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Evaluation of the Transcription Factor of the Gamma Receptor of the PPARG2 Pro12Ala Gene in the Pathogenesis of Vitiligo

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Abstract **Introduction:** Recently, in medical science, special importance has been attached to the study of the state of metabolism in the body of patients, taking into account the evaluation of molecular genetic studies of genes that control metabolic processes. **Objevtives:** The aim of our research was to study allelic variants and association genotypes of the PPARG2 Pro12Ala gene polymorphism in patients with Vitiligo and to identify predictors of the development of the disease. **Research material and methods:** The object and subject of the research were patients with Vitiligo, DNA samples from patients and healthy donors, the PPARG2 Pro12Ala gene. The research included 109 patients with Vitiligo aged 5 to 62 years, who were observed at the Republican Specialized Scientific and Practical Medical Center for Pediatrics of the Ministry of Health of the Republic of Uzbekistan and "Ixlos Med Servis" LLC. Among 109 patients, 52 were women and 57 were men. **Conclusions:** Thus, the G allele and the heterozygous genotype of the C/G polymorphism of the PPARG2 gene are markers of an increased risk of developing vitiligo in the Uzbek population of the Bukhara region, especially a localized and generalized form of dermatosis ($\chi2$=20.9; p<0,00001; OR=13,9; 95%CI 3,29-59,1; $\chi2$=17,3; p<0,0002; OR=8,9; 95% CI 2,04-39,6). The C allele and the functionally favorable C/C genotype are reliable protective markers for the development of pathology ($\chi2$=17,3; p<0,0002; OR=0,08; 95%CI 0,02-0,35).

Keywords Vitiligo, Genetics, Uzbek population, PPARG2 gene, Clinic, Prognosis

1. Introduction

Recently, in medical science, special importance has been attached to the study of the state of metabolism in the body of patients, taking into account the evaluation of molecular genetic studies of genes that control metabolic processes. Among these genes, special attention is paid to studies of allelic variants and the association of polymorphisms of the genotypes of the y-receptor gene, which activates the proliferation of peroxisomes (PPARG).

Peroxisome proliferator-activated receptor gamma 2 (PPARG2) Y is an intracellular transcription factor that plays an important role in adipogenesis, glucose and fat homeostasis. The functions of this transcription factor are to regulate genes associated with fat accumulation, adipocyte and myoblast differentiation, and insulin sensitivity [5,8,15]. PPARG2) - is expressed mainly in adipose tissue, to a lesser extent in many other cell types, such as macrophages, smooth muscle fibers, endothelial cells, cardiac myocytes [2,7,10,16].

As a result of the analysis of networks regulating the intracellular cholesterol level in hepatocytes and lipid metabolism in adipocytes, it was shown that the PPARG2-factor is one of the key regulators of lipid metabolism gene expression [4,13,20]. The genes from the adipocyte gene network regulated by PPARG2y factors include genes for 1) proteins that transport fatty acids, 2) LXRa and 1NiO-1 proteins, regulators of expression and maturation of the transcription factor SREBP-1c; 3) PEPCK-C enzyme.

Researches have proven the influence of this polymorphism on metabolic processes that affect the properties of muscle tissue and physical qualities, which allows us to consider it as a genetic marker of predisposition to sports in which competitive exercises are provided mainly by anaerobic energy supply mechanisms [3,11].

In this regard, we are of great interest to study the transcription factor of the gamma receptor of the PPARG2 Pro12Ala gene in the process of body metabolism in patients with vitiligo.

The aim of our research was to study allelic variants and association genotypes of the PPARG2 Pro12Ala gene

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polymorphism in patients with vitiligo and to identify predictors of the development of the disease.

2. Research Material and Methods

The object and subject of the research were patients with vitiligo, DNA samples from patients and healthy donors, the PPARG2 Pro12Ala gene.

The research included 109 patients with vitiligo aged 5 to 62 years, who were observed at the Republican Specialized Scientific and Practical Medical Center for Pediatrics of the Ministry of Health of the Republic of Uzbekistan and "Ixlos Med Servis" LLC. Among 109 patients, 52 were women and 57 were men. The diagnosis in all patients was confirmed by the results of clinical examination (dermatoscopy). The control group consisted of 81 healthy individuals without skin pathology of the corresponding age.

Among 109 patients with vitiligo under the age of 18 years, there were 41 (37,6%) (in children 2-11 years old – 17 and adolescents 12-18 years old – 23), 19-30 years old – 25 (22,9%), 31-40 years old – 19 (17,4%), 41-50 years old – 13 (11,9%) and over 51 years old (49,8%) – 11 patients.

Based on the clinical form, 40 patients were diagnosed with a localized form, which accounted for 36,7%, and 46 patients with a generalized form, which accounted for 42,2% of cases. The universal form was diagnosed in 23 out of 109, which accounted for 21,1% of cases, respectively. In the group of patients with a localized form among 40 patients, 15 (37,5%) of them noted the focal form and 25 (62,5%) the segmental form of vitiligo. Among 46 patients with a generalized form, 11 (23,9%) were diagnosed with a vulgar form and 35 with an acrofacial form, which accounted for 76,1% of cases.

Molecular genetic examination of biomaterials (DNA) was carried out on the basis of "GENOTEXNOLOGIYA" LLC according to a scientific agreement. The object and subject of the research were DNA samples of sick and healthy individuals, the Ala54Thr gene of the FABP2 gene.

DNA samples were isolated from peripheral blood lymphocytes according to a modified method. The concentration and purity of the isolated DNA were evaluated by measuring the optical density of DNA-containing solutions at a wavelength of 260 and 280 nm against TE on a NanoDrop 2000 spectrophotometer (USA). Genotyping of the polymorphism of the PPARG2 Pro12Ala gene was carried out on a real-time PCR amplifier Rotor Gene 6000 Model 65H0-100 (Australia), using the test system of the company "Synthol" Cat. No.-NP_555_100_RG (Russia), according to the manufacturer's instructions. Statistical analysis of the results was carried out using the statistical software package "Open Epi 2009, Version 2.3". The frequency of variants of alleles and genotypes (f) was calculated by the formula: f=n/2N and f=n/N, where n is the occurrence of the variant (allele and genotype), N is the sample size.

Statistical analysis of the results was carried out using the statistical software package "Open Epi 2009, Version 2.3".

3. Research Results

The results of molecular genetic studies of the PPARG2 Pro12Ala gene (rs1801282) are presented in Table 1.

The results of molecular genetic studies of the PPARG2 Pro12Ala gene showed that in the control group of healthy individuals, the functional allele C of the PPARG2 gene was determined in 98.8% of cases (162/164), while in the group of patients with vitiligo in the general population, this allele was detected in 85,3% of cases (186/218), respectively, which was 1,2 times lower than in the control group (χ^2=20,9; p<0,00001; OR=0,07; 95%CI 0,02-0,3). The mutant allele G of the PPARG2 gene in the group of healthy individuals was determined in 1,2% of cases (2/164), and in the main group of patients – 14,7% (32/218), which was 12,3 times higher than in control individuals (χ^2=20,9; p<0,00001; OR=13,9; 95%CI 3,29-59,1).

Analysis of the obtained results indicates that the frequency of occurrence of the mutant variant of the G allele among patients with vitiligo (14,7%) and in controls (1,2%) showed a significant difference in the values of the studied parameter (χ^2=20,9; p<0,00001). The obtained result may indicate the connection of the "G" allele of the Pro12Ala polymorphism of the PPARG2 gene, which leads to the replacement of the cytosine nucleotide for guanine, leading to the replacement of the amino acid proline for alanine in the protein at position 12 of the amino acid sequence, with the development of metabolic disorders in patients with vitiligo. At the same time, the risk of developing vitiligo in the presence of a variant G allele of polymorphism in the genome increased by 13,9 times (OR=13,94).

Table 1. The frequency of distribution of alleles and genotypes of the PPARG2 gene polymorphism c.34 C>G; Pro12Ala in patient and control groups

No.	groups	Allel efrequency				Frequency distributio nof genotypes					
		C		G		C/C		C/G		G/G	
		*n	%	*n	%	n	%	n	%	n	%
1.	Main group n=109 (218)	186	85,3	32	14,7	83	76,1	20	18,3	6	5,5
2	Control group n=82 (164)	162	98,8	2	1,2	80	97,6	2	2,4		

n –number of examined patients; *****n – number of alleles studied

Analysis of the genotyping association of the polymorphism of the Pro12Ala gene of the PPARG2 gene showed that in the group of healthy individuals, the functional C/C genotypes were determined in 80 patients, which accounted for 97,6% of cases (80/82), and in the main group of patients with vitiligo, the C/C genotype was determined in 83 patients out of 109, which accounted for 76,1% of cases (83/109), respectively, which was 1,3 times lower compared to control individuals (χ^2=17,3; p<0,0002; OR=0,08; 95%CI 0,02-0,35).

The heterozygous C/G variant of the PPARG2 gene in the control group was detected in 2,4% of cases (2/82), while in the main group of patients with vitiligo– 18,3% of cases (20/109), which is 7.6 times higher than in healthy individuals (χ^2=17,3; p<0,0002; OR=8,9; 95%CI 2,04-39,7).

The homozygous mutant G/G variant of the PPARG2 gene was detected in 6 out of 109 patients with vitiligo, which accounted for 5,5% (6/109), and this genotype was not detected in the group of healthy individuals (χ^2=17,3; p<0,0002; OR=10,4; 95%CI 0,58-186,6).

The analysis of the obtained results indicates that the heterozygous C/G and homozygous G/G variants of the genotypes of the PPARG2 gene polymorphism are a genetic determinant involved in the formation of melanogenesis disorders, and its carriage is a factor of predisposition to the development of vitiligo, which increases its risk by 8,9-10,4 times (OR=8,9; OR=10,4).

The results of molecular genetic studies were analyzed taking into account the clinical course of Vitiligo (Table 3).

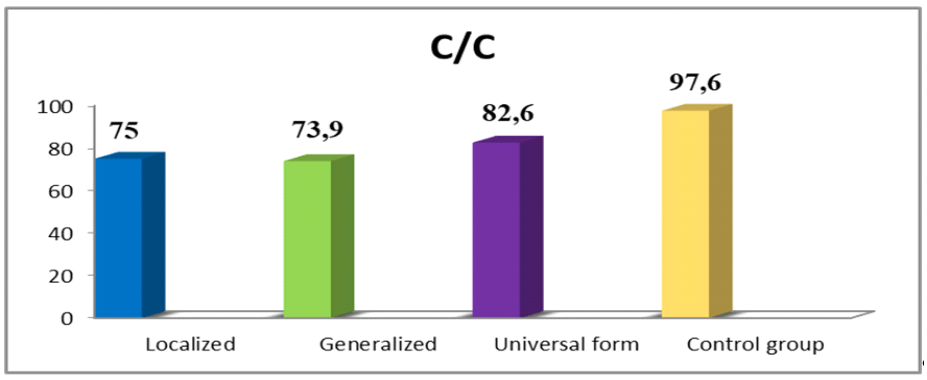
Table 2. Differences in the frequency of occurrence of alleles and genotypes of the polymorphism (c.34 C>G) Pro12Ala of the PPARG2 gene in the main and control groups

Alleles and genotypes	Number of examined alleles and genotypes		Statistical difference
	Main group	*Control group*	
Allele C	186	162	χ^2=20,9; p<0,00001; OR=13,9; 95%CI 3,29-59,1
Allele G	32	2	
Genotype C/C	83	80	χ^2=17,3; p<0,0002; OR=0,08; 95%CI 0,02-0,35
Genotype C/G	20	2	χ^2=17,3; p<0,0002; OR=8,9; 95%CI 2,04-39,6
Genotype G/G	6		χ^2=17,3; p<0,0002; OR=10,4; 95%CI 0,58-186,6

Table 3. Frequency distribution of alleles and genotypes of polymorphism (c.34 C>G) Pro12Ala of the PPARG2 gene in groups of patients

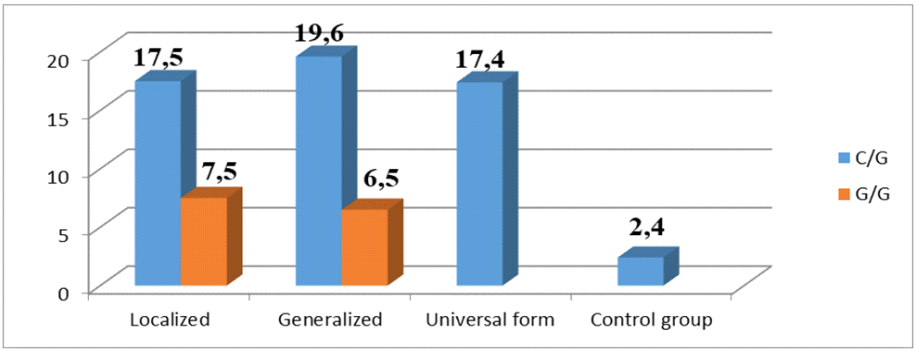
Group	n	Allele frequency				Frequency distribution of FABP2 genotypes					
		C		G		C/C		C/G		G/G	
		n	%	n	%	n	%	N	%	n	%
The main group of them:	109 (218)	186	85,3	32	14,7	83	76,1	20	18,3	6	5,5
Localized form of Vitiligo	40 (80)	67	83,8	13	16,3	30	75	7	17,5	3	7,5
Generalized form of Vitiligo	46 (92)	77	83,7	15	16,3	34	73,9	9	19,6	3	6,5
Universal form	23 (46)	42	91,3	2	4,3	19	82,6	4	17,4	-	-
Control group	82 (164)	162	98,8	2	1,2	80	97,6	2	2,4		

n – number of examined patients; *n – number of alleles studied



Picture 1. Indicators of detectability of functional C/C genotypes of association of PPARG2 gene polymorphism in patients with vitiligo and control healthy group (%)

As shown in picture 1, in the group of patients with vitiligo, depending on the clinical form, the detection of functional C/C genotypes of the PPARG2 gene had distinctive features: thus, in patients with a localized form, the C/C genotype was detected in 30 out of 40, patients accounted for 75% of cases, which was 2,6 times lower than in control individuals (χ^2=15,9; p<0,0004; OR=0,08; 95%CI 0,02-0,36). In patients with a generalized form of C/C, the genotype was determined in 34 out of 46 patients, which amounted to 73,9%, which was 2,4 times lower than in control healthy individuals (χ^2=17,3 p<0,0002; OR=0,07; 95%CI 0,02-0,33). Then, in patients with the universal form, the C/C genotype was determined in 82,6% of cases (in 19 out of 23), which was 4,2 times lower than in the control group (χ^2=7,5; p<0,002; OR=0,12; 95%CI 0,02-0,7). There sultsobtained were statistically significant (P<0,05).



Picture 2. Indicators of detection of heterozygous (C/G) and homozygous G/G genotypes of the PPARG2 gene in patients with vitiligo, taking into account the clinical form and the control healthy group (%)

As follows from the picture, in patients with Vitiligo with a localized form, the heterozygous C/G variant of the PPARG2 gene genotypes was determined in 7 patients out of 40, which accounted for 17,5% of cases (χ^2=15,9 p<0,0004; OR=8,48; 95%CI 1,7-43,0) and the homozygous variant – in 7,5% of cases (3/40), respectively (χ^2=15,9 p<0,0004; OR=15,4; 95%CI 0,78-305,7). The results obtained are statistically significant (P<0,001).

In patients with the generalized form, the heterozygous C/G variant of the PPARG2 gene was identified in 19,5% of cases (9/46) (χ^2=17,3 p<0,0002; OR=9,7; 95%CI 2,0-47,3) while the homozygous mutant G/G variant of the PPARG2 gene in 6,5% of cases (3/46) (χ^2=17,3 p<0,0002; OR=13,3; 95%CI 0,67-262,9).

Whereas, in patients with the universal form of Vitiligo in 17,4% of cases, the heterozygous variant C/G of the PPARG2 gene (4/23), respectively, was detected (χ^2=7,5 p<0,02; OR=8,4; 95%CI 1,4-49,4). The results obtained were statistically significant (P<0,05).

Analysis of the obtained results indicates that the mutant G allele and the heterozygous C/G variant of the PPARG2 gene is a significant prognostic criterion for the risk of developing Vitiligo (P<0,05).

Thus, the results of molecular genetic studies determined a significant association of the unfavorable variant allele G of the Pro12Ala polymorphism of the PPARG2 gene, leading to the replacement of Pro with Ala at position 12 of the amino acid sequence, with the development of vitiligo. It was found that the risk of developing this pathology in the presence of a variant G allele and a heterozygous genotype of C/G polymorphism in the genome increased by 13,9 times and 8,9 times (OR=13,9; OR=8,9, respectively). The obtained result also indicates that the heterozygous C/G genotype and the homozygous G/G genotype of the Pro12Ala polymorphism of the PPARG2 gene are a genetic determinant that determines the formation of skin depigmentation of the vitiliginous lesion, and carriage of the C/G genotype is a factor of predisposition to the development of this pathology, increasing its risk by 8,9 (OR=8,9; P<00002).

It should be noted that an important step in the research of polymorphic genes potentially associated with the development and pathogenesis of diseases is the analysis of the expected and observed frequency of the genotypes of the studied polymorphisms and the correspondence of the frequency distribution to the *Hardy-Weinberg equilibrium (HWE)* (Table 4).

Table 4. Expected and observed frequency of distribution of genotypes according to HWE polymorphism (c.34 C>G) Pro12Ala of the PPARG2 gene in the main group of patients with Vitiligo

Genotypes	Genotype frequency		χ^2	P
	observed	expected		
C/C	76,2	54,01	0,728	0,08
C/G	18,4	38,9	0,250	
G/G	5,5	7,03	0,022	
Total	100,00	100,00	3,14	

As follows from table 4, the frequency distribution of genotypes according to the HWE polymorphism (c.34 C>G) Pro12Ala of the PPARG2 gene in the main group of patients with vitiligo revealed thatthe observed frequency of functional homozygous C/C genotypes was found in 76,2%, and the expected frequency was 54,01% of cases. While the observed heterozygous C/G genotype was 18,4%, and the expected heterozygous genotype was 38,9% of cases, which was 2,1 times higher than the observed frequencies. And the homozygous unfavorable variant of genotypes – G/G of the

PPARG2 gene in the observed frequencies was 5,5%, and in the expected ones it was 7,03%, which increased by 1,2 compared to the observed frequencies of homozygous mutant genotypes, respectively. The results obtained are important indicators as a criterion for predicting the risk of developing morbidity.

Whereas in the control group, the observed and expected frequency of favorable C/C genotypes of the PPARG2 gene was 97,6% and 60,6%, respectively, and the observed frequency of the heterozygous C/G variant was 2.4% and the expected frequency was 34.5%, respectively, which was 14,4 times higher than the observed frequencies. (P<0.05).

The homozygotic variant of the favorable G/G genotypes of the observed frequency was 0, and the expected frequency was 4,9%, respectively (Table 5).

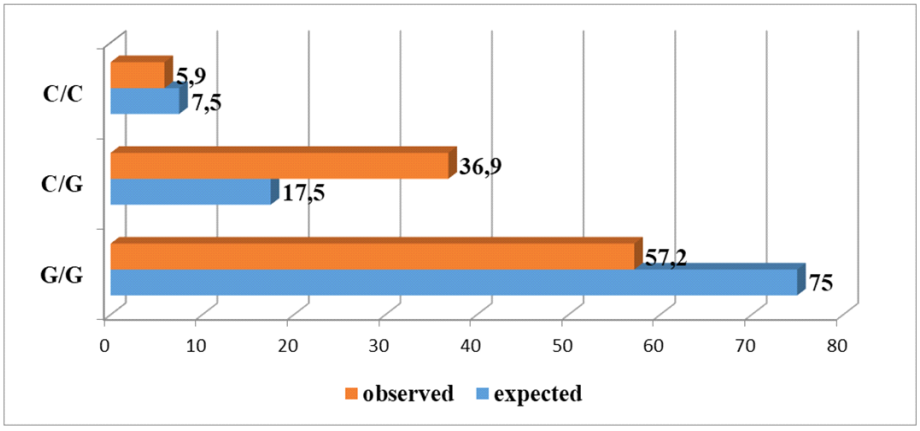
Table 5. Expected and observed frequency of distribution of genotypes according to the HWE polymorphism (c.34 C>G) Pro12Ala of the PPARG2 gene in the control group of healthy individuals

Genotypes	Genotype frequency		χ^2	P
	observed	expected		
C/C	97,6	60,6	0,939	1
C/G	2,4	34,5	0,060	
G/G	0	4,9	0,001	
Total	100,00	100,00	0	

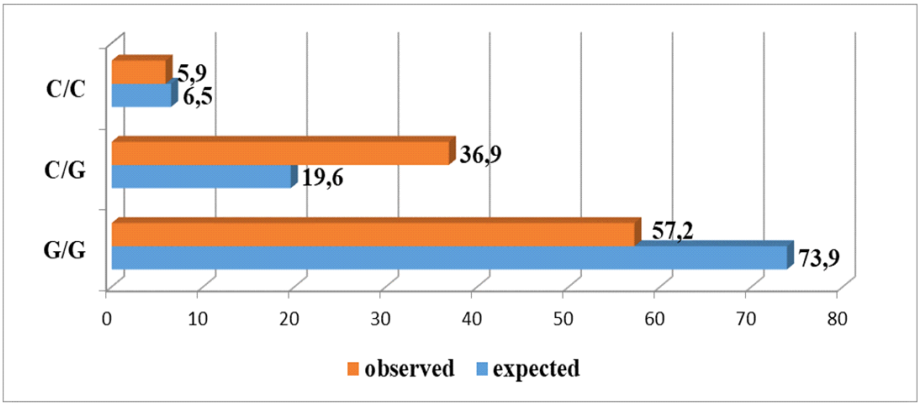
Comparative characteristics of the expected and observed frequencies of the genotypes of the polymorphism (c.34 C>G) Pro12Ala of the PPARG2 gene showed a statistically significant deviation of the indicators (P<0,05) in all the studied groups and subgroups, which indicates that the observed proportion of genotypes in the studied samples corresponds to the Hardy-Weinberg equilibrium.

The analysis of the obtained results showed that both in the control and in the main groups with Vitiligo, the indicators of the expected and observed heterozygosity of the studied polymorphism were statistically significant, characterized by an increase in the frequency of expected C/G heterozygosity by 1.12 times and G/G homozygosity by 1.4 times associations of genotype polymorphism (c.34 C>G) Pro12Ala of the PPARG2 gene, which is important in predicting the risk of developing vitiligo in all clinical forms of morbidity.

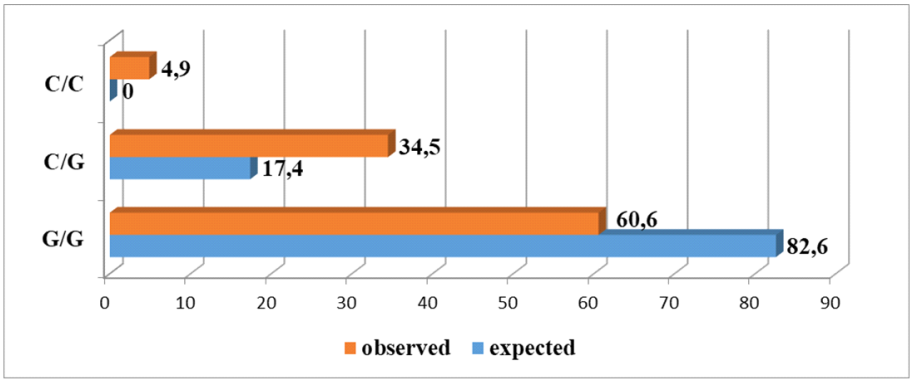
Whereas, taking into account the clinical form of the incidence, the increase in the observed frequency of heterozygous genotypes of the C/G genotypes of the PPARG2 gene was 17,5% of cases, and the expected frequencies of the heterozygous C/G variant were 36,9% of the PPARG2 gene cases, respectively, which was 2,1 times higher than the observed frequencies in patients with a localized form of vitiligo (Picture 4).



Picture 3. Indicators of observed and expected association frequencies ofPPARG2 genotype polymorphisms in patients with localized vitiligo (%)



Picture 4. Indicators of observed and expected association frequencies of PPARG2 gene polymorphisms in patients with generalized form of vitiligo (%)



Picture 5. Indicators of observed and expected association frequencies of PPARG2 genotype polymorphisms in patients with universal vitiligo (%)

The same trend was noted in patients with a generalized form of vitiligo, characterized by an increase in the frequency of expected frequencies of heterozygous C/G variants of the PPARG2 gene by 1.8 times compared with the observed frequencies of PPARG2 gene heterozygosity (Picture 5).

Whereas in the group of patients with the universal form, the expected frequency of the heterozygous C/G variant was 34,5% and the G/G mutant variant was 4,9%, respectively, which was 1,9 and 4 times higher than the rates of the frequently observed genotypes of the PPARG2 gene (picture 4).

Analysis of the obtained results shows that the distribution of all genotypes of the (c.34 C>G) Pro12Ala polymorphism of the PPARG2 gene in the group of patients and controls corresponds to HWE, indicating the absence of the influence of systematic or random factors that can change the genetic structure of populations. The study of the genetic structure of this marker revealed a relatively high level of expected C/G heterozygosity of the PPARG2 gene in the main group of vitiligo patients in relation to the control group (38,9% and 34,5%, respectively). In both groups, the indicator D is to the left of 0, that is, it is negative (D<0). The revealed fact testifies to higher frequencies of expected heterozygotes, but not actually calculated heterozygotes.

Thus, the G allele and the heterozygous genotype of the C/G polymorphism of the PPARG2 gene are markers of an increased risk of developing vitiligo in the Uzbek population of the Bukhara region, especially the localized and generalized form of dermatosis (χ^2=20,9; p<0,00001; OR=13,9; 95%CI 3,29-59,1; χ^2=17,3; p<0,0002; OR=8,9; 95% CI 2,04-39,6). Allele C and functionally favorable C/C genotype are reliable protective markers for the development of pathology (χ^2=17,3; p<0,0002; OR=0,08; 95%CI 0,02-0,35).

Considering the fact that in the main group there was a significant detectability of the association of polymorphism of unfavorable heterozygous genotypes 7,6 times more compared to the control group, the data obtained may indicate that carrying the heterozygous C/G genotype of the PPARG2 gene may be a predisposition factor for the development of this pathology, increasing its risk by 8,9 times (OR=8,9).

4. Conclusions

1. The results of molecular genetic studies of the PPARG2 Pro12Ala gene showed that the mutant allele G of the PPARG2 gene in patients with Vitiligo was determined 12,3 times more than 14,7% (32/218) compared with control healthy individuals (χ^2=20,9; p<0,00001; OR=13,9; 95%CI 3,29-59,1).
2. Heterozygous C/G variant of the PPARG2 gene in the control group was detected in 2,4% of cases (2/82), while in the main group of patients with Vitiligo– 18,3% of cases (20/109), which is 7,6 times higher than in healthy individuals (χ^2=17,3; p<0,0002; OR=8,9; 95%CI 2,04-39,7). The homozygous mutant G/G variant of the PPARG2 gene was detected in 6 out of 109 patients with Vitiligo, which accounted for 5,5% (6/109), and this genotype was not detected in the group of healthy individuals (χ^2=17,3; p<0,0002; OR=10,4; 95%CI 0,58-186,6).
3. Thus, the G allele and the heterozygous genotype of the C/G polymorphism of the PPARG2 gene are markers of an increased risk of developing Vitiligo in the Uzbek population of the Bukhara region, especially a localized and generalized form of dermatosis (χ^2=20.9; p<0,00001; OR=13,9; 95%CI 3,29-59,1; χ^2=17,3; p<0,0002; OR=8,9; 95% CI 2,04-39,6). The C allele and the functionally favorable C/C genotype are reliable protective markers for the development of pathology (χ^2=17,3; p<0,0002; OR=0,08; 95%CI 0,02-0,35).

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