ANALYSIS OF THE ROLE OF POLYMORPHISM 1997C/A OF THE COL1A1 GENE IN THE FORMATION OF ATROPHIC POST-ACNE SCARS IN THE UZBEK POPULATION

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Abstract. *The study of the genetic and biochemical basis of the problem of the formation of post-acne scar changes, as well as the establishment of significant molecular genetic and biochemical markers is almost at the very initial stage of development[7,8,9,10,11,12,13]. Recently, the literature very often states the presence of a pathogenetic connection between unfavorable genotypes with the formation of an atrophic form of post-acne[1], which became the goal of our study.*

Of these, works devoted to assessing the significance of the 1997C/A polymorphism of the COL1A1 gene (including indirectly) in the formation of post-acne scar changes are limited to single studies[1,14,15,16] In addition to these, there are works devoted to the role of epigenetic factors in disruption of COL1A1 collagen synthesis and the development of scars post-acne[17,18,19]. At the same time, our results are consistent with the data of the above researchers.

Keywords*: genotypes, acnescars, hypertrophic, atrophic, keloid, post-acne scars.*

Purpose of the study: to study the pathogenetic relationship between clinical forms of post-acne and unfavorable genotypic variantspolymorphism 1997C/A of the COL1/A1 gene.

Materials and research methods. Molecular genetic studies of the frequency distribution of genotypes of the 1997C/A polymorphism of the COL1/A1 gene were carried out in 107 patients with post-acne (of which: 55 men, 52 women). The control group consisted of 103 conditionally healthy persons of Uzbek nationality, corresponding by gender and age, without any dermatological diseases, including post-acne.

An analysis of associations in the studied areas was carried out using a comparison of two samples according to the “case-control” type. Patients, depending on the clinical course of the disease, were divided into 2 subgroups (with acne and post-acne scars) and 3 subgroups: atrophic, hypertrophic and keloid form.

Results.

In both groups, the empirical distribution of genotypes of the 1997C/A polymorphism of the COL1/A1 gene corresponded to the theoretical ones expected at Hardy-Weinberg equilibrium (PHB, $p>0.05$, according to Fisher’s exact test).

Comparative analysis of the distribution of allele frequencies of genotypes of a polymorphic locus 1997C/A of the COL1/A1 gene showed a significant difference in the studied groups of acnescars and conditionally healthy individuals.

In patients with acnescars, compared with healthy individuals, there was a significant increase in the frequency of the A allele (23.8% versus 9.7%, respectively), and a decrease in the

frequency of the wild C allele (76.2% versus 90.3%, respectively). According to the odds ratio, when carrying the 1997A allele, the risk of developing acnescars significantly increases by more than 2.9 times (OR=2.9; 95%Cl:1.69 – 5.72). At the same time, the variant allele 1997Cshowed an association with a reduced risk of developing this pathology (90.3% in the control group; 76.2% in the patient group; χ2=14.9; p=0.01; OR=0.3; 95%Cl:0.2 - 0.59).

Variant frequencies of genotypes C/C, C/A and A/A of the geneCOL1A1in the groups with acnescars was 60.7%, 30.8% and 8.4%, respectively, and in the control group – 82.5%, 15.5% and 1.9%, respectively.

It has been established that deficiency, i.e., carriage of a genotypic variant A/A of the COL1/A1 gene was most associated with a 4.6-fold increase in the risk of developing scarring in patients with acne (χ2=4.4; p=0.05; OR=4.6; 95%Cl: 1.11 - 19.37). Carriage of the heterozygous genotype C/A also increased the risk of disruption of the connective tissue fiber structure in patients with acne and the development of acnescars by more than 2 times (χ2=6.9; p=0.01; OR=2.4; 95%Cl: 1.25 - 4.7).

Table 1. Differences in the frequency of allelic and genotypic variants of the 1997C/A polymorphism in the COL1/A1 gene in patient groups

Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	OR	95%CI
	Main group		Control group					
	n	%	n	%				
WITH	163	76.2	186	90.3	14.9	0.01	0.3	0.2 - 0.59
A	51	23.8	20	9.7	14.9	0.01	2.9	1.69 – 5.7
S/S	65	60.7	85	82.5	12.2	0.01	0.3	0.18 - 0.61
C/A	33	30.8	16	15.5	6.9	0.01	2.4	1.25 - 4.7
A/A	9	8.4	2	1.9	4.4	0.05	4.6	1.11 - 19.37

The following presents the results of the analysis of genotypic startificationpolymorphism 1997A of the COL1/A1 gene with the risk of acnescars in subgroups with different clinical forms of pathology.

No statistically significant difference was found in the distribution of allele frequencies and genotypes of the 1997C/A polymorphism of the COL1/A1 gene in the subgroup of patients with the hypertrophic form and the control group. The frequency distribution of alleles C and A in this subgroup of patients was 85.7% and 14.3%, respectively, and in the control group – 90.3% and 9.7%, respectively. The calculated relative chance of detecting an unfavorable allele A among patients with hypertrophic form of post-acne compared to the control group was OR=1.6 with confidence interval95%CI:0.65 - 3.71 (χ2=1.0 and p=0.4). Based on these data, we can conclude that this locus is not associated with the risk of hypertrophic form of post-acne (Table 1).

The frequency of occurrence of genotypic variants C/C, C/A and A/A in the subgroup of patients was 78.6%, 14.3% and 7.1%, respectively, while in the control group, respectively, 82.5%, 15.5% and 1.9% (Table 2). Although carriage of the homozygous A/A genotype was associated with an almost 4-fold increase in the risk of the hypertrophic form of post-acne compared to conditionally healthy individuals, the differences did not reach the stated level of statistical significance (7.1% versus 1.9%, respectively; χ2=2.0; p=0.2; OR=3.9; 95%Cl:0.6 - 25.34).

The following presents the results of an analysis of the association of allelic and genotypic variants of the 1997C/A polymorphism of the COL1A1 gene with clinical variants of acnescars. The genotyping results are presented in Table 3.

Table 2. Differences in the frequency of allelic and genotypic variants of the 1997C/A polymorphism of the COL1/A1 gene in the subgroup of patients with the hypertrophic form of acne scars and controls

Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	OR	95%CI
	Hypertrophic form		Control group					
	n	%	n	%				
WITH	48	85.7	186	90.3	1.0	0.4	0.6	0.27 - 1.55
A	8	14.3	20	9.7	1.0	0.4	1.6	0.65 - 3.71
S/S	22	78.6	85	82.5	0.2	0.7	0.8	0.28 - 2.18
C/A	4	14.3	16	15.5	0.0	0.9	0.9	0.28 - 2.96
A/A	2	7.1	2	1.9	2.0	0.2	3.9	0.6 - 25.34

In the subgroup of patients with the atrophic form of acne scars, the carriage frequency of the C/C, C/A and A/A genotypes was 53.3%, 37.3% and 9.3%, respectively (Table 3). In the control group, the frequency of genotype distribution was, respectively: 82.5%, 15.5% and 1.9%. The frequency of alleles C and A in the subgroup of patients and the control sample was 72.0% and 28.0% versus 90.3% and 9.7%, respectively.

Table 3. Differences in the frequency of allelic and genotypic variants of the 1997C/A polymorphism of the COL1A1 gene in the subgroup of patients with atrophic forms of acnescars and controls

Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	OR	95%CI
	Atrophic form		Control group					
	n	%	n	%				
WITH	108	72.0	186	90.3	20.2	0.01	0.3	0.16 - 0.48
A	42	28.0	20	9.7	20.2	0.01	3.6	2.06 - 6.34
S/S	40	53.3	85	82.5	17.7	0.01	0.2	0.12 - 0.47
C/A	28	37.3	16	15.5	11.1	0.01	3.2	1.62 - 6.47
A/A	7	9.3	2	1.9	4.9	0.05	5.2	1.21 - 22.24

In this subgroup of patients, a statistically significant predominance in the number of carriers of unfavorable genotypes C/A and A/A and a decrease in the number of carriers of the wild genotype C/C was found compared to the control group. According to the odds ratio, carriage of these genotypic variants of the 1997C/A polymorphism of the COL1/A1 gene can significantly increase the risk of this form of the disease by 3.2 (χ2=11.1; p=0.01; OR=3.2; 95%Cl: 1.62 - 6.47) and 5.2 (χ2=4.9; p=0.05; OR=5.3; 95%Cl: 1.21 - 22.24) times.

The prevalence of unfavorable genotypes of the 1997C/A locus of the COL1A1 gene in the group of acne scars patients confirms that carriage of these genotypes is more susceptible to scar formation compared to carriage of the phenotypically favorable genotype C/C. The increase

in the frequency of carriage of unfavorable genotypes C/A and A/A in the group of patients may be explained by the more significant role of these genotypic variants in disrupting the expression of the COL1A1 protein, the possible consequences of which may be the formation of an atrophic post-acne scar.

The discussion of the results. Thus, the data obtained indicate the involvement of the 1997C/A polymorphism of the COL1A1 gene in the formation of predisposition to post-acne. The genetic predictor of the development of acnescars is allelic variant A. Carriages of unfavorable genotypic variants of the 1997C/A polymorphism of the COL1/A1 gene, leading to functional defects of the connective tissue, can provoke the development of scar changes associated with acne. It is noteworthy that the development of an exclusively atrophic form of post-acne was associated mainly with functionally unfavorable genotypes of the 1997C/A locus of the COL1/A1 gene, while other forms more often developed independently of "functionally unfavorable" allelic variants of the collagen gene. This may be due to the fact that mutant variants of the COL1A1 gene lead to a change in the ratio of alpha-1 and alpha-2 chains and to disruption of the collagen structure, which does not allow the organization of fibers. It has been established that unfavorable genotypic variants of this gene lead to an increase in the level of expression of the COL1A1 gene and an increase in the synthesis of the α1 chain, which leads to disorganization, i.e., atrophy of the connective tissue[2,3].

Conclusions. Summarizing the results obtained, we can conclude that the work we carried out is undoubtedly of great scientific and practical interest in terms of studying the genetic basis of development and searching for prognostic markers for the development of this post-acne condition. A significant associative relationship was found between the 1997C/A polymorphism of the COL1/A1 gene with the formation of acne scars. Perhaps in the coming years, such work will be continued and will give impetus to the development of new effective methods of prediction and individual means of treating and preventing this disease.

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