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Impaired regulation of genome stability may be the key mechanism of left ventricular hypertrophy development in arterial hypertension

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Summary

Objective

To investigate association between PPAR gene family polymorphisms and PARP, PARG and NOS3 genes with left ventricular hypertrophy (LVH) in patients with arterial hypertension (AH).

Materials and methods

This study involved 2012 patients, 127 of them had LVH. We performed transthoracic echocardiography and used determination of alleles and genotypes of polymorphic candidate genes using phenol-chloroform DNA extraction from venous blood of patients. Amplificator "Tercic" ("DNA-technology, Russia) has been used for polymorphic genetic loci amplification. Statistical analysis has been performed with SPSS software.

Results

We demonstrated the association of LVH with 4a allele of NOS3 (OR 1,68, p=0.016) and GC genotype of PARG gene (OR 3.61, p=0.024). Multifactor regression analysis demonstrated independent relationship of left ventricular hypertrophy with 4a NOS3 allele, GG genotype of PARG gene, patient's age and maximal levels of systolic blood pressure.

Conclusion

Impaired balance of processes that lead to genome destabilization/stabilization may be one of the mechanisms responsible for LVH developing in patients with AH.

Key words

PARG, NOS3, arterial hypertension, left ventricular hypertrophy.

Modern guidelines for management of patients with arterial hypertension (AH) mark out target organs lesions like left ventricular hypertrophy (LVH), hypertensive nephropathy as a separate problem and suggest to put much diagnostic efforts into their detection [1]. These lesions are referred to additional risk factors that negatively influence patients' prognosis. Lack of strict correlation between level, severity, duration of AH and the beginning of developing target organ lesions proves that some additional causes influence the formation of these complications. Recently discovered new experimental data demonstrate that DNA (deoxyribonucleic acid) stability regulation can play a key role in this process. It is supposed to think that NO (nitrogen oxide) causes activation of peroxide oxidation that leads to peroxynitrite synthesis. DNA is identified to be one of the targets of peroxynitrite. NO-synthases expression is regulated by PPAR (peroxisome proliferator-activated receptors) family of nuclear receptors. The opposite process of DNA repair starts with involvement of poly ADP(adenosine diphosphate) ribose polymerase I type (PARP I) [2] and poly ADP ribose glycohydrolase (PARG). Changes of genome stability are actively investigated as a possible pathogenetic mechanism of various diseases. There are some evidences proving the role of these mechanisms in development of AH complications [3]. Associative genetic approach allows to test the hypothesis of the role of the protein of interest in pathogenesis of disease by studying patients with different genotypes of this protein that influence differently its activity.

According with this, the current study aimed to investigate possible association of PPAR nuclear receptor family genes polymorphic markers and endothelial NO-synthase with developing LVH in AH.

Characterization of patients and methods

This study has been approved by local ethic commitee. This study involved 212 patients with AH. Exclusion criteria were lack of patient's to participate in study, presence of myocardial scars and evident valvular heart disease.

Clinical characterization of patients 94 male patients (44.3%) and 118 female patients (55.7%). Average age of patients: 60.23 ± 0.74 years, AH duration at the moment of examination:– 14.2±0.79 years. 22 patients(10.4%) at the moment of inclusion into study had AH stage 1, 67 patients (31.6%) had AH stage 2, and 123 patients (58%) had AH stage 3. 115 patients (54.2%) were diagnosed with coronary artery disease (CAD), 35 (16.5%) were diagnosed with diabetes mellitus type 2, 17 (8.1%) survived stroke. Average body mass index (BMI) was 29.2±0.34 kg/m^2, 168 (79.2%) patients had excessive body weight, 37 (17.4%) patients had glomerular filtration rate (GFR) < 60 ml/min.

Methods. End-diastolic dimensions (EDD), end-systolic dimensions (ESD), interventricular septum thickness (IST), posterior left ventricular wall thickness

Table 1. **Investigated candidate genes**

Candidate gene	Polymorphic marker	Genotype frequency distribution		χ^2, p
		Observed	Expected (according with Hardy Weinberg principle)	
Endothelial NO-synthase gene (NOS3)	4a/4b Glu298Asp	4b4b-68 4a4b-101 4a4a-5	80,7 57,6 17,7	19,65 <0,001
Peroxisome proliferator-activated receptor α gene (PPARA)	C24313G	CC-150 CG-56 GG-6	149,4 57,1 5,5	0,08
Peroxisome proliferator-activated receptor γ2 gene (PPARG2)	Pro12Ala	Pro/Pro-149 Pro/Ala-53 Ala/Ala-8	146,6 57,6 5,67	1,37
Peroxisome proliferator-activated receptor γ3 gene (PPARG3)	C(–681)G	CC -104 CG -48 GG -12	99,9 56,2 7,9	3,49
Peroxisome Proliferator-Activated Receptor Gamma, Coactivator 1 Alpha gene (PPARGC1A)	Gly482Ser	Gly/Gly -71 Gly/Ser- 83 Ser/Ser-10	77,2 70,6 16,2	5,01 <0,05
Peroxisome Proliferator-Activated Receptor Delta gene (PPARD)	T(–87)C	CC -59 CT -26 TT -79	31,6 80,8 51,6	75,4 <0,001
poly(ADP-ribose) polymerase 1gene (ADPRT1)	Leu54Phe	Leu/Leu -44 Leu/Phe -62 Phe/Phe- 58	34,3 81,4 48,3	9,32 <0,005
	Val762Ala	Ala/Ala-127 Ala/Val-28 Val/Val-9	121,2 39,5 3,2	13,98 <0,001
Poly(ADP-ribose) glycohydrolase gene (PARG)	A(–431)G	AA-97 AG-48 GG-19	89,3 68,5 11,2	9,72 <0,005

(PLVWT) were evaluated using transthoracic echocardiography. This measurement was performed in M-mode on the level of mitral valve chords and parasternal long axis view. Ejection fraction (EF) was determined using Simpson's formula in apical 4-chamber position. Left ventricular myocardium mass (LVMM) was measured using Devereus RB formula [5], $LVMM=1,04*[(IST+PLWT+EDD)^3 – EDD^3]-13,6$.

Left ventricular myocardium mass index (LVMMI) was quantified as the LVMM ratio to body surface area. LVMMI >95 g/m^2 was considered as LVH for woman and >110g/m^2 for men respectively.

Phenol-chloroform extraction of genomic DNA from venous blood of patients was used for determination of alleles and genotypes of polymorphic candidate genes Amplificator "Tercic" ("DNA-technology, Russia) was used for polymorphic genetic loci amplification. Agarose gels were stained with ethidium bromide and polyacrilamide gels were stained with silver nitrate. Investigated candidate genes are listed in Table 1.

Statistical analysis Statistical analysis was performed using standard package of SPSS software. For quantitative variables average values and errors of average were quantified. Statistical analysis was done using Mann-Whitney and Kruskal-Wallis tests. Discrete variables were estimated using Pearson's chi-squared test x^2 . When expected number of observations in any square of the contingency table was <5 we used Fisher's exact test and used p-value derived from two-sided test. Independent influence of clinical and genetic factors on LVH degree was estimated with logistic regression. Clinical factors that had significant relation with AH clinical course according with single-factor regression analysis (p<0,05) were included into multifactor regression analysis. Binary logistic regression with Wilks test has been used as multifactor analysis approach. for all tests p-value <0.05 was considered significant. Accordance between observed genotype frequencies and expected ones quantified using Hardy-Weinberg equilibrium was checked with online-calculator. (http://www.oege.org/software/hardy-weinberg.html).

Results

Between observed patients 127 had LVH, 85 patients had no signs of LVH. Patients with LVH were older, there were more female than male between them, these patients had longer AH duration and higher numbers of maximal systolic blood pressure (SBP) (Table 2).

Significant differences in the frequency of alleles and genotypes of polymorphic markers of *PPARG2, PPARG3, PPARA, PPARGC1A, PARP1* genes in the

Table 2. **Clinical characterization of patients**

Parameter	All patients (n=212)	Patients without LVH (n=85)	Patients with LVH (n=127)	p
Gender male/ female	94/118	49/36	45/82	0,001
Age, years	60,2±0,74	54,8±1,04	63,8**±0,**93	0,01
Diabetes mellitus type 2, n(%)	35 (16,5)	9(10,6)	26(20,5)	ns
AH duration, years	14,2±0,79	10,9±0,92	16,7±1,15	0,001
BMI, kg/m	29,2±0,34	28,7±0,44	29,5±0,22	ns
Excessive body weight, n(%)	168 (79,2)	63(74,1)	105(82,7)	ns
SBP max, mm Hg..	198,3±1,53	186,9±3,27	205,9±1,71	0,01
DBP max mm Hg.	110,9±0,79	108,3±1,84	112,8±0,86	ns
GFR, ml\min	81,36±1,43	83,5±2,63	77,2**±1,69**	ns
GFR < 60 ml / min, n(%)	37 (17,4)	12(14,1)	25(19,6)	ns
Stroke, n(%)	17 (8,1)	4(4,7)	13(10,2)	ns
CAD, n(%)	115 (54,2)	40(47,1)	75(59,1)	ns

Comments: DBD – diastolic blood pressure, ns – not significant

groups of patients with and without LVH were not present (Table 1).

Distribution of polymorphic markers of PPARA, PPARG2, PPARG3 genes frequencies corresponded to Hardy-Weinberg equation. Other markers declined from expected distribution (Table 1).

Genotype frequencies of polymorphic markers *PPARG2, PPARG3, PPARA, PPARGC1A, PARP1, ADPRT1* genes had no significant differences between patients with LVH and without LVH (Table 3).

Table 3. **The frequency of polymorphic markers of genes alleles and genotypes polymorphic markers of genes expression products of which participate in metabolic regulation in patients with and without LVH**

	No LVH n= 85	LVH n= 127	p	*OR[95%CI]*
Polymorphic marker *C24313G* of *PPARA* gene				
Genotypes CC CG GG	 61 (71,8%) 23 (27,1%) 1 (1,2%)	 89 (70,1%) 33 (26,0%) 5 (3,9%)	 ns ns ns	 1,01[0,59-2,04] 0,94[0,51-1,76] 3,34[0,39-30,00]
Alleles: *C* *G*	145 (85,3%) 25 (14,3%)	211 (83,1%) 43 (16,9%)	ns ns	0,84[0,49-1,84] 1,18[0,69-2,02]
Polymorphic marker *Pro12Ala* of *PPARG2* gene				
Genotypes Pro/Pro Pro/Ala Ala/Ala	 64 (75,3%) 18 (21,2%) 3 (3,5%)	 85 (67,5%) 36 (28,6%) 5 (4,0%)	 ns ns ns	 0,68[0,36-1,86] 1,48[0,77-2,84] 1,04[0,44-4,48]
Alleles: Pro Ala	146 (85,9%) 24 (14,1%)	206 (81,7%) 46 (18,3%)	ns ns	0,73[0,23-1,45] 1,35[0,79-2,32]
Polymorphic marker *C(–681)G* of *PPARG3* gene				
Genotypes *CC* *CG* *GG*	 44 (64,7%) 19 (27,9%) 5 (7,4%)	 69 (63,3%) 33 (30,3%) 7 (6,4%)	 ns ns ns	 0,94[0,50-1,76] 1,12[0,57-2,18] 0,84[0,26-2,84]
Alleles: *C* *G*	107 (77,5%) 29 (22,5%)	171 (78,4%) 47 (21,6%)	ns ns	0,98[0,58-1,66] 1,01[0,60-1,70]
Polymorphic marker *T(–87)C* of *PPARD* gene				
Genotypes *CC* *CT* *TT*	 23 (33,8%) 18 (26,5%) 27 (39,7%)	 39 (35,8%) 13 (11,9%) 57 (52,3%)	 ns 0,012 ns	 1,09[0,57-0,06] 0,36[0,16-0,81] 1,66[0,90-3,07]
Alleles *C* *T*	64 (47,1%) 72 (52,9%)	91 (41,7%) 127 (58,3%)	ns ns	0,80[0,52-1,24] 1,24[0,80-1,90]
Polymorphic marker *Gly482Ser* of *PPARGC1A* gene				
Genotypes *Gly/Gly* *Gly/Ser* *Ser/Ser*	 29 (42,6%) 36 (52,9%) 3 (4,4%)	 47 (43,1%) 54 (49,5%) 8 (7,3%)	 ns ns ns	 1,01[0,55-1,88] 0,87[0,47-1,60] 1,71[0,44-6,70]
Alleles: *Gly* *Ser*	94 (69,1%) 42 (30,9%)	148 (64,9%) 70 (35,1%)	ns ns	0,94[0,59-1,49] 1,05[0,67-1,66]
Polymorphic marker *Leu64Phe* of *ADPRT1* gene				
Genotypes *Leu/Leu* *Leu/Phe* *Phe/Phe*	 16 (23,5%) 25 (36,8%) 27 (39,7%)	 31 (28,4%) 42 (38,57%) 36 (33,0%)	 ns ns ns	 1,54[0,77-3,06] 1,32[0,72-2,45] 0,74[0,39-1,40]
Alleles *Leu* *Phe*	 57 (41,9%) 79 (58,1%)	 104 (47,7%) 114 (52,3%)	 ns ns	 1,26[0,82-1,94] 0,79[0,51-1,21]
Polymorphic marker *Val762Ala* of *ADPRT1* gene				
Genotypes *Ala/Ala* *Ala/Val* *Val/Val*	 50 (73,5%) 15 (22,1%) 3 (4,4%)	 87 (79,8%) 16 (14,7%) 6 (5,5%)	 ns ns ns	 1,42[0,69-2,90] 0,60[0,27-1,32] 1,26[0,30-5,22]
Alleles *Ala* *Val*	 115 (84,6%) 21 (15,4%)	 180 (86,5%) 28 (13,5%)	 ns ns	 1,17[0,63-2,16] 0,85[0,47-1,57]
Polymorphic marker *A(–431)G* of *PARG* gene				
Genotypes *AA* *AG* *GG*	 44 (64,7%) 21 (30,9%) 3 (4,4%)	 61 (56,0%) 32 (29,4%) 16(14,7%)	 ns ns 0,024	 0,69[0,27-1,29] 0,93[0,48-1,79] 3,61 [1,21-12,91]
Alleles *A* *G*	 109 (80,1%) 27 (19,9%)	 154 (70,6%) 64 (29,4%)	 0,03 0,03	 0,27 [0,07-0,98] 1,64[1,01-2,67]
Polymorphic marker *4a/4b* of *NOS3* gene				
Genotypes *4b/4b* *4b/4a* *4a/4a*	 36 (53,7%) 30 (44,8%) 1 (1,5%)	 38 (33,3%) 72 (63,2%) 4 (3,5%)	 0,005 0,012 ns	 0,43 [0,23-0,79] 2,10 [1,14-3,86] 2,36[0,26-23,53]
Alleles *4b* *4a*	 102 (76,1%) 32 (23,9%)	 148 (64,9%) 80 (35,1%)	 0,016 0,016	0,59 [0,37 – 0,93] 1,68 [1,07-2.62]
Polymorphic marker *Glu298Asp* of *NOS3* gene				
Genotypes *Glu/Glu* *Glu/Asp* *Asp/Asp*	 41 (62,1%) 24 (36,4%) 1 (1,5%)	 62 (52,5%) 52 (44,1%) 4 (3,4%)	 ns ns ns	 0,67[0,36-1,24] 1,37[0,74-2,56] 2,24[0,24-20,84]
Alleles *Glu* *Asp*	 106 (80,3%) 26 (19,7%)	 176 (74,6%) 60 (25,4%)	 ns ns	 0,72[0,42-1,21] 1,39[0,82-2,33]

Patients with LVH had significantly higher frequency of 4a allele of polymorphic marker of NOS3 gene (p=0.016, OR 1.68 [1.07-2.62]). These patients had significantly higher frequency of GG polymorphic marker *A(–431)*G of PARG gene (p=0.024) [OR 3.61 CI 1.21-12.91]. The frequency of A allele was significant-

Table 4. **Echocardiography (EchoCG) results in relation to PARG, PPARA and NOS3 genotypes**

EchoCG parameter	4a|4b of NOS3 gene		C24313G of PPARA gene		A(–431)G of PARG gene	
	Genotype *4b/4b* (n=74)	Genotypes *4a/4a* and *4a/4b* (n=107)	Genotype CC (n=150)	Genotypes CG and GG (n=62)	Genotypes AA and AG (n=158)	Genotype GG (n=19)
PLVWT, cm	1,10±0,050	1,22±0,025	1,19±0,020	1,11±0,024	1,16±0,016	1,23±0,051
p	0,017	0,045	нд			
IST, cm	1,12±0,023	1,21±0,022	1,17±0,017	1,09±0,024	1,14±0,015	1,21±0,048
p	0,004	0,014	ns			
EDD, cm	4,79±0,077	4,85±0,058	4,82±0,047	4,81±0,063	4,82±0,044	5,00±0,154
p	ns	ns	ns			
EF, %	58,5±0,89	56,5±1,04	56,3±0,77	58,5±1,11	55,50±0,72	57,3±02,92
p	ns	ns	ns			
LVMM, g	245,3±9,25	270,6±9,09	262,3±7,54	236,8±9,25	251,9±6,46	298,6±26,50
p	0,053	0,051	0,025			
LVMMI, g/m^2	127,4±4,65	144,6±4,44	138,5±3,70	125,5±4,33	133,8±3,24	157,6±20,02
p	0,032	0,044	0,023			

ly lower [OR 0.27 CI 0.07-0.98], and the frequency of G allele – significantly higher (OR=1.64[1.01-2.67]) comparing with the group of patients without LVH. In the group of patients with LVH the frequency of *T(–87)C* marker heterozygote genotype of PPARD gene was significantly lower.

We also compared main characteristics of left ventricle myocardium in patients with different genotypes of investigated polymorphic markers. Significant differences were obtained just for *NOS3*, *PARG* and *PPARA* genes (Table 4).

It was demonstrated that for polymorphic marker *A(–431)G* of PARG gene patients with rare genotype GG have significantly higher LVMM and LVMMI comparing with the patients with A allele. The association of this marker and systolic and diastolic function parameters was not identified. There were no differences in condition of LV systolic function.

It was shown that for polymorphic marker *C24313G* of *PPARA* gene carriers of CC genotype have significantly more thick walls of LV myocardium, LVMM and LVMMI.

It was demonstrated that in case of polymorphic marker *4a/4b* of NOS3 gene patients who carry 4a allele have significantly more thick walls of LV myocardium and LVMMI.

To evaluate independence of clinical and genetic factors influence on LVH risk we performed regression analysis (Table 5). Single-factor regression analysis demonstrated that male gender, age, SBP levels and NOS3 gene polymorphism were related to LVH development. factors that had significant connection with LVH according with single-factor analysis were included into multifactor analysis.

Multifactor analysis revealed that the presence of 4a allele of 4a/4b polymorphic marker of NOS3 gene, GG genotype of polymorphic marker *A(–431)*G of PARG gene, age of patients and maximal SBP levels in patients with AH are associated independently with LVH

Discussion

According with modern ideas, genome stability is connected with several simultaneous processes. First of them is activity of factors that destabilize DNA, for example peroxynitrite, second – activity of DNA repair, key regulator of which is PARP1 and PARG interaction. Regulation of all these processes is another important factor o genome stability.

Our study demonstrated association of polymorphic markers of NOS3, PPARA, PARG genes with developing LVH in patients with AH. This association proves that LVH development is not only the di-

Table 5. **Clinical and genetic factors that influence independently LVH developing**

Factor	OR (single-factor analysis)	p	OR (multifactor analysis)	p
Male gender	2,59 [1,86-5,72]	0,0001		ns
Age	1,09 [1,02-1,14]	0,0001	1,12 [1,07-1,17]	0,0001
SBP max levels	1,03 [1,01-1,06]	0,001	1,18 [1,02-1,58]	0,023
Allele *4a* of polymorphic marker *4a/4b* of *NOS3* gene	2,32 [1,34-4,11]	0,008	2,58 [1,09-6,09]	0,031
Genotype *GG* of polymorphic marker *A(–431)*G of *PARG* gene	3,72[1,04-13,72]	0,043	8,52 [1,71-42,38]	0,028

rect consequence of increased hemodynamic load on myocardium, but also is the result of impaired balance of factors that maintain genome stability.

NO from one side is considered to be one of the key endothelial factors that regulate vascular tone, from another side it is one of the toxic factors that damage tissues and trigger apoptosis [4]. NO is synthesized from L-arginine by NO-synthase family of enzymes in several tissues. NO-synthase 3 type (NOS3) is responsible for NO production in endothelium where NO activates guanylyl cyclase system and works either as the main vasodilating factor or interacts with peroxide forming peroxynitrite. Peroxynitrite has strong genotoxic effect and it has significant role in poly(ADP-ribose) polymerase expression regulation. Association of polymorphic markers genotypes 4a/4b of NO-synthase gene with LVH development was demonstrated before [7], and in this study it has been proved in a big group of patients. This polymorphism is associated with increased level of basal NO secretion and reduced release of NO as a response to stimuli that activate NOS3, by this creating favorable conditions for peroxynitrite formation [8].

Peroxisome proliferator activating receptors (PPAR) are nuclear receptors that regulate transcription. Apart of it their stimulation can change NO-synthases activity. These receptors are present in 3 isoforms – alpha, gamma and beta/delta. Each of them is coded by its own gene (PPARA, PPARG, PPARD). Each isoform has tissue and substrate specificity. These receptors regulate proliferation, angiogenesis, inflammation, lipid metabolism and lipid peroxidation. PPARA cardioprotective action hasn't been fully understood so far. It has been shown in cell cultures that PPARA reduces cardiomyocyte proliferation in response to endothelin [9]. One of possible mechanisms of this protection, including protection from LVH, can be turning on the mechanism of PPARA-mediated inhibition of apoptosis stimulated with insulin-like growth factor [5, 10]. Another possible way to influence LVH with PPARA activation can be related to sirtuin1(Sirt1), important mediator of energetic metabolism [11]. Sirt1 participates in protein deacetylation and regulates activity of different processes, including NOS3 activity [12]. Important feature of its action is that its substrate NAD+(Nicotinamide adenine dinucleotide) is used also for DNA repair. According with some studies, these processes compete for restricted amount of NAD+. Administration of PPARA blockers SIRT1 effects to LVH development disappear [6]. PPARA activation prevents the development of myocardial fibrosis [13].

One of possible mechanisms of PPARA cardioprotective action in relation to LVH can be its interaction with NO-sythases. PPARA agonist fenofibrate that is used as lipid-lowering agent reduces bronchial response to methacholine, action of which is related with insufficient activity of NO-synthases [14]. Alpha type receptor is expressed mostly in the heart. Gamma type receptors have coactivators, proteins that cause receptor's conformational change and participate in its activation. Alpha1 coactivator is expressed mainly in cardiac tissue and participates in cardiomyocyte energetic metabolism.

PPARA role in LVH is proved with clinical evidences. Previously it has been shown that LVH hypertrophy is associated with CC genotype of C24313G polymorphic marker of PPARA gene [15]. In our study this association has been confirmed for another time in a big group of patients.

Majority of works that investigated LVH development aimed to prove the participation of other nuclear receptors of PPAR family and this relation hasn't been confirmed. Likely it can be explained with low functional significance of selected polymorphisms.

PARP1 is the sensor of DNA damage and starts DNA repair process [16]. PARP1 binds intensively single and double strand DNA breaks that were formed as the result of direct DNA damage or during DNA repair as a result of enzyme action. Further poly(ADP-ribose) synthesis precedes the beginning of damaged DNA repair. At the same time poly(ADP-ribose) promotes apoptosis. Change of poly(ADP-ribose) polymerase activity can lead to hereditary retinal dystrophy. and predisposes to several cancers and autoimmune diseases [17]. PARP family genes activation mediates cell protection from genotoxic, oxidative and other agents. Probably PARP participates in some metabolic processes, particularly in lipid metabolism, Poly(ADP-ribose)polymerases family can be associated with myocardial hypertrophy development [18]. Some myocardial hypertrophy mediators ,like angiotensin II, interleukin-6, are activators of PARP family enzymes, and it is possible that activation of this system mediates LVH development. This fact allowed to consider the association of PARP polymorphism with developing LVH.

PARP1 gene is located in 13q34 chromosome. ADPRT1 gene that codes poly(ADP-ribose)polymerase PARP1 contains two functionally different parts: N-terminal DNA-binding domain and

C-terminal catalytic domain. There is an automodification domain between them. Several polymorphisms are known for this gen, Leu54Phe (located at exon 2) and Val762Ala (located at exon 17 in the beginning of catalytic domain) are the best investigated ones. Val762Ala polymorphic marker is associated with increased risk of several oncologic diseases development [19], Leu54Phe marker is associated with the risk of diabetic nephropathy development [20]. It was shown in experiments that PARP1 can participate in myocardial lesions formation and myocardial hypertrophy [21]. It was demonstrated that PARP1 blockers can prevent LVH development in animal models and in the culture of cardiomyocytes [22, 23]. Clinical data that would be able to prove this hypothesis are still absent. Results related to more studied polymorphic markers didn't demonstrate the association between LVH developing and PARP1 polymorphism.

Poly(ADP-ribose)glycohydrolase is a physiological antagonist of poly(ADP-ribose)polymerase. Poly(ADP-ribose)glycohydrolase is responsible for degradation of poly(ADP-ribose) that is the product of PARP family enzymes. Poly(ADP-ribose) chains that are synthetized in nuclei as a response to mutagenic factors dedrade during 1-2 minutes after termination of their synthesis because of PARG action

This enzyme's function is related to apoptosis system. Poly (ADP-ribose)glycohydrolase slows down apoptosis. The main catalytic center of poly (ADP ribose) glycohydrolase is complementary to ADP-ribose. Poly (ADP ribose) glycohydrolase is located at 10q11.23 chromosome. It is known that PARG activity increases as a response to ischemia. It has been shown that increased expression of this gene in the brain of ischemic mice, and also in abdominal organs if mesenteric artery is ischemic. So far there were no data about PARG gene polymorphic markers association with human disease pathogenesis. This study demonstrated that carrying G allele of polymorphic marker A(-431)G of PARG gene predisposed to developing LVH. Reduced activity of PARG and impaired degradation of ADP-ribose that makes cells more sensitive to growth factor action can be a possible mechanism of this phenomenon.

The limitation of this study was comparably small number of patients. But the results of this study can become a foundation for further studies in this field.

Thus one of the mechanisms responsible for developing LVH in patients with AH can be impaired balance of processes that lead to genome destabilization/stabilization.

Conflict of interest: None declared

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