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Results of Frequency Analysis Distribution of A1188c Rs3212227 Polymorphism in the IL12b Gene among Patients with Chronic Polypoid Rhinosinusitis

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Abstract: ***Our data confirm the complexity of the genetic mechanism for the development of polyposis processes in patients with CPRS and indicate the necessity and importance of understanding complex gene interactions in the analysis of the development and clinical stage of the studied pathology. Material and methods. In accordance with the purpose of the study and to fulfill the assigned tasks, clinical studies were carried out in 140 patients with CPRS and with chronic rhinosinusitis, who were examined and treated at the ENT department of the multidisciplinary clinic of the Tashkent Medical Academy in 2017-2019. To study the diallelic polymorphism of the promoter regions of the genes of the studied interleukins, 50 healthy (no CPRS) donors, men and women, were examined. The average age of the examined donors was 51.3 ± 1.44 years. Conclusion. Analyzing the prevalence of genotypic variants of this polymorphism, we revealed a direct association of the C / C monogenotype of the A1188C rs3212227 polymorphism in the IL12B gene with the development of polyposis processes. The study of the distribution of genotypes showed that the homozygous genotype A / A was insignificant, almost 1.2 times more often found in group 1 (80.64%), while the frequency of detection of the heterozygous genotype A / C was insignificantly 1.1 times higher among patients with HRC 2 groups. The opposite situation could be observed in the study of the homozygous C / C genotype, which was not identified among all study groups.***

Keywords: Polymorphism, Gene, Genotypes, Polyposis Processes, Allele.

I. INTRODUCTION

Diseases of the paranasal sinuses are among the most common pathologies in otorhinolaryngology, which is facilitated by the modern environmental situation, the widespread prevalence of allergic and viral respiratory diseases, and a decrease in local and general immunity.

All researchers agree that in recent years in the world there has been a tendency to an increase in the incidence of chronic sinusitis, including chronic polypous rhinosinusitis (CPRS) [1, 2, 3].

Epidemiological studies of CPRS in Russia, which were carried out with an interval of 5 years, indicate that in selected time intervals in each specific region, the prevalence of the disease does not change significantly. For a number of reasons (environmental conditions, social and drug load, changes in the functional indicators of the most important homeostatic systems of the human body, etc.), one cannot expect a decrease in the incidence of CPRS. The stability of CPRS incidence rates, regardless of regional characteristics or other external factors, is considered by leading otolaryngologists to be the basis for a more detailed study of the causes of this nosology [4], primarily the genetic predisposition to CPRS development. Many facts speak in favor of the genetic hypothesis of CPRS development. It has been proven that the risk of CPRS in the presence of polyposis heredity is 25 times higher, with a heterozygous carrier of the MZ phenotype (deficiency of alpha-1 antitrypsinase) - 4 times, with dry earwax - 3 times [5]; revealed changes in the karyotypes of peripheral blood cells in patients with CPRS [6]. Since chromosomal polymorphism can determine individual sensitivity to the occurrence of any disease, i.e. individual response of the organism to a damaging factor, persons with karyotype variants that differ from the norm are at risk of developing certain diseases that depend on hypo-, hyper, or norm-sensitivity of the hereditary apparatus [7,8,9,10].

Numerous studies of the last decade have demonstrated the dependence of the immune response on allelic polymorphism of cytokine genes. The result of such works in vitro is the identification of individual alleles of genes associated with increased or decreased production of the corresponding cytokine [11]. The data obtained to date suggest that polymorphic cytokine genes are capable of taking an active part in the formation of a specific immune response to pathological conditions in humans. Individual allelic variants can be associated with the level of production of the corresponding protein, which also affects the course of the disease and the development of a number of complications. However, it remains unclear which mutations and which cytokines are of decisive importance in the development of certain diseases.

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Therefore, a promising area of molecular genetic research is the study of the contribution of specific alleles to the propensity to infection in the development of pathology [12,13,14,15,16].

The modern stage in the development of cytology, histology and clinical anatomy, as well as progress in diagnostic technologies have led to the concept of the nasal cavity as a complex morphofunctional system [17]. The modern knowledge obtained in the process of scientific research about anatomy, histology and physiology, as well as the morphogenesis of various pathological processes in the nasal cavity and paranasal sinuses, has significantly expanded the idea of the functional significance of these structures in the adaptive capabilities of the nasal cavity to breathing conditions, their role in the respiratory system as a whole [18,19].

Modern histological and clinical-functional studies made it possible to state the growth of chronic diseases of the mucous membrane of the nasal cavity and paranasal sinuses, the formation of various endonasal formations [20]. This is due to the deterioration of the ecological and social situation, an increase in the virulence of the microbial flora, a change in its composition and resistance to antibacterial drugs. In the pathogenesis of diseases of the ENT organs, in addition to the infectious agent, the leading role belongs to the immune system of the mucous membranes of the nose and pharynx, as well as the general reactions of humoral and cellular immunity [21].

The body's resistance to exo- and endogenous pathological factors is largely associated with the ability to quickly adapt to changing environmental conditions. The mucous membrane of the nasal cavity serves as the first protective barrier where local immunity reactions take place.

It is known that in many organs and tissues, including the mucous membrane of the nasal cavity of the human body, there are neuroendocrine cells related to the link of autonomous regulation of organs. Moreover, the structural and functional features of neuroendocrine cells and their bioamine profile in patients with signs of polyposis rhinosinusitis have not been practically studied. Therefore, the study of the morphophysiological organization of the mucous membrane of the nasal cavity in humans is an urgent problem of modern cytology, histology and cell biology.

Considering the above, we conducted a study of the genetic polymorphism of cytokine genes in patients with CPRS, the results of which demonstrate genetically determined features of the immune response that contribute to the development of CPRS, as well as determining some of the clinical features of the disease.

II. MATERIAL AND METHODS

In accordance with the purpose of the study and to fulfill the assigned tasks, clinical studies were carried out in 140 patients with CPRS and with chronic rhinosinusitis, who were examined and treated at the ENT department of the multidisciplinary clinic of the Tashkent Medical Academy in 2017-2019. The examined patients met the following criteria: the presence of polyposis tissue in the nasal cavity that obstructs the common nasal passage completely or by at least 50%; complaints of prolonged difficulty in nasal breathing; according to the patient, the disease significantly reduces the quality of his life; absence of acute inflammatory pathology; written informed consent for surgical treatment and morphological examination of the surgical material (attached to the case history).

To study the diallelic polymorphism of the promoter regions of the genes of the studied interleukins, 50 healthy (no CPRS) donors, men and women, were examined. The average age of the examined donors was 51.3 ± 1.44 years.

For real-time PCR, a commercial kit with SYBRGreen I dye (Litekh, Russia) was used. The polymorphism of five positions of the IL10 rs1800895 592C> A gene was studied. Genotyping of the samples was carried out using allele-specific polymerase chain reaction (PCR) in real time on a DT-96 device (DNA-Technology) using the SYBR Green I intercalating dye. The reaction mixture corresponded to the manufacturer's recommendations.

The reaction began with the activation phase of Taq polymerase (93 ° C, 1 min). The next 35 PCR cycles consisted of denaturation (93 ° C, 10 sec.), Annealing (64 ° C, 15 sec.) And elongation (72 ° C, 20 sec.) Phases. The signal was read at the stage of elongation.

III. RESULTS AND DISCUSSION

The values of the distribution of alleles and genotypes of the A1188C rs3212227 polymorphism in the IL 12B gene in the 1-2 group and controls presented in Table 1.

Table 1 Frequency of distribution of alleles and genotypes of A1188C rs3212227 polymorphism in the IL 12B gene in patient and control groups

№	Group	Allele frequency				Genotype distribution frequency					
		A		C		A\A		A\C		C\C	
		n	%	n	%	n	%	n	%	n	%
1	CPRS n=31	56	90.32	6	9.67	25	80.64	6	19.35	0	0
2	CRS n=40	71	88.75	9	11.25	31	77.5	9	22.5	0	0
3	Control group n=73	130	89	16	11	57	78.1	16	21.9	0	0

Taking into account the fact that the detection rate of allele A prevailed in all study groups. It should be borne in mind that the frequency of detection of allele A in group 1 slightly prevailed relative to its values in group 2 and control. The frequency of detection of allele C, on the contrary, was slightly higher among patients of group 2, relative to its frequency in group 1 and the population sample.

The study of the distribution of genotypes showed that the homozygous genotype A / A was insignificant, almost 1.2 times more often found in group 1 (80.64%), while the frequency of detection of the heterozygous genotype A / C was insignificantly 1.1 times higher among patients with HRC 2 groups. The opposite situation could be observed in the study of the homozygous C / C genotype, which was not identified among all study groups.

Table 2 shows the results of the analysis of the distribution of alleles and genotypes among representatives of the population sample and patients in groups 1-2.

Table 2 Differences in the frequency of occurrence of alleles and genotypes of A1188C rs3212227 polymorphism in the IL 12B gene in 1- and control groups

Alleles and genotypes	Number of examined alleles and genotypes				Xi2	p	RR	+ 95%CI	OR	+95%CI
	CPRS		Control							
	n	%	n	%						
A	56	90,32	130	89,04	0,076	0,273	1,014	4,130	1,149	3,093
C	6	9,68	16	10,96	0,076	0,727	0,986	1,683	0,871	2,332
A/A	25	80,65	57	78,08	0,086	0,273	1,033	4,550	1,170	3,347
A/C	6	19,35	16	21,92	0,086	0,305	0,883	3,890	0,855	2,440

The analysis showed that if the frequency of detection of allele A did not have statistically significant differences in detection in 1 and control groups, however, there was a tendency to an increase in its detection among patients with CPRS ($\chi2$ = 0.07; P = 0.2; RR = 1.01; OR = 1.14; 95% CI: 4.13- 3.09), while for the C allele, on the contrary, there was a tendency to an increase in its occurrence among conventionally healthy individuals ($\chi2$ = 0.07; P = 0.7; RR = 0.98; OR = 0.87 ; 95% CI: 1.68- 2.33).

An analysis of the frequencies of detecting the A / A genotype showed that among patients with CPRS this genotype was detected statistically insignificantly less than 1.1 times more often than in the group of conventionally healthy individuals ($\chi2$ = 0.08; P = 0.2; RR = 1.03 ; OR = 1.17; 95% CI: 4.55- 3.34). The study of the distribution of the A / C genotype showed the same picture, in accordance with which an insignificant and statistically insignificant prevalence was found - 1.1 times the frequency of its detection in the control group of conventionally healthy individuals, relative to the detection rates of this genotype in patients of group 1 with CPRS ($\chi2$ = 0.08; P = 0.3; RR = 0.88; OR = 0.85; 95% CI: 3.890-2.44).

The results of the analysis of the distribution of alleles and genotypes of the A1188C rs3212227 polymorphism in the IL 12B gene presented in Table 3 demonstrate the same indicators in patients with CRS and among conventionally healthy individuals.

Analysis of the distribution of alleles A and C showed the presence of insignificant less than 1.0 times and statistically insignificant prevalence of allele A in the control sample ($\chi2$ = 0.004; P = 0.36; RR = 0.99; OR = 0.97; 95% CI: 2.95-2.30) , and also a statistically insignificant, less than 1.0 times prevalence of the C allele among patients with CRS was noted ($\chi2$ = 0.04; P = 0.6; RR = 1.0; OR = 1.03; 95% CI: 1.84- 2.45).

It was found that the A / A genotype among conventionally healthy individuals is insignificant, less than 1.0 times higher than its detection frequency among patients with CRS ($\chi2$ = 0.005; P = 0.35; RR = 0.99; OR = 0.96; 95% CI: 3.18-2.43).

Table 3 Differences in the frequency of alleles and genotypes of the A1188C rs3212227 polymorphism in the IL 12B gene in the 2- and control groups

Alleles and genotypes	Number of examined alleles and genotypes				Xi2	p	RR	+ 95%CI	OR	+95%CI
	CRS		Control							
	n	%	n	%						
A	71	88,75	130	89,04	0,004	0,360	0,997	2,959	0,971	2,305
C	9	11,25	16	10,96	0,004	0,640	1,003	1,846	1,030	2,454
A/A	31	77,5	57	78,08	0,005	0,360	0,993	3,184	0,967	2,432
A/C	9	22,5	16	21,92	0,005	0,352	1,027	3,293	1,034	2,592

It was also found that the heterozygous genotype A / C of the polymorphic locus A1188C rs3212227 in the IL 12B gene was evenly distributed in group 2 and in the control group, and its detection frequency was practically at the same level in both studied samples, with extremely insignificant and statistically insignificant prevalence in the subgroup of patients with CRS ($\chi2$ = 0.005; P = 0.3; RR = 1.02; OR = 1.03; 95% CI: 3.29-2.59).

The results of the analysis of the distribution of alleles and genotypes of the polymorphic locus A1188C rs3212227 in the IL 12B gene among patients with CPRS in comparison with group 2 are presented in Table 4.

Analysis of the distribution of alleles A and G did not reveal statistically significant differences in the frequency of their detection in subgroup 1b and in the control sample. Thus, the G genotype did not have significant and statistically significant differences in both study groups, being in them practically at the same level, only extremely slightly prevailing among conditionally healthy individuals.

Table 4 Differences in the frequency of occurrence of alleles and genotypes of genotypes polymorphism A1188C rs3212227 in the IL 12B gene in groups 1 and 2

Alleles and genotypes	Number of examined alleles and genotypes				Xi2	p	RR	+ 95%CI	OR	+95%CI
	CPRS		CRS							
	n	%	n	%						
A	56	90,32	71	88,75	0,091	0,400	1,018	3,639	1,183	3,516
C	6	9,68	9	11,25	0,091	0,600	0,983	2,333	0,845	2,517
A/A	25	80,65	31	77,5	0,104	0,400	1,041	3,985	1,210	3,861
A/C	6	19,35	9	22,5	0,104	0,446	0,860	3,292	0,827	2,628

However, it was noted that genotype A, which also did not have significant and significant differences in the frequency of its distribution, insignificantly prevailed among patients with CPRS ($\chi 2 = 0.09$; P = 0.4; RR = 1.01; OR = 1.18; 95% CI: 3.63-3.51) ...

The frequency of the A / A genotype was statistically insignificant, less than 1.0 times, prevailed among patients with CPRS, relative to patients with CRS ($\chi 2 = 0.1$; P = 0.40; RR = 1.04; OR = 1.21; 95% CI: 3.985 -3.86).

The A / C genotype, on the other hand, was insignificantly 1.1 times more likely to be detected among patients with CRS ($\chi 2 = 0.1$; P=0.44; RR=0.86; OR=0.82; 95% CI: 3.292-2.62).

IV. CONCLUSION

Thus, our data confirm the complexity of the genetic mechanism for the development of polyposis processes in patients with CPRS and indicate the need and importance of understanding complex gene interactions when analyzing the development and clinical stage of the studied pathology. Analyzing the prevalence of genotypic variants of this polymorphism, we revealed a direct association of the C / C monogenotype of the A1188C rs3212227 polymorphism in the IL12B gene with the development of polyposis processes.

In addition, these data emphasize the prognostic significance of the C / C genotype of the IL-12B gene rs1800896 polymorphism in the development of CPRS. In carriers of this genotype, the relative risk of developing CPRS increases more than 3 times, compared with carriers of other genotypic variants of the rs3212227 polymorphism of the IL12B gene.

The absence of significant differences in the prevalence of IL12B genotypes among conventionally healthy donors and CRS patients is possibly explained by the fact that the presence of unfavorable polymorphism, in itself, is still insufficient for the development of this disease. In genetically predisposed individuals CPRS will develop according to the interaction scheme in the "genotype-phenotype" system (genetic-environmental). At the same time, the presence of unfavorable genotypic variants can affect the clinical course of the disease.

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