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Association Between Il17a G197a Polymorphism and Rosacea in the Uzbek Population

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Abstract Rosacea is a chronic, progressive, inflammatory disease manifested by recurrent course, erythema, telangiectasia, papules or pustules on the central part of the face. Currently, the etiology and pathogenesis of rosacea are not fully understood, and treatment requires improvements. Currently, there is a growing interest in the entire interleukin family - in the pathophysiology of many human diseases, including skin diseases. Several studies have been devoted to the study of IL-17 in rosacea patients, but the results of these studies are contradictory to each other. With this in mind, this article will focus on the key role of interleukin 17 (IL-17) in the development and progression of the disease based on our own research conducted.

Keywords: *rosacea, IL17A gene polymorphism, clinical stages of rosacea, IL17A genotypes, Uzbek population*

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1. Introduction

Rosacea is a chronic, progressive, inflammatory disease manifested by recurrent courses, erythema, telangiectasias, papules or pustules on the central face. [1]. At present, the etiology and pathogenesis of rosacea are not fully understood, and treatment requires refinements.

In recent years, numerous studies have been conducted on the role of pro- and anti-inflammatory cytokines (TNF-α, IL-1β, IL-4, IL -6, IL-8, IL-10, IL-18, etc.), growth factors (VEGF, FGF) in the mechanism of rosacea development. However, the results are mixed and contradictory [2]. For example, Slesarenko N.A. et. al. found high levels of IL-6, IL-8, IL-10, IL-17 and IL-18 in the serum of rosacea patients [3], whereas, Salamon et. al. (2008) found a significant decrease in serum IL-6 and IL-17 levels in 60 rosacea patients compared to controls [4].

Some studies suggest a link between rosacea and the gene encoding interleukin-17 (IL-17), a cytokine involved in inflammation. Researchers are studying genetic variations in the gene encoding IL-17 to determine if they affect susceptibility to rosacea [5].

To date, several single nucleotide polymorphisms of the IL17A gene have been identified, but the most pathogenetically significant and studied are polymorphisms G197A(rs2275913) of the IL17A gene, localized on chromosome 6p.12.2. The G197A polymorphism affects the expression level of IL17A produced by CD4+ Th cells, which has both pro-inflammatory and protective activity. Functionally unfavorable A/A genotype is associated with impaired gene expression and high activity of proinflammatory cytokine IL17A [6].

2. Study Objective

Polymorphism G197A, which affects the level of expression of proinflammatory cytokine IL17A, has a pronounced ethnic specificity, but in information databases data on association with inflammatory skin diseases, including rosacea, are few, and in Uzbekistan are practically not presented, which determined the purpose of this study.

3. Materials and Methods of Research

Molecular genetic study of biomaterials from rosacea patients and conditionally healthy donors was carried out on the basis of Research Institute of Hematology and Blood Transfusion in the Department of Molecular Medicine and Cell Technologies (Head - Prof. Karimov H.Y.). To study genetic markers of interleukin IL-17 genes was carried out on 102 DNA samples isolated from peripheral blood lymphocytes of patients with rosacea and 95 unrelated conditionally healthy donors of Uzbek nationality (control sample). A set of equipment for PCR-diagnostics was used in the work.

4. Results of the Study

We carried out a comparative analysis of observed

(empirical) and expected frequencies of genotypes at locus G197A of IL17A gene in groups of patients with rosacea and controls. Tables 1.1, 1.2 and 1.3 show the results of testing the presented G197A polymorphism of IL17A gene for compliance with Hardy-Weinberg equilibrium. According to the data obtained in both groups the distribution of genotype prevalence (empirical) of polymorphic locus G-197A of IL-17A gene in the group of patients with rosacea and control sample did not reveal the shift of equilibrium, i.e., the distribution of genotypes corresponded to the Hardy-Weinberg equilibrium. The frequencies of wild G and minor A alleles were 0.6 and 0.4 in the patient group and 0.72 and 0.28 in the control group.

In the total group of rosacea patients, the empirically-observed and theoretically-expected frequencies of G/G, G/A and A/A genotypes were: 0.37/0.36, 0.45/0.48 and 0.18/0.16, respectively, in the control sample: 0.54/0.52, 0.37/0.4 and 0.09/0.08, respectively. In both groups, this marker was characterised by a high level of polymorphism, where the heterozygosity level was 0.48 and 0.4, respectively. The difference between the expected and observed frequencies of G197A genotypes of IL17A gene in the studied groups of patients and controls was statistically insignificant.

At the same time, the expected number of ancestral and minor G/G and A/A homozygotes in both studied groups were slightly higher than the observed one at 0.36/0.37 and 0.18/0.16, respectively. When comparing allele frequencies by Fisher's exact test, the differences were not statistically reliable ($p>0.05$), and the level of empirical heterozygosity was less than expected (D=-0.06 and D=-0.08, respectively).

Thus, the distribution of actual and theoretical frequencies of the G197A locus of the IL17A gene both in the population and in the studied samples of patients are in equilibrium with the Hardy-Weinberg law, which indicates the representativeness of our results. These data allow us to analyses the associative relationship of this polymorphism with the formation and development of rosacea.

The next stage of our research was to study the association of polymorphic marker G197A of IL17A gene with clinical stages of rosacea. When comparing the genotype frequency distribution of the G197A locus of the IL17A gene, a significant difference between the main group with rosacea and conditionally healthy individuals was found ($p<0.05$) (Table 2).

In patients with rosacea, the unfavorable allele A was significantly detected 1.7 times more often with a frequency of 40.2% compared to the control group - 27.9% ($\chi2=6.6$; $p=0.03$), and the favorable allele G was significantly prevalent among healthy individuals with a frequency of 72.1%, which was 1.7 times significantly more often than in the patient group - 59.8% ($\chi2=6.6$; $p=0.03$).

Based on the data obtained on the distribution of allele and genotype frequencies of polymorphism G197A of IL17A gene, the risk of rosacea development increases in individuals carrying minor allele A (OR=1.7 with 95%CI:1.14 - 2.65). In contrast, the presence of the G allele in the genome is associated with a reduced risk of rosacea (OR=0.6 with 95%CI: 0.38 - 0.88).

Carrying the ancestral G/G genotype was characteristic of 38 (37.3%) patients in the main group and 51 (53.7%) of the control sample. Calculation of the relative risk showed that the probability of rosacea formation in individuals with the G/G genotype variant of G197A polymorphism is statistically significantly lower than in case of other genotypes of this polymorphism of IL17 gene ($\chi2=5.4$; $p=0.03$; OR=0.5; 95%CI:0.29 - 0.9), which suggests that this genotype is associated with a protective effect on rosacea development.

Carriers of unfavorable heterozygous G/A genotype in the studied group were 46 (45.1%) patients with rosacea and 35 (36.8%) in the examined population sample. Functionally unfavorable A/A genotype was characteristic of 18 (17.6%) patients in the main group and 9 (9.5%) individuals in the control group. According to the odds ratio, the risk of rosacea development in carriers of G/A and A/A genotypic variants of G197A polymorphism G197A of IL17A gene increases 1.4 ($\chi2=1.4$; $p=0.3$; OR=1.4; 95%CI: 0.8 - 2.49) and 2 ($\chi2=2.8$; $p=0.1$; OR=2.0; 95%CI:0.88-4.76) times, respectively (Table 3).

Table 1.1. Expected and observed frequencies of genotype distribution of the locus genotype by RXB of the G197A polymorphism in the IL17A gene in a group of patients with rosacea

Main group					
Alleles	Allele frequency				
G	0,6				
A	0,4				
Genotypes	Genotype frequency		$\chi2$	p	df
	observed	expected			
G/G	0,37	0,36	0,06		
G/A	0,45	0,48	0,19		
A/A	0,18	0,16	0,14		
Total	1	1	0,39	0,5>	1

Table 1.2. Expected and observed genotype distribution frequencies of the locus genotypes for the RXB polymorphism G197A of the IL17A gene in the control sample

Main group					
Alleles	Allele frequency				
G	0,72				
A	0,28				
Genotypes	Genotype frequency		$\chi2$	p	df
	observed	expected			
G/G	0,54	0,52	0,05		
G/A	0,37	0,4	0,27		
A/A	0,09	0,08	0,35		
Total	1	1	0,67	0,4	1

Table 1.3. Heterozygosity level of G197A polymorphism of IL17A gene in groups of patients and controls

Groups	Ho	He	D*
Main group	0,45	0,48	-0,06
Control group	0,37	0,4	-0,08

Note: D = (Ho - He)/He

Table 2. Frequency of distribution of alleles and genotypes of polymorphism G197A of IL17A gene G197A in groups of patients and controls

N	Group	Allele frequency				Genotype distribution frequency					
		G		A		G/G		G/A		A/A	
		n	%	n	%	n	%	n	%	n	%
1	Main group n=102	122	59,8	82	40,2	38	37,2	46	45,1	18	17,6
2	Stage 1 n=26	32	61,5	20	38,5	10	38,5	12	46,1	4	15,4
3	Stage 2 n=56	70	62,5	42	37,5	23	41,1	24	42,9	9	16,1
4	Stage 3 n=20	20	50,0	20	50,0	5	25.0	10	50,0	5	25,0
5	Control group n=95	137	72,1	53	27,9	51	53,7	35	36,8	9	9,5

Table 3. Comparative statistical differences of G197A polymorphism of IL17A gene in the main group of rosacea patients and control sample

Alleles and genotypes	Number of alleles and genotypes				χ2	p	OR	95%CI
	Main group		Control group					
	n	%	n	%				
G	122	59,8	137	72,1	6,6	0,03	0,6	0,38 - 0,88
A	82	40,2	53	27,9	6,6	0,03	1,7	1,14 - 2,65
G/G	38	37,3	51	53,7	5,4	0,03	0,5	0,29 - 0,9
G/A	46	45,1	35	36,8	1,4	0,3	1,4	0,8 - 2,49
A/A	18	17,6	9	9,5	2,8	0,1	2,0	0,88 - 4,76

Given the high risk of rosacea development when carrying the unfavorable allelic variant of the G197A polymorphism of the IL17A gene, we analysed the effect of this locus on the course of the pathology determined by the severity of the disease. The data are presented in Tables 4.6, 4.7 and 4.8.

According to the results of genotyping, there was a tendency to increase the frequency of unfavourable allelic variant A among patients with stage 1 (erythematous-teleangiectatic) (38.5%) and stage 2 (papular-pustular) (37.5%) rosacea compared to the control group (27.9%). The risk of developing stages 1 and 2 of rosacea when carrying this allele is increased more than 1.6-fold ($\chi2$=2.2; p=0.2; OR=1.6; 95%CI:0.85 to 3.06 and $\chi2$=3.0; p=0.1; OR=1.6; 95%CI:0.95 to 2.55, respectively).

The proportion of carriers of the favourable G allele was non-significantly (trend) higher among conventionally healthy donors (72.1%) compared to these subgroups (61.5% and 62.5%, respectively) (Table 2). However, these differences only reached the reported level of statistical trend ($\chi2$=2.2; p=0.2; OR=0.6; 95%CI: 0.33 - 1.17; $\chi2$=3.0; p=0.1; OR=0.6; 95%CI: 0.39 - 1.06) due to the small number of these patient subgroups.

When analysing the genotype frequency distribution of this polymorphism in patients with erythematous-teleangiectatic and papulo-pustular stages of rosacea, there was also an insignificant increase in the proportion of carriers of unfavourable G/A and A/A genotypes (46.2% and 15.4%) and (42.9% and 16.1%) compared to the control group (36.8% and 9.5%), respectively. Moreover, the odds ratio of detection of G/A and A/A genotypes in these subgroups was OR=1.3 and 1.5 (stage 1) and OR=1.3 and 1.5 (stage 2).

It should be noted that when analyzing the genotype distribution for the G197A polymorphism, there is a tendency to decrease the frequency of the wild genotype G/G in the subgroups of stage 1 and 2 patients with rosacea (38.5% and 41.1%, respectively) compared to the control group (53.7%). This may confirm the genetic protective effect of carriers of this genotype to the development of rosacea, i.e., in this case our results confirm the previously established association of the wild genotype with the protective effect in relation to the development of this pathology (Table 4 and Table 5).

Table 4. Comparative statistical differences of G197A polymorphism of IL17A gene in a subgroup of patients with rosacea (stage 1) and controls

Alleles and genotypes	Number of alleles and genotypes				χ2	p	OR	95% CI
	1 stage		Control group					
	n	%	n	%				
G	32	61,5	137	72,1	2,2	0,2	0,6	0,33 - 1,17
A	20	38,5	53	27,9	2,2	0,2	1,6	0,85 - 3,06
G/G	10	38,5	51	53,7	1,9	0,2	0,5	0,22 - 1,3
G/A	12	46,2	35	36,8	0,7	0,4	1,5	0,61 - 3,52
A/A	4	15,4	9	9,5	0,7	0,4	1,7	0,5 - 6,1

Table 5. Comparative statistical differences of G197A polymorphism of IL17A gene in a subgroup of patients with rosacea (stage 2) and controls

Alleles and genotypes	Number of alleles and genotypes				χ2	p	OR	95%CI
	2 stage		Control group					
	n	%	n	%				
G	70	62,5	137	72,1	3,0	0,1	0,6	0,39 - 1,06
A	42	37,5	53	27,9	3,0	0,1	1,6	0,95 - 2,55
G/G	23	41,1	51	53,7	2,2	0,2	0,6	0,31 - 1,17
G/A	24	42,9	35	36,8	0,5	0,5	1,3	0,66 - 2,52
A/A	9	16,1	9	9,5	1,5	0,3	1,8	0,69 - 4,87

A significant difference was revealed when comparing the frequencies of genotypes and alleles of polymorphism G197A of IL17A gene among the patients with stage 3 rosacea (pustular nodular) and in the control group. The results of comparative analysis of genotype and allele

frequency distribution of this polymorphism are presented in Table 6. In this subgroup of patients with rosacea, the common G/G genotype was statistically significantly less frequent than in the control group (25.0% vs 53.7%, respectively; $\chi2$=5.4; p=0.03; OR=0.3; 95%CI:0.1 - 0.82). In contrast, the heterozygous G/A genotype was predominant in patients (50.0%) compared to controls (36.8%). When calculating the odds ratio (OR), it was found that this marker at the trend level may be involved in the pathogenesis of rosacea development (OR=1.7; 95%CI: 0.65 - 4.5).

Table 6. Comparative statistical differences of G197A polymorphism of IL17A gene in a subgroup of patients with rosacea (stage 3) and controls

Alleles and genotypes	Number of alleles and genotypes				$\chi2$	p	OR	95% CI
	3 stage		Control group					
	n	%	n	%				
G	20	50,0	137	72,1	7,5	0,01	0,4	0,2 - 0,77
A	20	50,0	53	27,9	7,5	0,01	2,6	1,31 - 5,11
G/G	5	25,0	51	53,7	5,4	0,03	0,3	0,1 - 0,82
G/A	10	50,0	35	36,8	1,2	0,3	1,7	0,65 - 4,5
A/A	5	25,0	9	9,5	3,7	0,1	3,2	0,98 - 10,33

Differences were also found in the frequency distribution of the unfavourable homozygous genotype A/A in the subgroup of stage 3 rosacea patients and controls. The frequency of this genotype among patients and controls was 25.0% and 9.5%, respectively, with OR=3.2 ($\chi2$=3.7; p=0.1), which suggests that this genotype is also associated with the risk of rosacea development.

When calculating the odds ratio, convincing data were obtained indicating that carriage of an unfavourable allele of this locus is associated with a high probability of realization of pathological skin events of chronic inflammatory nature. Thus, in the investigated subgroup when carrying an unfavourable allele the probability of rosacea development was 2.6 times higher than in the comparison group (50.0% vs. 27.9%, respectively; $\chi2$=7.5; p=0.01; OR=2.6; 95%CI: 1.31 - 5.11). At the same time, a significant high frequency of the G allele in the control group compared to the subgroup of patients was found, indicating the presence of a protective effect of this allelic variant on rosacea manifestation (72.1% vs. 50.0%, respectively; $\chi2$=7.5; p=0.01; OR=0.4; 95%CI:0.2 - 0.77).

5. Conclusion

Thus, statistically significant differences in the distribution of alleles and genotypes in groups of rosacea patients and individuals without this pathology indicate a reliable association of polymorphic marker G197A of the IL17A gene with the pathogenesis of the clinical picture of this pathology. Carriage of allele A and related genotypes is a risk factor of rosacea development (OR>1), and carriage of ancestral G allele and genotype G/G is associated with a reduced risk of this pathology development (OR<1).

A direct correlation between carriage of unfavourable genotypes of the proinflammatory cytokine IL17A gene (G197A) and rosacea progression was observed, which confirms the importance of autoimmune inflammation (process) in the development and clinical course of such a multicomponent disease as rosacea. The results obtained reveal some aspects of rosacea genetics and indicate the advisability of further study of other functional autoimmune inflammation genes (IL17F and IL23R) involved in the pathogenesis of acneiform dermatoses.

Accumulation of scientific knowledge about genetic bases of inflammatory dermatoses, study of contributions of system genes and their combinations in susceptibility to these pathologies, will provide invaluable help in the development of new effective methods of therapy, in the creation of a comprehensive programme for individual primary prevention of rosacea, taking into account the genetic characteristics, predicting the development of this pathology in the offspring of patients.

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