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Molecular Genetic Study of the Association of the GJB2 G/A (35DELG) Gene Polymorphism in Patients with Ichthyosis.

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KEYWORDS

Molecular Genetic Study, Gene Polymorphism

ABSTRACT:
The article presents research on the gene GJB2 G/A (35delG) in 56 patients with ichthyosis. Among the men, there were 34 patients and 22 women. All patients underwent clinical, molecular genetic, and statistical studies. All patients consulted with related specialists: a therapist, pediatrician, neurologist, ophthalmologist, endocrinologist, and others. The control group consisted of 40 healthy individuals of the corresponding age without any skin diseases.

RESUME

The article presents research on the gene GJB2 G/A (35delG) in 56 patients with ichthyosis. Among the men, there were 34 patients and 22 women. All patients underwent clinical, molecular genetic, and statistical studies. All patients consulted with related specialists: a therapist, pediatrician, neurologist, ophthalmologist, endocrinologist, and others. The control group consisted of 40 healthy individuals of the corresponding age without any skin diseases.

Analysis of the results of molecular genetic studies indicates that the A allele and heterozygous genotypes of the GJB2 G/A (35delG) polymorphism are significant molecular genetic markers of risk for the development of a severe form of ichthyosis - neuroichthyosis in the Uzbek population ($P<0.05$), which can be used for early prediction of dermatosis. ($\chi 2=13.89$; $P=0.0002$; OR = 0.21; 95% CI 0.0888-0.5041)

Ichthyosis is a group of rare hereditary dermatoses caused by mutations in genes responsible for keratinization of the skin, resulting in disruption of the barrier function of the epidermis and sometimes affecting the nervous system, leading to sensory problems such as neuropathic pain, loss of sensation (touch, vibration, temperature), and peripheral neuropathy, especially in severe genetic forms. [1-8] Studying genetic markers in the clinical course of ichthyosis is a prognostic aspect in the early diagnosis of severe forms of the disease. [9-11]

The purpose of our research was to assess the detection of allelic variants and the association of genotype polymorphism of the GJB2 G/A (35delG) gene in patients with ichthyosis in the Uzbek population.

Research material and methods. 56 patients with ichthyosis aged 13 to 48 years were examined. Among the men, there were 34 patients and 22 women. All patients underwent clinical, molecular genetic, and statistical studies. All patients consulted with related specialists: a therapist, pediatrician, neurologist, ophthalmologist, endocrinologist, and others. The control group consisted of 40 healthy individuals of the corresponding age without any skin diseases.

Molecular genetic studies were conducted at the "Geno Texnologiya" LLC clinic in accordance with the concluded scientific contract. The object and subject of the study were patients' DNA samples and the GJB2 G/A (35delG) gene. Genotipization of the GJB2 G/A (35delG) gene polymorphism was performed on a real-time PCR amplifier Rotor Gene 6000 Model 65H0-100 (Australia), using the "Sintol" Kat. No-NP_555_100_RG (Russia) test system, according to the manufacturer's instructions. Statistical analysis of the results was carried out using the "OpenEpi 2009, Version 2.3" statistical software package. The frequency of variants of alleles and genotypes (f) was calculated using 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. Research results: In terms of clinical form, among 56

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patients with the vulgar non-syndromic form - 49 and the syndromic form - 7 patients, respectively.

Research results: In terms of clinical form, among 56 patients with the vulgar non-syndromic form - 49 and the syndromic form - 7 patients, respectively.

The results of molecular genetic studies of the distribution of the GJB2 G/A (35delG) enzyme gene polymorphism in patients with ichthyosis and the control healthy group are presented in Table 1.

Table 1. Frequency of distribution of alleles and genotypes of the GJB2 G/A (35delG) gene polymorphism in the groups of patients with ichthyosis and the control group of healthy individuals.

№	Group	Allele frequency				Frequency of genotype distribution					
		G		A		G/G		G/A		A/A	
		*n	%	*n	%	n	%	n	%	n	%
1.	Main group n= 59 (118)	79	66,9	39	33,1	28	47,5	23	38,9	8	13,5
2	control group n= 37 (74)	67	90,5	7	9,5	32	86,5	3	8,1	2	5,4

n - number of examined patients; *n - number of chromosomes studied

As can be seen from the table, a comparative analysis of the frequency distribution of alleles and genotypes of the GJB2 G/A (35delG) gene polymorphism among 118 DNA samples in 59 patients with ichthyosis revealed the presence of a normal G allele in 66.9% (79/118) of cases and a nonfunctional A allele in 33.1% (39/118) of cases, respectively. (χ2=13.89; P=0.0002; OR = 0.21; 95% CI 0.0888-0.5041)

Whereas, in the control group of 37 healthy individuals, the frequency of the normal G allele of the GJB2 gene G/A (35delG) was 90.5% (67/74), and the mutant A allele of the GJB2 gene G/A (35delG) was 9.5% (7/74), respectively.

Analysis of the distribution of allelic variants of the GJB2 G/A (35delG) gene revealed a high frequency of the mutant A allele in the group of patients with ichthyosis, which exceeded the indicators of healthy individuals by 3.5 times. (P<0.05).

Assessment of the frequency of distribution of genotypes of this polymorphism also revealed significant differences between the main group of patients with ichthyosis and the control group of healthy individuals (P<0.05). Thus, in the control group of healthy individuals, the detection of functioning G/G genotypes was detected in 32 out of 37, which constituted 86.5%, while heterozygous G/A genotypes were detected in 3 (8.1%), and mutant homozygous A/A genotypes of the GJB2 gene were detected in 2 cases, which constituted 5.4% of cases, respectively.

Meanwhile, an association of functional G/G genotype polymorphism was found in 28/59 patients with ichthyosis, which constituted 47.5% of cases. Heterozygous G/A genotypes of the GJB2 gene were detected in 23 out of 59 patients, which constituted 38.9% and exceeded the indicators of healthy individuals by 4.8 times (P <0.05). Mutant A/A genotypes were

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detected 2.5 times more frequently compared to the control group and constituted 13.5% (8/59) of cases.

According to the odds ratio coefficient, the risk of developing non-syndromic forms of ichthyosis, manifested by impaired sensory function, especially the hearing apparatus, in the main group with the presence of G /A GJB2 G/A (35delG) polymorphism, is 4.8 times higher compared to the control healthy group. (P<0.05)

Thus, the results of molecular genetic studies have shown a significant relationship with the unfavorable variant of the "A" allele of polymorphism (GJB2 G/A (35delG) with the development of severe ichthyosis. It has been established that the risk of developing syndromic forms of ichthyosis increases 3.5 times if there is a variant A allele of polymorphism in the genome.

According to literature data, the population frequency of occurrence of different allelic variants and genotypes of polymorphic genes can be an unstable value, as it is influenced by various dynamic factors involved in creating the genetic structure of the population. At the same time, it is important to assess the expected and observed frequency of genotypes of the studied polymorphic genes, potentially associated with the development and pathogenesis of diseases, which can be determined according to the distribution of frequencies to the Hardy-Weinberg equilibrium (HP).

Table 2. Expected and observed frequency distribution of GJB2 gene G/A (35delG) polymorphism genotypes for RFV in the group of patients with ichthyosis.

Genotypes	**Genotype frequency**		χ^2	**P**
	Observed	***Expected***		
G/G	47,5	44,8	0,091	0.36
G/A	38,9	44,3	0,370	
A/A	13,6	10.9	0,375	
Total	1,00	1,00	0,837	

As can be seen from the table, the frequency distribution of genotypes according to the RF of the GJB2 gene G/A (35delG) polymorphism in the main group of patients with ichthyosis showed that the observed frequency of functional G/G genotypes was 47.5%, the expected - 44.8%, while heterozygous G/A genotypes - 38.9%, the expected 1.1 times exceeded the observed indicators and amounted to 44.3%, and the observed mutant homozygous genotypes - A/A - 7.5%, while the expected frequency of genotypes was -10.9%, respectively. For the GJB2 G/A (35delG) gene in the group of patients with ichthyosis, the empirical (Hobs) distribution of genotypes corresponds to the theoretically expected (Hexp) in RFV (p <0.05).

Table 3. Expected and observed frequency distribution of GJB2 gene G/A (35delG) polymorphism genotypes by RFV in the group of healthy individuals

Genotypes	**Genotype frequency**		χ^2	P
	Observed	***Expected***		
G/G	86,5	81,9	0,092	
G/A	8,11	17,13	1,758	
A/A	5,41	0,89	8,413	

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Всего	100,00	100,00	10,262	0.014

In the control healthy group, the observed frequency of G/G genotypes occurred in 86.5% of cases, and the expected frequency of genotypes was 81.9%, while the observed frequency of heterozygous G/A genotypes occurred in 8.11% and the expected frequency in 17.13 cases, and homozygous mutant A/A genotypes occurred in 5.4 and 0.69% of cases, respectively. (Table 3).

For this locus in the control group, the empirical (Hobs) distribution of genotypes practically corresponds to the theoretically expected (Hexp) at RFV ($p>0.05$). However, there is a tendency towards deviation.

Analysis of the obtained results shows that the distribution of all genotypes of the GJB2 G/A (35delG) gene polymorphism in the group of patients with ichthyosis and control healthy individuals corresponds to RFV. The study of the genetic structure of this marker revealed an increase in the expected mutation in the main group of patients with ichthyosis by 2.5 times compared to the healthy group.

Conclusion: Analysis of the results of molecular genetic studies indicates that the A allele and heterozygous genotypes of the GJB2 G/A (35delG) polymorphism are significant molecular genetic markers of risk for the development of a severe form of ichthyosis - neuroichthyosis in the Uzbek population ($P<0.05$), which can be used for early prediction of dermatosis. ($\chi2=13.89$; $P=0.0002$; OR = 0.21; 95% CI 0.0888-0.5041)

Literature:

1. Ichthyosis in children: clinical recommendations. - Union of Pediatricians of Russia; 2016. - P. 6. Ikhtioz u detei: clinical guidelines. Union of Pediatricians of Russia; 2016. p. 6. (In Russian).
2. Murashkin N.N., Avetisyan K.O., Ivanov R.A., Makarova C.G. Congenital ichthyosis: clinical and genetic characteristics of the disease. Issues of modern pediatrics. 2022;21 (5):362-377. doi: https://doi.org/10.15690/vsp.v21i5.2459
3. Rakhmatov A.B., Khaldarbekov M.K. Prevalence and clinical polymorphism of congenital ichthyosis. // Prospects for the Development of Dermatovenereology in Childhood. Collection of theses. -2021-p.115-116.
4. A novel autosomal recessive GJB2-associated disorder: Ichthyosis follicularis, bilateral severe sensorineural hearing loss, and punctate palmoplantar keratoderma. Youssefian L, Vahidnezhad H, Saeidian AH, Mahmoudi H, Karamzadeh R, Kariminejad A, Huang J, Li L, Jannace TF, Fortina P, Zeinali S, White TW, Uitto J.Hum Mutat. 2019 Feb;40(2):217-229. doi: 10.1002/humu.23686. Epub 2018 Dec 1.PMID: 3043168
5. Demerdjian M, Crumrine DA, Milstone LM, Williams ML, Elias PM. Barrier dysfunction and the pathogenesis of neutral lipid storage disease in ichthyosis (Chanarin-Dorfman syndrome). J Invest Dermatol. 2006;126(9):2032–2038. doi: 10.1038/sj.jid.5700332. [DOI] [PubMed] [Google Scholar]
6. Irurzun I, Natale MI, Agostinelli ML et al. Ichthyosis follicularis, atrichia and photophobia (IFAP) and hereditary mucoepithelial dysplasia: two syndromes that share a common clinical spectrum. Pediatr Dermatol 2021; 38: 568-74.
7. Perera NJ, Lewis B, Tran H, Fitz M, Sullivan DR. Refsum disease: a novel therapeutic approach to the treatment of a complex disorder using the intestinal lipase inhibitor orlistat. J Obes. 2011;2011 doi: 10.1155/3011/482021. [DOI] [PMC free article] [PubMed] [Google Scholar]
8. Rizzo VB, S'Aulis D, Jennings MA, Crumrine DA, Williams ML, Elias PM. Ichthyosis in Sjögren-Larsson syndrome reflects barrier dysfunction due to abnormal lamellar

epithelial structure and secretion. Arch Dermatol Res. 2010;302(6):443–451. doi: 10.1007/s00403-009-1022-y. [DOI] [PubMed] [Google Scholar]

9. A novel autosomal recessive GJB2-associated disorder: Ichthyosis follicularis, bilateral severe sensorineural hearing loss, and punctate palmoplantar keratoderma. Youssefian L, Vahidnezhad H, Saeidian AH, Mahmoudi H, Karamzadeh R, Kariminejad A, Huang J, Li L, Jannace TF, Fortina P, Zeinali S, White TW, Uitto J.Hum Mutat. 2019 Feb;40(2):217-229. doi: 10.1002/humu.23686. Epub 2018 Dec 1.PMID: 3043168

10. Youssefian L, Naji M, Park JS, Rajabi F, Abdollahimajd F, F, Mahmoudi H, Kamyab-Hesari K, Ghalamkarpour F, Zabihi M, Teimoorian M, Youssefian L, Zeinali S, Vahidnezhad H, Uitto J. Ichthyosis follicularis syndromes in patients with mutations in GJB2. Clin Exp Dermatol. 2022 Aug;47(8):1561-1566. doi: 10.1111/ced.15217. Epub 2022 Jun 23. PMID: 35396755.

11. Youssefian L, Vahidnezhad H, Saeidian AH et al. A novel autosomal recessive GJB2-associated disorder: ichthyosis follicularis, bilateral severe sensorineural hearing loss, and punctate palmoplantar keratoderma. Hum Mutat 2019; 40: 217-29.