JOURNAL OF MULTIDISCIPLINARY SCIENCES AND INNOVATIONS

VOLUME 5, ISSUE 05
MONTHLY JOURNALS

ISSN NUMBER: 2751-4390
IMPACT FACTOR: 9,08

UDC: 575:577.2: 616.155.392-036-07

IL23R GENE POLYMORPHISM IN APLASTIC ANEMIA IN THE UZBEK POPULATION

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https://doi.org/10.5281/zenodo.20430324

RESUME

This article examines the role of interleukin-23 receptor (IL23R) genetic polymorphism in the pathogenesis of acquired aplastic anemia (AA). The aim of the study was to investigate the distribution of allele and genotype frequencies of the rs11209026 (G/A) locus and their association with the risk of developing and the severity of pancytopenia in patients of Uzbek nationality. A comparative analysis of 86 AA cases and 98 controls was conducted. RT-PCR revealed a predominance of the G/G genotype in all groups. Despite the lack of a statistically significant association ($P > 0.05$), the obtained data contribute to a better understanding of the population genetics of blood diseases in Central Asia.

Key words: aplastic anemia, IL23R, cytokines, genetic polymorphism, Th17 cells, Uzbek population, pancytopenia.

Introduction. Aplastic anemia (AA) is a critical condition characterized by pancytopenia and fatty replacement of bone marrow [9]. The pathogenesis is based on T-cell attack on stem cells (HSCs) under the influence of proinflammatory cytokines [10]. Disruption of the Th1/Th2 balance and activation of the Th17 axis lead to loss of immune tolerance.

A key link in the activation of Th17 lymphocytes is interleukin-23 [1], which stimulates the secretion of IL-17 and TNF-α through the IL23R receptor. Genetic polymorphisms can alter receptor affinity and the intensity of the immune response [5]. In particular, the rs11209026 variant of the IL23R gene is recognized as a risk factor for autoimmune diseases [3], but its role in hematology remains a subject of debate.

The pathogenesis of AA in eastern populations has ethnic characteristics [8], which requires the evaluation of regional markers for personalized therapy [7]. The Treg/Th17 balance is modulated by interleukin gene variants [6]. Given that the prognostic value of polymorphisms depends on the severity of the disease [4], and the population of Uzbekistan is genetically heterogeneous, studying the IL23R (G/A) locus in the region is extremely important [2].

Methods. The study involved 86 patients with acquired aplastic anemia (AA) treated at the Republican Scientific and Practical Medical Center of Hematology. The control group consisted of 98 apparently healthy donors without any blood pathologies. The main inclusion criteria were a confirmed diagnosis of acquired AA, Uzbek ethnicity, and voluntary informed consent. According to Kamitta's criteria, patients were divided into three groups based on disease severity: 16 patients had mild AA, 46 had severe AA, and 24 had ultra-severe AA. Molecular genetic analysis of the IL23R (G/A) polymorphism was performed using real-time PCR (RT-PCR) using DNA isolated from peripheral blood. Statistical processing of the obtained results included the mandatory test for Hardy-Weinberg equilibrium, as well as the calculation of the $\chi 2$ criterion,

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relative risk (RR) and odds ratio (OR) with the determination of the 95% confidence interval (CI).

Results. An analysis of the observed frequencies to theoretically expected values showed that the distribution of genotypes in both groups obeys the Hardy-Weinberg law (in the main group: $\chi 2=0.05$; P=0.79; df=1, in the control group: $\chi 2=0.01$; P=0.876; df=1). In the IL23R gene structure (G/A), the dominant variant in all samples was the G allele. In the control group, its frequency was 99.0%, while the frequency of the mutant A allele was only 1.0% (see Table 1).

Table 1

Structural analysis of IL23R gene polymorphism (G/A) in healthy controls and patients with AA

No.	Group	Alleles (n/%)				Genotypes (n/%)					
		G		A		G/G		G/A		A/A	
		n	%	N	%	N	%	n	%		%
1	Primary with AA, n=86	168	97.7	4	2.3	82	95.3	4	4.7	0	0.0
2	Mild AA, n=16	31	96.9	1	3.1	15	93.8	1	6.2	0	0.0
3	Severe AA, n=46	90	97.8	2	2.2	44	95.7	2	4.3	0	0.0
4	Super heavy, n=24	47	98.0	1	2.0	23	95.8	1	4.2	0	0.0
5	Comparison control, n=98	194	99.0	2	1.0	96	98.0	2	2.0	0	0.0

When comparing the main group of patients with healthy individuals, a slight increase in the frequency of the mutant allele A (2.3% versus 1.0%) and heterozygote G/A (4.7% versus 2.0%) was noted, but these differences were not statistically significant (see Table 2).

Table2

Two-way analysis of differences in the IL23R gene polymorphism (G/A) in the study and control groups

Alleles and genotypes	Groups				χ^2	P	RR	DI	CRR	DI
	I-st - basic AA		V – I – control							
	n	%	n	%						
G	168	97.7	194	99.0	1.0	0.4	1.0	0.32-3.05	0.4	0.08-2.28
A	4	2.3	2	1.0	1.0	0.4	1.0	0.11-9.38	2.3	0.44-12.2
G/G	82	95.3	96	98.0	1.0	0.4	1.0	0.31-3.08	0.4	0.08-2.28
G/A	4	4.7	2	2.0	1.0	0.4	2.3	0.72-7.21	2.3	0.44-12.5

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These results indicate the absence of an independent association of the IL23R locus (rs11209026) with the risk of developing the disease in the studied population.

An assessment of the impact of polymorphism on the severity of AA also revealed no significant correlations. The highest frequency of the unfavorable G/A variant (6.3%) was observed in the mild form, while in the severe form it was 4.2% (see Table 3).

Table3

Two-way analysis of differences in the IL23R gene polymorphism (G/A) between a group of patients with mild AA and healthy controls

Alleles and genotypes	Groups				χ2		RR	DI	CR	DI
	II-nd - mild AA		V – I – control							
	n	%	N	%						
G	31	96.9	194	99.0	0.9	.4	1.0	0.04-24.0	0.3	0.03-3.21
A	1	3.1	2	1.0	0.9	.4	1.0	0.21-4.92	3.1	0.31-31.5
G/G	15	93.8	96	98.0	1.0	.4	1.0	0.04-25.1	0.3	0.03-3.24
G/A	1	6.3	2	2.0	1.0	.4	3.1	0.12-80.5	3.2	0.3-33.14

At the same time, in the group of patients with severe AA, in comparison with healthy individuals, the differences in the distribution of alleles and genotypes of the IL23R polymorphic gene (G/A) also did not differ in significance between the allelic variants (G allele – 97.8% versus 99.0%; $\chi2=0.6$; P=0.5; RR=1.0; CI: 0.14-6.94; OR=0.5; CI: 0.07 - 3.2 and A allele – 2.2% versus 1.0%; $\chi2=0.6$; P=0.5; RR=1.0; CI: 0.15-6.95; OR=2.2; CI: 0.31-14.8) and genotypic variants (G/G genotype – 95.7% versus 98.0%; $\chi2=0.6$; P=0.5; RR=1.0; CI: 0.13-7.07; OR=0.5; CI: 0.07-3.21 and G/A genotype - 4.3% versus 2.0%; $\chi2=0.6$; P=0.5; RR=2.1; CI: 0.29-5.42; OR=2.2; CI: 0.31-15.3) (see Table 4).

Table 4

Two-way analysis of differences in the IL23R gene polymorphism (G/A) between a group of patients with mild AA and healthy controls

Alleles and genotatios	Groups				χ2	P	RR	DI	CR	DI
	III - severe AA		V – I – control							
	n	%	N	%						
G	90	97.8	194	99.0	0.6	0.5	1.0	0.14-6.94	0.5	0.07 - 3.2
A	2	2.2	2	1.0	0.6	0.5	1.0	0.15-6.95	2.2	0.31-14.8
G/G	44	95.7	96	98.0	0.6	0.5	1.0	0.13-7.07	0.5	0.07-3.21
G/A	2	4.3	2	2.0	0.6	0.5	2.1	0.29-5.42	2.2	0.31-15.3

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In the group of patients with severe AA, in relation to the control group, the distribution of alleles and genotypes of the polymorphic geneIL23R (G/A) the established differences were not significant (G allele – 97.9% vs. 99.0%; $\chi2$=0.4; P=0.6; RR=1.0; CI: 0.04-23.7; OR=0.5; CI: 0.05-5.19 and A allele – 2.1% vs. 1.0%; $\chi2$=0.4; P=0.6; RR=1.0; CI: 0.21-4.87; OR=2.1; CI: 0.19-22.1) and genotypic variants (G/G genotype – 95.8% vs. 98.0%; $\chi2$=0.4; P=0.6; RR=1.1; CI: 0.04-24.4; OR=0.5; CI: 0.04-5.24 and G/A genotype – 4.2% vs. 2.0%; $\chi2$=0.4; P=0.6; RR=2.0; CI: 0.08-51.0; OR=2.1; CI: 0.19-22.8) (see Table 5).

Table 5

Two-way analysis of differences in the IL23R gene polymorphism (G/A) between a group of patients with mild AA and healthy controls

Alleles and genotypes	Groups				χ2		RR	DI	CRR	DI
	IV-th – super heavy AA		V – I – control							
	n	%	N	%						
G	47	97.9	194	99.0	0.4	0.6	1.0	0.04-23.7	0.5	0.05-5.19
A	1	2.1	2	1.0	0.4	0.6	1.0	0.21-4.87	2.1	0.19-22.1
G/G	23	95.8	196	98.0	0.4	0.6	1.0	0.04-24.4	0.5	0.04-5.24
G/A	1	4.2	2	2.0	0.4	0.6	2.0	0.08-51.0	2.1	0.19-22.8

Comparative analysis between subgroups (e.g., mild vs. severe) showed identical results (P = 0.8), which excludes this polymorphism from the factors determining disease progression.

The biological role of the IL-23/STAT3/IL-17 pathway in the pathogenesis of autoimmune bone marrow destruction is undisputed. Interleukin-23 promotes cell differentiation and the secretion of inflammatory cytokines, which should theoretically correlate with the severity of AA. However, our study showed that in the Uzbek population, genetic variability at the rs11209026 locus is not a determining factor in this process.

The lack of statistical significance may be due to several factors. First, the low frequency of the mutant A allele in the studied population (only 1–2%), which is typical of many Asian ethnic groups, as opposed to European ones. Second, it is possible that other loci of the IL23R gene or associated genes in the STAT3 signaling pathway have a greater influence on the disease phenotype.

However, the trend towards a twofold increase in the frequency of the G/A genotype in patients (4.7%) compared to healthy controls (2.0%) is noteworthy and may indicate the presence of a weak effect that can be detected in larger samples.

Conclusion. In the Uzbek population, the IL23R (G/A) gene polymorphism is characterized by a high frequency of the dominant G allele (more than 97%) and a low prevalence of the mutant A allele. No statistically significant association was found between allelic variants of the rs11209026 locus and the risk of developing aplastic anemia (P = 0.4). The IL23R (G/A) genetic variant is not a marker of the severity of the clinical course of AA, since the distribution of genotypes between groups with different degrees of pancytopenia was uniform (P > 0.05). The

study results allow us to revise the list of potential prognostic markers for the region and focus further research on other links in the IL-23/Th17 signaling pathway.

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