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Contribution of Tumor Necrosis Factor Alpha Polymorphic Gene (rs1800629) to the Mechanisms of Immune Microthrombocytosis and Immune Thrombocytopenia in Adults in Uzbekistan

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Abstract

We studied the association of the genetic polymorphism rs1800629 TNFα in the development of immune microthrombocytosis (Shenlein-Genoch purpura) and immune thrombocytopenia in adults of Uzbek nationality. The rs1800629 gene TNFα polymorphism was assessed using DNA samples obtained from peripheral blood through standard PCR analysis. The research results showed a significant difference in the distribution of allele A and genotype G/A of the TNFα gene (rs1800629) among patients with immune microthrombocytosis (allele A: $\chi 2=4.89$; P=0.027; OR=2.53; 95% CI 1.09-5.89 and genotype G/A: $\chi 2=5.58$; P=0.018; OR=2.92; 95% CI 1.18-7.26) and immune thrombocytopenia (allele A: $\chi 2=5.05$; P=0.024; OR=2.44; 95% CI: 1.10-5.40 and genotype G/A: OR=2.37; $\chi 2=3.86$; P=0.049; 95% CI: 1.99-5.67) during the active phase of the disease compared to the control group. This suggests the potential involvement of this polymorphism in the development of immune microthrombocytosis and

immune thrombocytopenia.
Key words: rs1800629 TNFα gene polymorphism, immune microthrombocytosis (Shenlein-Genoch purpura), immune thrombocytopenia, carrier, frequency, allele, genotype, association.

Relevance. Immune microthrombocytosis (IMT) and immune thrombocytopenia (ITP) are immune complex diseases with unclear etiology [2,5].

Studies aimed at investigating the etiological and pathogenetic mechanisms of IMT and ITP have shown that these diseases are associated with the influence of multiple factors, making them multifactorial [1,3].

The molecular basis underlying the development of IMT and ITP is not yet fully understood, but some evidence supports the role of genes in the pathogenesis of these diseases [7,12,18,20, 27].

It is known that cytokine genes, particularly those with polymorphic changes, play a crucial role in regulating inflammation and the immune response [10,11, 25]. Among the numerous cytokine genes, the gene encoding the proinflammatory cytokine TNF-α, primarily produced by activated macrophages, is considered significant [22].

It is assumed that TNF-α increases during the acute stage of IMT and may enhance the binding activity of IgA antibodies against endothelial cells. Therefore, the potential role of the TNFα gene polymorphism (rs1800629; G 308A) in the pathogenesis of IMT has been evaluated in various studies [8,21,24, 26]. However, some authors present data showing no link between the genetic polymorphism of TNF-α (rs1800629) and the development of the disease [21], while others claim the opposite [8].

The role of this cytokine gene has also been evaluated in the development of ITP [16,19]. For example, Turkish researchers T. Sever, S. Oguzkan, T. Babacan (2011) established a high expression of the TNFα (-308) gene (OR= 0.249, 95% CI: 0.076-0.815, $p < 0.05$) in patients with chronic ITP (OR=0.318; 95% CI: 0.103-0.987) [19].

Conversely, E. Okulu, T. İleri, V. K. Çulha, et al. (2011), when studying the role of tumor necrosis factor-alpha (TNF-α) -308 G/A in the development and clinical progression of ITP in 50 patients, concluded that the risk of ITP development and clinical progression is not associated with the TNFα gene polymorphism (G308A) (OR=0.738; 95% CI: 0.275-1.981 and OR=0.762, 95% CI: 0.179-3.249) [14].

Therefore, existing data on the association of TNF-α with the development of IMT and ITP are contradictory. Due to these conflicting opinions, the study of the association of the rs1800629 gene TNF-α polymorphism with the risk of developing IMT and ITP appears to be of interest.

Materials and methods. The study included 169 unrelated individuals of Uzbek nationality, among them 75 (Group 1) were patients diagnosed with immune microthrombocytosis (IMT) based on modern EULAR, PRINTO, and PreS classification criteria (2010) [15], and 89 (Group 2) were patients with immune thrombocytopenia (ITP), verified according to international expert recommendations (2009) [17]. All patients (aged 16 to 80) were observed at the Republican Specialized Scientific-Practical Medical Center of Hematology (Tashkent, Uzbekistan) from 2017 to 2020. Depending on the stage of the disease, each group was subdivided into two subgroups: "A" subgroup - active stage, and "B" subgroup - remission

stage of the disease. The control group consisted of healthy unrelated individuals of Uzbek nationality, matched by gender and age to the examined patient groups. Informed consent was obtained from all participants.

DNA was extracted from leukocytes in venous blood according to a standard DNA extraction protocol [13]. Detection of the rs1800629 gene TNFα polymorphism was performed using SNP-PCR on an "Applied Biosystems" 2720 programmable thermal cycler (USA), with the use of test systems from the "Litekh" company (Russia), following the manufacturer's instructions.

Statistical analysis of the results was conducted using the "OpenEpi 2009, Version 9.3" statistical software package.

Results and Discussion: We investigated the biallelic polymorphism rs1800629 of the TNF-α gene, which represents the substitution of a single guanine nucleotide with adenine (G/A) in the groups of patients with IMT, ITP, and the healthy control group.

The distribution frequencies of observed (Hobs) and expected (Hexp) genotypes of the rs1800629 TNFα gene polymorphism in the main groups of patients with IMT and ITP, as well as in the control group, did not deviate from their canonical Hardy-Weinberg equilibrium distribution (P>0.05).

In our observations, among the examined patients with immune microthrombocytosis (n=75), the frequency of the unfavorable A allele increased by 1.7 times in comparison to the control group, rising from 7.3% (in the control group) to 12.7% (in the main group), with fluctuations ranging from 10.3% in subgroup "B" of patients to 14.6% in subgroup "A" of patients (Table 1).

Table 1.

Analysis of the results of the rs1800629 gene TNF-α polymorphism study in the groups of patients with immune microthrombovasculithis and the control group.

Group	n	The allele frequencies				Genotype distribution frequency					
		G		A		G/G		G/A		A/A	
		n	%	n	%	n	%	n	%	n	%
Main group IMTV	75	131	87.3	19	12.7	56	74.7	19	25.3	0	0.0
«A» subgroup	41	70	85.4	12	14.6	29	70.7	12	29.3	0	0.0
«B» subgroup	34	61	89.7	7	10.3	27	79.4	7	20.6	0	0.0
Control group	73	135	92.3	11	7.3	62	84.9	11	15.1	-	0.0

The significant increase in the frequency of carrying the unfavorable A allele in the main group of patients with immune microthrombocytosis ($\chi 2=3.21$; P=0.073; OR=2.0; 95% CI 0.93-4.31) and in the subgroups of patients "A" - up to 14.6% ($\chi 2=4.89$; P=0.027; OR=2.53; 95% CI 1.09-5.89) and "B" - up to 10.3% ($\chi 2=0.46$; P=0.50; OR=1.41; 95% CI 0.52-3.81) indicates an association of this allele with an increased risk of developing immune microthrombocytosis in the "A" subgroup (Table 2).

Table 2.
Associative Link between the rs1800629 TNF-α Gene Polymorphism and the Risk of Developing IMT in Comparison to the Control

Poly-morphism		Alleles, genotypes	Control group, (n=73)		Main group, (n=75)		Reliability
			n	%	n	%	
308 G/A TNF-α	Alleles	308G	135	92,5	129	86,0	χ^2=3.208; p=0.07329; OR=1.998; 95% CI: 0.9266-4.308)
		308A	11	7,5	21	14,0	
	Genotypes	308 G/G	62	84,9	54	72,0	χ^2=3.65; p=0.05606; OR=2.192; 95% CI: 0.9697-4.955)
		308 G/A	11	15,1	21	28,0	
		308 A/A	0	0	0	0	

It should be noted that in the control sample and in patients with immune microthrombocytosis, only the wild-type G/G and heterozygous G/A genotypes were found, and the presence of the unfavorable rare A/A genotype was not detected. Additionally, in the patient group, heterozygous G/A genotype was observed 1.7 times more frequently (25.3% vs. 15.1%) compared to the control group, with the highest percentage of carriers of this genotype noted in the "A" subgroup of patients (29.3%).

The frequency distribution of carriers of the heterozygous G/A genotype in the main group of patients with immune microthrombocytosis (25.3% vs. 15.1%; χ2=3.65; P=0.056; OR=2.19; 95% CI 0.97-4.96), and in the subgroups of patients "A" (29.3% vs. 15.1%; χ2=5.58; P=0.018; OR=2.92; 95% CI 1.18-7.26) and "B" (20.6% vs. 15.1%; χ2=0.51; P=0.48; OR=1.46; 95% CI 0.51-4.18) indicates an association of this allele with an increased risk of developing immune microthrombocytosis in the "A" subgroup.

Frequency analysis of allele distribution in the ITP patient group (n=89) showed a decrease in the frequency of the G allele (83.7% vs. 92.3%) compared to the control group. At the same time, there was a significant increase in the frequency of the unfavorable A allele, from 7.4% in the control group to 16.3%. This same trend was observed in the ITP patient subgroups: in the "A" subgroup (n=49), the proportion of alleles G and A was 83.7% and 16.3%, respectively, while in the "B" subgroup (n=40), their values were 83.8% and 16.2%.

In the main group of patients, the frequency of the homozygous G/G genotype was found in 68.5% (n=61), and the heterozygous G/A genotype in 30.3% (n=27) of cases. In contrast, in the control group, the frequency of the G/G genotype was higher (85.2%), and the G/A genotype was lower (14.8%). It is worth noting that alongside these mentioned genotypes, in one case in the main group of patients, mainly attributed to the "A" subgroup, the mutant homozygous A/A genotype was observed (1.1%), while in the control group, the presence of this genotype was not observed (Table 3).

Table 3.
Frequency distribution of alleles and genotypes of the TNF-α gene polymorphism (rs1800629) in the control group and in ITP patients.

Group	n	Alleles' frequency				Genotype distributions frequency					
		G		A		G/G		G/A		A/A	
		n	%	n	%	n	%	n	%	n	%
Main ITP group, from them:	89	149	83.7	29	16.3	61	68.5	27	30.3	1	1.1
«A» - subgroup	49	82	83.7	16	16.3	34	69.4	14	28.6	1	2.0
«B» - subgroups	40	67	83.8	13	16.2	27	67.5	13	32.5	0	0.0
Control group	81	150	92.3	12	7.4	69	85.2	12	14.8	0	0.0

The analysis of differences in the distribution of allele and genotype frequencies of the TNF-α gene polymorphism (rs1800629) shows that in the main group of patients compared to the control group, the G allele was significantly lower by 1.1 times, while the frequency of the A allele increased by almost two times ($\chi2=3.208$; $p=0.07329$; OR=1.998; 95% CI: 0.9266-4.308). Regarding genotypes, the frequency of the G/G genotype was higher (85.2%), while the G/A genotype was lower (14.8%) ($\chi2=3.65$; $p=0.05606$; OR=2.192; 95% CI: 0.9697-4.955) (Table 4).

Table 4.
Differences in the distribution of allele and genotype frequencies of the TNF-α gene polymorphism (rs1800629) in the control group and in ITP patients.

Poly-morphism		Alleles, genotypes	Control group, (n=81)		Main group, (n=89)		Reliability
			n	%	n	%	
308 G/A TNF-α	Alleles	308G	150	92.3	149	83.7	$\chi^2=6.31$; $p=0.0012$; OR=1.998; 95% CI: 1.9266-4.308)
		308A	12	7.4	29	16.3	
	Genotypes	308 G/G	69	85.2	61	68.6	$\chi^2=3.65$; $p=0.05606$; OR=2.192; 95% CI: 1.9697-4.955)
		308 G/A	12	14.8	27	30.3	
		308 A/A	0	0	1	1.1	

In the "A" subgroup of ITP patients in the active stage of the disease, the percentage of carriers of the favorable G allele was more than one time lower, and the frequency of the unfavorable A allele was statistically significantly 2.44 times higher than the values in the control group ($\chi2=5.05$; $p=0.024$; OR=2.44; 95% CI: 1.10-5.40). Furthermore, in comparison to the control group, homozygous G/G genotype was significantly 1.23 times lower, while the

heterozygous G/A genotype statistically significantly exceeded it by 2.9 times ($\chi2$=5.581; p=0.01815; OR=2.923; 95% CI: 1.177-7.259). It is important to note that, although in a single case, only in this subgroup of patients was the mutant A/A genotype detected (2.0%).

The analysis of differences in the "B" subgroup of ITP patients in the remission stage shows that the percentage of carriers of the unfavorable A allele was statistically significantly 2.5 times higher than in the control group ($\chi2$=4.894; p=0.02695; OR=2.527; 95% CI: 1.089-5.863), while the percentage of the homozygous G/G genotype was significantly lower, and the heterozygous G/A genotype statistically significantly exceeded those in the control group ($\chi2$=5.581; p=0.01815; OR=2.923; 95% CI: 1.177-7.259).

This circumstance allows us to assert that the heterozygous G/A genotype of the rs1800629 gene TNF-α polymorphism is significantly associated with the development of immune microthrombocytosis and immune thrombocytopenia in individuals of Uzbek nationality. This is likely due to the loss of the protective effect of the wild-type G/G genotype in individuals with the heterozygous type of the TNF-α gene polymorphism (rs1800629). These results contribute to the formation of fundamental insights into the molecular-genetic basis and pathogenetic mechanisms of these diseases in individuals of Uzbek nationality.

Conclusion. *И*mmune microthrombocytosis and immune thrombocytopenia are diseases for which the etiopathogenetic mechanisms have not been fully elucidated to this day [2,5]. Currently, there are various opinions and claims that suggest a crucial role of genetic polymorphisms in the pathogenesis of these diseases [1,4]. A multitude of molecular-genetic studies have been conducted to investigate the role of genes in the development of immune microthrombocytosis and immune thrombocytopenia. However, the results of these studies in different populations are often contradictory, which may be attributed to ethnic differences in predisposition to these diseases. Literature describes studies on the role of the tumor necrosis factor-alpha (TNF-α) gene - an inflammatory cytokine involved in systemic inflammation and the pathogenesis of inflammatory diseases [24]. According to Ding GX et al. (2016) [8], the A allele of the G308A polymorphism of the TNF-α gene increases the risk of developing immune microthrombocytosis, while other authors have not found an association between the TNF-α gene and the development of the disease [21]. Similarly, contradictory data have been obtained in studying the contribution of this genetic marker to the development of immune thrombocytopenia [9,22,23]. For example, Yadav D. K., Tripathi A. K. et al. (2016), while studying the characteristics of the polymorphism of the tumor necrosis factor gene TNF-α (G308A) in Indian patients with immune thrombocytopenia, did not find significant differences in the distribution of the heterozygous genotype of the TNF-α gene (G308A) among patients and controls [23]. However, the results of studies by El Sissy A.H., Elanwary Sh. (2014) showed a significant sixfold increase in the frequency of the homozygous A/A genotype and an almost twofold increase in the frequency of the heterozygous G/A genotype of the TNF-α gene (G308A) polymorphism in patients with immune thrombocytopenia compared to the control group [9].

In the present study, genetic association of the TNF-α gene polymorphism (rs1800629) with the development of immune microthrombocytosis and immune thrombocytopenia was examined. The results of our research showed that during the active phase, the frequency of the unfavorable A allele (14.6% compared to 7.3%) and the heterozygous G/A genotype (29.3% compared to 15.1%) of the TNF-α gene (rs1800629) in the group of patients with immune microthrombocytosis, as well as the frequency of the A allele (16.3% compared to 7.4%) and

the heterozygous G/A genotype (28.6% compared to 14.8%) of the TNF-α gene (rs1800629) in the group of patients with immune thrombocytopenia, were significantly higher compared to the control group. This, in turn, suggests a potential involvement of this genetic polymorphism in the pathogenesis of these diseases.

Analyzing the results of current studies on the molecular-genetic mechanisms of immune microthrombocytosis and immune thrombocytopenia, considering their contradictory nature, it becomes evident that the genetic mechanism of disease development is highly complex and not yet fully understood.

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