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Original Article

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

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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,

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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 ≥140 mmHg and/or diastolic BP (DBP) values ≥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 – 2nd stage (asymptomatic EAH), moderate-high CV risk, from the 1st through to the 3rd 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±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±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^2), 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

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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^2). LVMI cutoff values of echocardiographic LVH diagnostic criteria were >115 g/m^2 for men and >95 g/m^2 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 (χ^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 (χ2) (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 ≥160/≥100 mmHg) by 15% (χ^2=4.02; p=0.045). Moreover, SBP/DBP ≥160/≥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% (χ^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% (χ^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 із SBP/DBP mmHg, n (%)		χ^2, p
		<160/<100, n=60	≥160/≥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)	χ^2=4.02 p=0.045
Concentric LVH, n (%)	0	52 (86.67)	30 (75.0)	χ^2=2.21 p>0.05

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

Geometric model of the LV		Concentric remodeling of the LV, n (%)	Eccentric LV hypertrophy, n (%)	Concentric LV hypertrophy, n (%)
AGT gene (rs4762, 521C>T), n (%)	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)
χ^2; P		p>0.05	χ^2=3.88; p=0.015	χ^2=4.50; p=0.01
GNB3 gene (rs5443, 825C>T), n (%)	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)
χ^2; P		p>0.05	χ^2=5.67; p=0.017	χ^2=5.14; p=0.023

in homozygous C-allele patients of the AGT gene by 29.13% (χ^2=4.50; p=0.01) and in the T-allele subjects of the GNB3 gene by 22.22% (χ^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
Concentric LV remodeling	2.50	0.15–41.94	>0.05	0.4	0.02–6.71	>0.05
Eccentric LV hypertrophy	4.62	1.35–15.72	0.019	0.22	0.06–0.74	0.015
Concentric LV hypertrophy	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
Concentric LV remodeling	1.0	0.06–16.63	>0.05	1.0	0.06–16.63	>0.05
Eccentric LV hypertrophy	4.86	1.22–19.21	0.017	0.21	0.05–0.82	0.037
Concentric LV hypertrophy	0.25	0.07–0.87	0.047	4.0	1.15–13.95	0.022

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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 β-myosin chain, α-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 (≥160/≥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.

References

1. Bornstein AB, Rao SS, Marwaha K. Left Ventricular Hypertrophy. [Updated 2022 Jul 15]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557534/
2. Gregoire Wuerzner, Murielle Bochud, Carole Zweiacker, *et al*. Step Count is Associated with Lower Nighttime Systolic Blood Pressure and In-creased Dipping. Am J Hypertens 26(4):527-534, 2013. doi:10.1093/ajh/hps094
3. Stewart MH, Lavie CJ, Shah S, *et al*. Prognostic implications of left ventricular hypertrophy. Prog Cardiovasc Dis 61(5-6):446-55, 2018. https://doi.org/10.1016/j.pcad.2018.11.002
4. Deschepper CF, Boutin-Ganache I, Zahabi A, Jiang Z. In search of cardiovascular genes. Interaction between phenotypes and genotypes. J Hypertension 39:332-336, 2002.
5. Sydorchuk LP, Gaborets IY, Sydorchuk AR *et al*. Combined Effects of ACE (I/D) and eNOS (894T>G) Genes Polymorphism in

 https://doi.org/10.46389/rjd-2023-1269 © 2023 The Authors

Patients with Arterial Hypertension in the Realization of Molecular Mechanisms of Left Ventricular Hypertrophy. New Armenian Medical Journal 7(2):32-42, 2013.

6. Palmieri V, Bella JN, Arnett DK *et al*. Effect of type 2 diabetes mellitus on left ventricular geometry and systolic function in hypertensive subjects: Hypertension Genetic Epidemiology Network (HyperGEN) study. Circulation 103(1):102–72, 2001. https://doi.org/10.1161/01.cir.103.1.102
7. Soltész B, Pikó P, Sándor J, Kósa Z, Ádány R, Fiatal S. The genetic risk for hypertension is lower among the Hungarian Roma population compared to the general population. PLoS ONE 15(6): e0234547, 2020. https://doi.org/10.1371/journal.pone.0234547
8. Tegegne BS, Man T, van Roon AM, *et al*. Heritability and the Genetic Correlation of Heart Rate Variability and Blood Pressure in >29 000 Families: The Lifelines Cohort Study. Hypertension 76(4):1256-1262, 2020. doi: 10.1161/HYPERTENSIONAHA.120.15227
9. Sydorchuk A, Sydorchuk L, Gutnitska A, *et al*. Linkage of Metabolic Disorders, Endothelial Dysfunction and NOS3 (rs2070744) and GNB3 (rs5443) Genes Polymorphisms in Hypertensive Patients. Biointerface Research in Applied Chemistry Open-Access Journal 13(2):1-12, 2022. DOI: https://doi.org/10.33263/BRIAC132.123
10. Repchuk Y, Sydorchuk LP, Sydorchuk AR, *et al*. Linkage of blood pressure, obesity and diabetes mellitus with angiotensinogen gene (AGT 704T>C/rs699) polymorphism in hypertensive patients. Bratisl Lek Listy 122(10):715-720, 2021. https://doi.org/10.4149/BLL_2021_114
11. Charbonier FW, Zamani M, Huang NF. Endothelial cell mechanotransduction in the dynamic vascular environment. Adv Biosyst 3(2), 2019. https://doi.org/10.1002/adbi.201800252
12. Ji LD, Li JY, Yao BB, Cai XB, Shen QJ, Xu J. Are genetic polymorphisms in the renin-angiotensin-aldosterone system associated with essential hypertension? Evidence from genome-wide association studies. J Hum. Hypertens 31(11):695-8, 2017. https://doi.org/10.1038/jhh.2017.29
13. Sydorchuk LP, Ursuliak YV. Genes allele status of angiotensin-converting enzyme (I/D) and endothelial nitric oxide synthase (894 G>T) in patients with acute coronary syndrome. Lik Sprava 5-6:24-34, 2015.
14. Sydorchuk AR, Sydorchuk LP, Gutnitska AF, *et al*. Endothelium function regulation markers and carotid intima-media thickness in arterial hypertension depending on NOS3 (rs2070744) and GNB3 (rs5443) genes polymorphism: a prospective case-control study. Endocrine Regulations 56(2):104-114, 2022. DOI: 10.2478/enr-2022-0012
15. Visseren FLJ, Mach F, Smulders YM, *et al*. ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J, 42(34):3227-3337, 2021. http://doi.org/10.1093/eurheartj/ehab484
16. Bryan W, Mancia G, Spiering W, *et al*. 2018 ESC/ESH Guidelines for the management of arterial hypertension. The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). European Heart Journal 39:3021-3104, 2018. https://doi.org/10.1093/eurheartj/ehy339
17. Dzhuryak V, Sydorchuk L, Sydorchuk A, *et al*. The cytochrome 11B2 aldosterone synthase gene CYP11B2 (RS1799998) polymorphism associates with chronic kidney disease in hypertensive patients. Biointerface Research in Applied Chemistry 10(3):5406-5411, 2020. doi:10.33263/BRIAC103.406411
18. Sydorchuk L, Dzhuryak V, Sydorchuk A, *et al*. The cytochrome 11B2 aldosterone synthase gene rs1799998 single nucleotide polymorphism determines elevated aldosterone, higher blood pressure, and reduced glomerular filtration, especially in diabetic female patients. Endocrine Regulations 54(3):101-110, 2020. DOI: 10.2478/enr-2020-0024
19. Charoen P, Eu-Ahsunthornwattana J, Thongmung N, *et al*. Contribution of Four Polymorphisms in Renin-Angiotensin-Aldosterone-Related Genes to Hypertension in a Thai Population. Int J Hypertens 4861081, 2019. https://doi.org/10.1155/2019/4861081
20. Repchuk Y, Sydorchuk L, Fedoniuk L, *et al*. Association of Lipids' Metabolism with Vitamin D Receptor (rs10735810, rs222857) and Angiotensinogen (rs699) Genes Polymorphism in Essential Hypertensive Patients. Open Access Maced J Med Sci 9(A): 1052-6, 2021. https://doi.org/10.3889/oamjms.2021.6975
21. Semianiv M, Sydorchuk L, Fedonyuk L, *et al*. Metabolic and Hormonal Prognostic Markers of Essential Arterial Hypertension Considering the Genes Polymorphism AGTR1 (rs5186) and VDR (rs2228570). Romanian Journal of Diabetes Nutrition and Metabolic Diseases 28(3): 284-91, 2021. https://www.rjdnmd.org/index.php/RJDNMD/article/view/1049
22. Marushchak M, Krynytska I. Insulin Receptor Substrate 1 Gene and Glucose Metabolism Characteristics in Type 2 Diabetes Mellitus with Comorbidities. Ethiop J Health Sci. Sep 31(5):1001-1010, 2021. doi: 10.4314/ejhs.v31i5.12
23. Shipilova T, Pshenichnikov I, Kaik J. *et al*. Echocardiographic as-sessment of the different left ventricular geometric patterns in middle-aged men and women in Tallinn. Blood Press 12: 284-290, 2003.
24. Gerdts E, Cramariuc D, de Simone G, *et al*. Impact of left ventricular geometry on prognosis in hypertensive patients with left ventricular hypertrophy (the LIFE study). Eur. J. Echocardiogr 9(6):809-815, 2008.
25. Isa MS, Bala GS, Oyati AI, *et al*. Patterns of left ventricular hypertrophy and ge-ometry in newly diagnosed hypertensive adults in Northern Nigerians. J. of Diabetes and Endocrin 1(1):1-5, 2010.
26. Lieb W, Gona P, Larson MG, *et al*. The natural history of left ventricular geome-try in the community: clinical correlates and prognostic significance of change in LV geometric pattern. JACC Cardiovasc Imaging 7(9):870–8, 2014. https://doi.org/10.1016/j.jcmg.2014.05.008
27. Sayin BY, Oto A. Left Ventricular Hypertrophy: Etiology-Based Therapeutic Options. Cardiol Ther 11(2):203-230, 2022. doi: 10.1007/s40119-022-00260-y
28. Marketou ME, Parthenakis F, Vardas PE. Pathological Left Ventricular Hypertrophy and Stem Cells: Current Evidence and New Perspectives. Stem Cells Int 2016:5720758, 2016. DOI: 10.1155/2016/5720758
29. Dias-Peixoto MF, Ferreira AJ, Almeida PW, Braga VB, Coutinho DC. The cardiac expression of Mas receptor is responsive to different physiological and pathological stimuli. Peptides 35(2): 196-201, 2012.
30. Verdecchia P, Gentile G, Angeli F, Reboldi G. Beyond blood pressure: evidence for cardiovascular, cerebrovascular, and renal protective effects of renin-angiotensin system blockers. Ther. Adv. Cardiovasc. Dis 6(2): 81-91, 2012.

© 2023 The Authors

31. Palmieri V, Bella JN, Arnett DK, *et al*. Effect of type 2 diabetes mellitus on left ventricular geometry and systolic function in hypertensive subjects: Hypertension Genetic Epidemiology Network (HyperGEN) Study. Circulation 103:102–1072001, 2001. DOI: 10.1161/01.cir.103.1.102
32. Juo SHH, DiTullio M, Lin HF, *et al*. Heritability of left ventricular mass and other morphologic variables in Caribbean Hispanic subjects: The Northern Manhattan Study. J Am Coll Cardiol 46:730–742, 2005. DOI: 10.1016/j.jacc.2005.05.025
33. Chein KL, Hsu HC, Su TC, Chen MF, Lee YT. Heritability and major gene effects on left ventricular mass in the Chinese population: a family study. BMC Cardiovasc Disor 6:37, 2006. DOI: 10.1186/1471-2261-6-37
34. Fox ER, Klos KL, Penman AD, *et al*. Heritability and genetic linkage of left ventricular mass, systolic and diastolic function in hypertensive African Americans (from the GENOA Study) Am J Hypertens 23:870–875, 2010. DOI: 10.1038/ajh.2010.67
35. Bella JN, Göring HH. Genetic epidemiology of left ventricular hypertrophy. Am J Cardiovasc Dis 2(4):267-78, 2012.

 https://doi.org/10.46389/rjd-2023-1269 © 2023 The Authors