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ANALYSIS OF ASSOCIATIONS OF *PPARGC1A* AND *PPARG* GENE POLYMORPHISMS WITH METABOLIC SYNDROME IN PERSONS WITH VIBRATION DISEASE

Abstract. Vibration disease (VD) has a significant authority in the structure of occupational pathology and is often accompanied by diseases associated with impaired lipid and carbohydrate metabolism. The increased risk of their development may be due to a genetic predisposition to them. Information about the associations of polymorphisms of the peroxisome proliferation activating gamma receptor (PPARγ) gene and its coactivator with metabolic syndrome is presented in the literature. The aim of this work was to study the relationship between the Pro12Ala polymorphisms of the *PPARG* gene and Gly482Ser of the *PPARGC 1A* gene with metabolic syndrome in individuals with VD. The frequency of alleles and genotypes of these polymorphisms was studied in patients with VD and in the comparison group, and their role in the development of metabolic syndrome (MS) was assessed. It was found that the frequency of MS among individuals with VD was higher with the same distribution of alleles and genotypes of Pro12Ala polymorphisms of the *PPARG* gene and Gly482Ser of the *PPARGC1A* gene in the examined groups. Carriage of the ProPro genotype of the *PPARG* gene is associated with resistance to MS development in the comparison group. A significant effect of the Pro12Ala polymorphisms of the *PPARG* gene and Gly482Ser of the *PPARGC1A* gene on the formation of MS was not revealed in patients with vibration disease.

Key words: polymorphisms, PPARG, PPARG coactivator, vibration disease, metabolic syndrome.

Introduction. From 2007 to 2017, about 7% of employees of enterprises in the Far North of the Russian Federation who have contact with hazardous production factors were exposed to general and local vibration [10]. The combined effect of unfavorable production factors (vibration, pronounced cooling and functional overstrain of the musculoskeletal system) leads to the development of vibration disease (VD). This disease takes a significant place in the structure of occupational pathology and is 20-22% [9, 10]. It is characterized as a concomitant pathology of cardiovascular disease (CVD), disorders of lipid and carbohydrate metabolism [13]. It is possible that the sensitivity of people to the action of industrial vibration, as well as an increased risk of metabolic disorders and CVD, can be determined, among other things, by the peculiarities of their genetic status. Associations have been identified between some genotypes of the protease inhibitor alpha-I-antitrypsin, acid phosphatase isoenzyme and vibration disease [7]. Relationships have been established between polymorphic variants of genes for nitric oxide synthase, endothelin, plasminogen activator type 1 and arterial hypertension [1, 3]. It has been shown that polymorphisms of the peroxisome proliferation-activating gamma receptor (PPARγ) gene are associated with changes in the levels of fatty acids, cholesterol and its fractions in blood lipoproteins and tissue sensitivity to insulin, metabolic syndrome (MS) [12, 14, 18]. However, data on the influence of minor allele of the Pro12Ala polymorphism of the *PPARG* gene on metabolic processes and lipid metabolism are ambiguous, the peculiarities of its phenotypic manifestations may be due to the combined influence of race, the presence of mutations in other genes, and the action of external factors, including industrial factors [5, 18]. The functioning of the PPARγ receptor depends on its coactivator, which is encoded by the *PPARGC1A* and *PPARGC1B* genes [4, 16, 17]. The literature provides data on the association between the Gly482Ser polymorphism of the *PPARGC1A* gene and arterial hypertension in men with type 2 diabetes [20]. The **aim** of this work was to study the relationship between the Pro12Ala polymorphisms of the *PPARG* gene and Gly482Ser of the *PPARGC1A* gene with metabolic syndrome in individuals with vibration disease.

Materials and methods. The study included men after they signed an informed consent for examination approved by the Biomedical Ethics Committee of the East Siberian Institute of Medical and Environmental Research, who had no history of cancer, renal, liver failure, stroke, myocardial infarction and coronary heart disease. There were two groups: main group included 121 patients with VD (age 51.0 ± 0.6 years), the comparison group – 69 men who were not exposed to vibration in their professional activity (mean age 51.4 ± 0.8 years).

Individuals with MS were identified in each of the surveyed groups. They had abdominal obesity (waist volume> 94 cm) and two of any of the criterion indicators of impaired lipid or carbohydrate metabolism, blood pressure (triglyceride content more than 1.7 mmol / L, high-density lipoprotein cholesterol below 1.0 mmol / L, lipoprotein cholesterol low density above 3.0 mmol / l, blood pressure more than 140/90 mm Hg, plasma glucose levels above 6.1 mmol / l or impaired glucose tolerance). Individuals without this syndrome and those with it were subgroups 1 and 2 in the comparison group, in main group – 3 and 4, respectively. Subgroup 1 included 45 people aged 50.3 ± 1.0 years, subgroup 2 – 24 mens 53.5 ± 1.0 years old, the 3rd subgroup consisted of 60 patients 50.4 ± 0.9 years old, 4th – 61 individuals (average age 52.5 ± 0.9 years).

We ascertained the ethnicity of the respondents using a questionnaire to ascertain the ethnicity of their parents. Persons of the Caucasian race (Russians, Ukrainians) accounted for 89%, individuals of the Mongoloid race (Buryats, Ya-

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kuts, Tatars) among the surveyed were 11%. The incidence of representatives of the Mongoloid race did not differ significantly in subgroups 1-4 and amounted to 8.9%, 12.5%, 11.6% and 9.8%, respectively.

Whole blood using K3 EDTA as an anticoagulant was used for genetic studies. DNA was isolated from blood leukocytes using a DNA-express reagent (Litekh, Russia) by a modified method [2]. Genotyping of the Gly482Ser polymorphisms of the *PPARGC1A* gene and Pro12Ala of the *PPARG* gene was performed by real-time PCR with allele-specific primers in accordance with the protocol of the manufacturer of reagent kits (Litekh, Russia).

The analysis of the research results was performed using the STATISTICA 6.0 and SNPstats software (access https://www.snpstats.net/start.htm). The chi-square test ($\chi 2$) was used to compare genotype frequencies. The assessment of the association of the genotype with the disease was determined by the odds ratio (OR), taking into account the 95% confidence interval (95% CI). The critical level of statistical significance of the differences (p) was 0.05. When describing the age characteristics of the studied samples, the values of the arithmetic mean and its error (M ± m) were used.

Results and discussion. The Pro-12Ala mutation (rs1801282) is most common for the *PPARG* gene localized on chromosome 3 (3p25.2), the Gly-482Ser polymorphism (rs8192678) - for the *PPARGC1A* gene, which is located on chromosome 4 (4p15.1) [5, 16, 17, 21, 22]. Data on the frequency of allelic variants and genotypes of these polymorphisms in the comparison group and patients with VD are presented in Table 1.

It was found that the distribution of the studied genotypes in the investigated samples corresponded to the expected values at the Hardy-Weinberg equilibrium. The Ala allele of rs1801282 polymorphism was carried by 17% of individuals from the comparison group and 15% from group I. Our data are consistent with the results of studies carried out on the European population and residents of Russia, in which the frequency of the Ala allele of the *PPARG* gene was 20% and 13.9 % respectively [4, 21]. The occurrence of alleles and genotypes of the Pro12Ala polymorphic locus of the *PPARG* gene among persons with and without occupational pathology did not differ. The frequencies of nucleotide substitutions in the Gly482Ser polymorphism of the *PPARGC1A* gene were also comparable in the groups. The incidence of carriers of the minor allele Ser in the studied groups was the same as the average for the population of Russia (32.6%) and amounted to 32-37% [21]. The absence of differences in the frequencies of alleles and genotypes of the studied polymorphisms of the *PPARG* and *PPARGC1A* genes between the groups indicates that the cohorts had a similar pattern of genetic predisposition to the development of dyslipidemia and impaired glucose metabolism, since these receptors are involved in the metabolism of fats and carbohydrates. Due to the fact that PPARγ and its coactivator are involved in the pathogenesis of a number of diseases, including obesity, MS and diabetes mellitus, at the next stage of the study, we analyzed the occurrence of MS in the comparison group and among patients with VB.

The number of individuals with MS among patients with an occupational disease was higher than in the comparison group (50.4% and 34.8%, p = 0.037). According to the literature, metabolic syndrome is detected in 20-50% of the population of Russia, it is observed in 30-40% of cases in people over 30 years old, and its frequency varies depending on the region, age, gender [8, 19]. Higher numbers of MS incidence among patients with VD are consistent with the data of other studies, which examined the individual components of the syndrome – abdominal obesity, dyslipidemia and arterial hypertension, detected in 34%, 59% and 94% of people with vibration pathology, respectively [6].

Further analysis of the association of gene polymorphism was carried out in the subgroups identified taking into account the presence of MS. It was found that the risk of MS is reduced in persons who are not in contact with vibration in professional activities and who are carriers of the ProPro genotype of the *PPARG* gene (OR = 0.43; 95% CI 0.21-0.91, p=0.046). The *PPARG* gene belongs to the key regulators of adipogenesis, and the presence of the minor allele Ala of the Pro12Ala polymorphism leads to a decrease in the binding of the receptor to its target (lipoprotein lipase and acetyl-CoA synthetase), and, as a consequence, to a change in the intensity of lipid metabolism, an increase in free fatty acids in adipocytes, insulin resistance [4, 18, 21, 22]. Therefore, the carriage of the Pro allele can have a protective effect and be a marker of resistance to the development of MS in the absence of vibration. In the presence of vibration pathology, the protective effect of the considered genetic factors is leveled. In this study, we did not reveal a relationship between the Gly-482Ser polymorphism of the *PPARGC1A* gene and the risk of developing MS in the examined groups.

This syndrome was less common among the examined patients with the protective ProPro genotype of rs1801282 polymorphism in the comparison group than among patients with VD (p=0.025) (Table 2). This shows that under the influence of external factors, in particular, vibration, the role of genetic predisposition in the development of MS decreases.

Among individuals with the GlySer genotype of rs8192678 polymorphism, the frequency of MS in the comparison group was lower (p = 0.061) compared to the group of patients with occupational pathology. This fact may also indicate that nucleotide substitutions in the genes of the PPARγ receptor and its coactivator,

Table 1

Frequency distribution of alleles and genotypes of polymorphic variants of the PPARG and PPARGC1A genes

Gen/SNP	Allele / Genotype	All examined % (number)	Comparison group % (number)	Main group % (number)	p
PPARG Pro12Ala (rs1801282)	Pro	84 (320)	83 (115)	85 (205)	0.606
	Ala	16 (60)	17 (23)	15 (37)	
	ProPro	71 (134)	70 (48)	71 (86)	0.884
	ProAla	27 (52)	27 (19)	27 (33)	1.00
	AlaAla	2 (4)	3 (2)	2 (2)	0.663
PPARGC1A Gly482Ser (rs8192678)	Gly	66 (198)	63 (87)	68 (111)	0.327
	Ser	34 (104)	37 (51)	32 (53)	
	GlyGly	45 (68)	42 (29)	48 (39)	0.425
	GlySer	42 (64)	45 (31)	40 (33)	0.502
	SerSer	13 (19)	13 (9)	12 (10)	0.840

Note: p - level of statistical significance of differences in allele and genotype frequencies between groups.

Table 2

The incidence of metabolic syndrome among individuals with different genotypes of polymorphic loci Pro12Ala of the PPARG gene and Gly482Ser of the PPARGC1A gene

Gen/SNP	Genotype	Comparison group, % (quantity)	Main group, % (quantity)	p
PPARG Pro12Ala	ProPro	31 (15)	51 (44)	0.025
	ProAla	47 (9)	45 (15)	0.889
	AlaAla	0 (0)	100 (2)	1.000
PPARGC1A Gly482Ser	GlyGly	41 (11)	41 (16)	1.000
	GlySer	29(9)	52 (17)	0.061
	SerSer	44 (4)	50 (5)	0.794

Notes: p is the level of statistical significance of differences between groups.

causing changes in their functional activity, do not significantly affect the development of MS in individuals with VD. It can be assumed that its formation is caused by a violation of other mechanisms of regulation of lipid and carbohydrate metabolism, which are characteristic, among other things, for persons with vibration pathology. [3, 15]. Since MS is one of the main causes of atherosclerotic lesions of the coronary arteries [11], in order to reduce the risk of developing cardiovascular disease, it is necessary to carry out diagnostic and preventive measures aimed at identifying this syndrome and reducing its frequency in people with VD.

Conclusion. As a result of the study, it was found that, despite the same distribution of alleles and genotypes of the Pro12Ala polymorphism of the *PPARG* gene and Gly482Ser of the *PPARGC1A* gene in the examined groups, the frequency of MS among persons with WD was higher. It was shown that the carriage of the ProPro genotype of the *PPARG* gene in the comparison group marks resistance to the development of MS, while the role of genetic factors in patients with occupational pathology has not been established. It can be concluded that in the examined persons exposed to vibration, the formation of MS is caused by disturbances in the mechanisms of regulation of lipid and carbohydrate metabolism, which are not associated with the Pro12Ala polymorphisms of the *PPARG* gene and Gly482Ser of the *PPARGC1A* gene.

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VARIANTS OF SINGLE NUCTEOTIDE SUBSTITUTIONS IN THE GENES OF MATRIX METALLOPROTEINASES *(MMP-2 AND MMP-9)* IN ARTERIAL HYPERTENSION IN PEOPLE OF WORKING AGE

Point substitutions were studied in the genes MMP-2 c.-1306C> T (rs243865) and MMP-9 c.-1562C> T (rs3918242) in people under the age of 60 living in the Primorsky Territory. It was found that the differences between the shares of the MMP-2 CC, CT, and TT genotypes in the groups of persons with AH and the control group were statistically insignificant (mid-p = 0.16), while for the MMP-9 CC, CT, and TT genotypes, these differences were determined (α = 0.05). In the distribution of patients with hypertension, depending on the indicators of relative cardiovascular risk (CVR) in persons with hypertension under 40 years of age in the group with a CVR value of 2, a significant increase in the minor alleles of MMP-9 1562 C/T was found, compared with individuals with a CVR value 1, the presence of the T allele in the MMP-9 gene c.-1562C> T (rs3918242) is associated with a higher risk of cardiovascular catastrophes in young people with hypertension. Thus, the definition of the aforementioned polymorphism is of particular importance for young patients.

Keywords: arterial hypertension, metabolic syndrome, matrix metalloproteinases MMP-2 and MMP-9, genetic polymorphisms

Introduction. One of the discussed problems in the risk of occurrence and prognosis of an unfavorable course of AH is the search for genetic polymorphisms and other significant biomarkers that allow to assess the individual cardiovascular risk with a high degree of accuracy and timely carry out personalized corrective preventive measures [3].

The direction of predictive medicine associated with the search for genes encoding enzymes of connective tissue metabolism, the imbalance in the state of which, in turn, determines early damage to target organs, regardless of the degree of increase in blood pressure (ABP) is of interest. The processes of cardiovascular remodeling in hypertension (AH) and preclinical damage to target organs are associated with the inversion of the phenotypes of the smooth muscle cell of the vessel from contractile to proliferative, changes in the state of the cytoskeleton and cellular memory of cardiomyocytes, restructuring of the extracellular matrix as a result of the action of factors that activate hemodynamic stress, and as a result of discoordination of the response at the genetic level [3]. The family of matrix metalloproteinases (MMP) occupies a special place in the formation of the proinflammatory potential of the cell microenvironment, followed by elastin degradation and accumulation of collagen I, II, and III and fibronectin [8]. The unbalanced activity of the *MMP-2* and *MMP-9* genes caused by single nucleotide substitutions in the promoter zone at the rs243865 and *rs3918242* loci, respectively, in hypertension (AH) attracts the attention of many researchers, and their results are not unambiguous. Interest in studying the contribution of SNV to the *MMP-2* and *MMP-9* genes at the *-1306 C / T* and *-1562 C / T* loci indicates the need to accumulate data for their identification in the population of persons with AH in order to be able to use them as predictors of the risk of AH, predicting the occurrence of target organ damage and organizing personalized prevention of cardiovascular accidents, which is especially important for people of working age and young people, including due to the high prevalence of "masked" hypertension (AH) in this category of patients.

Objective: to determine the conjugation of SNV in genes *MMP-2 c.-1306C>T* (rs243865) and *MMP-9 c.-1562C> T (rs3918242)* with the presence of hypertension (АГ) in people of working age.

Materials and methods. The study included 271 volunteers aged 25 to 60 years of Caucasian race, Slavic ethnicity, living for at least three generations in the Primorsky Territory. These individuals took part in the ESSE-RF study. Of these, 161 patients with hypertension (AH), 91 men and 70 women, the control group

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