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ALLELIC POLYMORPHISM OF THE IL-1β (rs1143627) GENE IN PATIENTS WITH IMMUNE THROMBOCYTOPENIA

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ABSTRACT

Purpose of the study. To study the features of the frequency distribution of alleles and genotypes of IL-1β (rs1143627) gene polymorphism, its role in the development of ITP in people of the Uzbek ethnic group.

Material and methods: The study included 89 patients with ITP (median age - 41 ± 1.7 years) (main group) who were admitted for examination by the RSPMCH in the period from 2012 to 2018. Detection of IL-1β (rs1143627) polymorphism was carried out by SNP-PCR.

Results and its discussion. Carriage of the IL-1β gene polymorphism (rs1143627) is not associated with the risk of developing immune thrombocytopenia.

Key-words: immune thrombocytopenia, IL-1β (rs1143627) gene polymorphism, allele, genotype, association, risk of development.

INTRODUCTION

Immune thrombocytopenia (ITP) is characterized by a variety of clinical manifestations and heterogeneity of the course, expressed in varying degrees of severity of hemorrhagic syndrome, which is determined by a number of important factors [1]. Recent studies have shown a high interest of scientists in terms of studying the contribution of polymorphic variants of proinflammatory cytokines to the risk of development and the severity of ITP [2, 3, 9].

The molecular basis underlying the development of ITP is not fully understood, however, some facts support the opinion that genes play a decisive role in the pathogenesis of these diseases [4,6].

It is known that cytokine genes play an important role in the realization of immune and inflammatory processes in the human body, polymorphic changes in which lead to disturbances in the regulation of inflammation and the immune response [7,8]. Of the large family of all cytokine genes, one of the most important is the proinflammatory cytokine gene IL-1 (α and β), which has a wide range of biological effects. Disturbances in the regulatory regions of the gene structure that occur due to the substitution of single nucleotides (SNP single-nucleotide polymorphism) most often lead to a change in its biological function, in particular to a decrease or increase in the production of IL-1, depending on the localization of the position of the nucleotide sequence replacement [4].

An important role of IL 1β has also been established in the pathogenesis of ITP. Thus, D. K. Yadav, A. K. Tripathi, D. Gupta et al. (2017) revealed a high frequency of the T allele (OR = 1.52; 95% CI = 1.04-2.22; P = 0.034), as well as homozygous (C / T) and heterozygous (T / T) variants of polymorphism genotypes gene IL-1β (C31T) (OR = 2.33, 95% CI = 1.069-5.09, P = 0.033 and OR = 2.044, 95% CI = 1.068-39, P = 0.034) among ITP patients, which emphasizes their significant influence on the risk of developing the disease [10]. J. Kim (2017) also notes a significant role of the IL1 β gene in the risk of developing ITP [5].

J.F. Vilela (2012) shows an analysis of the results of allele frequencies and genotypes of polymorphisms IL1β (C511T), IL1β (C3953T), IL6 (G174C) and other cytokines in patients with ITP compared with the control group, which did not reveal significant differences between the two groups. However, the presence of the CC genotype of the IL1β (C511T) gene polymorphism was associated in patients with ITP with a good response to splenectomy [10].

I. I. Zotova, S. I. Kapustin, Yu.S. Drijun et al. (2017) in the group of patients with early onset of ITP found an almost twofold increase in the incidence of the IL-1β –31CC genotype (15.8% versus 8.2%; OR = 2.1; 95% CI: 0.4–10.5; p = 0.39) and a 3-fold increase in carriers of the TNF-α –308A allele in the group of ITP patients under 50 years of age with late onset of ITP (26.7% versus 8.7%; OR = 3.8; 95% CI: 0.8–18.8; p = 0.12) [5].

Thus, the currently available research results characterized by the inconsistency of the data obtained. In this regard, the study of the pathogenetic significance of the polymorphism of genes of proinflammatory cytokines in the risk of ITP formation in the Uzbek ethnic group is of undoubted scientific and practical interest.

Purpose of the study. To study the features of the frequency distribution of alleles and genotypes of IL-1β (rs1143627) gene polymorphism, its role in the development of ITP in people of the Uzbek ethnic group.

Material and methods: The study included 89 patients with ITP (median age - 41 ± 1.7 years) (main group) who were admitted for examination and treatment at the Republican Specialized Scientific and Practical Medical Center of

Hematology (RSSPMCH) in the period from 2012 to 2018 biennium. The comparison group consisted of 81 persons (median age - 42 ± 1.4) without pathology of the hemostasis system. The main group is subdivided into two subgroups: A - ITP patients with hemorrhagic manifestations and B - ITP patients without hemorrhagic manifestations. The diagnosis of ITP was verified based on the recommendations of international experts (2009) [5]. Molecular genetic studies were carried out by the method of SNP-PCR analysis, using test systems of the company "Litech" (Russia), according to the manufacturer's instructions. Statistical analysis of the results was carried out using the statistical software package "Open Epi, Version 9.3".

Results and discussion. The results of the study to study the features of the polymorphic variant of the IL-1β gene (rs1143627) showed that in the main group of ITP patients, in relation to the control group, the frequency of the T allele was 75.8% (n = 135) versus 83.3% (n = 135), and allele C - 24.2% (n = 43) and 16.7% (n = 27). Analysis of the results depending on the stage of the disease revealed that in the "A" subgroup of ITP patients, the proportion of T and C alleles was 76.5% (n = 75) and 23.5% (n = 23); in the "B" subgroup, the carriage of these alleles was detected in 75.0% (n = 60) and 25.0% (n = 20) (see Table 1).

Table 1

Frequency of distribution of alleles and genotypes of IL1β gene polymorphism (rs1143627) in the control group and in ITP patients

Study groups	n	Allele frequency				Genotype distribution frequency					
		T		C		T/T		T/C		C/C	
		n	%	n	%	n	%	n	%	n	%
ITP main group of them:	89	135	75.8	43	24.2	51	57.3	33	37.1	5	5.6
"A" subgroup	49	75	76.5	23	23.5	29	59.2	17	34.7	3	6.1
"B" subgroup	40	60	75.0	20	25	22	55.0	16	40.0	2	5.0
Control group	81	135	83.3	27	16.7	56	69.1	23	28.4	2	2.5

The distribution of the observed frequency of all three genotypes revealed in our studies, both in the control group and in the group of patients, corresponded to the theoretically expected frequency and were in the Hardy-Weinberg equilibrium. Thus, in the control group and the main group of ITP patients, the frequency of the T / T polymorphism of the IL1β gene (rs1143627) was observed in 0.57 and 0.69 cases, respectively, and at the same time fully corresponded to this indicator in the expected frequency. With regard to genotypes T / C and C / C, a similar picture of practical correspondence between the observed and expected frequencies in both

groups was observed. The difference in the results both in the control and in the group of ITP patients was insignificant.

The observed along with this difference in the carriage of alleles and genotypes in the main group of patients in comparison with those in the control group, in particular, an increase in the proportion of carriers of the T allele (χ^2 = 2.91; p = 0.09; OR = 1.6; 95% CI: 0.93-2.7) and homozygous T / T genotype (χ^2 = 2.545; p = 0.11; OR = 1.7; 95% CI: 0.89-3.14), indicates a potentially protective role of this allele and genotype in relation to the formation of ITP.

At the same time, in the total sample of ITP patients, in comparison with those in the control group, there were almost no significant differences in the carriage of the C allele (χ^2 = 2.91; p = 0.09; OR = 1.6; 95% CI: 0.93-2.7), heterozygous genotype T/C (χ^2 = 1.5; p = 0.23; OR = 0.7; 95% CI: 0.35-1.3) and mutant genotype C/C (χ^2 = 1.1; p = 0.3; OR = 0.425; 95% CI = 0.08-2.26) (see Table 2).

Table 2

Difference in the frequency distribution of alleles and genotypes of IL1β gene polymorphism (rs1143627) in the control group and in the main ITP group

Polymorphism		Alleles, genotypes	Control group, (n = 81)		Main group, (n = 89)		Credibility
			n	%	n	%	
T31C gene IL1B	Alleles	T	135	83.3	135	75.8	χ^2=2.91; p=0.09; OR=1.6; 95%CI:0.93-2.7
		C	27	16.7	43	24.2	
	Genotypes	T/T	56	69.1	51	57.3	χ^2=2.5; p=0.11; OR=1.7; 95%CI:0.89-3.14
		T/C	23	28.4	33	37.1	χ^2=1.5; p=0.23; OR=0.7; 95%CI: 0.35-1.3
		C/C	2	2.5	5	5.6	χ^2=1.1; p=0.3; OR=0.43; 95%CI=0.08-2.26

Analyzing the results of the distribution of the frequencies of alleles and genotypes in ITP patients in the peak stage, it was revealed that the share of T allele carriage was slightly lower than the same indicator in the control group (76.5% versus 83.3%), while the C allele, on the contrary, was 1.53 times more common among ITP patients (23.5% versus 16.7%; $\chi2$ = 1.82; p = 0.18; OR = 1.53; 95% CI: 0.82-2.86). Carriage of the T / T genotype was characterized by a decrease in its share of 1.55 times (59.2% versus 69.1%; $\chi2$ = 1.34; p = 0.25; OR = 1.55; 95% CI: 0.74-3.24) and an insignificant increase in the share of the T / C genotype (37.1% versus 28.4%; $\chi2$ = 0.57; p = 0.45; OR = 0.75; 95% CI: 0.35-1.6) in patients in relation to the control group. It is also important to note that the carriage of the C / C mutant genotype in the "A" subgroup of patients was 6.1%

($\chi 2$ = 1.1; p = 0.3; OR = 0.4; 95% CI: 0.062-2.41), while in the control its values were 2.5% (see Table 3).

Table 3

Difference in the frequency distribution of alleles and genotypes of IL1β gene polymorphism (rs1143627) in the control group and in the "A" subgroup of ITP patients

Polymorphism		Alleles, genotypes	Control group, (n = 81)		"A" subgroup (n = 49)		Credibility
			n	%	n	%	
T31C gene IL1B	Alleles	T	135	83.3	75	76.5	χ^2=1.82; p=0.18; OR=1.53; 95%CI:0.82-2.86
		C	27	16.7	23	23.5	
	Genotypes	T/T	56	69.1	29	59.2	χ^2=1.34; p=0.25; OR=1.55; 95%CI:0.74-3.24
		T/C	23	28.4	17	34.7	χ^2=0.57; p=0.45; OR=0.75; 95%CI:0.35-1.6
		C/C	2	2.5	3	6.1	χ^2=1.1; p=0.3; OR=0.4; 95%CI:0.062-2.41

Among ITP patients in remission, the proportion of C allele carriage (25.0% versus 16.7%; $\chi 2$ = 2.4; p = 0.12; OR = 1.7; 95% CI: 0.87-3.2), T / T genotypes (55.0% versus 69.1%; $\chi 2$ = 2.34; p = 0.13; OR = 1.83; 95% CI: 0.84-4.0), T / C (40.0% versus 28.4%; $\chi 2$ = 1.651; p = 0.2; OR = 0.6; 95% CI: 0.27-1.32) and C / C (5.0% versus 2.5%; $\chi 2$ = 2.4; p = 0.12; OR = 1.7; 95% CI: 0.87-3.2) as well as in patients "A" subgroups did not differ significantly from those in the control group (see Table 4).

Thus, based on the absence of signs of a statistically significant genetic dependence of the risk of developing ITP with IL-1β gene polymorphism (rs1143634), revealed in a comparative analysis of genotype frequencies among ITP patients in comparison with similar indicators in the control group, it was found that IL-1β (rs1143634) cannot act as a genetic marker for the risk of developing ITP. In particular, the C allele and the C / C genotype of this gene do not have an independent role in the implementation of pathological processes of platelet destruction, leading to the development of ITP. The results obtained once again prove the fact that the role of one genetic polymorphism in the development of pathology is small [3,7], however, it can be associated with the interaction of several genes [8,10].

Table 4

Difference in the frequency distribution of alleles and genotypes of IL1β gene polymorphism (rs1143627) in the control group and in the "B" subgroup of ITP patients

Polymorphism		Alleles, genotypes	Control group, (n = 81)		"B" subgroup, (n = 40)		Credibility
			n	%	n	%	
T31C gene IL1B	Alleles	T	135	83.3	60	75	χ^2=2.4; p=0.12; OR=1.7; 95%CI:0.87-3.2
		C	27	16.7	20	25	
	Genotypes	T/T	56	69.1	22	55	χ^2=2.34; p=0.13; OR=1.83; 95%CI:0.84-4.0
		T/C	23	28.4	16	40	χ^2=1.65; p=0.2; OR=0.6; 95%CI:0.27-1.32
		C/C	2	2.5	2	5	χ^2=2.4; p=0.12; OR=1.7; 95%CI:0.87-3.2

Output:

1. The absence of dependence of the development of immune thrombocytopenia with the polymorphism of the IL-1β gene (rs1143627) was established.
2. The observed difference in the carriage of the T allele (χ2 = 2.91) and the homozygous T/T genotype (χ2 = 2.5) in the main group of patients in comparison with those in the control group indicates a potentially protective role of this allele and genotype in relation to the formation of ITP.

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