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Search for Age-Dependent Genetic Risk Factors for Predicting Early Myocardial Infarction in Men And Women

Aim	To assess the association of polymorphic variants of candidate genes, including two miR-375 microRNA target genes (*PRKCA* and *CDC42*) and *AGTR1*, *PAI1*, *IL10*, *IFNG*, and *TGFB1* genes involved in the pathogenesis of atherosclerosis as the major cause of myocardial infarction (MI), with the age of the first MI in groups of patients of different sexes.
Material and methods	Genotyping of DNA samples from peripheral blood of 548 ethnic Russian patients with a known age of MI onset was performed using real-time polymerase chain reaction. Differences in the frequencies of carriage of alleles and genotypes of the studied polymorphic variants, as well as their biallelic combinations, were analyzed in groups of patients with an age of MI onset less than and more than the median.
Results	In men, an association was found between the age of first MI and carriage of the *AGTR1* rs5186*C/C (p=0.016; odds ratio, OR, 2.58; 95% confidence interval, CI: 1.13-5.89) and *PRKCA* rs887797*A/A (p=0.033; OR, 2.03; 95% CI: 1.01-4.11) genotypes, as well as combinations of *AGTR1* rs5186*C/C + *PRKCA* rs1010544*A (p=0.0064; OR, 3.27; 95% CI: 1.32-8.07), *AGTR1* rs5186*A + *PRKCA* rs887797*G (p=0.0021; OR, 0.42; 95% CI: 0.24-0.75) and *AGTR1* rs5186*A/A + *CDC42* rs12038474*A (p=0.005; OR, 0.47; 95% CI: 0.27-0.82). In women, only combinations of *PRKCA* rs1010544*A + *IL10* rs1800896*A/A (p=0.032; OR, 1.94; 95% CI: 1.01-3.74) and *PRKCA* rs1010544*G + *IFNG* rs2430561*T/T (p=0.026; OR, 0.20; 95% CI: 0.044-0.96) were associated with the age at first MI.
Conclusion	A number of polymorphic variants of the genome associated with the age at first MI was identified. For the first time, it was shown that the set of such variants differs in men and women.

Keywords	Myocardial infarction; single-nucleotide polymorphism; age-dependent genetic predisposition
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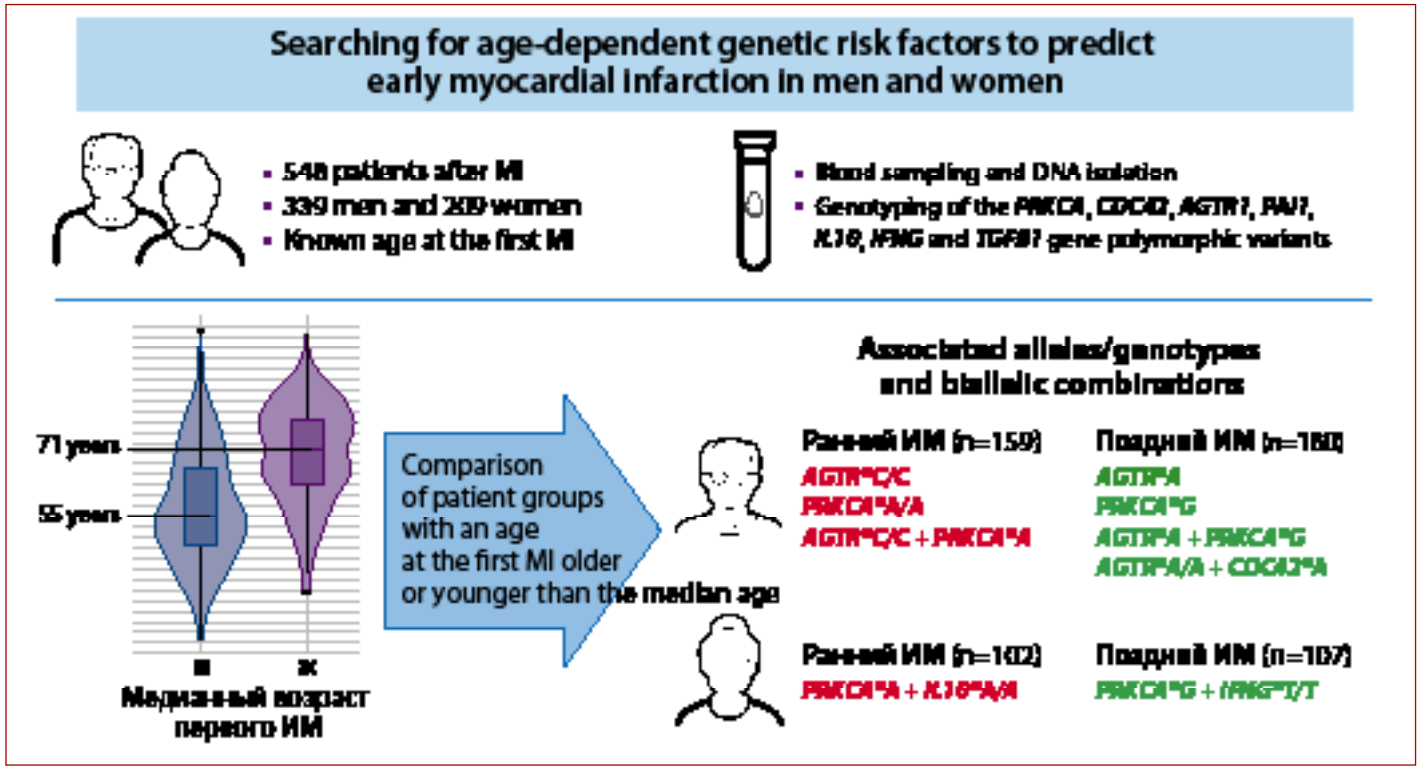
Introduction

Myocardial infarction (MI) is an acute form of ischemic heart disease (IHD) characterized by necrosis of a myocardial area due to cessation of its blood supply. MI is one of the most common causes of death in the Russian Federation (23.8%, according to 2023 data) [1]. It is a multifactorial (complex) disease, the risk of which is influenced by various external [2] and genetic factors. The non-Mendelian inheritance pattern of MI indicates the polygenic nature of this disease and results from the carriage of multiple variants of polymorphic genes [3].

To search for genes involved in the predisposition to polygenic diseases, the case-control method is traditionally used for comparing the frequencies of alleles and genotypes in patients and healthy individuals in the control group. With the development of high-throughput technologies for genome analysis, such studies are preferably carried out using the genome-wide association study (GWAS) method. The 2024 GWAS catalog [4] for MI as a separate disease presents 24 published studies conducted in various populations. Statistically significant associations of genetic variants with the risk of developing MI identified in these studies are characterized by p values in the range from 5×10^{-8} (the minimum significance level accepted for genome-wide studies) to 1×10^{-140} and small odds ratio (OR) values in the range of 1.03-1.39. Conducting such studies for each ethnic group requires significant resources while the reproducibility of GWAS results

Central illustration



can be relatively low, even for samples of several million people (for example, for the UK Biobank sample of 4,397,962 people, it was 58.1%) [5]. Therefore, the classical "candidate gene" approach remains relevant.

The spectrum of known risk factors (RFs), as well as some pathophysiological mechanisms underlying the development of MI, may differ significantly in young and elderly MI patients [6]. The RFs discussed in this review, which may be associated with the development of MI at different ages, also include genetic factors, but attention was mainly paid to one group of patients with the first MI at age <55 years ("early" MI) [7, 8]. The number of studies comparing the spectra of MI-associated genes in patients with early and late first MI using a control group of healthy individuals is limited. For example, R. Tomaiulo et al. [9] studied the possible participation of prothrombotic gene variants as a RF for the development of acute MI in subjects of different genders and ages from Southern Italy. In the study by B. V. Titov et al. [10], ethnic Russian patients with the first MI before the age of 60 had a significantly greater contribution of gene variants associated with inflammatory reactions to the risk of MI than patients with a later first MI. In the study by I. A. Goncharova et al. [11] also performed on a sample of Russian patients, early MI was associated with the carriage of polymorphic variants of the *ADAMDEC1* and *AQP2* genes, and late MI with the TAS2R38 polymorphism.

In the case of age-dependent diseases such as MI, the use of a standard case-control approach faces a number of difficulties [12], most of which arise at the stage of forming a control group. One way to overcome this problem in order to identify the features of the genetic architecture of MI at different ages may be to compare directly groups of young and elderly patients. However, we did not find a single such study in the literature.

The array of genetic variants associated with MI, an age-dependent disease with a polygenic type of inheritance, may vary significantly in patients with different ages of their first MI.

Aim

To assess the association of polymorphic variants of candidate genes, two miR-375 microRNA target genes (*PRKCA* and *CDC42*) and variants of the *AGTR1*, *PAI1*, *IL10*, *IFNG* and *TGFB1* genes involved in the pathogenesis of atherosclerosis as the main cause of MI, with the age of the first MI when comparing groups of patients of different sexes with different ages of its debut.

Material and methods

This retrospective study was approved by the Ethics Committee of the Chazov National Medical Research Center of Cardiology # 241 of 26.11.2018, and conducted in 2020-2023. The study included 548 patients after MI; 288 of them were managed at the Chazov National Medical Research Center of Cardiology of the Ministry

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of Health of the Russian Federation and 260 at Municipal Clinical Hospital # 51 of the Moscow Department of Health, who were followed up at the Department of Therapy, Cardiology, and Functional Diagnostics with a Course in Nephrology of the Central State Medical Academy at the Administrative Directorate of the President of the Russian Federation. MI was diagnosed according to the clinical criteria of the 2018 Fourth Universal Definition of MI [13]. All patients were ethnic Russians and provided their informed consent to participate in the study.

Frequencies of carrying individual alleles/genotypes of polymorphic regions and their biallelic combinations were compared directly in patients with the first MI at a younger and older age. Since the age of the first MI differs significantly between sexes [14], all comparisons were made separately for men and women. The gender segregation in the analysis was justified by the method used in clinical practice of forming risk scales for the development of cardiovascular diseases separately for men and women [15, 16].

These patients were divided into groups of men and women with the first MI at a younger and older age; the comparison groups were formed based on the median age of the first MI. Group 1 included patients whose age of the first MI was younger than the MI median age: <55 years for men (n=159) and <71 years for women (n=102). The remaining patients with the first MI at an older age were included in the respective comparison groups: ≥55 years for men (n=180) and ≥71 years for women (n=107).

The candidate genes and their polymorphic variants included in this study are listed in Table 1: *PRKCA* (rs887797, rs1010544), *CDC42* (rs12038474) [13], *AGTR1* (rs5186), *PAI1* (rs1799889), *IL10* (rs1800896), *IFNG* (rs2430561), and *TGFB1* (rs1800471).

DNA was isolated from peripheral blood using the QIAamp DNA Blood (QIAGEN) and ExtractDNA Blood (Eurogen) kits. Genotyping of polymorphic variants of the *AGTR1* (rs5186), *IL10* (rs1800896), *PRKCA* (rs887797, rs1010544), and *CDC42* (rs12038474) genes was performed by real-time polymerase chain reaction (PCR) using the TaqMan® Genotyping Master Mix PCR mixture and the TaqMan® SNP Genotyping Assay primers and fluorescently labeled probes. For the *IFNG* (rs2430561), *PAI1* (rs1799889), and *TGFB1* (rs1800471) genes, genotyping was performed by allele-specific PCR. To verify the obtained results, 10% of randomly selected DNA samples were re-typed.

Analysis of deviations of the observed genotype frequencies from the Hardy-Weinberg equilibrium using the chi-square test was performed with the Haploview 4.2 software (http://www.broad.mit.edu/mpg/haploview/index.php).

The association of the carriage of alleles and genotypes of the selected SNPs, as well as their biallelic combinations, with the age of the first MI was assessed with the APSampler software using the dynamic Monte Carlo method and Bayesian nonparametric statistics (https://sourceforge.net/projects/apsampler/). A MI-associated biallelic combination was understood as the joint carriage of two alleles/genotypes, each characterized by a lower significance of the association than the combination [17]. The significance levels of the found associations were assessed by the values of Fisher's exact test and OR. The p values were considered significant at a level of <0.05, provided that the values of the 95% confidence interval (CI) for the OR did not cross 1.

Results

Analysis of the genotype distribution in study patients showed that the Hardy-Weinberg genotype equilibrium was maintained (p>0.05) for the studied polymorphic regions of genes, except for rs5186 of the AGTR1 gene (p=0.0006).

The violin plot (see Fig. 1) visualizes the distribution of age at the first MI in men and women. The median age at the first MI in men was 55 years, and in women 71 years. Thus, the first MI occurred in ethnic Russian men earlier than in women.

Table 1. Candidate genes, their characteristics and single-nucleotide polymorphisms (SNPs) selected for the analysis of the association of their variants with myocardial infarction

Gene	Chromosomal localization	rs ID	SNP	Gene product
IL10	1q32.1	rs1800896	−1082G>A	Interleukin-10
CDC42	1p36.12	rs12038474	−864G>A	Cell division control protein 42 homolog
AGTR1	3q24	rs5186	1166A>C	Angiotensin II type 1 receptor
PAI1	7q22.1	rs1799889	−6754G>5G	Plasminogen activator inhibitor
IFNG	12q15	rs2430561	874A>T	Interferon gamma
PRKCA	17q24.2	rs887797	−1703G>A	Protein kinase C alpha
		rs1010544	−559T>C	
TGFB1	19q13.2	rs1800471	915G>C	Transforming growth factor beta-1

Comparison of the subgroups of men with an age at the first MI <55 years and ≥55 years (Table 2) revealed an association of earlier MI with carriage of the AGTR1 rs5186*C/C (OR 2.58; 95% CI 1.13-5.89; p=0.016) and PRKCA rs887797*A/A (OR 2.03; 95% CI 1.01-4.11; p=0.033) genotypes. Furthermore, a number of biallelic combinations associated with the age at the first MI was identified, all of which included the AGTR1 rs5186 variant and various variants of the PRKCA and CDC42 genes. The AGTR1*C/C genotype in combination with the PRKCA rs1010544*A allele (the allele alone was not significant) was more significantly associated with early MI (OR 3.27; 95% CI 1.32-8.07; p=0.0064) than the genotype alone. A later MI (≥55 years) was associated with combinations of the AGTR1*A and PRKCA rs887797*G alleles (OR 0.42; 95% CI 0.24-0.75; p=0.0021), as well as the AGTR1*A/A genotype and the CDC42 rs12038474*A allele (OR 0.47; 95% CI 0.27-0.82; p=0.005). Thus, the analysis of biallelic combinations formed as a result of the cumulative contribution of their polymorphic variants to the predisposition to the development of MI, identified another age-dependent variant of the PRKCA gene, rs1010544, as well as a variant of the CDC42 gene.

When comparing the subgroups of women divided according to the median age at the first MI, 71 years, no associations of individual alleles and genotypes were observed. As shown in Table 3, associations were found only between the combination of the PRKCA rs1010544*A allele and the IL10 rs1800896*A/A genotype with an age at the first MI <71 years (OR 1.94; 95% CI 1.01-3.74; p=0.032) and the combination of the PRKCA rs1010544*G allele and the IFNG rs2430561*T/T genotype (OR 0.20; 95% CI 0.044-0.96; p=0.026) with an age at the first MI >71 years.

Discussion

Long-term observations indicate that men are at a higher risk of developing cardiovascular diseases than women. Thus, the prevalence of MI among the population of Russian regions, according to 2022 data, was 5.2% among men and 1.5% among women [18]. One of the factors leading to such difference may be an earlier age at the first MI in men. According to the estimates we obtained from a representative sample of 549 ethnical Russian patients, the median age at the first MI was 55 years for men and 71 years for women. An earlier age at the first MI in men compared to women was also observed in other ethnic groups [14]. Based on these data, we performed an age-dependent analysis of genetic predisposition to MI separately for men and women. In contrast to previous studies, which compared each age-specific group with the same control group in the search for age-dependent genetic RFs for MI [9-11], in the present study we directly compared the carriage frequencies of alleles/genotypes of the studied polymorphic regions in groups of patients with the first MI at a younger and older age. In our opinion, this approach has a signif-

Table 2. Frequencies of carriage of alleles, genotypes and biallelic combinations of the studied genes significantly different in subgroups of men with an age at the first MI <55 years and ≥55 years

Gene, ID	Carriage of alleles, genotypes, and allelic combinations	Patients with the first MI at an age <55 years (n=159)	Patients with the first MI at an age ≥55 years (n=180)	p	OR (95% CI)
Alleles and genotypes					
AGTR1 rs5186	C (C/C+A/C)	0.39	0.36	—	—
	A (A/A+A/C)	0.88	0.95	0.016	0.39 (0.17-0.88)
	C/C	0.12	0.05	0.016	2.58 (1.13-5.89)
	A/C	0.27	0.31	—	—
	A/A	0.61	0.64	—	—
PRKCA rs887797	A (A/A+A/G)	0.57	0.52	—	—
	G (G/G+A/G)	0.86	0.93	0.033	0.49 (0.24-0.99)
	A/A	0.14	0.07	0.033	2.03 (1.01-4.11)
	A/G	0.43	0.45	—	—
	G/G	0.43	0.48	—	—
Biallelic combinations					
AGTR1 rs5186 + PRKCA rs1010544	C/C + A (A/A+A/G)	0.13	0.04	0.0064	3.27 (1.32-8.07)
AGTR1 rs5186 + PRKCA rs887797	A (A/A+A/C) + G (G/G+A/G)	0.75	0.87	0.0021	0.42 (0.24-0.75)
AGTR1 rs5186 + CDC42 rs12038474	A/A + A (A/A+A/G)	0.14	0.26	0.005	0.47 (0.27-0.82)

MI, myocardial infarction; OR, odds ratio; CI, confidence interval.

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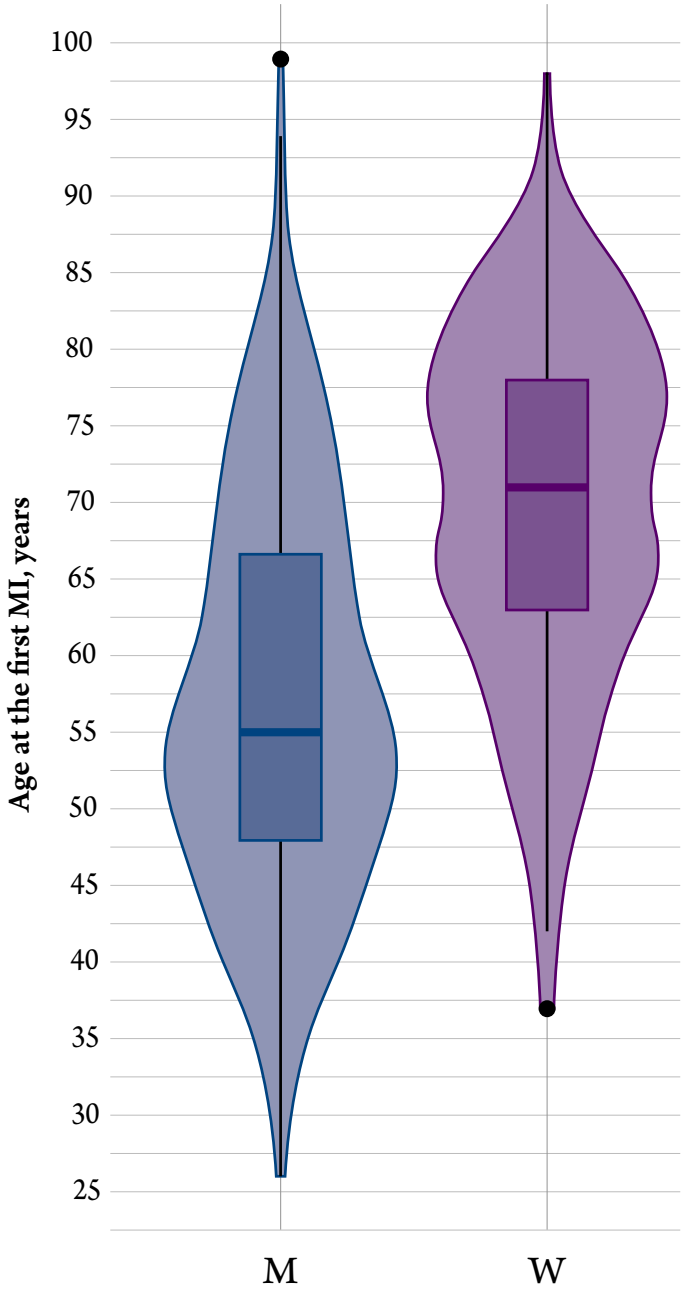
Figure 1. Figure 1. Violin plots of the distribution of age at the first MI in men (M; n=339) and women (W; n=209)



The rectangle in the center of each diagram represents the interquartile range; the thin black lines emanating from the rectangle are the boundaries of the 95% CI; the thick line inside the rectangle is the median; and the black dots are the values falling outside the CI. MI, myocardial infarction; CI, confidence interval.

icant advantage, since it is much more difficult to form balanced samples when comparing patients with age-dependent diseases with healthy individuals. For example, it cannot be guaranteed that the disease will not develop in subjects in the control group some time after the group formation. The results may also be distorted by different effects of other, non-genetic factors on the groups of patients and healthy subjects [19].

This study revealed an association between the age at the first MI and carriage of 6 polymorphic regions in 5 genes: AGTR1, PRKCA (rs887797 and rs1010544), and CDC42 in men and PRKCA (rs1010544), IL10, and IFNG in women, of which only one variant, PRKCA rs1010544, was identified in both men and women. Thus, the differences in the set of MI-associated genes in patients with early and late first MI were convincingly demonstrated. The level of significance of the associations identified in men and women also differed: in men, for the AGTR1 and PRKCA (rs887797) genes, individual polymorphic variants were associated with the age at MI, whereas in women, all age-associated variants were found only in biallelic combinations. For the PRKCA, CDC42, and IL10 gene products, an age-dependent association with MI was observed for the first time.

We have previously shown that one of the components in the pathogenesis of MI may be a disorder of the regulation of apoptosis and actin dynamics in the myocardium mediated by the effects of the regulatory non-coding miR-375 microRNA and several of its key target genes expressed in cardiomyocytes [20]. These genes include the PRKCA and CDC42 genes [21–23]. In addition, PRKCA may play an important role in changing the cardiomyocyte contractility [24], and CDC42 in modulating inflammatory responses [21]. All these processes are critical for the development of MI.

Of the five study genes that are related with inflammatory responses and involved in the pathogenesis of atherosclerosis as the main cause of MI (AGTR1, PAI1, IL10, IFNG, and TGFB1) [25] (see Table 1), associations with MI were found for three genes, AGTR1, IL10, and IFNG. The association of the AGTR1 gene variant

Table 3. Frequencies of carriage of biallelic combinations of the studied genes significantly different in subgroups of women with an age at the first MI <71 years and ≥71 years

Gene, ID	Carriage of biallelic combinations	Patients with the first MI at an age <71 years (n=102)	Patients with the first MI at an age ≥71 years(n=107)	p	OR (95% CI)
PRKCA rs1010544 + IL10 rs1800896	A (A/A+A/G) + A/A	0.34	0.21	0.032	1.94 (1.01–3.74)
PRKCA rs1010544 + IFNG rs2430561	G (G/G+A/G) + T/T	0.02	0.1	0.026	0.20 (0.044–0.96)

MI, myocardial infarction; OR, odds ratio; CI, confidence interval.

with the age at the first MI in men are in good consistency with our earlier results of the analysis of survival curves for carriers of various genetic variants in a total group of MI patients [26]. The IFNG variant had the opposite association with the risk of developing MI at a young age in the Turkish population [27]. This controversy can be explained by both ethnic characteristics and nonlinear epistatic interactions between the IFNG and PRKCA variants in the combination we identified.

It should be noted that the analysis conducted in the total group of patients, not segregated by gender and, therefore, characterized by an average median age at the first MI of 62 years, appeared non-informative, which reflects the ineffectiveness of this approach when applied to MI.

The study limitations include the need for verification of the study results on an independent ethnic Russian sample of MI patients. In addition, the results cannot be automatically transferred to other ethnic groups and populations.

Conclusion

This study demonstrated an association of several genome polymorphic variants with the age at the first MI, and a difference in the set of such variants between men and women. In the future, the study results can be used to improve the existing scales of cardiovascular risk in order to timely identify individuals of the Russian population, primarily men, at a high risk of MI at a young age, and to take prompt preventive measures.

Growing interest in the development of cell therapies for MI opens up another interesting perspective for the application of the obtained results. Genotyping of DNA samples of cell donors for variants of such genes as PRKCA and CDC42, involved in MI-associated pathological processes in the heart, can facilitate the selection of optimal biomaterial for transplantation, which is less susceptible to early pathological changes than the recipient's myocardium. This biomaterial may also have some protective effect by enhancing vascularization, stimulating the cardiomyocyte contractility, suppressing apoptotic reactions, etc.

In any case, only confirmation of our results on independent samples, which will be the subject of further research, will help to draw final conclusions about the contribution of the PRKCA, CDC42, AGTR1, IL10 and IFNG gene polymorphism to the development of MI.

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Conflict of interest

Authors declare no conflict of interest.

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