^2, $P < .05$). The frequency of male patients with BMI ≥25 was similar between the patients with G allele and those with CC genotype (55.1% vs 47.8%, P = not significant). No significant difference between the 2 groups was observed with regard to physical activity, blood pressure, and heart rate. At the end of follow-up, BMI was higher in male patients with G allele compared with patients with CC genotype (26.8 ± 0.3 vs 25.8 ± 0.2 kg/m^2, $P < .01$); and the frequency of male patients with BMI >25 kg/m^2 was greater in the former (69.0% vs 52.2%, $P < .01$). According to Cox regression, allele G was a significant predictor of developing overweight or obesity during follow-up. These epidemiologic relations were not significant in female patients. In young male patients with grade I hypertension, RGS2 1114G allele is associated with increased BMI and with greater risk of developing overweight or obesity. The RGS2 1114G allele may be considered a genetic marker that predicts an individual's predisposition to gaining weight.

1. Introduction

Obesity is a clinical condition that predisposes to several diseases, including hypertension and type 2 diabetes mellitus [1]. Hypertension is a common condition in obese individuals, with a prevalence of 42% among obese men and 38% among obese women [1]. On the other hand, weight gain is associated with an increased risk of developing hypertension [2].

The availability of abundant, energy-rich processed foods in the last few decades has resulted in a sharp rise in the prevalence of obesity in Westernized countries. However, a part of the variance in body mass index (BMI) is heritable; and heritability estimates for obesity are high (typically >0.70), comparing with other complex traits such as hypertension [3]. A large number of genes are involved in adipose tissue deposition, including genes coding for G protein signaling [4]. A family of proteins called *RGS* (*R*egulators of *G*-protein *S*ignaling) terminates G-protein signaling by accelerating the rate of guanosine triphosphate (GTP) hydrolysis by G_α subunits [5]. Among the members of the RGS family, RGS2 is the principal RGS protein for $G_{\alpha q}$-coupled membrane receptors of several hormones [6].

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0026-0495/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2007.10.021

RGS2 has an important and specific function during adipocyte differentiation [7,8]. Moreover, RGS2 may be involved in the regulation of basal metabolism, being a regulator of thyroid-stimulating hormone receptor–induced $G_{\alpha q}$ signal transduction [9]. Freson et al [10] showed that RGS2 may be involved in metabolic syndrome in white European men.

Recently, we investigated a common polymorphism (C1114G) in the 3′ untranslated region of the RGS2 gene [11]. RGS2 G allele frequency was increased in hypertensive patients compared with normotensive subjects [11]. Whether RGS2 predisposes the subjects to obesity, which, in turn, may lead to hypertension and metabolic syndrome, has not been determined. Therefore, we investigated the association of RGS2 C1114G polymorphism with the risk of weight gain in a homogeneous cohort of young, never-treated patients with stage I hypertension to clarify its relationship with obesity.

2. Research methods and procedures

2.1. Study population

The study was carried out in 406 white patients with grade I hypertension at low cardiovascular risk from hypertension clinics in Northern Italy that took part in the multicenter Hypertension and Ambulatory Recording Venetia Study (HARVEST), a long-term prospective study of 18- to 45-year-old individuals investigating the origin of hypertension with regard to clinical [12], physiological [13], and genetic [14] characteristics. Inclusion criteria were described previously [15]. Briefly, never-treated subjects screened for stage I hypertension (systolic blood pressure between 140 and 159 mm Hg and/or diastolic blood pressure between 90 and 99 mm Hg) were enrolled. The baseline data included a medical and family history and a questionnaire on lifestyle [13,14]. The interview was performed by the local investigator (physician). Current smokers were those who reported smoking 1 or more cigarettes per day and were divided into 3 categories, according to whether they smoked 1 to 5, 6 to 10, or >10 cigarettes per day. For physical activity habits, subjects were categorized as nonexercisers if they did not perform any sport activity on a regular basis and exercisers if they had performed the above-mentioned sports at least once in a week during the previous 2 months.

All participants underwent a physical examination, anthropometric measurements, office (mean of 3 readings) and 24-hour noninvasive ambulatory blood pressure measurement, resting electrocardiogram, and echocardiography [16]. Diabetes was ruled out by fasting serum glucose test; and renal impairment, by serum creatinine and urinalysis. None of the patients had cardiac failure or evidence of coronary heart disease.

The study was approved by the HARVEST Ethics Committee, and informed consent was obtained from all participants.

2.2. Study protocol

The subjects taking part in this subproject were all those recruited and followed up in 4 of the participating centers, who gave informed consent to blood sampling for genetic studies. After enrollment, the patients were seen in the outpatient clinic monthly during the first 3 months of follow-up, after 6 months, after 1 year, and every 6 months thereafter. At each visit, weight and office blood pressure were measured by the local investigator (physician) according to the recommendations of the British Society of Hypertension [17]. Subjects were followed until they developed sustained hypertension requiring antihypertensive treatment in accordance with international guidelines [14,17,18]. The definition of sustained hypertension was based on at least 6 clinic blood pressure readings taken on 2 subsequent visits within 1 month. Patients lost to follow-up were censored at the date of latest contact. Body mass index was calculated as weight in kilograms divided by the square of height in meters and was rounded to the nearest 10th. *Overweight* was defined as a BMI of 25.0 to 29.9 kg/m^2 and *obesity* as a BMI of 30.0 kg/m^2 or higher [19,20].

Among all the patients with BMI<25 kg/m^2 at enrollment, those who developed overweight and/or obesity during follow-up reached the end point for the purpose of the present substudy.

2.3. Genotyping

Cells were collected from the buffy coat obtained from heparinized blood (2 mL) from all subjects by centrifugation (400*g* for 30 minutes at 4°C). Genomic DNA was extracted from whole blood with a proprietary reagent (Macherey-Nagel, Düren, Germany), according to the manufacturer's protocol. Primers and probes for allelic discrimination analysis of SNP C1114G (ref SNP: rs4606) were designed from sequences derived as described elsewhere [11]. The probe for the G allele was labeled with a reporter 5,6-carboxyfluorescein (FAM) dye at its 5′-end and a quencher 4-(4′-dimethylaminophenylazo)benzoic acid (Black Hole 1) dye at its 3′-end, whereas the probe of the allele C was labeled with Texas Red dye at its 5′-end and Black Hole 2 at its 3′-end (dyes from MWG Biotech AG, Ebersberg, Germany). The sequence and amplicon length of both genes was previously described [11]. Briefly, 2 μL of purified DNA was amplified in a real-time polymerase chain reaction in the iCycler iQ system (Bio-Rad, Hercules, CA). All the reactions were performed in 96-well plates, using the iQ Supermix (Bio-Rad), as previously described [11]. Positive controls, genotyped by direct sequencing, were included in each run, together with a negative control containing no DNA template. The amplification was performed with the following thermal protocol: 94°C for 3 minutes to denature, 40 cycles at 94°C for 30 seconds for denaturing, and 53°C for 1 minute for annealing and extension.

2.4. Statistical analysis

Analysis was carried out with the use of the SPSS software package (version 15; SPSS, Chicago, IL). Relations between variables were assessed by means of the Pearson correlation for continuous variables and χ^2 or Fisher exact test for categorical variables. The Student *t* test and univariate analysis of variance with Bonferroni correction for multiple comparisons were used to compare means among alleles. Hardy-Weinberg equilibrium was assessed by χ^2 test with 1 *df*. To test the effect of the G allele on the risk of developing overweight and/or obesity during follow-up, a multivariate Cox proportional hazard model was used including all patients with BMI <25 kg/m^2 at enrollment. The significance level was set to $\alpha = .05$. Results are given as mean ± SEM.

3. Results

We studied 406 hypertensive patients; 189 were homozygous for the 1114C allele (CC genotype), 176 were heterozygous (CG genotype), and 41 were homozygous for the 1114G allele (GG genotype). The genotype distribution was in Hardy-Weinberg equilibrium.

Among male patients (n = 294), the 3 genotypes did not differ with regard to age, heart rate, and blood pressure values (Table 1). When patients homozygous or heterozygous for the G allele (CG and GG genotypes, respectively) were combined for analysis, BMI was higher in patients with G allele than in patients with CC genotype (26.1 ± 0.3 vs 25.3 ± 0.3 kg/m^2, *P* = .02) (Table 1). As shown in Fig. 1, the frequency of male patients with overweight was similar between the patients with G allele and those with CC genotype (43.7% vs 41.2%, *P* = not significant). In addition, the frequency of patients with obesity (11.4% vs 6.6%, *P* = not significant) did not differ significantly between the groups. Serum creatinine, glucose, triglycerides, total cholesterol, and high-density lipoprotein (HDL) cholesterol were also similar in the patients carrying the G allele in comparison with those with CC genotype (Table 1).

Among female patients (n = 112), the patients carrying the G allele did not differ from patients with CC genotype with regard to age, sex, BMI, heart rate, and blood pressure values (Table 2). Heart rate at ambulatory blood pressure monitoring was lower in patients with CG and GG genotype compared with patients with CC genotype (76.0 ± 1.0 vs 79.0 ± 1.0 beats per minute, *P* = .04) (Table 2). As shown in Fig. 1, the frequency of overweight and obesity in female patients with G allele was similar to that in patients with CC genotype. No significant difference between the genotypes was observed with regard to smoking, ethanol or coffee consumption, and physical activity in male and female patients (data not shown).

As shown in Fig. 1, the frequency of male patients with overweight or obesity at the end of follow-up was higher in the patients with G allele compared with those with CC genotype (50.0% vs 43.4% and 19.0% vs 8.8%, respectively; *P* < .01). At the end of follow-up, there was no significant difference between the patients with CC genotype and those with CG and GG genotypes with respect to heart rate and office and ambulatory blood pressure (Table 3). Furthermore, glucose, triglycerides, total cholesterol, and HDL cholesterol at the end of follow-up did not differ between the groups (data not shown). No significant difference between the genotypes was observed with regard to BMI, heart rate, and office and ambulatory blood pressure in female patients at the end of follow-up (Table 3).

Table 1
Baseline characteristics of the male population according to RGS2 C1114G polymorphism

	CC (n = 136)	CG (n = 130)	GG (n = 28)	*P*[a]	CG + GG	*P*[b]
Age (y)	31.9 ± 0.8	32.0 ± 0.8	33.9 ± 1.8	.518	32.4 ± 0.7	.624
BMI (kg/m^2)	25.3 ± 0.3	26.2 ± 0.3	25.6 ± 0.6	.051	26.1 ± 0.3	.022
SBP (mm Hg)	147.8 ± 0.9	146.3 ± 0.9	146.7 ± 1.9	.490	146.4 ± 0.8	.237
DBP (mm Hg)	92.5 ± 0.5	93.5 ± 0.6	93.1 ± 0.8	.370	93.5 ± 0.8	.175
HR (beats/min)	73.8 ± 0.8	73.6 ± 0.8	72.3 ± 1.5	.696	73.4 ± 0.7	.667
SBP 24 h (mm Hg)	133.7 ± 0.8	133.0 ± 0.8	134.6 ± 1.8	.688	133.3 ± 0.8	.704
DBP 24 h (mm Hg)	81.3 ± 0.6	80.4 ± 0.7	81.4 ± 1.3	.672	80.6 ± 0.6	.489
HR 24 h (beats/min)	70.9 ± 0.7	71.1 ± 0.7	70.6 ± 1.7	.945	71.0 ± 0.6	.883
Hemoglobin (g/dL)	14.9 ± 0.1	15.1 ± 0.1	14.9 ± 0.2	.528	15.0 ± 0.1	.392
Erythrocyte count (10^{12}/L)	5.05 ± 0.04	5.08 ± 0.04	4.90 ± 0.10	.177	5.06 ± 0.04	.976
Serum creatinine (mg/dL)	0.92 ± 0.02	0.93 ± 0.02	0.90 ± 0.04	.764	0.92 ± 0.02	.761
Serum glucose (mg/dL)	91.8 ± 0.8	95.0 ± 0.9	97.1 ± 2.3	.417	95.2 ± 1.1	.238
Total cholesterol (mg/dL)	190.3 ± 3.7	195.9 ± 4.4	189.4 ± 8.2	.573	194.5 ± 3.9	.409
HDL cholesterol (mg/dL)	48.6 ± 1.2	50.9 ± 1.3	53.9 ± 3.4	.189	51.5 ± 1.2	.114
Triglycerides (mg/dL)	123.7 ± 8.9	123.0 ± 7.4	110.5 ± 15.1	.805	121.0 ± 6.7	.805
Uric acid (mg/dL)	5.3 ± 0.1	5.4 ± 0.1	5.6 ± 0.3	.544	5.4 ± 0.1	.338
AER (mg/24 h)	10.9 ± 2.0	12.5 ± 2.9	11.5 ± 1.6	.838	12.0 ± 2.5	.728

Values are means ± SEM. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; AER, albumin excretion rate.

[a] The statistical analysis was performed by analysis of variance among the 3 genotypes.

[b] The statistical analysis was performed by Student *t* test for CG + GG vs CC genotypes.

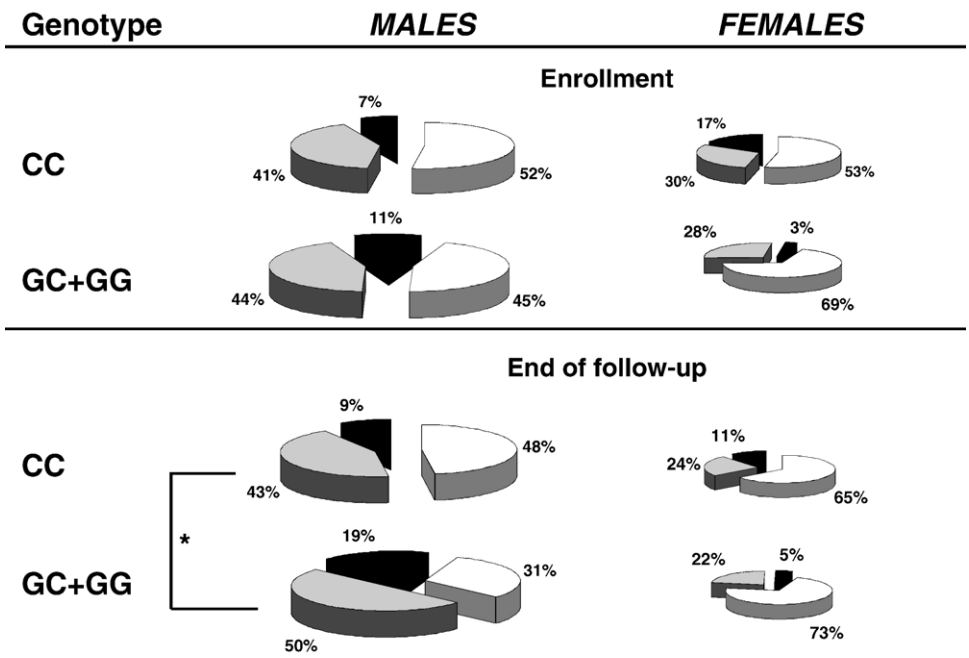

Fig. 1. Frequencies of overweight (▩) and obesity (■) according to the presence of RGS2 1114G allele in male and female patients at enrollment (upper panel) and at the end of follow-up (lower panel). *P <01.

During a median follow-up of 94.2 ± 2.6 months, among patients with BMI <25 kg/m^2 at baseline (male, n = 142; female, n = 69), a higher number of male patients developed obesity or overweight in comparison with female patients (19.0% vs 8.7%, respectively; P < .01). Among patients with BMI >25 kg/m^2 (n = 195), 18 male patients and 13 female patients lost enough weight to return to normal weight. According to a multivariate Cox model including all male patients with BMI <25 kg/m^2 at enrollment, presence of the G allele (95% confidence interval [CI], 1.110-3.952; P = .022), systolic blood pressure (95% CI, 1.007-1.067; P = .016), and age (95% CI, 1.008-1.083; P = .016) at enrollment were predictors of reaching overweight or obesity, whereas heart rate (95% CI, 0.929-0.996; P = .031) had a negative association (Table 4). Physical inactivity and smoking habits were not associated with overweight or obesity at the end of

Table 2
Baseline characteristics of the female population according to RGS2 C1114G polymorphism

	CC (n = 54)	CG (n = 44)	GG (n = 14)	P [a]	CG + GG	P [b]
Age (y)	35.8 ± 1.1	37.5 ± 1.1	35.0 ± 1.4	.388	36.9 ± 0.9	.415
BMI (kg/m^2)	24.8 ± 0.7	23.8 ± 0.6	23.1 ± 0.7	.316	23.6 ± 0.5	.154
SBP (mm Hg)	145.0 ± 1.3	143.2 ± 1.8	146.0 ± 3.4	.609	143.8 ± 1.6	.575
DBP (mm Hg)	95.0 ± 0.5	94.4 ± 0.7	94.3 ± 0.8	.761	94.4 ± 0.5	.462
HR (beats/min)	78.3 ± 1.4	75.3 ± 1.7	74.6 ± 1.8	.283	75.1 ± 1.4	.114
SBP 24 h (mm Hg)	128.5 ± 1.7	128.6 ± 1.8	129.0 ± 3.8	.992	128.7 ± 1.7	.932
DBP 24 h (mm Hg)	83.4 ± 1.0	83.1 ± 1.0	85.2 ± 2.5	.659	83.7 ± 1.0	.998
HR 24 h (beat/min)	79.0 ± 1.0	77.9 ± 1.2	73.1 ± 1.7	.030	76.0 ± 1.0	.041
Hemoglobin (g/dL)	13.5 ± 0.1	13.3 ± 0.2	13.1 ± 0.3	.445	13.3 ± 0.2	.254
Erythrocyte count (10^{12}/L)	4.51 ± 0.04	4.49 ± 0.05	4.47 ± 0.17	.141	4.49 ± 0.06	.710
Serum creatinine (mg/dL)	0.75 ± 0.02	0.76 ± 0.03	0.73 ± 0.06	.890	0.76 ± 0.03	.888
Serum glucose (mg/dL)	90.3 ± 1.3	93.8 ± 2.1	89.1 ± 1.3	.243	92.7 ± 1.7	.271
Total cholesterol (mg/dL)	197.8 ± 5.4	197.6 ± 6.0	186.1 ± 12.8	.616	194.9 ± 5.5	.708
HDL cholesterol (mg/dL)	60.3 ± 2.5	62.1 ± 3.5	54.3 ± 3.4	.536	60.6 ± 2.9	.929
Triglycerides (mg/dL)	95.9 ± 10.9	100.8 ± 10.7	85.5 ± 9.8	.797	97.5 ± 8.6	.908
Uric acid (mg/dL)	4.0 ± 0.2	4.0 ± 0.2	3.7 ± 0.4	.733	3.9 ± 0.2	.832
AER (mg/24 h)	14.9 ± 5.8	16.2 ± 4.7	11.5 ± 2.7	.916	15.1 ± 3.6	.974

Values are means ± SEM.

[a] The statistical analysis was performed by analysis of variance among the 3 genotypes.

[b] The statistical analysis was performed by Student t test for CG + GG vs CC genotypes.

Table 3
Characteristics of the study population according to RGS2 C1114G polymorphism at the end of follow-up

	Male			Female		
	CC	CG + GG	*P*	CC	CG + GG	*P*
Length of follow-up (mo)	89.6 ± 4.5	84.2 ± 4.1	.374	84.7 ± 7.4	89.7 ± 7.1	.624
BMI (kg/m^2)	25.8 ± 0.2	26.8 ± 0.3	.006	24.2 ± 0.6	23.7 ± 0.5	.480
SBP (mm Hg)	144.7 ± 1.2	146.1 ± 1.1	.407	145.6 ± 1.8	142.3 ± 2.1	.232
DBP (mm Hg)	93.7 ± 0.9	94.3 ± 0.9	.656	94.4 ± 1.3	91.7 ± 1.5	.181
HR (beats/min)	70.2 ± 0.7	70.6 ± 0.8	.684	73.7 ± 1.7	71.0 ± 1.0	.173
SBP 24 h (mm Hg)	134.8 ± 0.9	134.9 ± 0.9	.898	130.1 ± 1.9	131.5 ± 1.6	.579
DBP 24 h (mm Hg)	83.5 ± 0.7	83.3 ± 0.7	.858	83.7 ± 1.2	83.0 ± 1.1	.632
HR 24 h (beats/min)	70.6 ± 0.7	71.7 ± 0.7	.229	77.9 ± 1.2	75.2 ± 1.1	.103

follow-up (Table 4). In female patients, the G allele was not a significant predictor of outcome in the multivariate Cox model.

4. Discussion

The present study demonstrates that the 1114G allele of RGS2 gene is associated with increased BMI and with greater risk of developing overweight or obesity in hypertensive patients.

Several hormones modulate lipolysis through G-protein–coupled receptors [21]. G-protein–coupled receptor signal transduction is triggered by dissociation of the GTP-bound G_α from the $G_{\beta\gamma}$ dimer. The dissociated subunits interact with effector molecules to propagate the intracellular signal [22]. The duration and intensity of the cellular response to external signals are largely limited by guanosine triphosphatase activity, intrinsic to G_α, which, in turn, can reassociate with $G_{\beta\gamma}$ and receptors [22].

A family of proteins, called *RGS* (*R*egulators of *G*-protein *S*ignaling), terminates G-protein signaling by accelerating the rate of GTP hydrolysis by G_α subunits [5]. Among the members of the RGS family, RGS2 displays regulatory selectivity for the $G_{\alpha q}$ subclass of G proteins [23]. Once activated, RGS2 increases the guanosine triphosphatase activity of $G_{\alpha q}$, leading to a diminished cellular activation by $G_{\alpha q}$-coupled receptor [23,24].

In adipocytes, $G_{\alpha q}$ appears to play a necessary role in insulin-stimulated glucose transport; and it can transmit signals from the insulin receptor to the p110α subunit of PI3-kinase, which leads to glucose transporter 4 translocation [25]. Thus, RGS2 may be involved in glucose entrance in adipocytes.

In adipose tissue, activation of β-adrenoceptors by catecholamines leads to $G_{\alpha s}$ activation and, subsequently, to increased cyclic adenosine monophosphate production by adenylyl cyclase that is followed by activation of protein kinase A and hormone-sensitive lipase, the key enzyme of lipolysis [21]. On the contrary, activation of the $G_{\alpha i}$-coupled receptors leads to a decrease in intracellular cyclic adenosine monophosphate level, exerting an antilipolytic effect [21]. Interestingly, in the brain, RGS2 increases synaptic vesicle release by down-regulating the $G_{\alpha i}$ signaling [26]. Recently, we demonstrated that C1114G polymorphism was associated with RGS2 expression, with the lowest values in GG hypertensive subjects [11]. In patients with G allele, $G_{\alpha q}$-coupled receptor signaling, as angiotensin II–stimulated intracellular Ca^{++} increase and ERK1/2 phosphorylation, was higher compared with patients with CC genotype [11]. Thus, we can speculate that reduced expression of RGS2 may enhance both $G_{\alpha q}$ signaling, leading to enhanced glucose transporter 4 translocation, and $G_{\alpha i}$ signaling, leading to an antilipolytic effect.

Other experimental evidence showed that RGS2 acts as a regulator of transcription, inducing the expression of adipogenic markers [7,8]. In vitro studies show that RGS2 plays a crucial role in the program of adipocyte differentiation and may contribute to the function of peroxisome proliferator–activated receptor γ [7,8]. Furthermore, in βTC3 cells, overexpression of RGS2 decreased glucose-dependent insulinotropic polypeptide (GIP)–stimulated insulin secretion, attenuating the $G_{\alpha s}$-adenylate cyclase signaling pathway [27] and suggesting a potential role for RGS2 in modulating insulin secretion in pancreatic islet cells.

RGS2 is located on chromosome 1, and a growing number of studies [28-31] have reported linkage of the components of the metabolic syndrome to a region on human chromosome 1q. Regions of chromosome 1 are linked to the distribution of body fat in men [28], essential hypertension [29], and the metabolic syndrome [30]. Moreover, in a French Canadian population, the most prominent clusters of quantitative trait loci for hemodynamic, anthropometric, and metabolic phenotypes were found on chr 1 and chr 3 [31]. Two clusters regrouping >20 quantitative trait loci peaked at

Table 4
Relative risk of reaching overweight and/or obesity among male patients with BMI <25 kg/m^2 at enrollment, according to multivariate Cox analysis

	Relative risk	95% CI	*P*
Age	1.045	1.008-1.083	.016
Smoking	1.105	0.737-1.656	.629
Physical inactivity	1.312	0.708-2.429	.387
SBP at enrollment	1.036	1.007-1.067	.016
HR at enrollment	0.962	0.929-0.996	.031
G allele	2.094	1.110-3.952	.022

175 and 210 cM on chromosome 1. Bivariate analysis, including BMI and glucose-insulin, exceeded LOD of 5 at 175 cM on chromosome 1 [31], suggesting that genes in this region are relevant for the components of the metabolic syndrome including adiposity.

Diet clearly plays an important role in the development and progression of this condition. The genetic background can interact with habitual dietary fat composition, thereby affecting predisposition to overweight, and may modulate the responsiveness to altered dietary fat intake. Different diet regimens may explain the lack of association found in the present study in female patients, but we have no information on dietary fat intake in our cohort. Our female patients had lower BMI values than male patients and developed obesity less frequently. The G allele had no impact on body composition of female patients. This sexual dimorphism might be conditioned by the activity of sex hormones, differences in lifestyle, exposure to varying environmental factors, and/or epigenetic mechanisms involving genes mapping to the sex chromosomes. Sexual dimorphism was also reported in twins. Thus, Poulsen et al [32] observed divergent genetic influences on the components of the metabolic syndrome among male and female twins.

Recently, Freson et al [10] demonstrated that a C to G polymorphism at position −391 was associated with increased RGS2 expression in adipocytes and was associated with the metabolic syndrome in white European men. We did not find any association of the present polymorphism with glucose levels, triglycerides, total cholesterol, and HDL cholesterol in our cohort. We did not perform measurement of insulin sensitivity. However, in the study of Freson et al, among the components of the metabolic syndrome score, only triglycerides were significantly higher in G allele carriers than CC homozygotes [10]. Moreover, that study had a cross-sectional design and included a large population of patients treated with antihypertensive and antidiabetic agents. Longitudinal studies in a well-defined cohort can provide more meaningful data on the predictive power for outcome of a genotype. The HARVEST was designed with the purpose of studying prospectively a homogenous cohort of subjects at low cardiovascular risk. This allowed us to leave many patients untreated for long periods of time because their blood pressure remained below the threshold for treatment. We reasoned that in these young hypertensive patients with low cardiovascular risk profile, the genetic influences on BMI could be more pronounced than in obese older patients with long-lasting hypertension in whom the effects of environmental factors may prevail.

In mice, disruption of the RGS2 gene increases blood pressure and prolongs vasoconstrictor responses of the peripheral resistance vasculature in vivo and of aortic vascular smooth muscle cells in vitro [33]. Rare mutations in RGS2 have been associated with hypertension in a Japanese cohort [34]. In black population, the intronic 1891 to 1892TC and 2138 to 2139AA in/del, as well as haplotype B of RGS2 gene, were associated with hypertension, suggesting a potential ethnic-specific genetic contribution to hypertension [35]. We did not find any difference regarding blood pressure values both at the enrollment and at the end of follow-up. The patients enrolled in the present study already had mildly elevated blood pressure levels; and thus, the effect of RGS2 genotype could be diluted by the high blood pressure values at enrollment.

A limitation of the present study is the absence of waist-to-hip ratio or abdominal circumference. When the HARVEST study was started [16], the guidelines recommended only the measurement of height and weight and the calculation of BMI for hypertensive patients [17,18]. Nevertheless, we measured weight increase and showed that prospectively hypertensive patients carrying the G allele are more prone to body weight gain than those with CC genotype. Admittedly, the average BMI increase in the whole population was modest. However, a higher number of male patients with G allele developed obesity or overweight in comparison with male patients with CC genotype.

In conclusion, we propose that the RGS2 1114G allele may be regarded as one potential genetic marker for obesity in mild, never-treated hypertensive subjects. Nonpharmacologic measures addressed to prevent weight gain appear to be indicated in hypertensive subjects carrying the G allele. Further studies are needed to precisely define the biochemical mechanisms through which RGS2 signaling promotes the development of obesity.

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