International Journal of Studies in Natural and Medical Sciences
Volume 02 Issue 11, November, 2023
ISSN (E): 2949-8848
Scholarsdigest.org

Association of rs763780 Polymorphism of IL 17F Gene with Risk of Rheumatoid Arthritis in Uzbekistan

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Abstract:
As a result of our studies, we found that the G allele and the heterozygous A/G genotype of the IL 17F gene (rs763780) are significantly higher among patients with rheumatoid arthritis 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 the carrier 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 on the part of the heterozygous genotype A/G, there was a clear tendency to increase its frequency more than twice ($\chi2$=2.011; P=0.165; OR=2.068; 95% CI: 0758-5.645), which in turn indicates the possible participation of the studied polymorphism in pathogenesis of RA.

Keywords: rheumatoid arthritis, rs763780 polymorphism of IL 17F gene, allele carrier, genotype, risk of development.

Introduction

Among the variety of inflammatory diseases of the joints, rheumatoid arthritis (RA) is among the most common nosology, which affects about 1% of the adult population worldwide [5,7]. Along with this, among different populations of the world, large epidemiological studies have established differences in the prevalence of the disease [6,7,14]. Thus, RA is most often found in American Indians (up to 7%), while among other nationalities the incidence of the disease is in the range of 0.2–0.4% [14].

Pathogenetic aspects of RA development remain poorly understood [17]. However, it is known that in the implementation of the pathological process that gives rise to the disease, a connection is observed with respect to a number of factors such as environmental exposure, bad habits, microbial and viral agents, genetic polymorphisms, etc. [2,8,9,16].

Inflammation, being the basis of the development of RA, begins with changes in the articular tissue. The progression of inflammation in the subsequent passes to the bone tissue causing its destruction [3]. Many factors are involved in the regulation of inflammatory processes, among which the leading role is given to polymorphic variants of a number of proinflammatory cytokines (IL17F, etc.) [10,12]. Meanwhile, the results of studies assessing their participation in increasing the risk of developing RA are ambiguous [4,11,15, 10,12,18]. Thus, researchers C. N. Carvalho et al. (2015) did not

reveal an association between the polymorphism of the IL-17F (7488T/C) gene, the development and severity of RA [4]. Similar results with no differences between the IL 17F gene and the development of articular as well as extra-articular forms of the disease were obtained by A. Pawlik et al. (2016) when examining Polish RA patients (n=422) [15]. S. Louahchi et al. ((2016) also found no association of IL 17F (rs763780, rs2397084) with susceptibility to RA among Algerians (n=343) [15]. However, in the research results of Y. H. Lee, S.C. Bae, (2017), O. S. Marwa et al. (2017), M. Shao et al. ((2020) confirm the role of the IL 17F gene in the development of RA [10,12,18]. The differences obtained may be related to the characteristics of the studied populations. Analysis of the results of the conducted studies shows ambiguous conclusions regarding the contribution of the IL-17F gene to the mechanisms of the onset of RA. In this regard, conducting additional studies to assess the relationship of this gene with the development of RA is very interesting, and the data obtained will help to better understand and explain the degree of participation of the IL-17F gene in the formation of this complex disease.

Materials and Methods

The study included 106 adult (combined general group) unrelated patients living in the Republic of Uzbekistan with a diagnosis of RA, verified taking into account the criteria of ACR/EULAR (2010) [1]. All patients in the period from 2018 to 2021 were examined and inpatient treatment in 3 clinics of the Tashkent Medical Academy (Uzbekistan, Tashkent), where, depending on the form of the disease, divided into two subgroups 1A (n=74) – patients with articular RA and 1B (n=32) – patients with articular-visceral form of RA. As a control, conditionally healthy people (n=109) without autoimmune diseases in the anamnesis comparable in gender, age and living in the territory of the republic were examined. In order to comply with ethical standards, informed consent to participate was obtained from all persons included in the study.

To carry out molecular genetic studies, DNA was isolated from venous blood leukocytes using a set of "AmpliPrime RIBOT Prep, Russia" according to the standard methodology [13]. rs763780 polymorphism of IL 17F gene (SYNTOL, Russia) was detected by SNP-PCR (Applied Biosystems, thermocycler 2720 (USA)) with verification of specificity and number of amplified fragments by electrophoretic method in agarose gel.

The data obtained were statistically processed using the software package "OpenEpi 2009, version 9.3".

Results and Discussion

The distribution of genotypes of the polymorphic variant of the IL-17F gene (rs763780) in the study groups did not deviate from the Hardy-Weinberg equilibrium ($P > 0.05$). In particular, genotypes A/A, A/G and G/G in the combined group of RA patients were

equal to 0.79%, 0.2% and 0.01%, and in the control group their values were 0.88%, 0.12% and 0.0%, respectively.

Analysis of the distribution of allele frequencies showed a greater registration of the proportion of carriers of the G allele among RA patients in the general group compared with the control (10.8% vs. 6.0%). The increase in the frequency of this indicator was observed due to an increase in their share in both subgroups of patients, which in the subgroup "1A" of patients with articular RA reached 9.5%, and in the subgroup "1B" of patients with articular-visceral RA - 14.1% (Table 1).

Table 1. Analysis of the distribution of allelic and genotypic frequencies of IL 17F (rs763780) gene polymorphism in the study groups

Group	n	Frequency of alleles				Frequency of genotype distribution					
		A		G		A /A		A/G		G /G	
		n	%	n	%	n	%	n	%	n	%
1st - combined group of RA patients	106	189	89.2	23	10.8	84	79.3	21	19.8	1	0.9
"1A" subgroup	74	134	90.5	14	9.5	60	81.1	14	18.9	0	0.0
"1B" subgroup	32	55	85.9	9	14.1	24	75.0	7	21.9	1	3.1
2nd control group	109	205	94.0	13	6.0	96	88.1	13	11.9	0	0.0

If an increase in the proportion of the G allele of the polymorphic variant of the IL-17F gene (rs763780) in the 1st combined group of patients with RA and in the subgroup "1A" of patients with the articular form of the disease tended to increase the risk of developing RA by almost two times, then ($\chi2$=3.344; P=0.07; OR=1.919; 95%CI:0.954-3.859) and 1.65 times ($\chi2$=1.57; P=0.211; OR=1.65; 95%CI:0.756-3.594), then in the subgroup of patients "1B" with articular-visceral form in RA, the risk of developing the disease was statistically significantly increased by 2.58 times ($\chi2$=4,512; P=0.037; OR=2.58; 95%CI: 1,076-6,188) (Table 2).

The proportion of carriers of the A/A genotype of the polymorphic variant of the IL-17F gene (rs763780) in all groups had some differences: in the combined group of RA patients it was 79.3%, in the subgroups "1A" and "1B" - 81.1% and 75.0%, respectively, and in the subgroups in the control group – 88.1%. Along with this, the frequency of heterozygous genotype A/G had a clear difference in the groups of patients (group of combined RA - 19.8%; subgroup "1A" – 18.9%, "1B" – 21.9%) compared with the control (11.9%).

In addition, it is important to note that the mutant genotype G/G was registered only among patients with articular-visceral form of the disease (subgroup "1B"), the proportion of which was 3.1%.

The decrease in the frequency of wild genotype A/A among patients compared with the control did not differ in statistical significance (in the combined group of patients with RA - $\chi2$=3.073; P=0.084; OR=0.517; 95% CI: 0.247-1.081; in the subgroup "1A" -

χ2=1.713; P=0.193; OR=0.58; 95% CI: 0.257-1.311 and in subgroup "1B" - χ2=3.336; P=0.072; OR=0.406; 95% CI: 0.154-1.068) (Table 2).

Table 2. Evaluation of the relationship between IL 17F gene polymorphism (rs763780) and the risk of rheumatoid arthritis.

Study groups	Alleles and genotypes	The difference is statistically comparable to the control			
		OR	95% CI:	χ^2	P
1st group of RA patients (n=106)	A	3,344	0,072	0,521	0,259 - 1,048
	G	3,344	0,072	1,919	0,954 - 3,859
	A/A	3,073	0,084	0,517	0,247 - 1,081
	A/G	2,509	0,119	1,824	0,867 - 3,837
1A subgroup, articular form of RA (n=74)	A	1,577	0,211	0,607	0,278 - 1,323
	G	1,577	0,211	1,648	0,756 - 3,594
	A/A	1,713	0,193	0,580	0,257 - 1,311
	A/G	1,713	0,193	1,723	0,763 - 3,892
1B subgroup, articular-visceral form PA (n=32)	A	4,512	0,037	0,388	0,162 - 0,929
	G*	**4,512**	**0,037**	**2,580**	**1,076 - 6,186**
	A/A	3,336	0,072	0,406	0,154 - 1,068
	A/G	2,011	0,165	2,068	0,758 - 5,645

Meanwhile, the differences in the proportion of carriers of the heterozygous A/G genotype in the groups of RA patients compared with the control were more significant. So, if in the 1st combined group of RA patients this genotype increased by 1.8 times (χ2=2.509; P=0.119; OR=1.824; 95% CI: 0.867-3.837); then in the subgroup "1A" by 1.72 times (χ2=1.713; P=0.193; OR=1.723; 95% CI: 0.763-3.892) and in the subgroup "1B" more than twice (χ2=2.011; P=0.165; OR=2.068; 95% CI: 0758-5,645). The differences obtained indicate that there is a clear tendency to an increased risk of RA formation in carriers of the A/G genotype. Perhaps, with a larger coverage of the sample under study, the differences could be significantly significant.

Consequently, the differences we found in the frequency of distribution of the G allele and the A/G genotype among patients with RA compared to the control allow us to determine their role in increasing the risk of developing the disease, especially the suture-visceral form.

Conclusion

Rheumatoid arthritis is a very complex autoimmune disease, the genesis of which involves complex, not fully disclosed pathological mechanisms [14]. However, the results of modern studies emphasize the special role of genetic polymorphisms of proinflammatory cytokine genes, which are involved not only in increasing the risk of developing RA, but also in the severity of its course [7]. IL17F is considered as one of

such genes, which can serve as a potential candidate gene leading to the development of RA [10,12]. Meanwhile, with regard to this point of view, the views of researchers differ. So, if C. N. Carvalho et al. (2015), S. Louahchi et al. (2016), A. Pawlik et al. (2016) [4,11,15] in their studies did not find a link between the IL17F gene and the onset of RA, then the results of later works by Y. H. Lee, S.C. Bae, (2017), O. S. Marwa et al. (2017), M. Shao et al. ((2020) indicate the involvement of the IL 17F gene in the mechanisms of RA formation [10,12,18].

Taking into account the existing differences in this regard, it seemed interesting to us to assess the degree of participation of IL17F gene polymorphism (rs763780) in the risk of developing RA among the population of the Republic of Uzbekistan. As a result of our research, we found that the G allele and the heterozygous A/G genotype 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 articular-visceral form of the disease, in whom the G allele significantly exceeded the proportion of carriers in the control by 2.58 times ($\chi2$=4.512; P=0.037; OR=2.58; 95%CI:1.076-6.188), and on the part of the heterozygous A/G genotype, there was a clear tendency to increase its frequency more than twice ($\chi2$=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 for- pain. Moreover, only among patients with this form of RA, the presence of a mutant genotype G/G was detected (3.1%; $\chi2$=2.011; P=0.165; OR=2.068; 95% CI: 0758-5,645).

The obtained data emphasize the role of the polymorphic variant of the IL 17F gene (rs763780) in the development of RA among the population of Uzbekistan. In addition, these results contribute to a deeper understanding of the pathogenetic mechanisms of RA formation, which is very important when predicting the development of RA and finding the most effective methods of treating the disease.

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