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Association between Polymorphisms of Mtr Gene Rs1805087 and Coronavirus Infection

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Abstract. The most serious COVID-19 side effects brought on by SARS-CoV-2 infection is hypercoagulopathy-induced ischemia damage to important organs, which frequently results in COVID-19 infection-related impairment and death in patients. Therefore, it is possible to lower the above-mentioned indicators of morbidity and mortality by carefully examining the factors that contribute to hypercoagulopathy, selecting patients who are predisposed to the emergence of this pathological process, and performing specialized proliferative and therapeutic procedures for them. The MTR gene polymorphisms, which are thrombophilic genes and one of the causes of hypercoagulopathy, have been studied in COVID-19-infected Uzbek patients to better understand the relationship between the alleles of these genes and the amount of homocysteine in these patients as well as the role they may play in the pathogenesis of COVID-19.

Keywords. *MTR, rs1805087, wild allele, minor allele folate cycle, hyperhomocysteinemia, endothelial dysfunction.*

Introduction. The infection of COVID-19 has led to a pandemic that has affected millions of people around the world. The Chinese Center for Disease Control and Prevention confirmed that this condition was caused by a new type of beta-coronaviruses after examining throat swabs from patients [25]. The coronavirus has been found to cause various diseases, including respiratory, intestinal, nervous and liver diseases.

While the coronavirus infection mainly affects the respiratory tract, according to the latest data, COVID-19 is a systemic disease that affects the respiratory, cardiovascular, gastrointestinal, urinary, neurological, hematopoietic and immune systems [16]. The pathogenesis of the new coronavirus infection has not been studied to the end, the information on the epidemiology, clinical features, prevention and treatment of the disease is constantly being updated [17 , 26].According to the study of Assiri et al., a decrease in the number of platelets, leukopenia was noted in patients infected with COVID-19 [15].

In patients with coronavirus infection, symptoms of severe hypercoagulation are observed at all stages of hemostasis [10]. At the same time, in patients with COVID-19, platelet adhesion and aggregation activity increases, retraction time decreases. Platelet activity changes are related to the severity of COVID-19 [11].

Platelet activity does not reliably change in patients with mild coronavirus infection, while in moderate and severe coronavirus infection, platelet aggregation properties increase by 23-36%, and adhesion activity increases by 60-98%. This indicates that platelet hemostasis is shifted towards hypercoagulation [13]. Severe coronavirus infection is mainly observed in elderly patients, and these patients have a high risk of developing thromboembolic complications [18]. Thromboembolic

complications are mainly observed in the blood vessels of the heart and brain [2, 3, 12]. Patients with COVID-19 experience disability and death due to thromboses in vital organs [10, 11]. This is the result of Sars-CoV-2 induced endotheliocyte alteration and cytokine storm [13].

The spread of coronavirus in the body causes the development of a hyperimmune reaction - "cytokine storm": a large number of inflammatory interleukins, including S-reactive protein, serum ferritin, lactate dehydrogenase, D-dimer, 1-beta, 6, 2 interleukins, tumor necrosis factor and chemokines are produced [19].

In order to more accurately diagnose the state of thrombophilia, the study of the MTHFR gene A1298C (rs 1801131), C677T (rs 1801133) polymorphisms in the Uzbek population, and the significance of the C (rs 1801131) and T (rs 1801133) minor alleles of this gene in the pathogenesis of COVID-19 and hyperhomocysteinemia It is important to assess the extent of the disease of COVID-19 in observed patients [4, 8, 9]. By identifying this, various severe complications that can be caused by COVID-19 can be prevented by carrying out special preventive and therapeutic practices [5, 21, 22, 23].

Application of modern molecular diagnosis of genetic risk factors of thrombophilia to various fields of clinical medicine is very important for the prevention of many complications caused by thrombosis [14, 24].One of the main causes of death in coronavirus infection is the development of hypercoagulation, the development of thrombophilia and the increased risk of thrombosis [6, 7]. The development of pulmonary artery thromboembolism (PATE) in COVID-19 causes a decrease in blood circulation, increased tension in the right ventricle, increased troponin levels, development of cardiogenic shock, and short-term death [20].

Blood tests are important for doctors for early diagnosis of the disease, they provide information such as the inflammatory process, organ damage (kidney failure, liver failure), help to assess the severity of the disease. An increase in leukocytes, neutrophils or lymphocytes, and an increase in inflammatory markers (S-reactive protein) are characteristic of the inflammatory process. In addition, platelets also play an important role in the management of various inflammatory processes.

Material and methods. Eighty patients were investigated as the primary group in the scientific study. The patients of the main group were separated into three groups based on the severity of the disease and the clinical signs of COVID-19: Group I included 20 mild cases, Group II included 26 cases of moderate severity, and Group III included 34 cases of severe cases. We used the eighth revision of the document titled "Temporary recommendations on the treatment of patients with coronavirus infection" from the Ministry of Health of the Republic of Uzbekistan to divide the patients into groups in this sequence. To ascertain how the examined gene polymorphisms and the severity of the disease relate to one another, the groups were divided in this particular order.

In a clinical research, the blood of 80 patients with coronavirus infection had its thrombophilia genes evaluated. Nucleotide sequencing was done using polymerase chain reaction in a DT-Lite 48 amplifier, utilizing DNA-technology (Russia) reagents, to find the MTR gene rs1805087 polymorphisms in the venous blood of patients. By using the IFA method with the "Human" (Germany) reagent, the amount of homocysteine in the plasma of all group patients and healthy subjects was also

measured, and the relationship between their genotypes and the amount of homocysteine was examined.

Statistical processing of research results. The Hardy-Weinberg equilibrium was taken into consideration while evaluating genotypes, and the 2 criteria was employed to compare the degree of genotype and allele distribution. The relative risk (RR) and extimolar ratio (OR) with a 95% confidence interval (95% CI) were used to confirm the pathogenetic significance of alleles and genotypes in the studied disease if the 2 criterion was used to confirm the presence of a predisposition to the pathology under study through the association of alleles and genotypes. Statistical significance was defined as p 0.05. Statistica 6.1 (StatSoft, USA) was used to process the statistical data.

Results. The distribution frequency of genotypes and alleles of the MTR gene 2756 A>G (rs1805087) polymorphism, which was studied in the Uzbek population, are presented in the table below (table 1).

Table 1

Distribution frequency of alleles and genotypes of MTR gene in 2756 A>G (rs1805087) polymorphism

G groups	Distribution of alleles				Distribution of genotypes					
	A		G		A / A		A / G		G / G	
	n	%	n	%	n	%	n	%	n	%
Main group, (n = 80)	136	85	24	15	59	73.75	18	22.5	3	3.75
First group, (n = 20)	39	97.5	1	2.5	19	95	1	5	0	0
Second group, (n = 26)	46	88.46	6	11.54	20	76.92	6	23.08	0	0
Third group, (n = 34)	51	75	17	25	20	58.82	11	32,35	3	8.82
Control group, (n = 20)	38	95	2	5	18	90	2	10	0	0

The Hardy-Weinberg law was used to check the results of the genotype distribution of the MTR gene rs1805087 polymorphism, and the results did not significantly deviate from those results (2 3.84; R>0.05). (Table 2).

Table 2

Comparison of empirical - observed results with theoretical - expected results calculated by Hardy-Weinberg law of MTR gene rs1805087 polymorphism.

Main group					
Alleles	Distribution of alleles				
A	0.85				
G	0.15				
Genotypes	Distribution of genotypes		χ 2	p	df
	Observed	Expected			

A / A	0.7375	0.7225			
A/G	0.225	0.255			
G/G	0, 0 375	0.0225			
General	1	1	1.1	0.57	1

Control group					
Alleles	Distribution of alleles				
A	0.95				
G	0.05				
Genotypes	Distribution of genotypes		χ 2	p	df
	Observed	Expected			
A / A	0.90	0.905			
A / G	0.1	0.095			
G / G	0.0	0.0			
General	1	1	0.05	0.97	1

On the other hand, no evidence was found to support a causal link between the minor allele and the heterozygous genotype in the pathophysiology of Mild COVID-19 development when the relevance of the MTR gene 2756 A>G (rs1805087) polymorphism in various populations was studied. The frequency of alleles A and G and the genotypes A/A, A/G, and G/G were, respectively, 97.5%, 2.5%, and 95%, 5%, 0%. A reliable link between mild COVID-19 and various genotypes, particularly between heterozygous A/G and homozygous A/A genotypes, was not discovered when comparing the differences in the frequency of distribution of alleles and genotypes - 2 =0.4; R=0.6. (Table 3).

Table 3
Significance of different alleles and genotypes of MTR gene 2756 A>G (rs1805087) polymorphism in the development of mild COVID-19.

Alleles and genotypes	Number of alleles and genotypes				χ 2	p	RR	95% CI	OR	95% CI
	First group		Control group							
	n	%	N	%						
A	39	97.5	38	95.0	0.3	p = 0.6	1.0	0.04 - 24.33	2.1	0.19 - 22.52
G	1	2.5	2	5.0	0.3	p = 0.6	1.0	0.19 - 4.97	0.5	0.04 - 5.34
A / A	19	95.0	18	90.0	0.4	p = 0.6	1.1	0.04 - 25.79	2.1	0.18 - 24.21
A / G	1	5.0	2	10.0	0.4	p = 0.6	0.5	0.02 - 12.22	0.5	0.04 - 5.43

A/A, A/G, and G/G genotype frequencies in moderately severe COVID-19 were 88.46%, 11.54%, and 76.92%, 23.08%, and 0%, respectively. Although wild-type homozygous A/A genotype was protective (OR=0.4; 95% CI: 0.07-1.98), heterozygous

and genotype has an inducing effect (OR=2.7; 95% CI: 0.5-14.6), but these results were found to be statistically insignificant (2 =1.3; R=0.3) when analyzing the significance of the MTR gene 2756 A>G (rs1805087) polymorphism in moderate-severe(4- table).

Table 4

Significance of different alleles and genotypes of the MTR gene 2756 A>G (rs1805087) polymorphism in the development of moderate-severe COVID-19.

Alleles and genotypes	Number of alleles and genotypes				χ 2	P	RR	95% CI	OR	95% CI
	Second group		Control group							
	N	%	n	%						
A	46	88.5	38	95.0	1.2	p = 0.3	0.9	0.39 - 2.23	0.4	0.08 - 2.02
G	6	11.5	2	5.0	1.2	p = 0.3	1.1	0.1 - 11.8	2.5	0.49 - 12.43
A / A	20	76.9	18	90.0	1.3	p = 0.3	0.9	0.32 - 2.28	0.4	0.07 - 1.98
A / G	6	23.1	2	10.0	1.3	p = 0.3	2.3	0.86 - 6.16	2.7	0.5 - 14.46

The prevalence of the A and G alleles and the A/A, A/G, and G/G genotypes, on the other hand, were 75%, 25%, and 58.82%, 32.35%, and 8.82%, respectively, in the development of the severe form of COVID-19. When the significance of the alleles and genotypes of this gene polymorphism in the development of the severe form of COVID-19 was examined in patients in this group, there was no statistically significant relationship between the presence of the heterozygous A/G genotype and the severity of COVID-19: The A/A homozygous genotype - wild-type form was found to be protective in the development of severe COVID-19 (OR=0.2; 95%CI: 0.04-0, 7) and the statistical validity of this finding was established (2 =5.9; R=0.025) (table 5).

Table 5

The importance of different alleles and genotypes of MTR gene 2756 A>G (rs1805087) polymorphism in the development of severe form of COVID-19.

Alleles and genotypes	Number of alleles and genotypes				χ 2	P	RR	95% CI	OR	95% CI
	Third group		Control group							
	N	%	n	%						
A	51	75.0	38	95.0	6.9	)=0.01	0.8	0.5 - 1.26	0.2	0.04 - 0.62
G	17	25.0	2	5.0	6.9	)=0.01	1.3	0.09 - 17.26	6.3	1.61 - 24.98
A / A	20	58.8	18	90.0	5.9	)=0.025	0.7	0.33 - 1.31	0.2	0.04 - 0.7
A / G	11	32.4	2	10.0	3.4	) = 0.1	3.2	1.61 - 6.51	4.3	0.92 - 20.12

Discussion.

Additionally, it is interesting to note that while this difference was seen in the COVID-19-infected individuals, it was not consistently seen in the participants with the minor allele in the control group.In our opinion, this is due to the fact that the minor allele of the MTRR gene's rs1801394 polymorphism does not alter an individual's vulnerability to folate cycle insufficiency, which happens in such individuals and is compensated under normal circumstances. However, individuals with COVID-19 and the minor allele of the MTRR gene rs1801394 polymorphism are especially vulnerable to folate deficiency, and their relative reduced absorption may result in more pronounced and/or quicker manifestations of symptoms of folate cycle deficiency (such as elevated homocysteine).

Additionally, based on the findings of the examined gene polymorphisms, patients with the moderate and severe forms of COVID-19 differed considerably from the control group and patients with the mild form of COVID-19 in terms of the frequency of both mutant alleles of both genes. This is the rs1805087 polymorphism in the MTR gene and MTRR. Patients who carry the minor allele of the rs1801394 polymorphism are more prone to develop moderate and severe forms of COVID-19.

We believe that this is because an increase in homocysteine has a toxic effect on the endothelial system. As a result, the hyperproduction of cytokines during COVID-19 pathogenesis may have a cobormide effect on this process and result in a more severe inflammatory process in patients. Patients who carry the mutant allele may have decreased methyltetrahydrofolate reductase activity, which could put them at risk for moderate or severe illness in COVID-19 patients.

In conclusion, it can be said that thrombophilia risk gene polymorphisms, specifically the alleles and genotypes of MTRR A66G (rs1801394) and MTR A2756G (rs1805087), have not been proven to have protective-protective or inducing significance in the development of a mild level of COVID-19 pathogenesis.

The MTRR gene A66G polymorphism (rs1801394) heterozygous A/G genotype was found to be consistently high in moderate-severe COVID-19, and it was discovered that these genotypes have an inducing effect on this disease. The MTRR gene A66G polymorphism A/A genotypes were discovered to be more likely to cause moderate-severe COVID-19. It was discovered that the development of 19 has a protective impact. The MTR 2756 A>G (rs1805087) gene polymorphism, on the other hand, showed no statistically significant link with the heterozygous genotype, while the A/A genotype was found to be statistically reliable in the onset of the disease.

The MTRR gene A66G polymorphism A/A genotypes were also discovered to have an inducing effect on moderate-severe COVID-19, and the heterozygous A/G genotype of the MTRR gene A66G (rs1801394) polymorphism in severe COVID-19 was found to be consistently high. It has been discovered that it inhibits the growth of COVID-19. The MTR 2756 gene A>G (rs1805087) polymorphism heterozygous genotype, on the other hand, did not show a statistically significant link with the development of the disease, whereas the A/A genotype did. As a result, it was determined that the G/G genotype of the MTRR gene rs1801394 polymorphism is a statistically valid risk factor for the emergence of a severe form of COVID-19.

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