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ABSTRACT

The presence of a relationship between polymorphism of the IL23R gene receptor (11209026) and the risk of developing rheumatoid arthritis in Uzbekistan was studied. The polymorphism of the IL23R gene receptor (11209026) was assessed by analyzing DNA samples by standard PCR. The results of a study to study the polymorphism of the IL23R gene receptor (11209026) in the general group of patients with RA and in the subgroup 1A of patients with articular RA showed the presence of statistically significant differences in the carriage of the A allele (14.1% versus 7.8%; $\chi 2 = 4.46$; P = 0.04; OR = 1.95; 95% CI: 1.05-3.62) and (15.5% versus 7.8%; $\chi 2 = 5.43$; P = 0.02; OR = 2.176; 95% CI: 1.131-4.185), respectively, as well as a clear tendency towards an increased risk of developing RA in carriers of the G / A genotype (22.7% versus 15.6%; $\chi 2 = 1.73$; P = 0.19; OR = 1.58; 95% CI: 0.798-3.145) and (25.7% versus 15.6%; $\chi 2 = 2.83$; P = 0.09; OR = 1.87; 95% CI: 0.902-3.876), respectively. Therefore, allele A and genotype G / A can be considered as molecular genetic markers that increase the likelihood of developing articular RA.

Key words: rheumatoid arthritis, IL23R gene receptor polymorphism (11209026), allele, frequency, genotype, risk of development.

INTRODUCTION

Relevance. Rheumatoid arthritis (RA) is a common autoimmune disease in which many different genetic variants of functional gene polymorphisms may play a critical role in the underlying pathogenetic mechanism [9].

Among the genes of proinflammatory cytokines involved in the initiation and maintenance of inflammation in the body, an important representative is the heterodimeric cytokine IL-23 with two subunits α and β, which belongs to the superfamily of interleukins 6/12 (IL-6 / IL-12) [2,3,7 ,12]. Expressed by a number of activated cells such as macrophages, monocytes, T- and B-lymphocytes, endothelial cells, etc., this cytokine binds to the IL23R receptor [16,18]. The role of certain polymorphic variants of the IL-23R gene receptor in the development of inflammatory diseases has been studied both in clinical [20] and in experimental studies [5], in some of which the association was established [7,15,20], and in others it was absent [13, 21]. Considering this, we found it very interesting to study the peculiarities of the occurrence of allelic and genotypic variants of the rs11209026 polymorphism of the IL-23R gene receptor among RA patients and healthy people in order to identify the presence of an association between its carriage and the onset of RA.

Material and methods. This study was conducted with the participation of patients (n = 106) who were treated at 3 clinics of the Tashkent Medical Academy from 2018 to 2021, living in the territory of the Republic of Uzbekistan with a diagnosis of rheumatoid arthritis, verified according to the ACR/EULAR criteria (2010) [1]. Patients with RA (n=106), depending on the form of the disease, were divided into two subgroups 1A (n=74) - patients with articular RA and 1B (n=32) - patients with articular-visceral RA. The comparison group consisted of conditionally healthy individuals (n=109) also living in the republic without a history of autoimmune diseases. Molecular genetic studies were carried out in the laboratory of medical genetics of the Republican Specialized Scientific Practical Medical Center of Hematology (RSSPMCH, Republic of Uzbekistan, Tashkent). In accordance with the generally accepted technique, DNA was isolated from blood leukocytes. At the same time, the analysis (SNP-PCR) of the rs11209026 receptor polymorphism of the IL-23R gene was carried out using the “Applied Biosystems” 2720 (USA) system using the “Litex” test systems (Russia). Statistical analysis of the results was carried out using the program "OpenEpi 2009, Version 9.3".

Results and discussion. We analyzed the correspondence of the frequency distribution of genotypes (observed and expected) of the IL-23R gene receptor polymorphism rs11209026 to the Hardy-Weinberg equilibrium among patients of

the general group and healthy subjects in the control group. In the general group of RA patients, allelic frequencies G and A corresponded to 0.86 and 0.14, with their values equal to 0.92 and 0.08 among healthy ones. At the same time, in the group of patients, the observed genotypic frequencies of the rs11209026 polymorphism of the IL-23R gene receptor G/G, G/A, and A/A were 0.74, 0.23, and 0.03, while the expected frequencies were 0.74, 0.24, and 0.02 ($\chi 2$ = -. 49; p = 0.461). Whereas in the control, only the frequencies of the G/G and G/A genotypes (0.84 and 0.16) were observed with the expected frequency of the G/G genotypes - 0.85, G / A - 0.14, and A / A - 0.01 ($\chi 2$ = 0.78; p = 0.361). The absence of a discrepancy from Hardy–Weinberg principle (p> 0.05) in relation to the observed and expected frequencies of genotypic variants of the IL23R gene receptor polymorphism (11209026) in the studied groups made it possible to study the nature of the distribution of the allele and genotype frequencies of this gene among RA patients and healthy individuals. In the group of healthy individuals (n=109), alleles G and A were detected in 92.2% and 7.8% of the subjects. At the same time, the presence of genotypes G/G and G / A was found in 84.4% and 15.6%. Cases of carriage of the mutant genotype A/A were not identified in this group. In the general group of RA patients, the carriage of allele G was registered slightly less (85.9%), and the share of allele A, on the contrary, exceeded its frequency among healthy individuals (14.1%). As a rule, in the group of patients, the frequency of the wild genotype G/G (74.5%) was detected somewhat less often, while the frequency of the heterozygous genotype was detected in 22.7% of cases.

Moreover, in the group of RA patients, the carriage of the mutant genotype A / A was found in 2.8% of cases (Table 1).

Table 1

Analysis of the frequency distribution of alleles and genotypes of IL23R (11209026) gene receptor polymorphism among patients with RA and healthy individuals

Group	Allele frequency				Genotype distribution frequency					
	G		A		G /G		G /A		A /A	
	n	%	n	%	n	%	n	%	n	%
1st - general group RA (n = 106)	182	85.9	30	14.1	79	74.5	24	22.7	3	2.8
1A subgroup - articular form of RA (n = 74)	125	84.5	23	15.5	53	71.6	19	25.7	2	2.7
1B - articular-visceral form of RA (n = 32)	57	89.1	7	10.9	26	81.3	5	15.6	1	3.1
Control group (n = 109)	201	92.2	17	7.8	92	84.4	17	15.6	0	0.0

Analysis of the carriage of alleles and genotypes of the IL23R (11209026) gene receptor polymorphism, taking into account the clinical form of RA, showed the following:

- in subgroup 1A with articular RA, the cases of registration of alleles G and A of this polymorphism were 84.5% and 15.5%, respectively. The frequencies of genotypes G/G, G/A, and A/A were 71.6%, 25.7%, and 2.7%, respectively;

- in subgroup 1B with articular-visceral form of RA, the frequencies of the G and A alleles were found in 89.1% and 10.9%, respectively, and of the G/G, G/A, and A/A genotypes in 81.3%, 15.6% and 3.1% of cases, respectively.

From the data presented, it can be seen that the mutant genotype A/A of the IL23R gene receptor polymorphism (11209026) was most often detected among patients with the articular-visceral form of the disease, which may indicate the presence of a connection between the carriage of the A/A genotype and the development of a more severe course of the pathological process. extending beyond the joints. Evaluation of differences in the distribution of alleles and genotypes of the IL23R gene receptor polymorphism (11209026) between the examined general and control groups showed a statistically significant difference in the carriage of genotype A, the value of which was almost two times higher than its share among RA patients in comparison with its share in healthy persons (14.1% versus 7.8%; $\chi 2 = 4.46$; $p = 0.04$; OR = 1.95; 95% CI: 1.05-3.62) (Table 2).

Table 2

Comparative analysis of differences in the distribution of allelic and genotypic frequencies of IL23R (11209026) gene receptor polymorphism among RA patients and healthy individuals

Alleles and genotypes	Number of examined alleles and genotypes				χ^2	P	OR	95% CI
	General group		Control group					
	n	%	n	%				
G	182	85.9	201	92.2	4.46	0.04	0.51	0.28- 0.95
A	30	14.1	17	7.8	4.46	0.04	1.95	1.05-3.62
G /G	79	74.5	92	84.4	3.22	0.08	0.54	0.28-1.06
G /A	24	22.7	17	15.6	1.73	0.19	1.58	0.798 - 3.145
A /A	3	2.8	-	-	-	-	-	-

In these groups, the differences between the frequencies of the G/G genotype were not significant (74.5% versus 84.4%; $\chi^2 = 3.22$; $p = 0.08$; OR = 0.54; 95% CI: 0.28-1.06). At the same time, there was a tendency to an increase

in the frequency of the G/A genotype among RA patients by 1.58 times (22.7% versus 15.6%; $\chi 2 = 1.73$; p = 0.19; OR = 1.58; 95% CI: 0.798-3.145).

Further, we found it interesting to study the significance of differences in the carriage of alleles G and A, as well as genotypes G/G, G/A and A/A of the IL23R (11209026) gene receptor polymorphism, taking into account the forms of RA.

Thus, in subgroup 1A with the articular form of the disease, there was a significant difference in the carriage of allele A, which exceeded its frequency in comparison with the group of healthy individuals by more than two times (15.5% versus 7.8%; $\chi 2 = 5.43$; P = 0.02; OR = 2.176 ; 95% CI: 1.131-4.185) (Table 3).

Table 3

Comparative analysis of differences in the distribution of allelic and genotypic frequencies of IL23R gene receptor polymorphism (11209026) among patients of subgroup 1A with articular RA and healthy individuals

Alleles and genotypes	Number of examined alleles and genotypes				χ^2	P	OR	95% CI
	1A subgroup		Control group					
	n	%	n	%				
G	125	84.5	201	92.2	5.43	0.02	0.460	0.239-0.884
A	23	15.5	17	7.8	5.43	0.02	2.176	1.131-4.185
G /G	53	71.6	92	84.4	4.38	0.04	0.466	0.228-0.953
G /A	19	25.7	17	15.6	2.83	0.09	1.870	0.902-3.876
A /A	2	2.7	-	-	-	-	-	-

A decrease in the protective role of the wild genotype G/G in the development of articular RA was evidenced by its significant decrease in the 1A subgroup of patients (71.6% versus 84.4%; $\chi 2 = 4.38$; P = 0.04; OR = 0.466; 95% CI: 0.228-0.953). Moreover, an increase in the risk of developing this form of the disease was evidenced by the established clear trend in an increase in the carriage of the G / A genotype among patients of the 1A subgroup compared with healthy patients by almost two times (25.7% versus 15.6%; $\chi 2 = 2.83$; P = 0.09; OR = 1.87; 95% CI: 0.902-3.876). Statistical analysis of differences in the frequencies of alleles and genotypes of IL23R gene receptor polymorphism (11209026) in subgroup 1B with an articular-visceral form of the disease showed a slightly different picture. In particular, no significant differences were found in the carriage of both alleles and genotypes in the examined subgroup compared to the control (Table 4.).

Table 4

Comparative analysis of differences in the distribution of allelic and genotypic frequencies of IL23R gene receptor polymorphism (11209026) among patients 1B subgroup with articular-visceral RA and healthy individuals

Alleles and genotypes	Number of examined alleles and genotypes				χ^2	P	OR	95% CI
	1B subgroup		Control group					
	n	%	n	%				
G	57	89.1	201	92.2	0.63	0.45	0.689	0.274 – 1.734
A	7	10.9	17	7.8	0.63	0.45	1.452	0.576-3.658
G/G	26	81.3	92	84.4	0.18	0.68	0.801	0.287-2.233
G/A	5	15.6	17	15.6	0.00	1.00	1.002	-
A/A	1	3.1	-	-	-	-	-	-

For example, allele A, although it was found very often, almost 1.5 times among patients with articular-visceral form of RA, the established difference was not significant (10.9% versus 7.8%; $\chi2 = 0.63$; P = 0.45; OR = 1.452; 95% CI: 0.576-3.658). A similar trend was observed in relation to genotypes G/G (81.3% versus 84.4%; $\chi2 = 0.18$; P = 0.68; OR = 0.801; 95% CI: 0.287-2.233) and G / A (15.6% versus 15.6%; $\chi2 = 0.00$; P = 1.0).

A comparative assessment of the significance of differences in the carriage of alleles and genotypes of IL23R gene receptor polymorphism (11209026) between subgroups 1A and 1B revealed an insignificant increase in the frequency of allele A in 1A subgroup of patients compared to subgroup 1B by 1.5 times (Table 5).

Table 5

Comparative analysis of differences in the distribution of allelic and genotypic frequencies of IL23R gene receptor polymorphism (11209026) between patients 1A and 1B RA subgroups

Alleles and genotypes	Number of examined alleles and genotypes				χ^2	P	OR	95% CI
	1A subgroup		1B subgroup					
	n	%	n	%				
G	125	84.5	57	89.1	0.78	0.40	0.667	0.271-1.639
A	23	15.5	7	10.9	0.78	0.40	1.498	0.611-3.675
G /G	53	71.6	26	81.3	1.09	0.30	0.582	0.211-1.607
G /A	19	25.7	5	15.6	1.29	0.26	1.865	0.636-5.472
A /A	2	2.7	1	3.1	0.01	0.91	0.861	0.072-10.27

At the same time, insignificant differences were found in the frequencies of G/G genotypes (71.6% versus 81.3%; $\chi 2 = 1.09$; P = 0.30; OR = 0.582; 95% CI: 0.211-1.607) and A/A (2.7% versus 3.1%; $\chi 2 = 0.01$; P = 0.91; OR = 0.861; 95% CI: 0.072-10.27). However, in the carriage of the G/A genotype, there was a tendency to its increase almost twofold in the 1A subgroup of patients with articular RA (25.7% versus 15.6%; $\chi 2 = 1.29$; P = 0.26; OR = 1.865; 95% CI: 0.636- 5.472). The data obtained may indicate that somewhat different mechanisms are involved in the development of the articular-visceral form of RA, leading to damage to the joints and organs, which are also emphasized in the publications of foreign researchers [4].

Conclusion

Rheumatoid arthritis (RA) is a disease with an unexplored mechanism of development [16]. However, today there are a number of opinions and statements about the important role of polymorphic variants of proinflammatory cytokine genes in the pathogenesis of the development of the disease [8,14].

In particular, special attention of researchers is involved in studying the contribution of the genes of the IL23R cytokines (11209026) in the implementation of pathological processes accompanied by a failure of immunoregulation, and, as a result, leading to the onset of RA [11, 18].

Meanwhile, the results of studies carried out in different populations are ambiguous, which is possibly associated with population differences and the sample size of the surveyed contingent [6, 10].

Taking into account such disagreements, it seemed interesting to us to study the association of the polymorphic variant of the IL23R gene receptor (11209026) with the development of RA, depending on its clinical forms.

The results of a study to study the polymorphism of the IL-23R gene receptor (11209026) in the general group of RA patients and in the 1A subgroup of patients with articular RA showed the presence of statistically significant differences in the carriage of the A allele (14.1% versus 7.8%; $\chi 2 = 4.46$; P=0.04; OR=1.95; 95% CI: 1.05-3.62) and (15.5% versus 7.8%; $\chi 2 = 5.43$; P = 0.02; OR=2.176; 95% CI: 1.131-4.185), respectively, a decrease in the protective effect against the development of RA genotype G / G (74.5% versus 84.4%; $\chi 2 = 3.22$; P = 0.08; OR = 0.54; 95% CI: 0.28-1.06) and (71.6% versus 84.4%; $\chi 2 = 4.38$; P = 0.04; OR = 0.466; 95 % CI: 0.228-0.953), respectively, as well as a clear tendency to increase the risk of developing RA in carriers of the G/A genotype (22.7% versus 15.6%; $\chi 2 = 1.73$; P=0.19; OR=1.58; 95% CI: 0.798-3.145) and (25.7% versus 15.6%; $\chi 2 = 2.83$; P=0.09; OR=1.87; 95% CI: 0.902-3.876), respectively.

Therefore, allele A and genotype G/A can be considered as molecular genetic markers that increase the likelihood of developing articular RA.

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