ORIGINAL ARTICLE

Association between single nucleotide polymorphisms of the G-protein γ5 subunit and the risk of essential hypertension in the population of Poland

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KEY WORDS

essential hypertension, G-protein γ5 subunit, single nucleotide polymorphism

ABSTRACT

INTRODUCTION Polymorphisms in genes coding G-protein subunits (α, β, and γ) may affect the response of stimulated α_{2A}-adrenergic receptors, which are involved in the regulation of blood pressure.

OBJECTIVES The aim of the present study was to determine the association between the rs11559300 (A/G), rs199705300 (C/A), rs61754630 (C/T), rs13093 (C/A), and rs41284589 (C/T) single nucleotide polymorphisms (SNPs) of the gene coding G-protein γ5 subunit (*GNG5*) and the risk of essential hypertension in the population of Poland.

PATIENTS AND METHODS A total number of 838 subjects were included in the study: 536 patients with diagnosed essential hypertension and 302 controls. Genotyping was performed using the polymerase chain reaction–restriction length polymorphism (PCR-RFLP) method.

RESULTS Of the studied *GNG5* polymorphisms, only SNP rs13093 was significantly associated with an increased risk of essential hypertension (odds ratio [OR], 2.91; 95% confidence interval [CI], 1.68–5.05; $P = 0.0036$). In addition, the T allele of rs41284589 may protect against hypertriglyceridemia (OR, 0.32; 95% CI, 0.1–0.9).

CONCLUSIONS rs13093 in the promoter region of *GNG5* may be associated with an increased risk of essential hypertension in the Polish population. Further studies are needed to explain the molecular mechanism by which rs13093 affects blood pressure.

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Received: August 10, 2015.
Revision accepted: November 16, 2015.
Published online: November 16, 2015.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2015; 125 (12): 903-909

INTRODUCTION Essential hypertension is the most common cardiovascular disease, affecting from 20% to 50% of the adult population in developed countries.[1] Moreover, it accounts for 95% of all cases of hypertension[2] and is influenced both by environmental and by genetic factors.[3] Studies of families, as well as of monozygotic and dizygotic twins, have indicated that hypertension has a strong genetic component and that the coefficient of hypertension heritability ranges from 20% to 55%.[4,5]

Numerous epidemiological studies have shown that elevated blood pressure (BP) is a risk factor for coronary artery disease, heart failure, stroke, peripheral artery disease, and renal failure both in men and in women.[6-9] The NATPOL2011 study showed that about 10.5 million patients suffer from high BP in Poland, which represents 32% of the adult population. This number includes 9.5 million people aged from 18 to 79 years and almost 1 million aged 80 years or older.

One of the factors involved in the regulation of BP is the α_{2A}-adrenergic receptor. Its activation leads to BP lowering due to the inhibition of norepinephrine secretion from adrenergic fibers, which is controlled by a negative feedback.[10] The α_{2A}-adrenergic receptor belongs to the family of receptors coupled to the heterotrimeric

TABLE 1 Clinical characteristics of the study and control groups

Parameter	Study group (n = 536)		Control group (n = 302)		*P* value
	number	frequency	number	frequency	
sex (male)	250	0.47	156	0.52	0.38
essential hypertension	536	1	0	0	<0.05
hypercholesterolemia, >200 mg/dl	120	0.22	76	0.25	0.59
HDL-C (males <40 mg/dl; females <45 mg/dl)	40	0.07	–	–	–
LDL-C, >115 mg/dl	114	0.21	–	–	–
triglycerides, >150 mg/dl	100	0.19	–	–	–

a Yates-corrected χ^2

Conversion factors to SI units are as follows: for total cholesterol, HDL-C, and LDL-C, multiply by 0.02586; for triglycerides, multiply by 0.01129.

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol

G_i protein, which consists of α, β, and γ subunits. To date, 5 different Gβ subunits and 12 different Gγ subunits have been identified,[11] yielding 60 possible combinations of Gβγ dimers. However, biochemical studies have shown that the formation of a functional dimer does not occur randomly.[12,13] Studies based on Sf9 insect cells have indicated that β3 subunits and γ5 subunits interact with one another to form a functional βγ dimer associated with the $G\alpha_i2$ subunit of the G protein.[14] Richardson and Robishaw[15] reported that the β3γ5 dimer with the $G\alpha_i$ subunit demonstrates a substantially greater coupling with the recombinant α_{2A}-adrenergic receptor than other dimer combinations. The structure of the G-protein subunit is the key to achieve a physiological effect as a result of receptor stimulation. Dysfunction of the signal transduction pathway from the α_{2A}-adrenergic receptor may disrupt the physiological response and lead to the development of essential hypertension.

The aim of this study was to determine whether there is any association between the presence of essential hypertension and the occurrence of selected polymorphic variants of the *GNG5* gene coding the G-protein γ5 subunit in the Polish population. We tested 5 polymorphisms of the *GNG5* gene: 3 in the coding region (Ser6Gly, rs11559300; Leu48Met, rs199705300; Thr56Ile, rs61754630) and 2 in the promoter region (rs13093, recognized by the Sp1 transcription factor, and rs41284589, recognized by the Nfr1 transcription factor).

PATIENTS AND METHODS

Subjects The study group consisted of 536 patients with a diagnosis of essential hypertension based on the 2013 European Society of Hypertension and European Society of Cardiology guidelines for the management of arterial hypertension,[16] who had been treated with antihypertensive medications for at least 30 days before admission. All patients were Caucasians. Additional data obtained from hospital records included total cholesterol (mg/dl), high-density lipoprotein (HDL) cholesterol (mg/dl), low-density lipoprotein (LDL) cholesterol (mg/dl), and triglyceride (mg/dl) levels. The clinical characteristics of the study and control groups are provided in TABLE 1.

The control group consisted of 302 healthy Polish residents unrelated to patients. The inclusion criteria for the control group included the presence of normal BP confirmed by at least 2 separate BP measurements on 2 different days of hospitalization and no history of antihypertensive treatment. All control participants were selected randomly. The age of less than 18 years was the exclusion criterion both for the study and control groups.

The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Bioethics Committee of the Medical University of Lodz, Łódź, Poland.

DNA extraction and genotype determination Venous blood from all individuals was collected in vials containing sodium citrate at a concentration of 3.2% (Sarstedt, Nümbrecht, Germany). Samples were stored at –20°C until DNA isolation. Genomic DNA was isolated from blood leukocytes using a standard method (phenol/chloroform) or a Chemagic DNA Blood250 Kit (PerkinElmer, Waltham, Massachusetts, United States). The samples were examined using the polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) method, which was performed in a 25-µl volume containing 2.5 µl of 10 × PCR buffer (Bioron, Ludwigshafen, Germany), 1U DFS-Taq DNA Polymerase (Bioron, Ludwigshafen, Germany), 2 µl of 2 mM dNTP MIX (Thermo Scientific, Massachusetts, United States), 0.2 µl of 20 µM each primer (Genomed, Warsaw, Poland), 3 µl of extracted DNA, and 16.3 µl of distilled water. The PCR reactions were conducted in a Biometra T professional thermocycler (Analytik Jena Company, Jena, Germany). After an initial denaturation of 95°C for 5 minutes, the following cycle was performed 30 times: denaturation cycle, 95°C for 30 seconds; annealing, at a

TABLE 2 Conditions of polymerase chain reactions and expected length of dominant fragments after digestion

Polymorphism	Primers (5′-3′)	Annealing temperature, °C	Polymerase chain reaction product length, bp	Restriction fragment length polymorphism analysis	
				restriction enzyme	fragment length, bp
rs11559300 (A/G)	AGCACAGAACCGGAAACTTAG TCACTTTTACGCGGTTGAGTC	57	217	BsaHI	AA – 217 GG – 149+68
rs199705300 (C/A)	GTTCTCACCATCTGGCACTTC GGAACAGACTTTCTGGGGTC	59	160	MnlI	CC – 75+49+36 AA – 124+36
rs61754630 (C/T)	GTTCTCACCATCTGGCACTTC GGAACAGACTTTCTGGGGTC	59	160	CivQI	CC – 126+34 TT – 160
rs13093 (C/A)	TTCTCCTCCCCCTCCTCC GGGCTCCGAACTTTGTCTCTA	60	137	HaeIII	CC – 103+34 AA – 137
rs41284589 (C/T)	TTCTCCTCCCCCTCCTCC GGGCTCCGAACTTTGTCTCTA	60	137	CivQI	CC – 137 TT – 78+59

TABLE 3 Frequencies of genotypes and minor alleles in the study and control groups

Polymorphism		Study group (n = 536)		Control group (n = 302)	
		number	frequency	number	frequency
rs13093 (C/A)	CC	384	0.7164	266	0.8808
	CA	142	0.2649	36	0.1192
	AA	10	0.0187	0	0
	minor allele	162	0.1511	36	0.0598
	χ^2 for HWE	0.5692		1.2132	
	P for HWE	0.4506		0.2707	
rs41284589 (C/T)	CC	498	0.9123	292	0.9669
	CT	34	0.0634	8	0.0265
	TT	4	0.0075	2	0.0066
	minor allele	42	0.0391	12	0.0197
	χ^2 for HWE	13.2904		30.9800	
	P for HWE	0.000267		0.000000019	

Abbreviations: HWE, Hardy–Weinberg equilibrium

temperature specific for the individual SNP for 30 seconds; elongation, 72°C for 30 seconds; final extension, 72°C for 10 minutes; and then cooling to 16°C. The specific conditions for genotyping, including the choice of primer (Genomed) and annealing temperature and enzymes (Thermo Scientific), are presented in TABLE 2. The digestion products were separated by polyacrylamide gel electrophoresis in a Biometra Minigel-Twin (Analytik Jena Company) and visualized after staining with ethidium bromide (UVP PhotoDoc–It™ Imaging System, Upland, California, United States).

Statistical analysis Owing to its nonnormal distribution, age was expressed as means and standard deviations. The frequency of alleles was tested against the Hardy–Weinberg equilibrium (HWE). The Yates-corrected χ^2 test was used for data comparisons. A logistic regression analysis was performed to determine the relationship between individual factors and the occurrence of essential hypertension. Univariate comparisons were performed for all analyzed factors, and factors with *P* values lower than 0.15 were entered into a multivariate backward-stepwise model. The final *P* value of less than 0.05 was considered statistically significant in the multivariate analysis. The Statistica 8.0 (Statsoft, Tulsa, Oklahoma, United States) and Medcalc 9.36 (MedCalc Software, Ostend, Belgium) statistical packages were used for all computations.

RESULTS Of the 838 subjects included in the study, 302 constituted the control group (mean age, 65 ±9.8 years) and 536 constituted the study group (mean age, 66 ±12.7 years). The clinical characteristics of the study and control groups are provided in TABLE 1. The HWE was tested to compare expected and observed genotype frequencies using the χ^2 test. The distribution of the rs13093 polymorphism was consistent with the HWE (*P* = 0.2707), while the frequency of rs41284589 alleles significantly deviated from the expected value. No polymorphic variants for rs11559300, rs199705300, or rs61754630 were observed either in the study or control group.

The frequencies of the genotypes and minor alleles for rs13093 and rs41284589 between the

TABLE 4 Comparison of the distribution of rs13093 CA+AA vs CC in the study and control groups

Polymorphism		Study group (n = 536)	Control group (n = 302)	CA+AA vs.CC OR (95% CI)	*P* value[a]
rs13093	CA+AA	152	36	2.91 (1.68–5.05)	0.0036

a Yates-corrected χ^2

Abbreviations: CI, confidence interval; OR, odds ratio

TABLE 5 Distribution of clinical parameters in carriers of the T allele rs41284589 in the study group

Clinical parameter	Carriers of the T allele rs41284589 (C/T)	
	allele T (n = 38)[a]	*P* value[b]
total cholesterol, >200 mg/dl	16 (42.1%)	0.02
triglycerides, >150 mg/dl	14 (36.8%)	0.09
LDL-C, >115 mg/dl	10 (26.3%)	0.02
HDL-C (males <40 mg/dl; females <45 mg/dl)	8 (21.1%)	0.017

a the discrepancy between the number of patients with the T allele of rs41284589 (n = 38) and that of clinical parameters (n = 48) results from the fact that some patients presented with more than 1 clinical parameter

b Yates-corrected χ^2

For abbreviations and conversion factors, see **TABLE 1**.

study and control groups were compared, and the results are presented in **TABLE 3**. As rs41284589 did not meet the HWE in the control group, the subsequent multivariate analysis included only rs13093 (**TABLE 4**). Owing to the low percentage of polymorphic genotypes, the statistical analysis included the distributions of wild homozygotes vs mutant homozygotes and heterozygotes. A significant relationship was observed between the presence of rs13093 in the *GNG5* gene and the risk of essential hypertension.

Analysis in the study group The statistical analysis of rs13093, rs41284589, and the clinical parameters in the study group showed that the T allele of rs41284589 (C/T) is associated with elevated levels of total cholesterol, LDL cholesterol, and triglycerides, and decreased levels of HDL cholesterol, regardless of sex (**TABLE 5**). These parameters were entered into the multivariate analysis based on the multivariate backward-stepwise model, which showed that the T allele of the rs41284589 polymorphism (C/T) protects against elevated blood triglyceride levels (OR, 0.32; 95% CI, 0.1–0.9)

DISCUSSION Essential hypertension is the most common cardiovascular disease worldwide. The results of the present study indicate that rs13093 is a significant risk factor for essential hypertension in the Polish population, independent of primary hypertension risk factors.

In the sympathetic nervous system, 9 adrenergic receptor subtypes are activated by adrenaline and noradrenaline, but only the α_2-adrenergic receptor has been implicated as an inhibitory presynaptic autoreceptor. The α_{2A}-adrenergic receptor is known to be responsible for the control of BP homeostasis: its activation leads to a decrease in BP by inhibiting the central sympathetic outflow, as well as inhibiting noradrenaline release from sympathetic nerves.[17] Hein et al[18] reported that it is responsible for the normal presynaptic control of transmitter release from sympathetic nerves in the heart. Deletion of the α_{2A}-adrenergic receptor gene was found to cause tachycardia.[19] Moreover, increased noradrenaline turnover was observed in mice expressing a mutant α_{2A}-receptor (α_{2A}-D79N).[20] As coupling the receptor with an appropriately-composed G-protein subunit is required for the correct functioning of G protein-coupled receptor signaling pathways, this functioning may be disrupted by the presence of an SNP in the γ subunit of the G protein.

The G-protein γ5 subunit is a human protein encoded by the *GNG5* gene located on the short arm of chromosome 1 (1p22.3).[21] *GNG5* spans 6kb and consists of 4 exons and 3 introns. The coding region is localized at the 3'-end of exon 2 and in the most part of exon 3.[21] The analysis by PROMOTER SCAN (version 1.7) and a related study by Liu et al[22] indicated that the functional promoter region of *GNG5* lies within the ranges from –725 to –456 and from –342 to –92.[23]

Our findings indicate that the examined SNPs (rs11559300, rs199705300, and rs61754630) are not present in the G-protein γ5 subunit coding region within the Polish population. However, they do suggest that the carriers of the A allele of –195 C/A (rs13093) in the promoter region of the *GNG5* gene is associated with the risk of essential hypertension more than 2.9-fold greater than

that observed in carriers of the C allele among the Polish population (OR, 2.91; 95% CI, 1.68–5.05).

The rs13093 SNP is located in the recognition sequence of the Sp1 transcription factor. Sp1 is associated with many other transcription factors and can regulate the expression of TATA box-containing promoters, as well as those which do not contain the cassette.[24] The presence of the rs13093 (C >A) SNP in the recognition sequence of the Sp1 transcription factor may result in the loss of consensus sequences for Sp1 in this area, resulting in low levels of *GNG5* mRNA and γ5 protein. An insufficient amount of γ5 protein prevents the correct coupling of the G-protein complex (G α(i)2 with β3γ5) with the α_{2A}-adrenergic receptor. All the above may lead to the α_{2A}-adrenergic receptor displaying impaired hypotensive effects.

Interestingly, the multivariate analysis performed in the study group indicated that the T allele of the rs41284589 polymorphism may protect against elevated blood triglyceride levels (OR, 0.32; 95% CI, 0.1–0.9). The –152C/T polymorphism (rs41284589) occurs in the *GNG5* promoter sequence recognized by transcription factor Nrf1. It is hypothesized that this polymorphism may influence the level of the *GNG5* gene expression. The loss of consensus sequences for the Nrf1 transcription factor in the *GNG5* gene may lead to reduced levels of *GNG5* mRNA, resulting in reduced γ5 protein levels. In turn, as mentioned earlier, an insufficient amount of the γ5 protein prevents the G-protein complex (G α(i)2 with β3γ5) from coupling correctly with the α_{2A}-adrenergic receptor.

The hypotensive effect of the α_{2A}-adrenergic receptor causes numerous physiological responses, including the suppression of insulin release from pancreatic β cells.[25] Insulin is a major regulator of lipoprotein lipase (LPL) activity in adipose tissue. LPL hydrolyzes triglycerides present in the circulating blood lipoproteins, especially in chylomicrons and lipoproteins of very low density.[26] During adipocyte differentiation, insulin increases LPL gene transcription. In mature adipocytes or adipose tissue, insulin stimulates LPL activity by increasing the level of LPL mRNA and regulating LPL through both posttranscriptional and posttranslational mechanisms.[27-29] This mechanism of action could explain the reduced levels of triglycerides in patients with the T allele of SNP rs41284589 (C/T).

The study has 1 important limitation—it included a relatively small group of subjects; therefore, it is necessary to confirm these results in a larger cohort. Nevertheless, the study participants belonged to the same ethnic group, which arguably strengthens the results. Another strength of the study is the fact that this is the first analysis of the association between the rs13093 polymorphism and the risk of essential hypertension.

In conclusion, the results of this study confirm the necessity to look closer into the role of this polymorphism in the *GNG5* expression. Carrying the A allele at –195 C/A (rs13093) may be a potential genetic factor for primary essential hypertension and may help assess the risk profile in hypertensive patients, but further studies are needed to precisely define the effect of the A allele on the prognosis of these patients.

Contribution statement PH conceived the concept of the study. PH and AMS contributed to the design of the research. MM, AS, and JD were involved in data collection. AMS and PH analyzed the data. TP coordinated funding for the project. All authors edited and approved the final version of the manuscript.

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Związek między polimorfizmami pojedynczego nukleotydu genu kodującego podjednostkę γ5 białka G a rozwojem ryzyka pierwotnego nadciśnienia tętniczego w populacji polskiej

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pierwotne nadciśnienie tętnicze, podjednostka γ5 białka G, polimorfizm pojedynczego nukleotydu

STRESZCZENIE

WPROWADZENIE Zmienności polimorficzne w obrębie genów kodujących poszczególne podjednostki (α, β i γ) białka G mogą wpływać na odpowiedź stymulowanych receptorów α_{2A}-adrenergicznych, które biorą udział w regulacji ciśnienia krwi.

CELE Celem niniejszego badania było określenie związku pomiędzy występowaniem zmienności polimorficznych pojedynczego nukleotydu (*single nucleotide polymorphism* – SNP): rs11559300 (A/G), rs199705300 (C/A), rs61754630 (C/T), rs13093 (C/A) i rs41284589 (C/T) w genie kodującym podjednostkę γ5 białka G (*GNG5*) a ryzykiem rozwoju pierwotnego nadciśnienia tętniczego w populacji polskiej.

PACJENCI I METODY W badaniu udział wzięło łącznie 838 pacjentów: 536 pacjentów ze zdiagnozowanym pierwotnym nadciśnieniem tętniczym oraz 302 osoby z grupy kontrolnej. Genotypowanie przeprowadzono za pomocą metody reakcji łańcuchowej polimerazy i polimorfizmu długości fragmentu restrykcyjnego (PCR-RFLP).

WYNIKI Spośród przebadanych zmienności polimorficznych genu *GNG5* jedynie SNP rs13093 był istotnie związany ze zwiększonym ryzykiem pierwotnego nadciśnienia tętniczego (OR 2,91; 95% CI 1,68–5,05; p = 0,0036). Ponadto allel T rs41284589 może chronić przed hipertriglicerydemią (OR 0,32, 95% CI 0,1–0,9).

WNIOSKI rs13093 występujący w regionie promotorowym genu *GNG5* może się wiązać ze zwiększonym ryzykiem pierwotnego nadciśnienia tętniczego w populacji polskiej. Konieczne są dalsze badania w celu wyjaśnienia mechanizmu molekularnego tłumaczącego wpływ rs13093 na ciśnienie krwi.

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Praca wpłynęła: 10.08.2015.
Przyjęta do druku: 16.11.2015.
Publikacja *online*: 16.11.2015.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2015; 125 (12): 903-909