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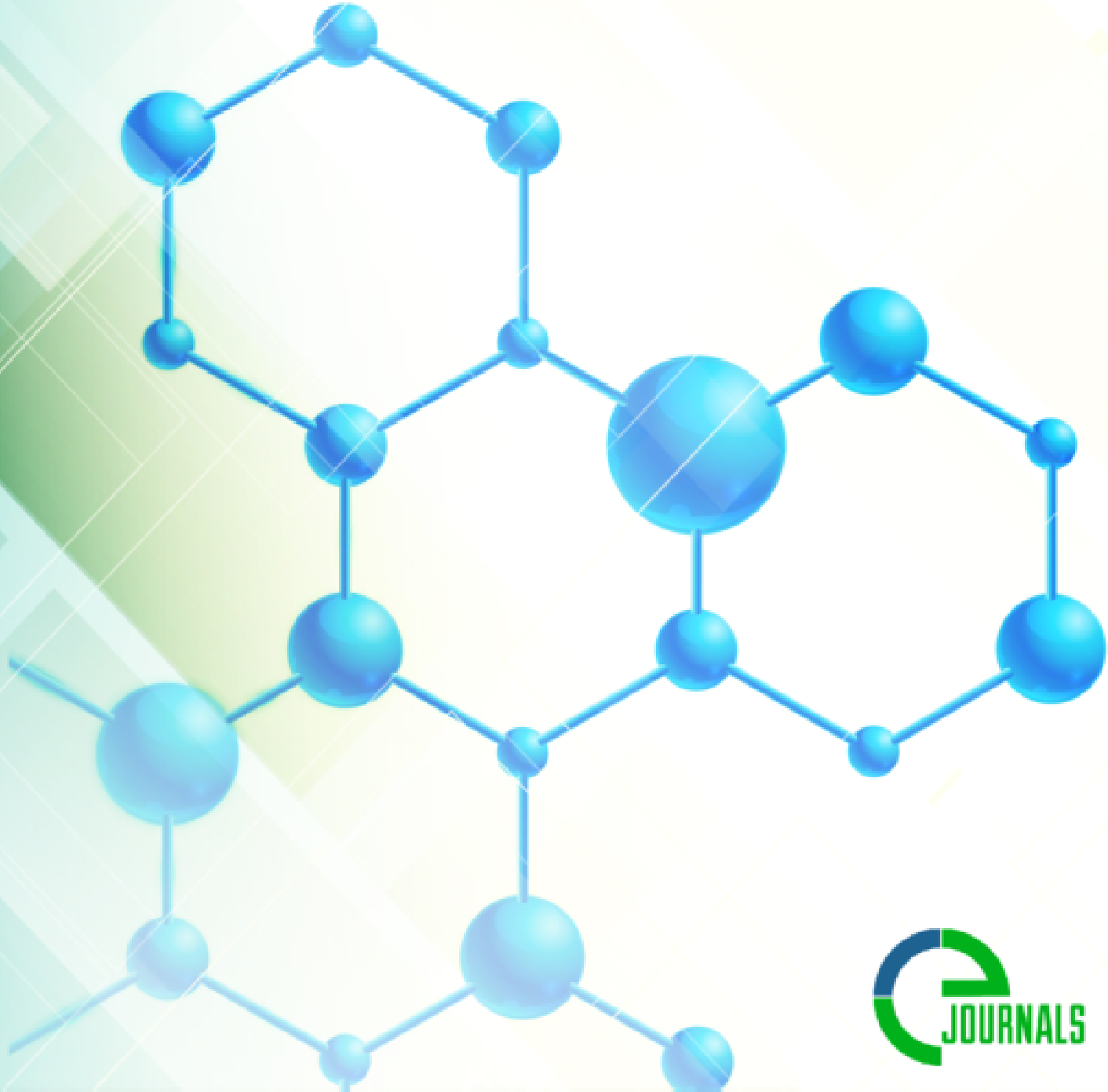

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ASP919GLY (A / G) MTR GENE POLYMORPHISM AS A CAUSE OF THROMBOPHILIA DEVELOPMENT IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstract: Chronic obstructive pulmonary disease (COPD) in modern medicine is one of the most common non-infectious diseases in the territory of the Republic of Uzbekistan. Thrombotic events are a common cause of hospitalizations and death in this category of patients.To clarify the etiology of frequent thrombosis in patients with COPD, the authors studied the occurrence of the Asp919Gly (A / G) polymorphism of the MTR gene as a cause of thrombophilia on the background of hyperhomocysteinemia as a state of high hypercoagulable risk.In the course of the study, the author established an association between the occurrence of this polymorphism among COPD patients with a history of thrombosis compared with patients without thrombotic complications, which is a sign of a causal relationship between the presence of a predisposing gene genotype and the development of thrombosis in this category of patients.

Keywords: Asp919Gly (A / G) polymorphism of the MTR gene, chronic obstructive pulmonary disease, thrombophilia.

Introduction. Thrombosis as a result of thrombophilic conditions makes a significant contribution to the overall morbidity and mortality of the world's population in all age groups, and therefore the interest in the study of thrombophilic conditions is steadily increasing. Every year, 1 in 250 people living on Earth dies from thrombosis. Three out of a thousand living people die from arterial thrombosis, which is the cause of acute ischemia of vital organs[5].

Almost 25% of the world's population develop venous thrombosis or pulmonary embolism at one time or another in life [1].

It should be emphasized that thrombophilia is not a disease in the generally accepted understanding and may not have clinical manifestations, which complicates its timely diagnosis, i.e. before the development of the first episode of thrombus formation. As a result of various "predictor" effects, the risk of thrombosis in a patient with hereditary thrombophilia increases significantly [2].

Chronic obstructive pulmonary disease (COPD) can also serve as a predictional factor.

Thrombophilia is an undisputed risk factor for the development of venous thrombosis and PE, however, their role in arterial thrombosis continues to be studied.

Mutations and polymorphisms in the genes of blood coagulation markers are of no small importance in the formation of thrombophilic conditions.

The MTR enzyme (methionine synthase) is an intracellular enzyme that catalyzes the repeated methylation of homocysteineto form methionine. The intermediate carrier of the methyl group in this reaction is a derivative of vitamin B12 - methylcobalamin, which acts as a coenzyme[3,4].

Several variants of the gene are known that affect the change in the function of the enzyme it encodes. The enzyme activity can be reduced as a result of nucleotide substitutions in the gene encoding it.

The most common polymorphism of the MTR gene, as a result, a decrease in the activity of the enzyme is observed, which leads to a violation of the metabolic pathway for the conversion of homocysteine, and its content in the blood plasma increases (hyperhomocysteinemia).

Hyperhomocysteinemia increases the likelihood of atherosclerosis and thrombosis. Accumulating in the body, homocysteinedamages the inner wall of the arteries, which leads to rupture of the endothelium. Cholesterol and calcium are deposited on the damaged surface, forming an atherosclerotic plaque, as a result of which the lumen of the vessel narrows and sometimes becomes clogged. This threatens with thrombosis or rupture of the vessel.

The interpretation of the research results should be carried out by the doctor in conjunction with other genetic, anamnestic, clinical and laboratory data.

Purpose. The aim of this study is to determine the role of the Asp919Gly (A / G) polymorphism of the MTR gene in the development of thrombotic events in patients with chronic obstructive pulmonary disease.

Material and research methods. The study included 92 patients with III-IV stages of COPD, who were inpatient treatment in the clinics of the Republican Scientific and Practical Medical Center for Phthisiology and Pulmonology during 2018-2019, as well as 46 healthy respondents who made up the control group.

To study the role of thrombophilia genes in the development of thrombotic episodes in patients with COPD, we studied the Asp919Gly polymorphism of the thrombophilia gene MTR in the group of patients with COPD (n = 92) with a history of thrombosis (n = 41) and without thrombosis (n = 51).

Genetic research methods. DNA diagnostics was held in Molecular Research and Cell Technologies Department of the Research Institute of Geology and Culture. DNA was isolated from blood leukocytes by the standard phenol-chloroform method (Maniatis T., 1984).

DNA extracted from peripheral blood by standard methods was used to diagnose mutational changes. The DNA diagnostic methods were based on polymerase chain reaction (PCR). Primary screening for the Leiden mutation was carried out according to the method of R.M. Bertina et al. (1994) and the Mnl 1 restriction enzyme. The G20210A mutation in the prothrombin gene was determined using the Taq 1 restriction enzyme after the introduction of an artificial restriction site into the PCR product. The allelic (homozygous or heterozygous) state of the identified mutation was confirmed using allele-specific primers.Blood in the amount of 5 ml was obtained by venipuncture into a disposable sterile tube with an anticoagulant. 0.5 M EDTA solution was used as an anticoagulant. The anticoagulant/blood ratio was 1/10. The blood was stored at -20?-80?C until DNA extraction.DNA was isolated from peripheral blood lymphocytes using Ribo Prep 200 reagent kits based on the use of guanidine thiocyanate and Nucleus sorbent (Isogene Lab. Ltd., Russia) in accordance with the method developed by the manufacturer. "SNP-EXPRESS CARDIOGENETICS" is designed to detect Asp919Gly polymorphism in the MTR gene in human genomic DNA isolated from whole blood leukocytes by the method of allele-specific polymerase PCR (AS) in real time. This set of reagents were used for detecting AS-PCR Asp919Gly polymorphism in the MTR gene.

All studies were carried out in accordance with the requirements of the Declaration of Helsinki (Recommendations for Physicians on Biomedical Research on Humans, 2000), regulatory documents of the Ministry of Health of the Republic of Uzbekistan.

Statistical software "OpenEpi, Version 2.9" was used for statistical analysis of the results.

Research results. Variations in the occurrence of genotypes for the Asp919Gly marker were identified to assess the results of the study. Assessment of the genotype using the Asp919Gly marker and the activity of the methionine synthase enzyme corresponding to this genotype was carried out in the following options:

I. Asp / Asp - normal enzyme activity
II. Asp / Gly - decreased enzyme activity
III. Gly / Gly - significantly reduced enzyme activity

Table 1
Frequency of occurrence of alleles and genotypes of polymorphism Asp919Gly(A / G)MTR gene

№	Groups	Alleles				Genotypes					
		Asp		Gly		Asp/Asp		Asp/Gly		Gly/Gly	
		n	%	n	%	n	%	n	%	n	%
1	Control group (n=46)	80	87	12	13	35	76,1	10	21,7	1	2,2
2	COPD group (n=92)	145	79	39	21,2	53	57,6	39	42,4	0	0
3	COPD without thrombosis (n=51)	86	84,3	16	15,7	35	68,6	16	31,4	0	0
4	COPD with thrombosis (n=41)	59	71,9	23	28,1	18	43,9	23	56,1	0	0

After analyzing the results of the study(Tab.1), we can say about a higher frequency of the Gly allele (21.2%) in the group of patients with COPD compared with the group of healthy respondents (13%).

When analyzing the occurrence of the genotypes of the Asp919Gly (Asp / Gly) polymorphism of the MTR gene in patients with COPD without a history of thrombosis, compared with patients with a history of thrombotic events, it was found that in the group without thrombosis, the frequency of the mutant Gly allele was found in 15.7%, while in patients with thrombosis, this indicator was 28.1%, which may indicate an association between the occurrence of mutant variants of the genotype and the incidence of hypercoagulable disorders in this group of patients. Whereas, the normal Asp allele prevailed in the group of patients without thrombosis - 84.3%, while in the group of patients with thrombosis it was 71.9%.

The normal genotype Asp/Asp, indicating the normal activity of the enzyme methionine synthase, prevailed in the group of patients without thrombosis (68.6%), while in the group of patients with thrombosis, this genotype was found in 43.9% ($p < 0.05$).

The Asp/Gly genotype predisposing to hyperhomocysteinemia, causing a decreased activity of the enzyme methionine synthase, was found in the group of COPD patients without thrombosis, and was found to be 31.4%, and in the group of patients with thrombosis, the occurrence of this genotype was 56.1% ($p < 0.05$). The mutant allele

Gly / Gly was found in 2.2% of cases in the control group of patients; this genotype was not found in the group of COPD patients.

Conclusions. In patients with COPD, Asp919Gly polymorphisms of the MTR gene predisposing to the development of dysfunction of the encoded enzyme were more common in comparison with the group of healthy respondents. Based on the results, it can be assumed that this Asp919Gly (A / G) polymorphism of the MTR gene plays a significant role in the development of thrombotic events in COPD patients, since the heterozygous variant of this gene, causing a decrease in methionine synthase activity, was found in the group with thrombosis in 56.1%, and in the group without thrombosis, this indicator was 31.4%.

The results obtained allow us to conclude that thrombotic events in patients with COPD may be associated with the state of hyperhomocysteinemia, which develops against the background of a decrease in the activity of the enzyme methionine synthase, which is a consequence of the mutant or heterozygous variant of Asp919Gly polymorphisms of the MTR gene.

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