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Association of Rs763780 Polymorphism of Gene IL17F with the Risk of Developing Rheumatoid Arthritis in Uzbekistan

By M. Sh. Karimov, A. A. Eshmurzaeva, Kh. M. Marufkhanov & M. V. Sibirkina

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I. Introduction

Among all the variety of inflammatory diseases of joints, rheumatoid arthritis (RA) is amid the most prevalent nosology which affects about 1% of adult population worldwide [5,7]. Along with this, within diverse populations of the world, large epidemiological studies have established differences in the prevalence of the disease [6,7,14]. Hence, on a frequently basis, RA occurs 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]. Pathogenic aspect of RA development remains poorly perceived. However, it is a fact that in the implementation of the pathological process that gives a rise to the disease, a connection is observed in conformity with a number of factors such as the impact of the environment, bad habits, microbial and viral agents, genetic polymorphisms, etc. [2,8,9,16]. Inflammation, being the basis for the development of RA, come to light with transformations in the articular tissue. The progression of inflammation in the subsequent passes to the bone tissue inducing its destruction [3]. The bulk of factors are involved in the regulation of inflammatory processes among which the leading role is played by polymorphic variants of a number of pro-inflammatory cytokines (IL17F, etc.) [10,12]. Meanwhile, the results of studies on the assessment of participation in increasing the risk of developing RA are ambiguous [4,11,15,10,12,18]. Thus, researchers C. N. Carvalho (2015) did not find a correlation between the IL-17F (7488T / C) gene polymorphism and the development and severity of RA [4]. Similar results with no differences between the IL17F gene and the development of articular and extra-articular forms of the disease were obtained by A. Pawlik (2016) when investigating Polish patients with RA (n = 422) [15]. S. Louahchi (2016) also did not find an association of IL17F (rs763780, rs2397084) with susceptibility to RA among Algerians (n = 343) [15]. Nevertheless, the results of studies by Y. H. Lee, S.C. Bae, (2017), O. S. Marwa (2017), M. Shao (2020) confirm the role of the IL17F gene in the development of RA [10,12,18]. The resulting disagreements are possibly related to the traits of the studied populations. Corollary analysis of the studies performed delineates ambiguous conclusions regarding the contribution of the IL-17F gene to the mechanisms of RA onset. In this regard, it is of significant magnitude to conduct supplementary examinations to assess the relationship of this gene with the development of RA. Furthermore, the data obtained will assist to better conceive and explain the degree of participation of the IL-17F gene in the formation of this complex disease.

II. Material and Methods

The study encompassed 106 adults (combined general group) of unrelated patients living in the Republic of Uzbekistan with a diagnosis of RA verified taking into account the ACR / EULAR criteria (2010) [1]. All patients, in the period of 2018 – 2021, were examined and hospitalized at 3 clinics of the Tashkent Medical Academy (Uzbekistan, Tashkent), which, depending on the form of the disease, were stratified into two subgroups 1A (n = 74) - patients with articular RA and

Author α: Doctor of Medical Sciences, Professor and Head of the Department of Internal Medicine Propedeutics, Tashkent Medical Academy, Tashkent, Uzbekistan. e-mail: author.uzb@mail.ru
Author σ: PhD, Assistant at the Department of Internal Medicine Propedeutics, Tashkent Medical Academy, Tashkent, Uzbekistan.
Author ρ: Doctor of Medical Sciences, Docent at the Department of Internal Medicine Propedeutics, Tashkent Medical Academy, Tashkent, Uzbekistan.
Author ω: Candidate of Medical Sciences, Docent at the Department of Internal Medicine Propedeutics, Tashkent Medical Academy, Tashkent, Uzbekistan.

1B (n = 32) - patients with articular-visceral form of RA. When it comes to control, conditionally healthy individuals (n = 109) without a history of autoimmune diseases, comparable in sex, age and living in the territory of the re-public, were examined. In order to comply with ethical standards, informed consent was resulted from all individuals included in the study. For molecular genetic studies, DNA was isolated from venous blood leukocytes using the "AmpliPrime RIBO-prep, Russia" kit according to the standard method [13]. Detection of rs763780 polymorphism of the IL17F gene (SYNTOL, Russia) was carried out by SNP-PCR (Applied Biosystems, thermocycler 2720 (USA)) with verification of the specificity and number of amplified fragments by electrophoretic method in agarose gel. The obtained data were statistically processed using the "OpenEpi 2009, Version 9.3" software package.

III. Results and Discussion

The distribution of genotypes of the polymorphic variant of the IL-17F gene (rs763780) in the studied 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 0.79%, 0.2%, and 0.01% while in the control group their values amounted to 0.88%, 0.12%, and 0.0%, respectively. Analysis of allele distribution frequencies represented a greater registration of the proportion of carriers of the G allele among RA patients in the general group compared to controls (10.8% versus 6.0%). There was ascendance in the frequency of this indicator due to an increase in their share in both subgroups of patients which reached 9.5% in subgroup 1A of patients with articular RA and 14.1% in subgroup 1B of patients with articular-visceral RA (Table 1).

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

Group	n	Allele frequency				Genotype distribution frequency					
		A		G		A /A		A/G		G /G	
		n	%	n	%	n	%	n	%	n	%
First combined group of RA patients	106	189	89.2	23	10.8	84	79.3	21	19.8	1	0.9
Subgroup «1A»	74	134	90.5	14	9.5	60	81.1	14	18.9	0	0.0
Subgroup «1B»	32	55	85.9	9	14.1	24	75.0	7	21.9	1	3.1
Second control group	109	205	94.0	13	6.0	96	88.1	13	11.9	0	0.0

If the escalation in the proportion of allele G carriage of the polymorphic variant of the IL-17F gene (rs763780) in the 1st combined group of patients with RA and in the "1A" subgroup of patients with the articular form of the disease tended to amplify the risk of developing RA by almost twice ($\chi 2 = 3.344$; P = 0.07; OR = 1.919; 95% CI: 0.954-3.859) and 1.65 times ($\chi 2 = 1.57$; P = 0.211; OR = 1.65; 95% CI: 0.756-3.594). Then in the subgroup of patients "1B" with the articular-visceral form of RA, the risk of developing the disease was statistically significantly boosted by 2.58 times ($\chi 2 = 4.512$; P = 0.037; OR = 2.58; 95% CI: 1.076-6.188) (Table 2). Genotype A / A carriage proportion of the polymorphic variant of the IL-17F gene (rs763780) in all groups enabled particular differences: in the combined group of RA patients it was 79.3%, in subgroups "1A" and "1B" - 81.1% and 75.0%, respectively, and in the control group - 88.1%. Along with this, the frequency of the heterozygous genotype A / G had a clear discrepancy in the groups of patients (combined group RA - 19.8%; "1A" subgroup - 18.9%, "1B" - 21.9%) compared with the control (11.9%). In addition, it is important to note that the mutant G / G genotype was recorded only among patients with the articular-visceral form of the disease (subgroup 1B), the proportion of which was 3.1%. The decrease in the frequency of the wild A / A genotype among patients in contrast to the control did not differ statistically (in the combined group of RA patients - $\chi 2 = 3.073$; P = 0.084; OR = 0.517; 95% CI: 0.247-1.081; in the "1A" subgroup - $\chi 2 = 1.713$; P = 0.193; OR = 0.58; 95% CI: 0.257-1.311 and in subgroup "1B" - $\chi 2 = 3.336$; P = 0.072; OR = 0.406; 95% CI: 0.154-1.068) (Table 2).

Table 2: Assessment of the relationship between IL17F gene polymorphism (rs763780) and the risk of developing rheumatoid arthritis

Groups under scrutiny	Alleles and genotypes	Statistical difference compared to control			
		OR	95% CI:	χ^2	P
Group 1 RA (n=106) patients	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
Subgroup 1A, RA (n=74) articular form	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
Subgroup 1B, articular-visceral form of RA (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 the heterozygous genotype A / G carriage in the groups of RA patients compared with the controls turned out to be more paramount. So, if in the 1st combined group of RA patients this genotype boosted 1.8 times ($\chi 2$ = 2.509; P = 0.119; OR = 1.824; 95% CI: 0.867-3.837); then in "1A" subgroup 1.72 times ($\chi 2$ = 1.713; P = 0.193; OR = 1.723; 95% CI: 0.763-3.892) and in subgroup "1B" more than twice ($\chi 2$ = 2.011; P = 0.165; OR = 2.068; 95% CI: 0758-5.645). The obtained differences indicate the presence of a clear tendency towards an increased risk of RA formation in carriers of the A / G genotype. Perhaps, with a larger coverage of the sample under study, disparities could be reliably significant. Consequently, differences that we established in the frequency of distribution of the G allele and the A / G genotype among RA patients compared to controls allow us to determine their role in proliferating the risk of developing the disease, especially the articular-visceral form.

IV. Conclusion

Rheumatoid arthritis is induced by a complex autoimmune disease, the origin of which is complicated by the lack of pathological mechanisms [14]. However, the results of modern studies emphasize the special role of genetic polymorphisms of genes of proinflammatory cytokines 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 these genes, which can serve as a potential candidate gene leading to the development of RA [10, 12]. Meanwhile, in relation to this point of view, the views of researchers differ. So, if C. N. Carvalho (2015), S. Louahchi (2016), A. Pawlik (2016) [4, 11, 15] did not find an association between the IL17F gene and the onset of RA in their studies, the results of later works by Y. H. Lee, S.C. Bae, (2017), O. S. Marwa (2017), M. Shao (2020) indicate the participation of the IL17F gene in the mechanisms of RA formation [10, 12, 18]. Taking into account the existing disagreements in this regard, we found it interesting to assess the participation degree of the IL17F (rs763780) gene polymorphism in the risk of developing RA among the population of the Republic of Uzbekistan. As a result of our studies, we have encountered in that the G allele and the heterozygous A / G genotype of the IL17F gene (rs763780) among patients with RA are significantly higher than in the control group. In particular, the most significant differences were found in patients with articular-visceral form of the disease in which the G allele exceeded the proportion of carriage in the control statistically significantly 2.58 times ($\chi 2$ = 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 by more than twice ($\chi 2$ = 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 the carriage of the mutant genotype G / G (3.1%; $\chi 2$ = 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 IL17F 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 overly consequential in predicting the development of RA and searching for the most effective methods of treating the disease.

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