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The role of the genes of the natriuretic peptide systems and antioxidant protection in forming the risk of myocardial infarction

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Abstract.

Purpose of the study: to reveal the relationship between single nucleotide polymorphic variants (SNPV) of natriuretic peptide genes, antioxidant defense system and endothelial function with the development of myocardial infarction (MI). Material and methods: the study included 126 patients with MI and preserved or moderately reduced left ventricular ejection fraction. Among them were 92 men and 34 women, the average age of which was 57 ears. The control group included residents of Andijan without acute MI (n=110, 60 women and 50 men), whose mean age was 53 ears. Results of the study: in the sample of studied patients with MI without division by sex and age revealed significant associations with allelic variants of the CBR1 and CBR3 genes (carbonyl reductase 1 and 3 genes of the antioxidant defense system). When separating patients by gender, the following associations were revealed: in men, the NVC rs9024 CBR1 genotypes, as well as rs1056892 CBR3 genotypes, according to the dominant model of inheritance, have a protective effect in relation to predisposition to the development of myocardial infarction.

Conclusion: The obtained preliminary results indicate the need for further studies of the identified single nucleotide polymorphic variants in relation to the severity of myocardial infarction and the risk of recurrent cardiovascular events in the long term.

Key words: myocardial infarction, gene, natriuretic peptides, antioxidant protection, polymorphic variants.

Natriuretik peptid tizimlari genlarining va antioksidantlarni himoyasining miokard infarkti xavfini shakllanishdagi o'rni

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Annotatsiya.

Tadqiqot maqsadi: Miokard infarkti (MI) rivojlanishi bilan natriuretik peptid genlarining yagona nukleotidli polimorfik variantlari (SNPV), antioksidant himoya

tizimi va endotelial funktsiya o'rtasidagi bog'liqlikni aniqlash. Materiallar va usullar: Tadqiqot MI bilan og'rigan va chap qorincha chiqarish fraksiyasi saqlanib qolgan yoki o'rtacha darajada kamaygan 126 bemorni qamrab oldi. Ularning 92 nafari erkak va 34 nafari ayollar bo‘lib, ularning o‘rtacha yoshi 57 yoshni tashkil etgan. Nazorat guruhiga Andijon shahrida yashovchi o'tkir MI bo'lmagan (n=110, 60 ayol va 50 erkak) kirgan, ularning o'rtacha yoshi 53 yosh. Tadqiqot natijalari: O'rganilayotgan MI bilan og'rigan bemorlarning jinsi va yoshi bo'yicha bo'linmasdan namunasida CBR1 va CBR3 genlarining allel variantlari (antioksidant mudofaa tizimining karbonil reduktaza 1 va 3 genlari) bilan sezilarli aloqalar aniqlandi. Bemorlarni jinsi bo'yicha ajratishda quyidagi assotsiatsiyalar aniqlandi: erkaklarda NVC rs9024 CBR1 geno-tiplari, shuningdek, rs1056892 CBR3 genotiplari, dominant irsiyat shakllari miyokard infarkti rivojlanishiga himoya ta'siriga ega.

Xulosa: Olingan dastlabki natijalar miokard infarktining og'irligi va uzoq muddatda takroriy yurak-qon tomir hodisalari xavfi bilan bog'liq holda aniqlangan yagona nukleotidli polimorfik variantlarni keyingi tadqiqotlar zarurligini ko'rsatadi.

Kalit so'zlar: miokard infarkti, gen, natriuretik peptidlar, antioksidant himoya, polimorf variantlar.

Роль генов систем натриуретических пептидов и антиоксидантной защиты в формировании риска инфаркта миокарда

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Аннотация.

Цель исследования: выявить взаимосвязь однонуклеотидных полиморфных вариантов (ОНПВ) генов натрийуретических пептидов, системы антиоксидантной защиты и функции эндотелия с развитием инфаркта миокарда (ИМ). Материал и методы: в исследование включено 126 больных ИМ с сохраненной или умеренно сниженной фракцией выброса левого желудочка. Среди них было 92 мужчин и 34 женщин, средний возраст которых составил 57 лет. В контрольную группу вошли жители г. Андижана без острого ИМ (n=110, 60 женщин и 50 мужчин), средний возраст которых составил 53 года. Результаты исследования: в выборке обследованных больных ИМ без разделения по полу и возрасту выявлены достоверные ассоциатсии с аллельными вариантами генов CBR1 и CBR3 (гены карбонилредуктазы 1 и 3 системы антиоксидантной защиты). При разделении больных по половому признаку выявлены следующие ассоциатсии: у мужчин генотипы CBR1 rs9024, а также генотипы CBR3 rs1056892 по доминантной модели наследования

обладают протективным действием в отношении предрасположенности к развитию инфаркта миокарда.

Заключение. Полученные предварительные результаты свидетельствуют о необходимости дальнейшего изучения выявленных однонуклеотидных полиморфных вариантов в связи с тяжестью течения инфаркта миокарда и риском повторных сердечно-сосудистых событий в отдаленном периоде.

Ключевые слова: инфаркт миокарда, ген, натрийуретические пептиды, антиоксидантная защита, полиморфные варианты.

Introduction. Despite the encouraging results of the introduction of programs for primary and secondary prevention, as well as the treatment of atherothrombosis , cardiovascular disease (CVD) remains the main cause of death and disability worldwide [1]. The contribution of CVD to mortality rates will continue to increase, mainly due to the impact of the novel coronavirus pandemic , as well as due to lower coverage rates of prevention programs in low- and middle-income countries [2–3]. Acute forms of coronary heart disease (CHD), including myocardial infarction (MI), remain a significant cause of morbidity and mortality from CVD in developed countries [4–5]. It has been proven that diseases of the cardiovascular continuum are multifactorial in nature with a significant genetic component, including the hereditary risk of MI. [6–8]. CVDs are characterized by a complex genetic structure with various combinations of single nucleotide polymorphic variants (SNPs) [8]. Previous studies by domestic and foreign authors have shown the association of various ONVCs with the risk of development and adverse course of MI [9–10]. First of all, we are talking about hereditary disorders of lipid metabolism, regulation of vascular tone, hyperaggregative and hypercoagulable statuses [11–12].

A promising task is to study the relationship of SNPV genes for the inflammatory response, myocardial and endothelial dysfunction with developed MI in the Siberian population. Previously, a study evaluating the association of systemic inflammatory response genes was conducted in patients in Japan [13]. Studies evaluating the association of SNPV genes of the natriuretic peptide system have not been found in the available literature.

Purpose of the study: to reveal the relationship between SNPV of natriuretic peptide genes, the antioxidant defense system and endothelial function with the development of MI.

Material and methods

The study included 126 patients (mean age 57 years) with MI with preserved and moderately reduced left ventricular ejection fraction (LVEF) - 50%

hospitalized in the clinic Andijan State Medical Institute in 2021–2022 _ _ _ as part of a registry study. The registry and genetic testing protocol was approved by the local ethics committee. All patients before inclusion in the study signed an informed voluntary consent, its form was also approved by the local ethical committee.

Characteristics of patients with MI are presented in Table 1.

Table 1. Clinical characteristics of patients with MI

Clinical characteristics	Number of patients n(%)
Males	92 (73)
Females	34 (27)
Arterial hypertension	101 (80)
Medical history of chronic cardiac insufficiency	17 (13.5)
Medical history of angina	42 (32)
Diabetes mellitus type 2	27 (21.5)
Multifocal atherosclerosis	4 (3.4)
Chronic renal disease	92 (73.1)
Earlier percutaneous coronary intervention	7 (5.6)
Earlier coronary by-pass surgery	4 (3.2)

The control group for a comparative genetic study was represented by a population sample of residents of the city of Andijan without acute MI (n= 110 , 60 women and 50 men), whose average age was 53 years . The material for the study was genomic DNA isolated from peripheral blood according to a standard protocol. Genotyping selected SNPV were carried out by real-time PCR using TaqMan technology . A total of 5 genes were selected for SNPW. VNVCs of those genes were selected that had previously been studied for possible association with the risk of MI in genome-wide studies (GWAS) and in pilot studies of individual VNVCs. The studied genes reflected the hereditary characteristics of the functioning of natriuretic peptide systems, antioxidant protection, and endothelial function. Quantitative data are presented as median and interquartile range Me (25Q; 75Q). To analyze differences in the frequen-

cies of genotypes, Pearson's χ2 test or Fisher's exact test was used. The association of SNPV genes with a predisposition to the development of MI was assessed by calculating the odds ratio (OR) and 95% confidence interval (CI) to it. The frequency and effect of the considered genotypes were assessed using 4 statistical models of heredity (recessive, dominant, overdominant , additive). Differences were considered statistically significant if p <0.05.

Research results. The study of the links between the SNPV of the previously designated genes showed that the frequency distribution of almost all genotypes in the group with MI and in the control group corresponded to that expected at equilibrium. The rs4880 SOD2 polymorphic variant did not pass this distribution test and was therefore excluded from further analysis. In a sample of study patients with MI without division by sex and age revealed significant associations with allelic variants of the CBR1 and CBR3 genes.

When separating patients by gender, the following associations were revealed: in men, the NVC rs9024 CBR1 genotypes, as well as rs1056892 CBR3 genotypes, according to the dominant model of inheritance, have a protective effect in relation to predisposition to the development of myocardial infarction. Allelic variants of the NPR2 gene (atrial natriuretic peptide receptor type 2 gene) demonstrated a risk effect on the development of MI (Table 2).

Table 2. SNPV prevalence in males of the studiet groups

Gene	Polymorphism	Genotype	MI (n=92), n(%)	Control group (n=50), (N=%)	OR (95% CI)	P
NPR2	rs2236289	C/C	74 (80.1)	34(67)	1,00	0,035
		C/TT/T	18 (20.2)	16(32)	1,93 (1,04-3,58)	
	rs7034957	C/C	60 (65.2)	39(78)	1,00	0,038
		C/A-A/A	32(34.1)	11(21.4)	1,88 (1,03-3,45)	
CBR1	rs9024	G/G	36(39.3)	38(75.6)	1,00	<0,0001
		A/G-A/A	56(61)	12(24.4)	0,20 (0,11-0,36)	
CBR3	rs1056892	G/G	40(43.2)	14(28.5)	1,00	0,022
		A/G-A/A	52(56.6)	36(71.3)	0,51 (0,28-0,91)	

In women, the relationship of the studied genetic factors with the development of MI can be associated (according to the dominant inheritance model) with the NPV rs13288085 and rs7034957 of the NPR2 gene and rs9024 of the CBR1 gene, as well as rs1056892 of the CBR3 gene, which are characterized by a protective effect (Table 3)

Table 3. SNPV prevalence in females of the studiet groups

Gene	Polymorphism	Genotype	MI (n=34),n(%)	Control group (n=60),n(%)	OR(95%CI)	P
NPR2	rs13288085	C/C	30(89.1)	60(67)	1,00	0,0034
		C/T-T/T	4 (11)	19(32.3)	0,25 (0,08–0,73)	
	rs7034957	C/C	29 (86.1)	40(66.5)	1,00	0,007
		C/A-A/A	5 (13.2)	20(34.2)	0,30 (0,11–0,79)	
CBR1	rs9024	G/G	25(76.5)	24(40.2)	1,00	0,00001
		A/G-A/A	8(23.5)	36(59.8)	0,21 (0,09–0,47)	
CBR3	rs1056892	G/G	18 (55.5)	17(28.2)	1,00	0,0014
		A/G-A/A	15(44.5)	43(72.2)	0,31 (0,15–0,64)	

Discussion. In our study, the SNPV of the atrial natriuretic peptide B receptor gene , as well as carbonic anhydrase, an important component of the antioxidant defense system, showed an association with the development of MI, which can determine them as promising markers and cardiovascular risk factors in primary prevention, by analogy with existing ones. models of genetic prediction of the risk of MI. The enzyme carbonyl reductase is known to be one of several monomeric NADPH-dependent oxidoreductases with broad specificity for carbonyl compounds. Violations of the genetic determination of this enzyme may be associated with a decrease in the global antioxidant activity of the organism. Both carbonyl reductase genes studied by us are located nearby on chromosome 21q22.12. During normal translation of the CBR1 gene, its protein actively metabolizes many environmental toxins and pharmacological substrates during chemotherapy (doxorubicin). Experiments on animal models have demonstrated the antioxidant effect of the CBR1 gene. The manifestation of a number of SNPVs of the CBR1 gene and the associated decrease in the intensity of antioxidant protection may be associated with the progression of atherogenesis due to the angiotoxic effects of aeropollutants. Previous studies have shown that a number of other SNPs of the CBR1 gene are characterized by protective effects in relation to the development of oxidative stress, neurodegeneration , apoptosis , and cardiotoxicity. Four carbonyl reductase isoenzymes are known : CBR1, CBR2, CBR3, and CBR4. It was found that the rs9024 and rs1056892 polymorphic variants of the CBR1 and CBR3 genes are characterized by a myocardioprotective effect when exposed to cardiodepressant compounds (during chemotherapy). The presence of gender- specific translation of SNPV carbonyl reductase genes has not been previously reported in the literature. It has been proven that the concentrations of natriuretic peptides in circulating plasma can be used to assess the severity of manifesta-

tions of heart failure, as well as the clinical effects of remodeling of acute myocardial ischemia against the background of atherothrombosis and to predict the risk of adverse outcomes in patients with MI or after cardiac surgery . It was previously determined that a number of polymorphic variants of the genes of the natriuretic peptide system and their receptors are associated with CVD, such as arterial hypertension, stroke, and MI . It has been proven that the frequency and severity of perioperative left ventricular dysfunction after cardiac surgery were associated with the presence of some NPV genes of the natriuretic peptide system. Associations of a number of NPVs of the atrial natriuretic peptide gene with higher platelet aggregation activity and detection of CAD in various populations have also been previously shown. NPV of the brain natriuretic peptide gene have been associated with diabetes mellitus, pulmonary hypertension, and atherosclerotic renovascular disease. At the same time, the literature did not find a relationship between the polymorphisms of the natriuretic peptide type B receptor (NPR2) gene studied by us and the risk of developing MI, and the gender characteristics of these genetic markers were not described. In our opinion, the identified features of genetic factors can characterize unique cardiovascular risks in the population of Western Siberia, which was previously shown in our studies.

Conclusion.

The results of the pilot study showed that some SNPs of the genes for natriuretic peptides and antioxidant protection have a risky and protective effect in relation to predisposition to the development of MI. It is worth noting that the established associations have gender differences. Thus, in men, allelic variants rs2236289 and rs7034957 of the NPR2 gene (natriuretic peptide type B receptor) are associated with an increased risk of developing MI, and CBR1 rs9024, CBR3 rs1056892 reduce the risk of developing MI by 1.5 times. For women, the protective effect of polymorphic variants rs13288085 and rs7034957 of the NPR2 gene, as well as rs9024 of the CBR1 gene was shown. The obtained preliminary results indicate the need for further studies of identified NVC in relation to the severity of myocardial infarction and the risk of recurrent cardiovascular events in the long term.

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