

## Original Article

# Angiotensinogen (AGT RS4762) and guanine nucleotide-binding protein BETA-3 (GNB3 RS5443) genes predict left ventricular hypertrophy in hypertensive patients

Kseniia Voroniuk<sup>1\*</sup>, Larysa Sydorчук<sup>1</sup>, Valentina Dzhuryak<sup>2</sup>, Andrii Sydorчук<sup>3</sup>,  
Oleksandr Hinhuliak<sup>4</sup>, Ruslan Sydorчук<sup>5</sup>, Oksana Iftoda<sup>6</sup>, Oksana Kushnir<sup>6</sup>

<sup>1</sup> Department of Family Medicine, Bukovinian State Medical University, Chernivtsi, Ukraine

<sup>2</sup> Department of Microbiology and Virology, Bukovinian State Medical University, Chernivtsi, Ukraine

<sup>3</sup> Department of Emergency and Trauma Surgery, Donauklinik Neu-Ulm, Neu-Ulm, Germany

<sup>4</sup> Department of Internal Medicine, Physical Rehabilitation and Sport Medicine, Bukovinian State Medical University, Chernivtsi, Ukraine

<sup>5</sup> Department of General Surgery, Bukovinian State Medical University, Chernivtsi, Ukraine

<sup>6</sup> Department of Department of Hygiene and Ecology, Bukovinian State Medical University, Chernivtsi, Ukraine

\* Correspondence to: Kseniia Voroniuk, Department of Family Medicine, Bukovinian State Medical University, Chernivtsi, Ukraine, Holovna Str. 246V, Chernivtsi, 58000, Ukraine. Phone: +380990584893; E-mail: voroniuk.kseniia@bsmu.edu.ua

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## Abstract

This study aims to evaluate polymorphic variants of AGT (rs4762) and GNB3 (rs5443) genes as predictors of myocardium left ventricular hypertrophy (LVH) in patients with essential arterial hypertension (EAH). The case-control study involved 100 patients with EAH stage II, high-very high cardiovascular risk. There were 21% men, and 79% women; the average age was 59.86±6.22 years old. The control group consisted of 60 practically healthy subjects. AGT (rs4762) and GNB3 (rs5443) genotyping was performed by Real-Time PCR. As a result, centric LVH (ELVH) in EAH patients is more common in T-allele carriers of AGT gene (rs4762), CC-genotype subjects of GNB3 gene (rs5443) by 26.29% and 22.22%, respectively. Concentric LVH (CLVH) dominates in homozygous C-allele patients of AGT gene (rs4762), and T-allele of GNB3 gene (rs5443) by 29.13%, 22.22%, correspondingly. ELVH risk increases in hypertensive T-allele carriers of AGT gene (rs4762) 4.5 times and in CC-genotype of GNB3 gene (rs5443) almost 5 times. CLVH risk increases in CC-genotype patients of AGT gene (rs4762) almost 5 times, in T-allele of GNB3 gene more than 4 times. Blood pressure (BP) ≥160/≥100mmHg increases ELVH risk 3 times. In conclusion, LV hypertrophic models associate with AGT (rs4762) and GNB3 (rs5443) genes polymorphic variants in hypertensive patients, as well as ELVH with BP elevation.

**Keywords:** left ventricular hypertrophy, myocardium geometry, essential arterial hypertension, polymorphism of AGT (rs4762) and GNB3 (rs5443) genes.

## Introduction

Hypertensive-mediated left-ventricular hypertrophy (LVH) and myocardium remodeling are major pathophysiological manifestations of target-organ damage followed by an increased cardiovascular (CV) risk. LVH is present in 15-20% of the general population worldwide and is more common in African Americans,

the elderly, obese and hypertensive patients. Besides, arterial hypertension (AH) is the primary cause of LVH [1]. The review of echocardiographic data from 37.700 individuals revealed a 19-48% prevalence of LVH in untreated hypertensive subjects and 58-77% in high-risk essential arterial hypertensive (EAH) patients. The presence of obesity also doubles the LVH risk. The prevalence of LVH ranges from 36% to 41% in the population,



depending on the criteria used to define it. There is evidence that the predominance of LVH does not differ between men and women (range 36.0% vs. 37.9% and 43.5% vs. 46.2%). The high prevalence of LVH in EAH patients indicates that the blood pressure (BP) values also affect the LVH degree [2], although it has not been stated whether it determines the remodelling type [3].

Furthermore, a BP increase contributes to LVH development only in 25% of cases but in 60%, LVH is formed regardless of BP values [4]. Thus, hemodynamic overload does not reliably determine the LVH appearance and might be realized through hereditary predisposition or gene mutation peculiarities [5–8]. One of the possible genetic markers of heart muscle remodeling is the angiotensinogen gene AGT (rs4762, 521 C>T). The AGT gene's expression is an essential component of the renin-angiotensin-aldosterone system (RAAS) activity, as well as the guanine nucleotide-binding protein beta-3 gene (GNB3, rs5443, 825 C>T), which encodes a protein involved in the vascular smooth muscle cells and cardiomyocytes remodeling and proliferation [9]. Moreover, the AGT and GNB3 gene's code enzyme synthesis plays a pivotal role in atherogenesis, endothelial dysfunction, acute vascular disaster and metabolic disorders [9, 10–15]. However, the mechanisms that couple the LVH types with genetic factors in hypertensive patients still remain to be determined.

Therefore, the study aimed to establish the association of the AGT (rs4762) and GNB3 (rs5443) genes polymorphism with LV geometry changes in EAH patients.

## Method and materials

### Study design and patients

The study was conducted in full compliance with the main ethical principles of the European Convention on Human Rights and Biomedicine, according to the standards of the Helsinki Declaration, GLP and GCP, EUC directive #609 and other EU and international legislations on bioethics. The Ethics Committee of the Bukovinian State Medical University approved the Research Protocol. Each participant signed a consent form to participate in the study. The research is defined as a prospective, cohort, case-control study.

### Diagnosis. Inclusion/Exclusion criteria

Hypertension was defined according to European Societies of Hypertension and Cardiology (ESH/ESC)

recommendations: office systolic BP (SBP) values  $\geq 140$  mmHg and/or diastolic BP (DBP) values  $\geq 90$  mmHg at least for three measurements during a month [16, 17].

The study enrolled EAH patients with hypertensive-mediated organ damage (HMOD) estimated according to European Societies of Hypertension and Cardiology recommendations (ESH/ESC 2018, 2021) [16, 17]: target-organs damage – 2<sup>nd</sup> stage (asymptomatic EAH), moderate-high CV risk, from the 1<sup>st</sup> through to the 3<sup>rd</sup> grade of BP elevation.

Exclusion criteria were as follows: EAH patients with complicated/symptomatic HMOD (coronary heart disease, heart attack, stroke, heart failure, aneurysm, chronic kidney diseases, thickened, narrowed or torn blood vessels in the eyes, carotid arteries intima-media thickness enlargement and peripheral artery disease); secondary arterial hypertension; malignant or uncontrolled arterial hypertension; diabetes mellitus type I (DM1), sub- and decompensated diabetes mellitus (DM) type 2 (with diabetic target-organ damage); sub- and decompensated liver diseases; bronchial asthma, chronic obstructive pulmonary disease of III-IV stage with C or D risk value (GOLD 2019); exacerbated infectious diseases or during unstable remission of any location, including systemic immune system diseases; severe dementia; psychological/psychiatric disorders/diseases; malignancies of any location; multiple organ failure; use of oral corticosteroids or contraceptives; pregnancy or lactation.

A number of 100 patients were selected for further examination after screening of matching inclusion and exclusion criteria: 79% women, 21% men, mean age  $59.86 \pm 6.22$  yo. The control group included 60 practically healthy individuals who were not relatives of the patients, without reliable differences in age ( $49.13 \pm 6.28$ ) and gender distribution (63% - women, 37% - men) with the study group.

### Laboratory, anthropometric and clinical data collection

All enrolled patients underwent a complex of basic clinical examinations: clinical anamnesis recording, anthropometric parameters, body mass index (BMI, kg/m<sup>2</sup>), complete blood count, total cholesterol level, low/high-density level cholesterol (LDL-, HDL-C), serum uric acid, office SBP, DBP and heart rate (HR) measurement, ECG in 12 leads, EchoCG, kidneys' ultrasound examination and Daily Holter BP monitoring in undetermined conditions as well as consultations of ophthalmologist and neurologist according to Ukrainian

standards (2019) and European recommendations ESC/ESH (2018, 2021) [16, 17].

### Left ventricular hypertrophy patterns

The LVH was estimated using the established ECG criteria: Sokolow-Lyon index and Cornell scoring system.

The transthoracic echocardiography (Echo-CG) in M- and B-modes was utilized to confirm the LVH and the structural and functional myocardium state analysis, including the LV geometry. The standard linear Echo-CG indicators were measured by Ultrasonography complex “ACCUVIX A30” (Samsung Medison, South Korea). The LV mass (LVM) was calculated according to the Penn Convention. LVM index (LVMI) was assessed by LVM/body surface area ratio (g/m<sup>2</sup>). LVMI cutoff values of echocardiographic LVH diagnostic criteria were >115 g/m<sup>2</sup> for men and >95 g/m<sup>2</sup> for women (ESC/ESH, 2018). According to LVMI and LV relative wall thickness (RWT) the following geometric models of LV were identified (ESC/ESH, 2009): normal geometry of LV (NGLV), concentric remodeling of LV (CRLV), eccentric LVH (ELVH), concentric LVH (CLVH).

### Genotyping assay

Venous blood was collected in a sterile vacutainer and stabilized by K2-EDTA. DNA was isolated from the whole venous blood lymphocytes’ nuclei and purified according to the GeneJET Genomic DNA Purification Kit manufacturer’s instructions (Thermo Fisher Scientific, USA). DNA fragments of analyzed genes amplified by Quantitative Real-Time PCR (qRT-PCR) with specific for each gene TaqMan probes and genotyping with TaqMan Genotyping Master Mix on CFX96 Touch™ RT-PCR Detection System (Bio-Rad Laboratories, Inc., USA). The genotyping protocol was described in our former publications [18, 19]. Alleles’ discrimination of AGT (rs4762) and GNB3 (rs5443) genes polymorphisms

were analyzed by licensed CFX96 RT-PCR Detection System Software (Microsoft, USA). The genetic examination was performed for 72 patients and 48 healthy subjects.

### Statistical analysis

StatSoft Statistica® v.7.0 software was used for statistical analysis (StatSoft Inc., USA). The genotype distribution was assessed by the Pearson test ( $\chi^2$ ). Qualitative data analysis (categorical variables) and risk of pathology were calculated by a binary logistic regression model using relative risk (RelR); risk ratio (RR) was estimated by odds ratio (OR) with 95% confidence interval [95% CI] using a chi-square test ( $\chi^2$ ) (df=1). P value<0.05 was considered statistically significant.

### Results

The LVH development in the observed population was associated with dominating of Concentric LVH pattern (82% patients) 4.55 times over ELVH (16%) and CRLV (2%) subjects (Table1). The ELVH was revealed more often in EAH patients with 2-3 degrees of BP elevation (SBP/DBP  $\geq 160/\geq 100$  mmHg) by 15% ( $\chi^2=4.02$ ; p=0.045). Moreover, SBP/DBP  $\geq 160/\geq 100$  mmHg increases the risk of ELVH 3 times (OR=3.0; OR 95%CI:1.0-9.07; p=0.043).

The distribution of myocardium LV geometric models depending on the genes’ polymorphism AGT (rs4762, 521C>T) and GNB3 (rs5443, 825C>T) in hypertensive patients is presented in Table 2. ELVH was detected more often among the mutated T-allele carriers of the AGT gene (rs4762) than in the CC-genotype by 26.29% ( $\chi^2=3.88$ ; p=0.015) and in the CC-genotype patients of the GNB3 gene (rs5443) over the minor T-allele by 22.22% ( $\chi^2=5.67$ ; p=0.017) respectively. Whereas, on the contrary, CLVH was registered more often

Table 1: Geometric models of the left ventricle depending on the hypertension severity.

Geometric model of the LV	Control, n=60 (%)	EAH patients is SBP/DBP mmHg, n (%)		$\chi^2$ , p
		<160/<100, n=60	$\geq 160/\geq 100$ , n=40	
Normal geometry LV, n (%)	48 (80.0)	0	0	-
Concentric remodeling LV, n (%)	12 (20.0)	2 (3.33)	0	-
Eccentric LVH, n (%)	0	6 (10.0)	10 (25.0)	$\chi^2=4.02$ p=0.045
Concentric LVH, n (%)	0	52 (86.67)	30 (75.0)	$\chi^2=2.21$ p>0.05

Table 2: The myocardium left ventricle geometric models depending on the genes' polymorphism AGT (rs4762, 521C&gt;T), GNB3 (rs5443, 825C&gt;T) in hypertensive patients.

Geometric model of the LV		Concentric remodeling of the LV, n (%)	Eccentric LV hypertrophy, n (%)	Concentric LV hypertrophy, n (%)
<b>AGT gene (rs4762, 521C&gt;T), n (%)</b>	CC-genotype, n=51	1 (1.96)	6 (11.76)	44 (86.27)
	T-allele, n=21	1 (4.76)	8 (38.05)	12 (57.14)
<b>χ<sup>2</sup>; P</b>		p>0.05	χ <sup>2</sup> =3.88; p=0.015	χ <sup>2</sup> =4.50; p=0.01
<b>GNB3 gene (rs5443, 825C&gt;T), n (%)</b>	CC-genotype, n=36	1 (1.96)	11 (30.55)	24 (66.67)
	T-allele, n=36	1 (4.76)	3 (8.33)	32 (88.89)
<b>χ<sup>2</sup>; P</b>		p>0.05	χ <sup>2</sup> =5.67; p=0.017	χ <sup>2</sup> =5.14; p=0.023

in homozygous C-allele patients of the AGT gene by 29.13% ( $\chi^2=4.50$ ;  $p=0.01$ ) and in the T-allele subjects of the GNB3 gene by 22.22% ( $\chi^2=5.14$ ;  $p=0.023$ ) accordingly.

The epidemiological analysis confirmed an increased risk of ELVH in EAH patients with T-allele of the AGT gene (rs4762) more than 4.5 times (OR 95%CI:1.35-15.72;  $p=0.019$ ) followed by the low probability of ELVH model in the CC-genotype patients (OR=0.22;  $p=0.015$ ) (Table 3). Nevertheless, the CLVH risk increases in CC-genotype carriers of the AGT gene (rs4762) almost 5 times (OR 95%CI: 1.45-15.28;  $p=0.01$ ), with low chances in T-allele subjects (OR=0.21; OR 95%CI:0.06-0.69;  $p=0.012$ ).

Furthermore, the risk of ELVH in EAH patients increases almost 5 times in CC-genotype carriers of the

GNB3 gene (rs5443) (OR 95%CI:1.22-19.21;  $p=0.017$ ), with a low CLVH likelihood (OR=0.25; OR 95%CI: 0.07-0.87;  $p=0.047$ ) (Table 4). On the other hand, the risk of CLVH increases 4 times in the mutated T-allele patients of the GNB3 gene (OR 95%CI: 1.15-13.95;  $p=0.022$ ), with low odds of ELVH (OR=0.21; OR 95%CI: 0.05-0.82;  $p=0.037$ ).

## Discussion

Various studies demonstrate that LVH in hypertensive patients might be partially determined by genes coding RAAS or NO activity or regulating the enzymes' synthesis or expression and associated with endothelium dysfunction, vascular smooth muscle remodeling

Table 3: Polymorphic variants of the AGT gene (rs4762) as predictors of changes in the geometry of the left ventricle in patients with arterial hypertension.

LVH model	T-allele of the AGT gene			CC-genotype of the AGT gene		
	OR	OR 95%CI	p	OR	OR 95%CI	P
<b>Concentric LV remodeling</b>	2.50	0.15–41.94	>0.05	0.4	0.02–6.71	>0.05
<b>Eccentric LV hypertrophy</b>	4.62	1.35–15.72	0.019	0.22	0.06–0.74	0.015
<b>Concentric LV hypertrophy</b>	0.21	0.06–0.69	0.012	4.71	1.45–15.28	0.01

Table 4: Polymorphic variants of the GNB3 gene (rs5443) as predictors of changes in the geometry of the left ventricle in patients with arterial hypertension.

LVH model	CC-genotype of the GNB3 gene			T-allele of the GNB3 gene		
	OR	OR 95%CI	p	OR	OR 95%CI	P
<b>Concentric LV remodeling</b>	1.0	0.06–16.63	>0.05	1.0	0.06–16.63	>0.05
<b>Eccentric LV hypertrophy</b>	4.86	1.22–19.21	0.017	0.21	0.05–0.82	0.037
<b>Concentric LV hypertrophy</b>	0.25	0.07–0.87	0.047	4.0	1.15–13.95	0.022

or metabolic disorders [8, 12, 20–23]. However, the genetic's pathways of particular LV geometry pattern development remain underestimated [5].

Our research confirms the results of some studies in which the predominance of concentric LVH over other types of LV geometric models in EAH patients has been proven [3]. Moreover, CLVH increases the risk of CV events by 30%. In our research, the number of EAH patients with CLVH prevailed among the mutated T-allele carriers of the GNB3 gene (rs5443) and C-allele subjects of the AGT gene (rs4762) by 22.22% and 29.13%, respectively.

The eccentric or dilation model of the LVH (ELVH) is the second most common in EAH and is associated with myocardium contractile function decrease and CV risk increase by 15% [24]. On the other hand, the risk of CV complications with an isolated growth of LV RWT (concentric remodeling - CRLV) is unspecified [25, 26]. In our study, the ELVH was observed more often in the mutated T-allele carriers of the AGT gene (rs4762) and the CC-genotype of the GNB3 gene (rs5443) by 26.29% and 22.22% ( $p < 0.05$ ) correspondingly.

Generally, CLVH is caused by chronic pressure overload, which most often occurs as a result of arterioles vasoconstriction in chronic EAH or aortic stenosis. At the same time, ELVH is caused by increased LV filling pressure, known as diastolic overload, the primary mechanism of volume overload in patients with regurgitating valve lesions such as aortic or mitral regurgitation and dilated cardiomyopathy. However, transforming LV hypertrophic model from one type into another (ELVH vs. CLVH) is also possible [27, 28]. In patients with coronary artery disease (CAD), these mechanisms may play a significant role in attempts to compensate for ischemic or infarcted myocardial tissue. On the ischemia background, the cytokine release and neuro activation stimulate the myocardial hypertrophy development and cardiomyocyte thickness increase with extracellular matrix deposition. Therefore, one of the key pathophysiological components of LVH is the concomitant development of myocardial fibrosis. Initially, fibrosis is clinically manifested by diastolic dysfunction with possible CAD appearance and progression and further systolic dysfunction development [29]. Some studies have indicated that genetic factors influence myocardial fibrosis activity and LV mass, as well as heavy  $\beta$ -myosin chain,  $\alpha$ -actin, atrial natriuretic peptide synthesis, fetal isoforms of contractile proteins, increase, angiotensin-2 (AT2) production, promotes expression of "immediate-early" fetal genes such as *erg-1*, *jun-B*, *c-myc*, *c-jun*, *c-fos* which are responsible for the myocardial

intracellular protein synthesis, signal transducing and activate a fetal type of metabolism [30, 31]. However, there is little evidence that genetic variants of regulatory and pathway genes are functionally active to link with common forms of LVH [5, 32–34]. What is more, genetic research results are of limited clinical value. Although plenty genome-wide association studies in diverse populations were performed, the specific genes and functional variants in some chromosomal regions influencing LV mass have not yet been identified and require further research [35].

The linkage between LVH patterns and single-nucleotide polymorphisms of AGT (rs4762, 521C>T) and GNB3 (rs5443, 825C>T) genes in EAH patients we evidenced for the first time.

## Conclusion

T-allele of the AGT gene (rs4762) and CC-genotype of the GNB3 gene (rs5443) elevates the risk of Eccentric LVH in EAH patients 4.5-5 times. The risk of Concentric LVH increases 5 and 4 times as well in the CC-genotype patients of the AGT gene and in the T-allele of the GNB3 gene, accordingly. Systolic and diastolic BP elevation ( $\geq 160/\geq 100$  mmHg) increases the LVH risk 3 times in the observed population but only in the Eccentric geometry model.

## Conflict of interest

The authors declare no conflict of interest.

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