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# The role of a polymorphic variant of folate cycle genes in the clinical picture of rosacea.

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**Abstract**. The pathogenesis of rosacea remains not fully understood to date. The question remains open and debated as to how the severity and severity of the various clinical symptoms of rosacea in a particular patient can be explained. What mechanisms regulate progression of the process, leading to a combination of subtypes and a severe course in some patients and manifestation of the disease within one subtype without a tendency to worsen in others.

**Purpose of the study**: to study genetic markers 1298 A>C of the MTHFR gene (rs1801131), 677C>T of the MTHFR gene (rs1801133), 2756 A>G of the MTR gene (rs1805087) and 66A>G of the MTRR gene (rs1801394) in erythematous-telangiectatic and papulopustular subtypes Rosacea. Materials and methods of research. The study involved 27 people who, depending on the clinical picture of rosacea, were divided into three groups; the results were compared with 20 healthy volunteers.

**Keywords:** rosacea, genetic markers, genetic analysis of subtypes, combination of subtypes.

Rosacea is a chronic disease of predominantly centrofacial localization, in the pathogenesis of which the leading role belongs to vascular and immune disorders. According to epidemiological studies, the prevalence of rosacea makes up about 10% of the world's population[2,6,16,26]. Most often, dermatosis occurs on streets with skin phototype 1-2, but it is also diagnosed in Asians, Latin Americans, African Americans and Africans [3,5,11,16]. Women over 30 years of age are more susceptible to this disease [6,16].

The question remains open and debated as to how can explain the severity and severity of various clinical symptoms of rosacea in a particular patient. Thanks to

what mechanisms are responsible for the progression of the process, leading to a combination of subtypes and a severe course in some patients and the manifestation of the disease within one subtype without a tendency to worsen in others.

In this regard, the study of the genetic component is promising. Genetic predisposition was first shown in a retrospective study in which the risk of developing the disease in family members of patients with rosacea was increased by more than fourfold [1], as well as reports of the development of dermatosis in monozygotic twins [17]. In addition, a recent cohort study twins with rosacea found a higher correlation between monozygotic than heterozygous twins [2]. In another study, genetic analysis demonstrated the potential significance of glutathione S-transferase (GST) gene polymorphisms in rosacea, where the GSTT1 and GSTM1 nucleotide genotypes were found to be closely associated with an increased risk of the disease [28]. Because GST

encodes an enzyme required for the catalytic reduction of reactive oxygen species (ROS), polymorphisms in GST may lead to significant oxidative stress and influence the pathogenesis of rosacea.

At the same time, a recent genome-wide association search (GWAS) study identified two single nucleotide polymorphisms (SNPs), rs763035 and rs111314066, among Europeans with rosacea [8]. In addition, three major major histocompatibility complex (MHC) class 2 alleles were identified: HLA-DRB1, HLA-DQB1 and HLADQA1 which are also associated with rosacea [16].

In another study, patients with rosacea were found to have a genetic predisposition to carry the rs3733631 polymorphic variant in the tachykinin receptor genes TACR3, which is located close to the TLR2 locusugene on 4q25 [17].

Currently, there is a number of reliable information about the role

genes of folate cycle enzymes in methylation reactions, which are responsible for many enzymatic transformations. The MTHFR gene, encoding methylenetetrahydrofolate reductase, one of the key enzymes of the folate cycle, is located at position 1p36.3. The two most common polymorphisms of the MTHFR gene - 677 C>T (rs1801133) and 1298 A>C (rs1801131) - are associated with a decrease in enzyme activity. Single nucleotide substitutions (SNP) rs1801133 (677C>T) and rs1801131 (1298A>C) in this gene lead to the formation of a thermolabile form of the enzyme, a decrease in its activity and, as a consequence, an increase in the level of homocysteine in the blood and a decrease in methionine synthesis. Homocysteine is a sulfur-containing amino acid produced by the metabolism of methionine. Homocysteine is converted to methionine with vitamin B12 and folic acid as cofactors. In the metabolic cycle of homocysteine synthesis, the lack of these vitamin-containing cofactors leads to increased homocysteine levels. Hyperhomocysteinemia is associated with various systemic diseases, including cardiovascular, cerebrovascular and neuropsychiatric conditions. A number of studies have identified potential mechanisms by which homocysteine may contribute to endothelial dysfunction, including platelet activation. Many studies have demonstrated an increased incidence of hyperhomocysteinemia in patients with various inflammatory skin diseases, including acne, vitiligo, psoriasis, and hidradenitis suppurativa. The accumulation of homocysteine causes damage to the vascular endothelium, has both atherogenic and thrombovascular effects, and also has a neurotoxic effect. In this regard, the study of the distribution of polymorphism of folate cycle genes in rosacea is an urgent problem in dermatology.

**Materials and methods**: We studied the pathogenetic significance of genotypic variants of polymorphisms 1298 A>C of the MTHFR gene (rs1801131), 677C>T of the MTHFR gene (rs1801133), 2756 A>G of the MTR gene (rs1805087) and 66A>G of the MTRR gene (rs1801394) in the formation and severity of rosacea in patients living in Uzbekistan. Genotyping of samples was carried out using the polymerase chain reaction method in real time. To obtain genomic DNA, a two-stage method of blood cell lysis was used: 1) obtaining a lysate concentrate of leukocyte cells; 2) further purification of

the buffy cell lysates was carried out by the alcohol-salt treatment method [Ausubel, F. M., Brent, R., Kingston, R. E., Moore, D. D., Seidman, J. G., Smith, J. A. & Struhl, K. Current Protocols in Molecular Biology - Wiley, New York, 2001.] in a modernized form. In the present study, we adjusted the DNA concentration to 100 ng/µl. DNA concentration was measured using a NanoDrop™ Lite spectrophotometer (ThermoFisher Scientific, USA). Real-time DNA sequence analysis based on Q-PCR HRM technology and PCR detection by microchip electrophoresis. To type polymorphic variants of the studied candidate genes (Table 1), the HRM-qPCR methods (Stratagene M*3005P, Agilent Technologies, Germany; DT-Prime, Russia) and the microarray PCR detection method (MCE 202 MultiNA, Zhimadzu, Japan) were used ). In total, we examined 47 DNA samples. Of these, 27 patients had rosacea and 20 were relatively healthy.

**Discussion of results:** When studying polymorphisms of folate cycle genes, data were obtained suggesting the influence of impaired folic acid metabolism on the mechanism of rosacea development. Variants of folate metabolism genes leading to an increase in the level of homocysteine in the blood contribute to traumatization of the vascular endothelium. The study identified genes believed to be involved in the occurrence and mechanism of development of rosacea, as well as influencing the severity of the disease. Unfavorable variants of folate metabolism genes: MTHFR: 1298 A>Crs1801131, MTHFR: 677C>rs1801133.

When studying the frequency of alleles of the 1298 A>C polymorphism of the MTHFR gene (rs1801131), a comparative analysis of subgroups (ETP and PPP) of the comparison group with the control group was carried out. For groups in which significant differences were identified, OR (odds ratio) and RR (relative risk) values were calculated. According to the data obtained, the homozygous A/A genotype in the PPP group is significantly less common than in the control group. These data prove that this genotype is a genetic factor of relative resistance to the development of the disease (OR=0.5; RR=0.7; 95%CI=0.23-1.08). The A/C genotype is significantly more common in both the group comparisons in general and in the PPP group when compared with the control group. OR = 8 in the comparison group and OR = 14 in the PPP subgroup, respectively, the chance of developing rosacea in general and the PPP subtype in the presence of the A/C genotype of the MTHFR gene (rs1801131) is 8 and 14 times higher, respectively, in the study group than in the control group. Relative risk indicator was equal to 2.9 (the upper and lower limits of the 95% CI did not include 1), which suggests that in people who are carriers of the A/C genotype of the MTHFR gene (rs1801131), rosacea occurs 2.9 times more often than in people having other variants of this gene.

Thus, molecular genetic studies of allelic variants of the 1298 A>C polymorphism of the MTHFR gene (rs1801131) allow us to draw conclusions about the genetic basis of the formation of rosacea. In the presence of a heterozygous genotype 1298 A/C (possibly also genotype 1298 C/C), the risk of developing the disease increases, i.e. this

polymorphism is a genetic marker of an increased risk of developing rosacea, while the A/A genotype is capable of performing a protective function.

When studying the 677C>T polymorphism of the MTHFR gene (rs1801133), a predominance of the frequency of the normal allele "C" was observed with a simultaneous decrease in the frequency of occurrence of the functionally inferior allele "T" (Table 7). The frequency of occurrence of the C/C genotype was 48.1%, of the C/T genotype - 33.3%, T/T genotype – 18.6%. The frequency distribution of "S/S", "S/T", "T/T" genotypes in the control group was 80.0%, 5% and 15%, respectively. The prevalence of alleles of the 677C>T polymorphism of the MTHFR gene (rs1801133) in the comparison group was : C – 64.8% (35/54), T – 35.2% (19/54); in the control group: C – 82.5% (33/40), T – 17.5% (7/40).

The data obtained by studying the frequency distribution of the 677C>T polymorphism of the MTHFR gene (rs1801133) in patients with rosacea depending on the clinical form of the disease were as follows. In the distribution of genotypes among those examined in the comparison group with ETP rosacea, an increase in the proportion of the homozygous genotype C/C was observed due to a decrease in the content of the heterozygous genotype C/T (53.8% versus 30.8%, respectively) and the homozygous genotype T/T (15.4%). When studying the genotypes of the comparison group for PPP rosacea, the frequency of occurrence of the homozygous subtype C/C was 42.9%, the proportion of the heterozygous genotype C/T was 35.7% and the homozygous genotype T/T was 21.4%. Depending on the clinical form of rosacea, the frequency of occurrence of normal rosacea changed. allele and functionally inferior allele "T". In ETP, the "C" allele was 69.2% (18/26), the frequency of occurrence of the "T" allele was 30.8% (8/26). In PPP, the frequency of occurrence of the "C" allele was 60.7% (17/28), the frequency of the "T" allele was 39.3% (11/28).

**Conclusion**. In conclusion, we can conclude that there is a relationship between the distribution of alleles of the 1298 A>C MTHFR gene (rs1801131) and the 677C>TMTHFR gene (rs1801133) and rosacea subtypes. Allele codes have been identified that indicate a tendency to the severity of the process. These results raise questions about the prospects for a more in-depth study of genetic predictors in order to predict predisposition to the development of a more severe course of the disease, timely prescription of preventive measures and the development of a personalized approach to the treatment of rosacea.

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