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ANALYSIS OF MTHFR GENE GLU429ALA POLYMORPHISM SIGNIFICANCE IN THE RISK OF MYOCARDIAL INFARCTION

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ABSTRACT
Alleles and haplotypes of the Glu429Ala polymorphism of the MTHFR gene did not affect the risk of developing MI. In all likelihood, the prothrombotic effect of polymorphisms of this gene can manifest itself when it is combined with other genetic mutations that affect the risk of developing MI or when a combination of hereditary and acquired factors is present. Such combinations are a much greater threat than the presence of one genetic disorder of the coagulation system.
KEY WORDS: *myocardial infarction, COVID-19, Glu429Ala genetic polymorphism of MTHFR gene.*

1. INTRODUCTION

Over the past two years, the results of cohort studies, a number of reviews and descriptions of clinical observations on complications caused by the SARS-CoV-2 virus, in particular in the cardiovascular system, have been published. The development of cardiovascular disorders exacerbated the severity of the patients' condition and increased the risk of mortality [4, p.1745-1756]. For example, doctors in Italy reported a case of a 53-year-old patient whose clinical manifestations of COVID-19 were severe pericarditis with fever rather than pneumonia [3, p.3-14; 6, p.2121-2138]. In patients who died from COVID-19, biomarker levels before death were 12 times higher in the presence of morphological signs of myocardial damage than in their absence [1, p.1071-1076].

An increase in biomarker values is a sign of an unfavorable outcome of an existing disease. Undoubtedly, further research is needed on the diagnostic and prognostic role of biomarkers of myocardial stress in COVID-19 [2, p.883-884]. To this end, we studied the role of the Glu429Ala polymorphism in the MTHFR in the risk of myocardial infarction (MI) in patients with a history of COVID-19 viral infection and in patients who did not have a history of transferred COVID-19 [5, p.28-35].

2. PURPOSE OF THE STUDY

To study and evaluate the contribution of the Glu429Ala polymorphism in the MTHFR gene to the risk of myocardial infarction (MI) in patients with a history of COVID-19 viral infection and in patients who did not have a history of COVID-19.

3. MATERIAL AND METHODS OF RESEARCH

In a specialized center for the treatment of patients infected with COVID-19 in the Andijan branch of the Republican Specialized Scientific and Practical Medical Center for Cardiology, in the cardiology department of the Andijan Regional Multidisciplinary Center and in the Andijan branch of the Republican Scientific Center for Emergency Medical Care, clinical and laboratory materials were collected from patients being treated for cardiovascular disease. In particular, patients with myocardial infarction were involved in the study. These patients were divided into two groups: patients with myocardial infarction with a history of COVID-19 viral infection and patients with myocardial infarction without a history of viral infection with COVID-19. In total, 94 patients with myocardial infarction aged over 18 years were involved in the study. Of them:

- The first group - 53 patients with myocardial infarction who had a history of viral infection with COVID-19;
- The second group - 41 patients with myocardial infarction who did not have a history of viral infection COVID-19
- The third group - a control group of 90 conditionally healthy donors.

Statistical processing of the results was performed using the standard software package OpenEpi V.9.2. Analysis of the deviation of empirical genotype frequencies from the theoretically expected Hardy–Weinberg distribution was carried out using the Statistica software package.

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4. THE RESULTS OBTAINED AND THEIR DISCUSSION

The calculated probability coefficient showed that the proportion of detection of the functionally unfavorable Ala allele in respondents with COVID-19 associated MI was slightly lower, while the wild Glu allele was slightly higher compared to representatives of the control group (20.8% vs. 23.9% and 79.2% versus 76.1%, respectively). Calculation data suggest that the presence of these alleles does not increase the risk of developing COVID-19 associated MI ($\chi2$=0.4; OR=0.8; 95%CI:0.47-1.49; p=0.6) and ($\chi2$=0.4; OR=1.2; 95%CI:0.67-2.14; p=0.6). It was revealed that the statistical difference between the homozygous variant of the Glu/Glu haplotype ($\chi2$=1.0; OR=1.4; 95%CI:0.7-2.87; p=0.4), the heterozygous Glu/Ala haplotype ($\chi2$ =1.6; OR=0.6; 95%CI:0.29-1.3; p=0.3) and unfavorable haplotype Ala/Ala ($\chi2$=0.2; OR=1.4; 95% CI:0.36-5.39; p=0.7) in patients with virus-associated MI was irrelevant. And this indicates that in the presence of these

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haplotypes, there is no risk of the formation of this pathology in patients with COVID-19. (Tab. 1).

Table 1. Association between the Glu429Ala polymorphism in the MTHFR gene in groups of patients with COVID-19 associated MI and controls.

Alleles and genotypes	Number of examined alleles and genotypes				χ2	p	OR	95%CI
	COVID-19 associated MI		Control group					
	n	%	n	%				
Glu	84	79,2	137	76,1	0,4	p = 0,6	1,2	0,67 - 2,14
Ala	22	20,8	43	23,9	0,4	p = 0,6	0,8	0,47 - 1,49
Glu/Glu	35	66,0	52	57,8	1,0	p = 0,4	1,4	0,7 - 2,87
Glu/Ala	14	26,4	33	36,7	1,6	p = 0,3	0,6	0,29 - 1,3
Ala/Ala	4	7,5	5	5,6	0,2	p = 0,7	1,4	0,36 - 5,39

In patients with MI without COVID-19, despite insignificant differences, an increase in the frequency of the favorable Glu allele was detected (76.8% and 76.1%, respectively) and a decrease in the frequency of the mutant Ala marker (23.2% and 23.9%, respectively). respectively). The results show that the presence of these alleles is not the cause of the development of MI (χ2=0.0; OR=1.0; 95%CI:0.56-1.93; p=0.9 and χ2=0.0; OR =1.0; 95%CI:0.52-1.78; p=0.9). The frequency of detection of haplotypes Glu/Glu, Glu/Ala, Ala/Ala in patients with MI and in the control group was: 58.5%, 36.6% and 4.9% versus57.8%, 36.7% and 5 .6% respectively. The study of the associative relationship between alleles and haplotia of the Glu429Ala polymorphism of the MTHFR gene in this group of patients showed that the statistical difference in identifying the wild Glu/Glu haplotype (with χ2=0.0; OR=1.0; 95%CI:0.49-2 .18; p=0.9) and unfavorable haplotypes Glu/Ala and Ala/Ala, was small (with χ2=0.0; OR=1.0; 95%CI: 0.46-2.14; p= 0.9 and χ2=0.0; OR=0.9; 95%CI: 0.16-4.69; p=0.9). (see table 3.22). This indicates the absence of influence of these markers on the development of MI. (Table 2).

Table 2. Association between the Glu429Ala polymorphism in the MTHFR gene in groups of patients with myocardial infarction without a history of COVID-19 virus infection and controls.

Alleles and genotypes	Number of examined alleles and genotypes				χ2	p	OR	95%CI
	MI without COVID-19		Control group					
	n	%	n	%				
Glu	63	76,8	137	76,1	0,0	p = 0,9	1,0	0,56 - 1,93
Ala	19	23,2	43	23,9	0,0	p = 0,9	1,0	0,52 - 1,78
Glu/Glu	24	58,5	52	57,8	0,0	p = 0,9	1,0	0,49 - 2,18
Glu/Ala	15	36,6	33	36,7	0,0	p = 0,9	1,0	0,46 - 2,14
Ala/Ala	2	4,9	5	5,6	0,0	p = 0,9	0,9	0,16 - 4,69

Statistical calculations of the data showed that the frequency of detection of the major Glu allele and the minor Ala allele in patients with COVID-19 associated MI was insignificant compared to MI without a history of COVID-19 (79.2% versus 76.8% and 20.8% versus 23.2%, respectively, with χ2=0.2; 95%CI: 0.57-2.31; p=0.7 and χ2=0.9; %CI:0.43-1.74; p=0.7).

The distribution frequency of Glu/Glu, Glu/Ala, Ala/Ala haplotypes in patients with COVID-19 associated MI and MI without COVID-19 was: 66.0%, 26.4% and 7.5% versus 58.5% , 36.6% and 4.9%, respectively. The study revealed a slight increase in the frequency of the ancestral Glu/Glu haplotype and the mutant marker Ala/Ala in the group of patients with COVID-19 associated MI relative to the group of patients with MI without COVID-19 (χ2=0.6; OR=1.4; 95 %CI:0.59-3.19; p=0.5) and (χ2=0.3; OR=1.6; 95%CI:0.28-9.03; p=0.6). The results of the analyzes showed that the unfavorable heterozygous haplotype Glu/Ala was insignificantly lower in the group of patients with COVID-19 associated MI compared to the group of patients with MI without COVID-19 (26.4% and 36.6%, respectively, with χ2=1, 1; OR=0.6; 95%CI: 0.26-1.5; p=0.3). (see table 3.23). This indicates that carriage of these polymorphisms does not increase the risk of developing MI. (Table 3).

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Table 3. Association between the Glu429Ala polymorphism in the MTHFR gene in groups of patients with MI without a history of COVID-19 virus infection and those with COVID-19 associated MI.

Alleles and genotypes	Number of examined alleles and genotypes				χ2	p	OR	95%CI
	COVID-19 associated MI		MI without COVID-19					
	n	%	n	%				
Glu	84	79,2	63	76,8	0,2	p = 0,7	1,2	0,57 - 2,31
Ala	22	20,8	19	23,2	0,2	p = 0,7	0,9	0,43 - 1,74
Glu/Glu	35	66,0	24	58,5	0,6	p = 0,5	1,4	0,59 - 3,19
Glu/Ala	14	26,4	15	36,6	1,1	p = 0,3	0,6	0,26 - 1,5
Ala/Ala	4	7,5	2	4,9	0,3	p = 0,6	1,6	0,28 - 9,03

5. CONCLUSION

The detected alleles and haplotypes of the Glu429Ala polymorphism of the MTHFR gene did not affect the risk of developing MI. In all likelihood, the prothrombotic effect of polymorphisms of this gene can manifest itself when it is combined with other genetic mutations that affect the risk of developing MI or when a combination of hereditary and acquired factors is present. Such combinations are a much greater threat than the presence of one genetic disorder of the coagulation system.

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