

FGB, TNF α , IL-1 β , LPL, ITGB3, and TGFB1 genes polymorphism in patients with recurrent myocardial infarction

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ABSTRACT

The aim. To evaluate the association of fibrinogen (*FGB*), tumor necrosis factor α (*TNF α*), interleukin 1 β (*IL-1 β*), lipoprotein lipase (*LPL*), platelet glycoprotein (*ITGB3*), and transforming growth factor β (*TGFB1*) genes with the incidence of recurrent myocardial infarction (MI) in patients living in the middle Volga region.

Materials and methods. The study included 104 people with recurrent MI compared to 280 people who had just one episode of MI. *TNF α* (rs1800629), *IL1B* (rs16944), *TGFB1b* (rs1800469), *FGB* (rs1800788), *ITGB3* (rs5918) and *LPL* (rs328) gene polymorphism was determined in all patients using competing TaqMan probes. Association estimation was performed with multivariate logistic regression analysis.

Results. Patients with recurrent MI much more often had *TNF α* , *IL1B*, *TGFB1b*, *FGB*, *ITGB3* and *LPL* allele and genotype polymorphism. Moreover the risk of MI increased significantly in a case of combination of *FGB* (alleles and genotypes) and *TNF α* (alleles and genotypes) gene polymorphisms (OR = 4.04, 95% CI = (1.895–8.615), $p = 0.0001$).

Conclusion. Thus, *FGB*, *LPL*, *TNF α* , *TGFB1b* and *ITGB3* gene polymorphism are associated with more severe coronary heart disease and may be a risk factor of recurrent MI development. The dominant total contribution of the *FGB* (rs1800788) and *TNF α* (rs1800629) polymorphic genes to the development of recurrent MI in the population of the middle Volga region was revealed.

Key words: recurrent myocardial infarction, gene polymorphism, *TNF α* , *IL1B*, *TGFB1b*, *FGB*, *ITGB3*, *LPL*.

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Особенности полиморфизма генов *FGB*, *TNF α* , *IL-1 β* , *LPL*, *ITGB3* и *TGFB1* у пациентов с повторным инфарктом миокарда

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РЕЗЮМЕ

Цель. Ассоциация полиморфизма генов фибриногена (*FGB*), фактора некроза опухоли α (*TNF α*), интерлейкина 1 β (*IL-1 β*), липопротеинлипазы (*LPL*), тромбоцитарного гликопротеина (*ITGB3*) и трансформирующего фактора роста β (*TGFB1*) с риском развития повторного инфаркта миокарда (ИМ) у пациентов, проживающих на территории Среднего Поволжья.

Материалы и методы. В исследование вошли 280 человек с однократным и 104 человека с повторным ИМ. Генотипирование полиморфных локусов генов *TNF α* (rs1800629), *IL1B* (rs16944), *TGFB1b* (rs1800469), *FGB* (rs1800788), *ITGB3* (rs5918) и *LPL* (rs328) осуществляли с использованием TaqMan-зондов. Статистическую обработку данных проводили методом многофакторного логистического регрессионного анализа.

Результаты. Среди пациентов с повторным ИМ более часто встречались аллели и генотипы полиморфных маркеров генов *TNF α* , *IL1B*, *TGFB1b*, *FGB*, *ITGB3* и *LPL*. При оценке суммарного вклада полиморфизмов исследуемых генов риск повторного ИМ значительно возрастал при наличии комбинации полиморфизмов генов *FGB* (аллели и генотипы) и *TNF α* (аллели и генотипы), OR = 4,04; 95% CI 1,895–8,615; $p = 0,0001$.

Заключение. Таким образом, генотипы полиморфных локусов генов *FGB*, *LPL*, *TNF α* , *TGFB1b* и *ITGB3* могут быть ассоциированы с риском более тяжелого течения ишемической болезни сердца и приводить к развитию повторных инфарктов миокарда. Выявлен доминирующий суммарный вклад полиморфных локусов генов *FGB* (rs1800788) и *TNF α* (rs1800629) в развитие повторного ИМ у населения Среднего Поволжья.

Ключевые слова: повторный инфаркт миокарда, полиморфизм генов, *TNF α* , *IL1B*, *TGFB1b*, *FGB*, *ITGB3*, *LPL*.

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INTRODUCTION

Myocardial infarction is a severe cardiovascular disease with a multi-stage evolution consisting of different events. The genetic characteristics of each stage have a leading role in the determination of individual risk of atherosclerosis progression.

The key pathological processes that control coronary heart disease severity are lipid metabolism and hemostasis disorder, as well as activity of inflammatory process in atherosclerotic plaque. Several wide genome associated studies of recent years have revealed the responsibility of some gene polymorphisms for the amount and quality of production of various lipid metabolism and coagulation components and a number of cytokines, such as interleukins, transforming growth factors, adhesion molecules, etc. [1]. Remarkably, most of the studies of disease severity are mainly based on evaluating of fatal complications frequency among patients with a stable angina. However, it is assumed that a transforming growth factor is associated primarily with an increase in the size of the atherosclerotic plaque itself, and not with a thinning of its lining [2], and an increase in the activity of interleukin 1 β is associated with both aggravation of stenosis and the frequency of fatal complications [3]. The study of these genes polymorphism in aspect of cardiovascular disease progression is an essential step in understanding the pathogenetic mechanisms of coronary artery occlusion, including cases of recurrent MI. Based on a number of studies, it has been suggested that mutant alleles of cytokine cascade and thrombus formation genes, encoding main pathogenetic markers of restenosis and reocclusion of coronary vessels in patients with coronary artery disease (CAD), are quite frequent [2, 4].

Thus, the aim of the research is to study features of several genes polymorphism associated with inflammation activity, lipid metabolism and hemostasis for

a personalized prediction approach of recurrent MI development.

MATERIALS AND METHODS

A total of 384 participants aged 44 to 85 years (mean age 66 ± 10.7 years) who had undergone inpatient treatment in the cardiology department of City Clinical Hospital No. 7 in Kazan with acute myocardial infarction (AMI) with ST segment elevation and/or “Q”-positive MI were enrolled. All patients signed informed consent to participate in the study. AMI diagnosis was verified by biomarkers analysis results: troponins, ECG, and coronary angiography (CAG). In some patients (104 people), a previous MI was determined according to the anamnesis and previous research methods. A comparative study was conducted between a group of patients with single and repeated MI (280 and 104 patients, respectively).

All patients underwent genotyping of DNA samples isolated from peripheral blood leukocytes at the SNP of tumor necrosis factor alpha *TNF α* (rs1800629), transforming growth factor *TGFB1b* (rs1800469), interleukin 1 beta *IL1B* (rs16944), platelet glycoprotein *IT318GB* (rs16944), platelet glycoprotein chains of fibrinogen *FGB* (rs1800788) and lipoprotein lipase *LPL* (rs328) using competing TaqMan probes. Genotyping reliability was confirmed by sequencing. Oligonucleotide primers design and genes study were carried out in laboratory of pharmacogenomics of the Institute of Chemical Biology and Fundamental Medicine of the Siberian Branch of the Russian Academy of Sciences (ICBFM SB RAS).

“Genetics” and “Hardy Weinberg” statistics packages of the R-project software (www.r-project.org) were used for analysis. Compliance with the Hardy – Weinberg equilibrium was assessed using Fisher’s exact test. Association of genotype with severity of

CAD was carried out using multivariate logistic regression analysis, from which OR (odds ratios), its confidence interval (95% CI) and the significance level of the results obtained (p -value) were calculated. The odds ratio was calculated adjusted for race and risk factors (gender, age, smoking, the presence of hereditary burden, arterial hypertension (AH), dyslipidemia and obesity). Analysis was carried out for four models of inheritance: dominant, additive, recessive and co-dominant. The selection of the best of several

competing models was based on the Akaike Information Criterion (AIC). Data are presented as mean and mean error $M \pm m$.

RESULTS

All participants were preliminarily assessed for their clinical status and comorbidities to exclude their possible impact when analyzing association of genetic polymorphism with recurrent MI development (Table 1).

Table 1

Clinical characteristics of patients with MI ($n=384$)			
Parameters	1 group, $n=280$ (%)	2 group, $n=104$ (%)	p -value
Sex: male	1791 (64)	64 (61.5)	$p=0.61$
female	101 (36)	36 (38.5)	
Age (years)	64.1 ± 10.3	70.3 ± 7.2	$p=0.31$
Blood pressure	204 (72.8)	104 (100)	$p=0.02$
Smoking	186 (66.4)	63 (61)	$p=0.29$
TC	5.3 ± 0.98	5.19 ± 0.99	$p=0.38$
BMI	29.9 ± 6.2	28 ± 6.2	$p=0.07$
Hereditary burden	190 (67.8)	63 (60.5)	$p=0.16$
Type 2 diabetes	157 (56.0)	60 (57.6)	$p=0.8$
CHF:			$p=0.033$
with EF more 40%	194 (69.3)	60 (57.7)	
with EF less 40%	86 (30.7)	44 (42.3)	

Note. TC – total cholesterol; BMI – body mass index; CHF – chronic heart failure; EF – ejection fraction.

Thus, it was revealed that in the group with repeated MI, AH was detected significantly more often. Later, when conducting logistic regression analysis, corrections were made for this parameter, as well as for age. Taking stenosis into account, in the group with repeated MI lesions of the left coronary artery trunk and the anterior interventricular branch were observed more often. Allele frequencies were determined for all studied loci in patients in both groups. Alleles distribution of all genes in compar-

ison groups corresponded to the Hardy – Weinberg equation.

Association of gene polymorphism with the development frequency of single and repeated MI was calculated in two variants: by presence of a polymorphic allele, as well as by genotypes among all genes, except for the *LPL* and *TNFA* genes, as their pathological genotype frequency of occurrence is too rare for a reliable assessment. Alleles and genotypes in groups association is presented in Table 2.

Table 2

Association of polymorphic allele and genotype of the studied genes with the development of recurrent MI

ONP	1 group ($n=280$)	2 group ($n=104$)	Additive model OR 95% CI p -value	Co-dominant model	
				Heterozygous genotype OR 95% CI p -value	Homozygous genotype OR 95% CI p -value
<i>LPL</i>	CC 246 CG + GG 34 + 0	CC 78 CG + GG 21 + 5	2.92 [1.39–6.11] 0.005	–	–
<i>ITGB3</i>	TT 213 CT + CC 64 + 3	TT 82 CT + CC 11 + 11	1.21 [0.64–2.31] $p=0.13$	TC: 0.44 [0.15–1.29] $p=0.14$	CC: 7.08 [1.46–34.22] $p=0.005$
			AIC: 238.6	AIC: 231.86	

Table 2 (continued)

ONP	1 group (n = 280)	2 group (n = 104)	Additive model OR 95% CI p-value	Co-dominant model	
				Heterozygous genotype OR 95% CI p-value	Homozygous genotype OR 95% CI p-value
<i>FGB</i>	CC 145 CT + TT 110 + 25	CC 27 CT + TT 66 + 11	1.91 [1.15–3.17] p = 0.01	CT: 3.30 [1.51–7.23] p = 0.003	TT: 2.45 [0.70–8.60] p = 0.16
			AIC: 232.79	AIC: 230.94	
<i>TGFB1</i>	CC 139 CT + TT 118 + 23	CC 27 CT + TT 63 + 14	1.88 [1.12–3.16] p = 0.02	CT: 2.82 [1.28–6.20] p = 0.01	TT: 2.81 [0.86–9.23] p = 0.09
			AIC: 233.19	AIC: 233.23	
<i>IL1B</i>	CC 128 CT + TT 118 + 34	CC 41 CT + TT 47 + 16	1.36 [0.83–2.23] p = 0.23	CT: 1.31 [0.63–2.75] p = 0.47	TT: 1.89 [0.66–5.39] p = 0.23
			AIC: 239.48	TC: 0.44 [0.15–1.29] p = 0.14	
<i>TNFα</i>	GG 219 GA + AA 58 + 3	GG 96 GA + AA 3 + 5	0.21 [0.05–0.88] p = 0.03	-	-

Note. ONP – oligonucleotide primers; OR – odds ratio adjusted for risk factors; 95% CI – confidence interval; AIC – Akaike criterion; CC, CA, GG and others and others – genotype variants.

According to the data, five candidate genes under study were associated with recurrent MI development, taking into account corrections for comorbidities and age. As it can be seen from Table 3, polymorphism of *FGB* rs1800788, *LPL* rs328, *TNF α* rs1800629, *ITGB3* rs5918 and *TGFB1* rs1800469 had a statistically significant effect on the incidence of recurrent MI. Thus, for the *FGB* gene, a rare allele (–249T) presence (OR = 1.91, 95% CI = (1.15–3.17), p = 0.01) was associated with a higher frequency of recurrent MI development. For the *TNF* gene (–308G/A) it was possible to assess only the contribution of a rare allele, which is more common among patients without recurrent MI (OR = 0.21, 95% CI = (0.05–0.88), p = 0.03).

Besides, the rare –509T allele of *TGFB1* gene was significantly more often detected in patients with recurrent MI (OR = 1.88, 95% CI = (1.12–3.16), p = 0.002). And, finally, a strong correlation was demonstrated by genotype of the *ITGB3* gene (PIA2) homozygous for a rare allele (OR_{adj} = 7.08, 95% CI = (1.46–34.22), p = 0.005), while the presence of one rare allele had no significant pathological effect.

Assessment of contribution of cumulative genes polymorphism effect revealed the risk of MI significant increase in combination of *FGB* rs1800788 and *TNF α* rs1800629 polymorphisms (OR = 4.04, 95% CI = (1.895–8.615), p = 0.0001), while for *LPL* rs328 and *ITGB3* rs5918 this indicator turned out to be lower than in isolation for each of the genes (OR = 3.212, 95% CI = (1.165–8.853), p = 0.030 (Table 3).

Table 3

The combined contribution of <i>FGB</i> and <i>TNFα</i> gene polymorphism in the development of recurrent MINF α	
Parameter	OR [95% CI] p-value
<i>FGB</i> rs1800788 – T allele	OR = 4.04
<i>TNF</i> rs1800629 – A allele	95% CI 1.895–8.615 p = 0.0001
<i>LPL</i> rs328 – G allele	OR = 3.212,
<i>ITGB3</i> rs5918 – C allele	95% CI = (1.165–8.853), p = 0.030

Note. OR – odds ratio adjusted for risk factors; 95% C.I. – confidence interval.

DISCUSSION

Heredity contribution to the development of coronary atherosclerosis leaves no doubt, since numerous works are devoted to the influence of genetic polymorphism on the incidence of cardiovascular complications (CVC) of coronary artery disease.

In particular, there are data of the studied SNPs of *TNF α* tumor necrosis factor alpha (–308G/A), *TGFB1b* transforming growth factor (–509 C/T), *IL1B* interleukin 1 beta (–511C/T), *FGB* fibrinogen beta chain (–249C/T) and its *ITGB3* platelet glycoprotein (PIA1 / PIA2), as well as *LPL* lipoprotein lipase (rs328) effect on various manifestations of atherosclerosis.

Thus, presence of polymorphic T allele in SNP rs1800788 in *FGB* gene is associated with incidence of MI in population, although some early studies hadn't found connection between polymorphism and level

of fibrinogen in the blood and manifestations of IHD [5]. In many studies, *TNF α* gene polymorphism is also associated with the incidence of acute cardiovascular events [6]. C-509T polymorphism of *TGFB1b* gene has been considered a protective factor against atherosclerosis for a long time due to the anti-inflammatory effect of cytokine during atherogenesis [7]. However, in recent years, many studies have shown a negative effect of polymorphism on various manifestations of atherosclerosis, possibly due to development of proliferative changes in the intima, and note the relationship of the mutant -509 T allele with the incidence of fatal CVC [2].

In most studies, *LPL* gene polymorphism has not shown a significant effect on coronary atherosclerosis incidence and severity [8], however, it is assumed to be associated with an unfavorable course along with a number of concomitant factors. In a large number of studies PLA2 polymorphism of the *ITGB3* gene is associated with incidence of acute events, including in younger patients, but it is practically irrelevant for development of chronic conditions [9]. *IL1 β* -511C/T polymorphism presence is associated with frequency and degree of atherosclerotic stenosis in various localizations, while data on its effect on incidence of MI are rather contradictory [10].

At the same time, most of the studies are carried out in groups of patients with CVD compared to a relatively healthy population and reflect, first of all, the risks of disease occurrence, and not its dynamics. A distinctive feature of this work is a comparative assessment of genetic polymorphism among patients with complicated atherosclerosis, namely, depending on presence of single or repeated MI with the possibility of predicting it. It was found that patients with recurrent myocardial infarction showed a significant association with polymorphism of four genes, *FGB* rs1800788, *TNF* rs1800629, *LPL* rs328, *ITGB3* rs5918, and *TGF* rs180046.

T allele in SNP rs1800788 of the *FGB* gene with high statistical significance was more common in patients with recurrent MI, which fully correlates with the data of other studies and may be explained by an increased amount of pure fibrinogen and its effect on atherothrombosis [5]. At the same time, the opposite picture was observed with the *TNF α* rs1800629 SNP. The polymorphic A allele was significantly more common in patients without signs of acute or previous MI, while normal G/G genotype was associated with an increased incidence of the disease. Whereas other studies have noted a protective role of the G allele,

primarily in relation to acute events such as MI or unstable angina pectoris [11].

The *LPL* rs328 gene polymorphism contribution also manifested itself among patients with repeated MI and was highly associated with an increase in incidence of pathology. Taking into account some studies of mutant G allele effect on atherosclerosis development in patients after MI [12], a significance of this gene polymorphism specifically for patients with recurrent coronary artery occlusion can be assumed.

The polymorphism of the *ITGB3* rs5918 gene significantly increased the incidence of MI only in the case of the mutant homozygous genotype and was significant only in the group of patients who underwent repeated MI. In general, this does not contradict the data on the pathological effect of the mutant *ITGB3* rs5918 allele on the amount of fibrinogen and platelet reactivity in severe CVD [13]. The presence of the polymorphic G allele of the *TGF* rs1800469 gene was also significant only in the case of repeated MI, which may indicate the significance of excessive synthesis of the extracellular matrix in severe coronary artery disease [2].

Contribution assessment of the cumulative genes polymorphism effect allowed us to assume dominant role of polymorphic allele combinations in atherosclerosis progression risk prediction. Thus, with a combination of polymorphic alleles of the *FGB* rs1800788 and *TNF α* rs1800629 genes, the risk of recurrent myocardial infarction in patients with a single infarction increased significantly, even in comparison with the presence of a single gene polymorphism.

CONCLUSION

Thus, a correlation between *FGB* rs1800788, *LPL* rs328, *ITGB3* rs5918, *TNF α* rs1800629, and *TGF* rs1800469 genes polymorphisms and frequency of recurrent MI was revealed. Repeated MI is associated with the presence of any polymorphic genotype of the *FGB* rs1800788, *LPL* rs328, *TGFB1* rs1800469 genes and polymorphic homozygous genotype of the *ITGB3* rs5918 gene, as well as normal homozygous genotype of *TNF α* rs1800629 gene. On the contrary, the presence of polymorphic genotype of *TNF α* gene rs1800629 indicates its protective effect on the development of recurrent MI.

An increased incidence of some polymorphisms in group of patients with repeated MI compared to the group of patients with a single MI may indicate, first of all, an influence of these polymorphisms on atherosclerosis progression and enlarging of stenosis in

coronary arteries. However, this thesis requires further study.

Assessment of total contribution of *FGB* rs1800788 and *TNF α* rs1800629 genes polymorphism is appropriate to clarify both primary and recurrent myocardial infarction development risk in order to optimize diagnostic and therapeutic measures.

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Authors contribution

Mayanskaya S.D. – conception and plan of the research, analysis and interpretation of data. Garaeva L.A. – selection of patients for research, analysis and interpretation of data, article design. Teplyakov A.T. – advising on the concept of research and the results obtained, final approval of the manuscript for publication. Filipenko M.L. – development of the research concept, carrying out of the practical part of the study. Sokolova E.A. – carrying out of the practical part of the study, statistical processing of the results of work. Kravtsova O.A. – carrying out of the practical part of the study, editing of the article. Beresikova E.N. – clinical interpretation of the data obtained.

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