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The Role of Genes Enzymes Xenobiotics in The Mechanisms of Formation of Heavy Severity Level of Allergic Diseases in Uzbekistan

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Allergic skin diseases, Genes of enzymes of biotransformation of xenobiotics, Gene polymorphism, Clinic.

Allergic dermatosis occupies one of the leading places in structure of the general disease of a skin and hypodermic cellular tissue and makes 56,2 % among skin diseases [1,2,5,13]. On the basis of formation of allergic dermatosis lays interaction of various genetic factors with environmental factors [3,4,6-10,12]. One of the effective approaches to studying of mechanisms of allergic dermatosis development is connected with research of the genes, products which can be expressly or by implication involved in development of the given pathology [11,17-22].

The purpose of our researches is the studying of polymorphism of genes of enzymes of biotransformation of xenobiotics in patients with allergic skin diseases.

Material and Research Methods

Object and subject of research were the patients with allergic dermatosis (AlD), samples of DNA of sick and healthy donors, gluten transfusion genes GSTM1 (1p13.3), GSTT1 (22q11.2) and IIe 105Val genes of the GSTP1 gene were the object and subject of the study. The study included 88 patients with AlD age ranging from 5 to 67 years. Of these, 41 are women, 50 are men. The diagnosis in all patients is confirmed by the results of the clinical examination and laboratory researches.

All patients were surveyed, observed and passed treatment in branch of dermatology Medical Centre of Dermatovenereology and carried out molecular-genetic inspection of biomaterials on the basis of department of molecular medicine and cellular technologies of scientific research institute of haematology and blood transfusion of MinH of the Republic of Uzbekistan.

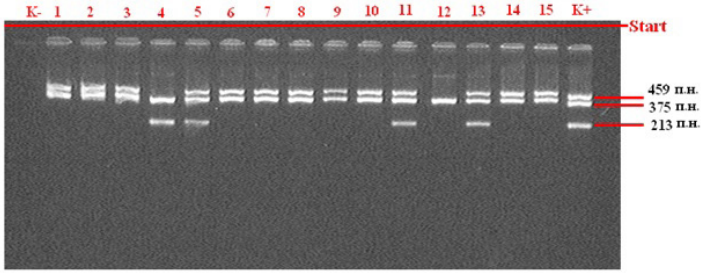

Figure 1: Electric phoregramme of genes detection GSTM1 and GSTT1 (459 items н. – gene GSTT1, 375 items н. – β - γλξαθν, 213 о. ν. – GSTM1).

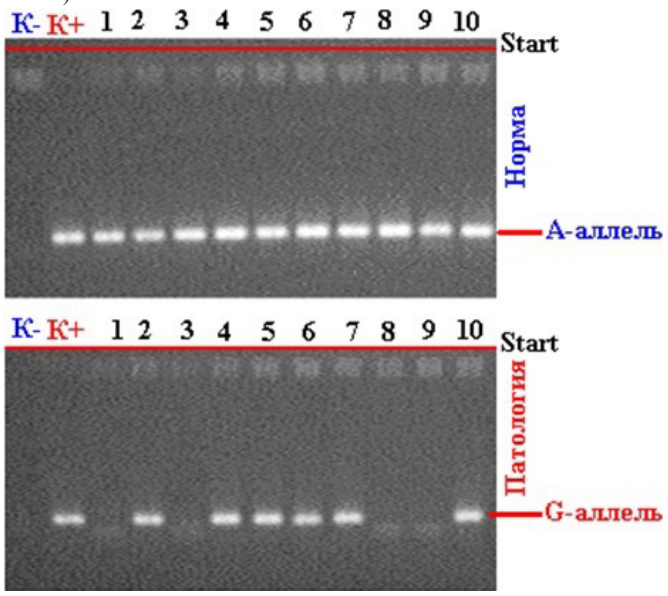

Figure 2: Detection of (A/G) gene polymorphism of glutathione S-transferase P1 (rs--) mutation -1:
K - negative control; K+ positive control; 1,3,8,9 – wild type A/A; 2,4,5,6,7,10 – heterozygous genotype A/G.

At carrying out of genetic researches as comparison group population control was used, which has been presented by samples of DNA (n=72) conditionally healthy donors (without any signs of atopic diseases) from bank of DNA of the given department.

The statistical analysis of results is spent with use of a package of statistical programs «OpenEpi 2009, Version 2.3».

Results of Research

On age aspect patients with AlD up to 14 years old have made – 13, 15-20-year olds – 12, 21-30 – 17, 31-40-year olds – 12, 41-50 – 10 and over 50 years old – 24 patients. Under the clinical form allergic dermatosis has been diagnosed accordingly among 88 patients, 49 patients with atopic dermatitis, 28 patients with nettle rush, 11 patients with allergic dertatitis. Taking into account index DIShS moderate severity level is diagnosed for 10 patients AlD (on the average 24,6+1,8 point) and 78 – heavy severity level (29,3 ± 0,5 point) diseases.

The characteristic of a genetic marker and sequence synthesised of oligoprimers are resulted in table 1.

№	Gene, localisation	Polymorphism	
1	GSTM1 (1p13.3)	deletion	F 5-'GAACTCCCTGAAAAGCTAAAGC-3' R 5 '-GTTGGGCTCAAATATAGGGTGG-3'
2	GSTT1 (22q11.2)	deletion	F 5 '-TTCCTTACTGGTCCTCACATCTC-3' R 5 '-TCACCGGATCATGGCCAGCA-3'
3	GSTP1 ((11 (11.g13)	deletion	5'-ACCAGGGCTCTATGGCCAA- 5'-TGACCCGAGAAGAACGGGT-3',

Table 1: Sequence of oligonucleotides primers used for carrying out PCR.

Results of molecular-genetic researches of polymorphism of genes enzymes xenobiotics in patients with AlD have revealed certain features of deletional polymorphism GSTM1 and GSTT1 (Table 2).

№	Groups	Frequency of distribution of genotypes							
		GSTM1 «+»		GSTM1 (0/0)		GSTT1 «+»		GSTT1 (0/0)	
		*n	%	*n	%	*n	%	*n	%
1	The basic group N=88	55	62.5	33	37.5	65	73.9	23	26.1
2	Contr. Group n=72	46	64.0	26	36.1	54	75.0	18	25.5

Table 2: Distribution frequency of alleles and polymorphism genotypes del/del genes GSTM1 and GSTT1 in groups of patients and the control.
n-number of the surveyed patients; *n - number of the investigated chromosomes.

Apparently from table 2, in the basic group of patients it was observed the tendency to insignificant increase in frequency of nonfunctional genotype GSTM1 (0/0) in comparison with the control (37,5% against 36,1%) accordingly. The risk of development of AlD in carriers of deletional genotype GSTM1 (0/0) has appeared in 1,1 times above in comparison with the individuals, having functional GSTM1 «+» a genotype. (OR=1.1; 95% CI0). However, calculation of frequencies of distribution of zero genotypes of gene GSTM1 between patients of AlD (the basic group) and the control has shown, statistically not significant distinctions (χ^2=0.3; П =0.1).

At the analysis of frequency of genotypes GSTT1 in group of patients of AlD following features are revealed. So, in patients with AlD frequency functional GSTT1 +/+ a genotype in 1,01 times was less in comparison with indicators control healthy group and has made 73.9% in comparison with control healthy group, against 75.0% accordingly. Whereas frequency of zero genotypes GSTT10/0 in group of patients with AlD has made 26.1%, that in 1,1 times was above in comparison with indicators of the healthy faces, however the obtained given indicators did not reach level of statistically significant indicators (χ^2=0.03; P=0.9; OR=1.1; 95% CI0. 0.519 2.169).

So, frequency studying of alleles and genotypes of genes FBC taking into account severity level of allergic dermatosis drew the following features (Figure 3).

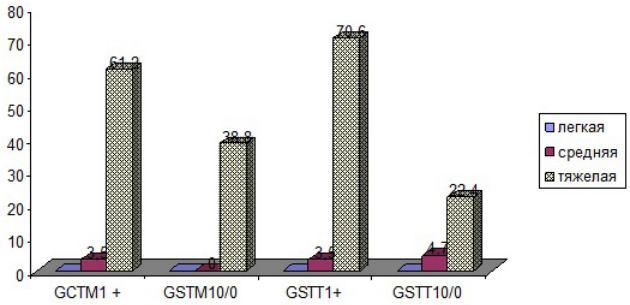

Figure 3: Indicators of distribution of genotypes ФБК in patients with AlD (%).

As follows from the figure, frequency of functional and zero genotypes GSTM1 and GSTT1 most often came to light in patients with heavy and moderate severity level. Thus, it is necessary to notice, that in patients with AlD frequency not functional genotype GSTM1 «0/0» in 38,8 % of cases and GSTT1 0/0 = 22,4 % of cases basically met in patients from heavy severity level.

The obtained data testifies that deletional polymorphisms GSTM1 and GSTT1 can be independent markers of the raised risk of development of heavy severity level of AlD.

№	Groups	Frequency of distribution of genotypes							
		GSTM1 0/0 + GSTT1 0/0		GSTM1 0/0 + GSTT1 «+»		GSTT1 0/0 + GSTM1 «+»		GSTM1 «+» + GSTT1 «+»	
		n	%	n	%	n	%	n	%
1	The basic group N=88	6	6,8	27	30,7	17	19,3	38	43,2
2	Contr. Group n=72	3	4.1	24	33.3	14	19.4	31	43.0

Table 3: Frequency distribution of combined genotypes of deletional polymorphisms genes GSTM1 and GSTT1 in the investigated groups.
The note: *n - quantity of the surveyed patients; 0/0 + 0/0: χ^2=0.5; P=0.4; OR=1.7; 95%CI 0.4058, 6.979 (there is a tendency).
Heterozygotic genotypes: χ^2=0.1; П =0.9; OR=1.0; 95%CI0.5221, 1.875.
Homozygous genotype: χ^2=0.1; П =0.9; OR=1.0; 95%CI 0.5359, 1.885.

Apparently from table 3, among patients with AlD, individuals with combined functionally defective genotypes GSTM10/0+GSTT10/0 met more often, than in group of healthy faces (6,8 % against 4,1 %, accordingly; χ^2=0.5; P=0.4; OR=1.7; 95%CI 0). The obtained data testifies that individuals with zero genotypes of genes enzymes xenobiotics GSTM1 and GSTT1 have a tendency to risk of allergic dermatosis development. Whereas, in combined variants – zero and functional genotypes of polymorphism of genes GSTM1 and GSTT1 between the investigated groups has not revealed statistically significant distinctions (p>0.05).

Molecular genetic studies showed that patients with allergic dermatosis have an increased frequency of occurrence of the association of "functionally unfavorable" genotypes A / G and G / G - 39.7% and 13.6%, respectively. According to the odds ratio, the risk of developing AlD in the main group in the presence of the G / A polymorphism (OR = 2.6; 95% CI 1.264–5.382) and G / G (OR = 11.2; 95% CI 1.421– 88.43) is 1.9 and 12 times higher compared to the control healthy group. Such indicators in the studied groups were statistically significant (χ^2 = 6.9; P <0.05; χ^2 = 8.0; P <0.05;).

The frequency of the distribution of genotypes by RCS IIe 105 Val polymorphism of the GSTP1 gene in the main group of patients with ALD showed that the observed frequency of A / A genotypes was found in 47.7%, heterozygous A / G genotypes - 39.7% and homozygous - G / G - 13 , 6%, respectively, whereas the expected frequency of the genotypes of group A / A and heterozygous - were 44.9 and 44.2%, respectively, and G / G - in 10.8% of cases.

While in the control group of healthy individuals, the observed and expected frequency of A / G heterozygous genotypes was found in 19.4% and 19.7% of cases, and homozygous non-functional G / G genotypes in 1.4 and 1.2%, respectively.

While the frequency distribution of the occurrence of alleles and genotypes of GSTP1 in the group of patients with allergodermatosis, in comparison with the control group, significant differences were found. The functionally unfavorable allele G of the GSTP1 gene was 3.4 times statistically significantly more prevalent in the studied chromosomes of allergic dermatoses than in the population sample (χ^2 = 10.8; P <0.05; OR = 3.4; 95% CI 1.6- 7.4).

The associations of "functionally unfavorable" A / G genotypes were identified (χ^2 = 6.9, P <0.05, OR = 2.6, 95% CI 1.264-5.382) and G / G (χ^2 = 8.0; P <0.05; OR = 11.2; 95% CI 1.421- 88.43) with the development of allergic dermatoses.

№	Groups	Allele frequency				Frequency of distribution of genotypes					
		A		G		A\A		A/G		G/G	
		n	%	n	%	n	%	n	%	n	%
1.	The basic group n=88	118	67.0	58	33.0	41	46.6	35	39.7	12	13.6
2	Contr. Group n=72	126	87.5	18	12.5	57	79.2	14	19.4	1	1.4

Table 4: The distribution frequency of alleles and genotypes of IIe 105 Val polymorphism of the GSTP1 gene in groups of patients and controls.
Note: n- number of examined patients, n*- number of chromosomes studied.

Alleles and genotypes	The number of examined alleles and genotypes		Statistical difference
	Основная группа	Контроль	
Allel A	118	126	χ^2=10.8;P<0.05;OR=3.4;95%CI 1.6- 7.4
Allel G	58	18	
genotyp A/A	41	57	χ^2=16.5;P<0.05;OR=0.2;95%CI 0.1186-0.4868
genotyp A/G	35	14	χ^2=6.9;P<0.05;OR=2.6;95%CI 1.264-5.382
genotyp G/G	12	1	χ^2=8.0;P<0.05;OR=11.2;95%CI 1.421- 88.43

Table 5: Differences in the frequency of occurrence of alleles and genotypes of IIe 105 Val polymorphism of the GSTP1 gene in the main and control groups.

Conclusion

Thus, results of research have shown, that in patients with allergic dermatosis the raised frequency of combined zero genotypes (GSTM10/0 + GSTT10/0) in comparison with population sample (6,8 % and 4,1 % accordingly) is marked. The obtained data testifies that in Uzbekistan individuals with combined zero genotypes of genes enzymes xenobiotics GSTM1 and GSTT1 have a tendency to risk of development of allergic dermatosis heavy severity level.

Whereas, the G allele and hetero / homozygous genotypes of IIe 105 Val polymorphism of the GSTP1 gene are significant markers of an increased risk of developing allergic skin diseases in Uzbekistan (P<0.05). Allele A and the functionally favorable A / A genotype are reliable protective markers for the development of pathology (χ^2 = 16.5; P <0.05; OR = 0.2; 95% CI 0.1186-0.4868).

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