ASSESSMENT OF THE DEGREE OF ASSOCIATION OF IL-17A GENE POLYMORPHISMS (rs2275913), IL-17F (rs763780) AND IL-23R (11209026) WITH THE SEVERITY OF CLINICAL AND INSTRUMENTAL MANIFESTATIONS OF RHEUMATOID ARTHRITIS

A.A. Eshmurzaeva[1], M.V. Sibirkina[2],M.Sh.Karimov[3]

[1]DSc, associate professor of the Department of the Propaedeutics of Internal Diseases No. 2 of Tashkentmedical academy
[2]PhD, associate professor of the Department of the Propaedeutics of Internal Diseases No. 2 of Tashkentmedical academy
[3]DSc, professor, head of the Department of the Propaedeutics of Internal Diseases No. 2 of Tashkentmedical academy

Abstract *The influence of the association of polymorphic genes IL17A (rs2275913), IL-17F (rs763780) and IL23R (11209026) on the clinical manifestations of RA in Uzbekistan was studied. The IL23R gene receptor polymorphism (11209026) was assessed by analyzing DNA samples using standard PCR. An association was found between carriage of unfavorable genotypes of the IL17A gene (rs2275913) and the duration of RA. There is a tendency to increase the duration of the articular form of the disease to 15 years or more in carriers of genotypes G/A + A/A of the IL17A polymorphic gene (rs2275913) by almost three times ($\chi 2=3.61$; $P=0.057$; $OR=2.57$; 95% CI: 0.96-6.86), which allows us to consider them as prognostic markers for the long-term course of RA. Unfavorable genotypes of the IL17A (rs2275913) and IL-17F (rs763780) genes as predictors of the development of severe FNS in patients with articular RA. There is a pronounced tendency towards an increase in unfavorable genotypes G/A + A/A of the IL17A polymorphic gene (rs2275913) by more than 5 times ($\chi 2=2.28$; $P=0.13$; $OR= 5.08$; 95% CI:0.50-51.38) and A/G +G/G polymorphism of the IL-17F gene (rs763780) almost 5 times ($\chi 2=2.66$; $P=0.10$; $OR=4.83$; 95% CI:0.62-37.77) among patients with FNS 3 with articular form of RA. Associations between the degree of RA activity and polymorphic genes IL17A (rs2275913), IL-17F (rs763780) and IL23R (11209026) with articular ($\chi 2<3.84$; $P>0.05$) and articular-visceral forms of the disease ($\chi 2<3.84$; $P>0.05$) not found.*

Keywords: *rheumatoid arthritis, IL-23R gene receptor polymorphism (11209026), IL-17A gene polymorphism (rs2275913), IL-17F gene polymorphism (rs763780), allele, frequency, genotype, carrier fraction, development risk, population of Uzbekistan.*

Introduction. Rheumatoid arthritis (RA) is an autoimmune disease with the versatility and severity of clinical manifestations, a high incidence of disability and poorly understood pathogenesis. It is known that in the implementation of the pathological process that gives rise to the disease, a connection has been observed in relation to a number of factors such as environmental influences, bad habits, microbial and viral agents, genetic polymorphisms, etc. [1].

The prevalence of the disease according to large epidemiological studies depends on the population [2,3,4], so the incidence of RA in American Indians (up to 7%), while among other nationalities the incidence of the disease is in the range of 0.2–0.4% [4].

Inflammation, being the basis for the development of RA, begins with changes in the joint tissue, and as the process progresses, it spreads to the bone tissue, causing its destruction [5]. The regulation of inflammatory processes involves many factors, among which the leading role is played by polymorphic variants of a number of proinflammatory cytokines (IL17A) [6, 7, 8, 9], (IL17F, etc.) [10,11] IL-23R [12,13, 14].

Meanwhile, the results of studies assessing their participation in increasing the risk of developing RA are ambiguous. In studies by C. N. Carvalho, R. F. do Carmo, A. L. P. Duarte, et al. (2015) found no connection between polymorphisms of the IL-17A (-197G/A) and IL-17F (7488T/C) genes and the severity of RA (n=100) and Sjögren's syndrome (n=31) [15]. Given the conflicting results, S. Zhang, Y. Wang, Q. Zhou et al. (2016) conducted a meta-analysis of the results of seven independent studies, including 3130 cases of RA and 3136 healthy individuals to study the role of IL17A in the development of RA, and, based on this, came to the conclusion that the rs 2275913 polymorphic variant of this gene has a protective effect on the development of the disease [16]. Research results Y. H. Lee, S.C. Bae, (2017), O. S. Marwa et al. (2017), M. Shao et al. (2020) confirm the role of the IL17F gene in the development of RA [10,11,17].

There is equally conflicting information about the role of certain polymorphic variants of the IL-23R gene receptor in the development of inflammatory diseases, in some of which an association was established [13,14], but in others it was absent [18,19]. The resulting discrepancies may be related to the characteristics of the populations studied.

In this regard, it seemed very interesting to us to conduct additional studies to assess the relationship of these genes with the development of RA and the influence of the association of polymorphic genes IL-17A (rs2275913), IL-17F (rs763780) and IL23R (11209026) on the clinical manifestations of RA.

Purpose of our study was to study the association of polymorphisms of the IL17A (rs2275913), IL-17F (rs763780) and IL-23R (11209026) genes with the severity of clinical and instrumental manifestations of rheumatoid arthritis among the population of Uzbekistan.

Material and methods. This study was conducted with the participation of 106 patients diagnosed with rheumatoid arthritis, verified according to the ACR/EULAR criteria (2010) with a median age of 43.5±3.8 years, who were treated at the 3rd clinic of the Tashkent Medical Academy from 2018 to 2021. living on the territory of the Republic of Uzbekistan. Patients with RA (n=106), depending on the form of the disease, are divided into two subgroups 1A (n=74) – patients with the articular form of RA and 1B (n=32) – patients with the articular-visceral form of RA.

The control group consisted of 109 conditionally healthy unrelated persons living in the territory of the republic without a history of autoimmune diseases, comparable age and gender in the general group of RA patients.

Molecular genetic studies were carried out in the laboratory of medical genetics of the Republican Specialized Scientific and Practical Medical Center for Hematology (Republic of Uzbekistan, Tashkent). To conduct molecular genetic studies, DNA was isolated from venous blood leukocytes using the AmpliPrime RIBO-prep, Russia kit according to the standard method [13]. At the same time, using the "Applied Biosystems" 2720 system (USA), an analysis (SNP-PCR) of the rs2275913 polymorphism of the IL17A gene receptor, rs763780 of the IL17F gene, rs11209026 of the IL-23R gene receptor was carried out using test systems "Litech" (Russia).

13Miller S.A., Dykes D.D., Polesky H.F. A simple salting out procedure for extracting DNA from human nucleated cells. Nucl Acids Res. 1988; 16:1215.

Mathematical analysis of the results was carried out using the OpenEpi 2009, Version 9.3 program.

Results. To carry out a statistical analysis of the occurrence of allelic and genotypic frequencies of polymorphisms of the genes IL17A (rs2275913), IL-17F (rs763780) and IL23R (11209026) in patients with RA (n=106) and individuals in the control group, an analysis of their compliance with the Hardy-Weinberg equilibrium (HW) was carried out , p>0.05). Analysis of the frequency distribution of genotypes of polymorphism of these genes in the studied groups showed no deviation from RCV (p>0.05).

First of all, we conducted a comparative analysis of the frequency of occurrence of functionally unfavorable genotypes of the studied gene variants among RA patients with articular and articular-visceral forms of the disease (see Table 1). The analysis showed a clear tendency to increase the frequency of unfavorable genotypes G/A + A/A for the genetic polymorphism IL17A (rs2275913) among patients with the articular form of RA with a disease duration of 15 years or more, almost three times compared to carriers of the favorable genotype G/G ($\chi 2$=3.61; P= 0.057; OR=2.57; 95% CI:0.96-6.86).

Table 1

Distribution of allele and genotype frequencies for the IL17A gene (rs2275913) among patients with the articular form of rheumatoid arthritis depending on duration

Patients	1-4 years		5-9 years		10-14 years		More than 15 years	
	n	%	n	%	n	%	n	%
G/A + A/A n=29	1	3.5	9	31.0	5	17.2	14	48.3
G/G n=45	4	8.8	17	37.8	12	26.7	12	26.7
Degreeofdifference	χ^2 =0.83; P=0.36; OR=0.37;95% CI:0.04-3.45		χ^2 =0.35; P=0.55; OR=0.74;95% CI:0.28-1.997		χ^2 =0.89; P=0.34; OR=0.57; 95% CI:0.18-1.84		χ^2=3.61; P=0.057; OR=2.57; 95% CI:0.96-6.86	

A similar analysis among patients with the articular-visceral form did not reveal any significant differences (see Table 2).

Table 2

Distribution of allele and genotype frequencies for the IL17A gene (rs2275913) among patients with articular-visceral form of rheumatoid arthritis depending on the duration of the disease

Patients	1-4 years		5-9 years		10-14 years		More than 15 years	
	n	%	n	%	n	%	n	%
G/A + A/A n=6	2	33.3	1	16.7	1	16.7	2	33.3
G/G n=26	0	0.0	4	15.4	11	42.3	11	42.3
Degreeofdifference	$\chi2$=9.24; P=0.002		$\chi2$=0.006; P=0.94; OR=1.10; 95% CI:0.10-12.08		$\chi2$=1.37; P = 0.24; OR=0.27; 95% CI:0.03-2.68		$\chi2$=0.16; P = 0.69; OR=0.6; 95% CI: 0.11-4.41	

Further analysis to assess the frequency of occurrence of functionally unfavorable genotypes of polymorphic genes IL-17F (rs763780) (for the articular form of RA with a duration of 15 years or more - A/G+G/G versus A/A: $\chi2$=0.45; P=0.50; OR =1.50; 95% CI:0.46-4.92 and for the articular-visceral form of RA with a duration of 15 years or more - A/G+G/G versus A/A: $\chi2$=1.08; P=0.30; OR=0.39; 95% CI:0.07-2.36) and IL23R (11209026) (for the articular form of RA with a duration of 15 years or more - G/A+A/A versus G/G: $\chi2$=0.04; P= 0.84; OR= 0.89; 95% CI :0.31-2.60 and for the articular-visceral form of RA with a duration of 15 years or more - G/A+A/A versus G/G: $\chi2$=0.27; P= 0.60; OR=1.60; 95% CI:0.27-9.53) depending on the duration of the disease showed no significant differences among patients with both articular and articular-visceral forms of RA.

Thus, the analysis of the frequency of occurrence of unfavorable genotypes of the IL17A (rs2275913), IL-17F (rs763780) and IL23R (11209026) genes showed only the presence of a clear tendency to increase genotypes G/A + A/A of the polymorphic IL17A gene (rs2275913), which proves its participation in maintaining the pathological process for 15 years or more ($\chi2$=3.61; P=0.057; OR=2.57; 95% CI:0.96-6.86). Therefore, genotypes G/A + A/A of the IL17A polymorphic gene (rs2275913) can be considered as prognostic markers for the long course of RA.

With regard to the severity and severity of the radiological stage of RA, differences in the carriage of unfavorable genotypes compared with favorable genotypes of the genes IL17A (rs2275913), IL-17F (rs763780) and IL23R (11209026) were not significantly significant among patients with articular disease ($\chi2$<3.84; P >0.05) and articular-visceral forms of RA ($\chi2$<3.84; P>0.05), which does not allow us to consider them as markers of the development of severity of radiological manifestations of the disease.

However, by studying the distribution of genotypes of the studied genes among patients with RA depending on the degree of functional joint insufficiency (FJD), we discovered interesting facts (see Table 3). For example, based on the polymorphism of the IL17A gene (rs2275913), a pronounced tendency has been established towards an increase in the frequency of unfavorable genotypes G/A + A/A among patients with FNS III with articular form of RA by more than 5 times compared to the frequency of the favorable genotype G/G ($\chi 2$ =2.28; P=0.13; OR= 5.08; 95% CI:0.50-51.38).

Table 3

Distribution of allele and genotype frequencies for the IL17A gene (rs2275913) among patients with the articular form of rheumatoid arthritis depending on the degree of FNS

Patients	FJF 1		FJF 2		FJF 3	
	n	%	n	%	n	%
G/A + A/A n=29	6	20.7	20	69.0	3	10.3
G/G n=45	5	11.1	39	86.7	1	2.2
Degreeofdifference	χ^2=1.28; P=0.26; OR= 2.09; 95% CI:0.57-7.60		χ^2=3.42; P=0.06; OR= 0.34; 95% CI: 0.11-1.1		χ^2=2.28; P=0.13; OR= 5.08; 95% CI:0.50-51.38	

In addition, the polymorphism of the IL-17F gene (rs763780) also revealed a pronounced tendency towards an increase in the frequency of unfavorable genotypes A/G+G/G among patients with FNS3 articular form of RA by almost 5 times compared to the frequency of the favorable genotype A/A ($\chi 2$ =2.66; P=0.10; OR=4.83; 95% CI:0.62-37.77) (see table 4).

Table 4

Distribution of allele and genotype frequencies for the IL-17F gene (rs763780) among patients with the articular form of rheumatoid arthritis depending on the degree of FNS

Patients	FJF 1		FJF 2		FJF 3	
	n	%	n	%	n	%
A/G+G/G n=14	2	14.3	10	71.4	2	14.3
A/A n=60	9	15.0	49	81.7	2	3.3
Degreeofdifference	χ^2=0.005; P=0.95; OR=0.94; 95% CI:0.18-4.95		χ^2=0.74; P=0.39; OR=0.56; 95% CI:0.15-2.12		χ^2=2.66; P=0.10; OR=4.83; 95% CI:0.62-37.77	

However, according to the polymorphism of the IL23R gene (11209026), no relationship with the severity of FNS was identified for the articular form of RA (see Table 5).

Table 5

Distribution of allele and genotype frequencies for the IL23R gene (11209026) among patients with the articular form of rheumatoid arthritis depending on the degree of FNS

Patients	FJF 1		FJF 2		FJF 3	
	n	%	n	%	n	%
G/A + A/A n=21	4	19.0	16	76.2	1	4.8
G/G n=53	7	13.2	43	81.1	3	5.7
Degreeofdifference	χ^2=0.41; P=0.52; OR=1.55; 95% CI:0.40-5.96		χ^2=0.23; P=0.63; OR=0.74; 95% CI: 0.22-2.51		χ^2=0.02; P=0.88; OR=0.83; 95% CI:0.08-8.50	

Along with these facts, among patients with the articular form of RA, for all three studied polymorphisms, no significant differences were identified between the carriage of unfavorable genotypes and the severity of FNS (see Table 6).

Table 6

Distribution of allele frequencies and genotypes for the IL17A (rs2275913), IL-17F (rs763780) and IL23R (11209026) genes among patients with the articular-visceral form of rheumatoid arthritis depending on the degree of FNS

IL17A (rs2275913)						
Patients	FJF 1		FJF 2		FJF 3	
	n	%	n	%	n	%
G/A + A/A n=6	2	33.3	4	66.7	0	0.0
G/G n=26	6	23.1	20	76.9	0	0.0
Degreeofdifference	χ^2=0.27; P=0.60; OR=1.67; 95% CI:0.24-11.44		χ^2=0.27; P=0.60; OR=0.60; 95% CI:0.09-4.12		-	
IL-17F (rs763780)						
Patients	FJF 1		FJF 2		FJF 3	
	n	%	n	%	n	%
A/G+G/G n=8	3	37.5	5	62.5	0	0.0
A/A n=24	5	20.8	19	79.2	0	0.0
Degreeofdifference	χ^2=0.89; P=0.35; OR=2.28; 95% CI:0.40-12.96		χ^2=0.89; P=0.35; OR=0.44; 95% CI:0.08-2.49		-	
IL23R (11209026)						
Patients	FJF 1		FJF 2		FJF 3	
	n	%	n	%	n	%
G/A + A/A n=6	1	16.7	5	83.3	0	0.0
G/G n=26	7	26.9	19	73.1	0	0.0
Degreeofdiffe	χ^2=0.27; P=0.60;		χ^2=0.27; P=0.60; OR=		-	

rence	OR=0.54; 95% CI: 0.05-5.50	1.84; 95% CI: 0.18-18.66	

Thus, the analysis of the frequency of occurrence of unfavorable genotypes of the IL17A (rs2275913), IL-17F (rs763780) and IL23R (11209026) genes showed only a pronounced tendency towards an increase in unfavorable genotypes G/A + A/A of the polymorphic IL17A gene (rs2275913) by more than 5 times ($\chi2$=2.28; P=0.13; OR= 5.08; 95% CI:0.50-51.38) and A/G+G/G polymorphism of the IL-17F gene (rs763780) among patients with FNS3 articular form of RA almost 5 times times ($\chi2$=2.66; P=0.10; OR=4.83; 95% CI:0.62-37.77) compared with the frequency of favorable genotypes of the studied genes. The results obtained allow us to consider unfavorable genotypes of the IL17A (rs2275913) and IL-17F (rs763780) genes as predictors of the development of severe FNS in patients with articular RA.

Studying the degree of differences in the frequency of distribution of unfavorable genotypes in relation to favorable genotypes of the genes IL17A (rs2275913), IL-17F (rs763780) and IL23R (11209026) in accordance with the degrees of RA activity, we did not find statistically significant differences among patients with articular disease ($\chi2$<3.84 ; P>0.05) and articular-visceral forms of the disease ($\chi2$<3.84; P>0.05). This is evidence of the lack of association between the degree of RA activity and the polymorphic genes IL17A (rs2275913), IL-17F (rs763780) and IL23R (11209026).

Discussion. Rheumatoid arthritis (RA) is a disease with a completely unknown mechanism of development [1]. 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 disease [15; 20].

In particular, special attention of researchers is involved in studying the contribution of the IL17A cytokine genes (rs2275913). IL-17F (rs763780). IL23R (11209026) in the implementation of pathological processes accompanied by a failure of immunoregulation, and, ultimately, leading to the onset of RA [21]. Meanwhile, the results of studies conducted in different populations are ambiguous, which may be due to population differences and the number of samples of the surveyed population [15].

Taking into account such disagreements, it seemed interesting to us to study the association of polymorphic variants of the genes IL17A (rs2275913), IL-17F (rs763780), IL23R (11209026) with the development of RA depending on its clinical forms.

In our studies on the characteristics of carriage of the rs2275913 gene polymorphism of the IL17A gene, the proportion of carriage of unfavorable allele A (20.3% versus 11.5%; $\chi2$=5.349; p=0.021; OR=1.963; 95%CI: 1.108-3.477) and heterozygous genotype G/A (32.4% versus 19.3%; $\chi2$=4.121; p=0.045; OR=2.011; 95%CI: 1.024-3.948) polymorphism of the rs2275913 gene of the IL17A gene in the group of patients with the articular form of RA is statistically significantly higher than those among conditionally healthy individuals. The data obtained may indicate the possible contribution of rs 2275913 of the IL17A gene to the mechanisms of RA development.

An assessment of the carrier characteristics of the IL17F gene polymorphism (rs763780) in groups of RA patients and healthy individuals among the population of

the Republic of Uzbekistan made it possible to establish. that the G allele and heterozygous genotype A/G of the IL17F gene (rs763780) are significantly higher among patients with RA compared to the control group. In particular, the most significant differences were found in patients with the articular-visceral form of the disease, in whom the G allele exceeded the proportion of carriers in the control statistically significantly by 2.58 times ($\chi2$=4.512; P=0.037; OR=2.58; 95%CI:1.076 -6.188), and for the heterozygous genotype A/G there was a clear tendency for its frequency to more than double ($\chi2$=2.011; P=0.165; OR=2.068; 95% CI: 0758-5.645).which in turn indicates the possible participation of this polymorphism in the pathogenesis of the disease. Moreover, only among patients with this form of RA was carriage of the G/G mutant genotype (3.1%; $\chi2$=2.011; P=0.165; OR=2.068; 95% CI: 0758-5.645).

Studies studying polymorphism of the IL23R gene receptor (11209026) showed the presence of statistically significant differences in the carriage of the A allele in the general group of RA patients (14.1% versus 7.8%; $\chi2$=4.46; P=0.04; OR=1.95; 95% CI: 1.05-3.62) and in the 1A subgroup of patients with the articular form of RA (15.5% versus 7.8%; $\chi2$=5.43; P=0.02; OR=2.176; 95% CI: 1.131-4.185). Besides. We found a decrease in the protective effect on the development of RA from the G/G genotype in the general group of RA patients (74.5% versus 84.4%; $\chi2$=3.22; P=0.08; OR=0.54; 95% CI: 0.28-1.06) and in 1A subgroup of patients (71.6% versus 84.4%; $\chi2$=4.38; P=0.04; OR=0.466; 95% CI: 0.228-0.953). Moreover, these features were accompanied by a clear tendency to increase the risk of developing RA in carriers of the G/A genotype in the overall group of patients (22.7% versus 15.6%; $\chi2$=1.73; P=0.19; OR=1.58; 95% CI: 0.798-3.145) and in the 1 A subgroup (25.7% versus 15.6%; $\chi2$=2.83; P=0.09; OR=1.87; 95% CI: 0.902-3.876), respectively. The results obtained allow us to consider the A allele and the G/A genotype as molecular genetic markers that increase the likelihood of developing the articular form of RA.

Conclusion.

1. Carriage of unfavorable alleles and heterozygous genotypes of polymorphic variants of the IL17A genes (rs2275913). IL-17F (rs763780), IL23R (11209026) in patients with RA indicates their involvement in the pathogenetic mechanisms of the disease.

2. An association was identified between carriage of unfavorable genotypes of the IL17A gene (rs2275913) and the duration of RA. There is a tendency to increase the duration of the articular form of the disease to 15 years or more in carriers of genotypes G/A + A/A of the IL17A polymorphic gene (rs2275913) by almost three times ($\chi2$=3.61; P=0.057; OR=2.57; 95% CI: 0.96-6.86), which allows us to consider them as prognostic markers for the long-term course of RA.

3. Associations between the severity of the radiological stage of RA and the carriage of unfavorable genotypes of the genes IL17A (rs2275913), IL-17F (rs763780) and IL23R (11209026) among patients with articular ($\chi2$<3.84; P>0.05) and articular-visceral forms of RA ($\chi2$ <3.84; P>0.05) not established.

4. Unfavorable genotypes of the IL17A (rs2275913) and IL-17F (rs763780) genes as predictors of the development of severe FNS in patients with articular RA. There is a

pronounced tendency towards an increase in unfavorable genotypes G/A + A/A of the IL17A polymorphic gene (rs2275913) by more than 5 times ($\chi2=2.28$; P=0.13; OR= 5.08; 95% CI:0.50-51.38) and A/G +G/G polymorphism of the IL-17F gene (rs763780) almost 5 times ($\chi2=2.66$; P=0.10; OR=4.83; 95% CI:0.62-37.77) among patients with FNS 3 with articular form of RA.

5. Associations between the degree of RA activity and the polymorphic genes IL17A (rs2275913), IL-17F (rs763780) and IL23R (11209026) with articular ($\chi2<3.84$; P>0.05) and articular-visceral forms of the disease ($\chi2<3.84$; P> 0.05) not detected.

References

1.Derksen V.F.A.M., Huizinga T.W.J., van der Woude D. The role of autoantibodies in the pathophysiology of rheumatoid arthritis. Semin. Immunopathol. 2017, 39, 437–446.

2.Cross M, Smith E, Hoy D, Carmona L, Wolfe F, Vos T. The global burden of rheumatoid arthritis: estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis. 2014; 73:1316-22. Medline:24550173 doi:10.1136/annrheumdis-2013-204627.

3. Firestein G. S. Pathogenesis of rheumatoid arthritis: the intersection of genetics and epigenetics. Trans Am ClinClimatol Assoc. 2018; 129: 171-182. PMCID: PMC6116585.

4. Nemtsova, M. V., Zaletaev, D. V., Bure, I. V., Mikhaylenko, D. S., Kuznetsova, E. B., Alekseeva, E. A., … Zamyatnin, A. A. (2019). Epigenetic Changes in the Pathogenesis of Rheumatoid Arthritis. Frontiers in Genetics, 10. doi:10.3389/fgene.2019.00570.

5.Boissier MC, Semerano L, Challal S, Saidenberg-Kermanac'h N, Falgarone G (2012) Rheumatoid arthritis: from autoimmunity to synovitis and joint destruction. J Autoimmun 39(3):222–228. doi:10.1016/j.jaut.2012.05.021.

6.Bogunia-Kubik, K., Świerkot, J., Malak, A., Wysoczańska, B., Nowak, B., Białowąs, K., … Wiland, P. (2015). IL-17A, IL-17F and IL-23R gene polymorphisms in Polish patients with rheumatoid arthritis. ArchivumImmunologiaeetTherapiaeExperimentalis, 63(3), 215–221.

7.Brzustewicz E. Bryl E. The role of cytokines in the pathogenesis of rheumatoid arthritis—Practical and potential application of cytokines as biomarkers and targets of personalized therapy. Cytokine. 2015, 76, 527.

8.Burska A. Boissinot M., Ponchel F. Cytokines as Biomarkers in Rheumatoid Arthritis. Med. Inflamm. 2014, 2014, 545493.

9. Hoboken N.J., Pfeifle R., Rothe T., Ipseiz N. et al., Regulation of autoantibody activity by the IL-23-TH17 axis determines the onset of autoimmune disease, Nat. Immunol. 18 (2017) 104–113.

10. Lee, Y. H., &Bae, S.-C. (2017). Associations between circulating IL-17 levels and rheumatoid arthritis and between IL-17 gene polymorphisms and disease susceptibility: a meta-analysis. Postgraduate Medical Journal, 93(1102), 465–471. doi:10.1136/postgradmedj-2016-134637.

11. Marwa, O. S., Kalthoum, T., Wajih, K., &Kamel, H. (2017). Association of IL17A and IL17F genes with rheumatoid arthritis disease and the impact of genetic polymorphisms on response to treatment. Immunology Letters, 183, 24–36. doi:10.1016/j.imlet.2017.01.013.

12. Hamdy G, Darweesh H, Khattab EA, Fawzy S, Fawzy E, Sheta M (2015) Evidence of association of interleukin-23 receptor gene polymorphisms with Egyptian rheumatoid arthritis patients. Hum Immunol 76:417–420.

13. Song GG, Bae SC, Choi SJ, Ji JD, Lee YH (2012) Associations between interleukin-23 receptor polymorphisms and susceptibility to rheumatoid arthritis: a meta-analysis. MolBiol Rep 39:10655–10663.

14. Zhai Y, Xu K, Huang F, Peng H, Feng CC, Zhu KK et al (2012) Association of interleukin 23 receptor gene polymorphisms (rs10489629, rs7517847) with rheumatoid arthritis in a European population: a meta-analysis. MolBiol Rep 39:8987–8994.

15.Carvalho, C. N., do Carmo, R. F., Duarte, Carvalho, A. A. T., Leão, J. C., &Gueiros, L. A. (2015). IL-17A and IL-17F polymorphisms in rheumatoid arthritis and Sjögren's syndrome. Clinical Oral Investigations, 20(3), 495–502. doi:10.1007/s00784-015-1540-2.

16. Zhang, S., Wang, Y., Zhou, Q., Yin, S., Chen, Y., Liu, C., ... Tang, W. (2016). Interleukin 17A rs2275913 G >A polymorphism is associated with the decreased risk of rheumatoid arthritis: A meta-analysis involving 6,266 subjects. International Journal of Clinical and Experimental Medicine, 9(10), 19222–19230.

17.Shao, M., Xu, S., Yang, H., Xu, W., Deng, J., Chen, Y., ... Pan, F. (2020). Association between IL-17A and IL-17F gene polymorphism and susceptibility in inflammatory arthritis: A meta-analysis. Clinical Immunology, 213, 108374. doi:10.1016/j.clim.2020.108374.

18.Paradowska-Gorycka, A., Malinowski, D., Haladyj, E., Olesinska, M., Safranow, K., &Pawlik, A. (2018). Lack of association between rheumatoid arthritis and genetic variants rs10889677, rs11209026 and rs2201841 of IL-23R gene. Medicina Clinic. doi:10.1016/j.medcli.2017.11.029.

19. Zou Q, Zhao Y, Wang Y, Fang Y, Liu Y (2019) Associations between IL-23R gene polymorphisms and the susceptibility of rheumatoid arthritis: a meta-analysis. Artif Cells NanomedBiotechnol 47:951–956.

20. Burska A. Boissinot M., Ponchel F. Cytokines as Biomarkers in Rheumatoid Arthritis. Med. Inflamm. 2014, R. 545-493.

21. da Silva, I. I. F. G., Angelo, H. D., Rushansky, E., Mariano, M. H., Maia, M. M. D., & de Souza, P. R. E. (2017). Interleukin (IL)-23 receptor, IL-17A and IL-17F gene polymorphisms in Brazilian patients with rheumatoid arthritis. ArchivumImmunologiaeetTherapiaeExperimentalis, 65(6), 537–543.

22. Eshmurzaeva, A. (2021). Study of the relationship between polymorphism of the il23r gene receptor (11209026) and the development of rheumatoid arthritis. InterConf.

23. Eshmurzaeva, A. (2021). Genetic polymorphism rs1805087 mtr and rheumatoid arthritis. InterConf.

24. Karimov, M. S., Eshmurzayeva, A. A., Shukurova, F. N., Sibirkina, M. V., &Gimadutdinova, A. R. (2023). Studying the Association of MTRR (rs1801394) Genetic Polymorphism with the risk of Developing Rheumatoid Arthritis in Uzbekistan. Eurasian Medical Research Periodical, 21, 15-19.