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## GENETIC CHARACTERISTICS OF CHILDREN WITH CELIAC DISEASE LIVING IN THE SOUTH OF RUSSIA

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## ГЕНЕТИЧЕСКАЯ ХАРАКТЕРИСТИКА ДЕТЕЙ С ЦЕЛИАКИЕЙ, ПРОЖИВАЮЩИХ НА ЮГЕ РОССИИ

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HLA-typing was performed on 110 children with celiac disease living in the South of Russia to identify HLA-DQ haplotypes. The diagnosis of celiac disease was established for all children following the criteria ESPGHAN 1999 and 2012. There were 50 (45.5 %) boys and 60 (54.5 %) girls. HLA-positive patients accounted for 108 (98.2 %) cases. The most common allele was DQ2 – 87 (79.1 %) children, DQ8 – 16 (14.6 %) people, and DQ7 – 5 (4.5 %) patients. DQ2 represented the DQ2.5 allele, 5 in 26 (29.9 %), a combination of DQ2.5 with DQ2.2 in 21 (24.1 %), only DQ2.2 in 7 (8.1 %) patients. The combination of DQ2 with DQ7 had 25 (28.7 %) children and 8 (9.2 %) children – the combination of DQ2 with DQ8. The DQ8 allele in 5 (31.3 %) was in combination DQ8 with DQ7.

Thereby, the clinical symptoms of the disease did not differ significantly from the type of allele. The highest titer characterized specific autoantibodies (anti-TTG, EMA) in children with the DQ2 allele.

*Keywords: celiac disease, children, HLA-haplotype, HLA-DQ2, HLA-DQ8, HLA-DQ7, degree of atrophy by Marsh*

Проведено HLA-типирование 110 детям с целиакией, проживающим на Юге России, с целью выявления гаплотипов HLA-DQ. Диагноз целиакии был установлен для всех детей в соответствии с критериями ESPGHAN 1999, 2012. Было 50 (45,5 %) мальчиков и 60 (54,5 %) девочек. HLA-позитивные пациенты составили 108 (98,2 %) случаев. Наиболее часто встречающимся аллелем был DQ2 – 87 (79,1 %) детей, DQ8 – 16 (14,6 %) человек и DQ7 – 5 (4,5 %) пациентов. Аллель DQ2 был представлен DQ2,2 – у 26 (29,9 %), комбинация DQ2,5 с DQ2,2 – у 21 (24,1 %), только DQ2,2 – у 7 (8,1 %) пациентов. Комбинацию DQ2 с DQ7 имели 25 (28,7 %) детей и 8 (9,2 %) детей – комбинацию DQ2 с DQ8. Аллель DQ8 в 5 (31,3 %) случаях был в комбинации DQ8 с DQ7.

Таким образом, клиническая симптоматика целиакии существенно не отличалась от вида аллели. Специфические аутоантитела (анти-ТТГ, ЭМА) у детей с аллелем DQ2 характеризовались максимально высоким титром.

*Ключевые слова: целиакия, дети, HLA-типирование, гаплотипы HLA, HLA-DQ2, HLA-DQ8, HLA-DQ7, степень атрофии Marsh*

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anti-DGP – antibodies to deamidated gliadin peptides  
 anti-TTG – antibodies to tissue transglutaminase  
 EMA – endomysial antibodies

ESPGHAN – European Society for Pediatric Gastroenterology,  
 Hepatology and Nutrition  
 HLA – human leukocyte antigen

**O**ver the past quarter-century, the incidence of autoimmune diseases, including celiac disease (celiac enteropathy), has been progressively increasing throughout the world [1, 2, 3]. Celiac disease is a systemic autoimmune disease, development of which requires the presence of HLA-DQ2/HLA-DQ8 haplotypes, involvement of autoantibodies – antibodies to tissue transglutaminase (anti-TTG), antibodies to endomysium (EMA), to deamidated gliadin peptides (anti-DGP) as well as an external trigger – gluten [1].

The most important genetic factor predisposing to the development of celiac disease is the presence of HLA-DQ2/DQ8 haplotypes, which are products of class II genes of the main histocompatibility complex (HLA system) [4, 5]. Genes of the HLA system of class II, which, by modern views, are an integral component of the pathogenesis of the disease, are located at the 6p21.3 locus of the short arm of chromosome VI. HLA genes are the main genes of celiac disease, whose contribution to the hereditary predisposition is about 40 % and without which the development of celiac disease seems unlikely [6]. The role of these genes is to bind exogenous immunodominant peptides and present them to T-lymphocytes, followed by selective activation and development of a pathological immune response [7, 8].

Numerous genetic studies in patients with celiac disease have shown that the HLA-DQ2 molecule (DQA1\*0201-DQB1\*0201 и DQA1\*0501-DQB1\*0201) occurs in 90–95 % of cases and only in 5–10 % – the HLA-DQ8 molecule (DQA1\*0301-DQB1\*0302) [6, 9, 10]. These HLA molecules can be encoded in cis or trans forms. Homozygotes with the HLA-DQ2.5 haplotype have the highest genetic risk, due to the high affinity for gluten protein binding. The HLA-DQ2.2 molecule has a lower effect on the risk of the celiac disease since it has a different amino acid (phenylalanine instead of tyrosine), which leads to a decrease in binding stability [11]. The risk of celiac disease is higher in individuals homozygous for HLA-DQ2.5 or HLA-DQ2.5/DQ2.2 vs. homozygous for HLA-DQ2.2 or heterozygous for HLA-DQ2.5 or DQ2.2 [6, 12, 13].

It is now generally accepted that HLA-DQ2/HLA-DQ8 genes in the general population are found in 30–40 % of healthy individuals and only 1–2 % of HLA-compatible people develop celiac disease [14, 15]. HLA typing has an extremely high (>99 %) negative predictive value. This is useful for analyzing patients with an ambiguous diagnosis (e.g., enteropathy with seronegative anti-TTG) or those already on a gluten-free diet. Genetic analysis can be used to rule out celiac disease and need for further testing in high-risk individuals due to family history. 60–70 % of the world's population without a genetic predisposition will never be affected by celiac disease. On the other hand, it is still not clear why, with a relatively high prevalence of predisposition alleles, only one out of every thirty of them manifests a disease [16, 17].

HLA class II genes are a necessary but insufficient factor for the development of the celiac disease. Studies of genomic associations have revealed other non-HLA genes (more than 40 loci) involved in the pathogenesis of celiac disease [18, 19]. However, individually, each of these non-HLA genes plays a relatively small role in the risk of developing celiac disease, but together these non-HLA genes are significant [20].

The recommendations of the European Society of Pediatric Gastroenterologists, Hepatologists and Nutritionists (ESPGHAN) allow diagnosis of celiac disease without jejunal biopsy in children with enteropathy symptoms, 10-fold or more anti-TSH IgA levels of the normal upper range, confirmed by the detection of EMA and positive HLA-DQ2/DQ8 haplotypes [21, 22, 23].

The presence/absence of HLA-DQ2/DQ8 system haplotypes is considered as the most important diagnostic and prognostic criterion [24, 25, 26]. The lack of HLA-DQ2 / DQ8 alleles with high probability indicates a slight risk of developing celiac disease [27, 28].

Over the course of two decades, in the Stavropol Region, on the background of improved diagnostics and the introduction of HLA typing, a marked increase in the frequency of celiac disease in the pediatric population has been noted, reflecting a global trend [29].

The study objective was to analyze the frequency and structure of HLA-DQ haplotypes in children with the celiac disease living in southern Russia and their possible relationship with the characteristics of the clinical, medical history, and morphological picture of the disease.

**Material and Methods.** The study enrolled 110 children living in the Stavropol and North Caucasus regions, who were examined and treated in the gastroenterological department of the Pediatric Hospital named after G. K. Philippskiy of Stavropol in 2010–2019.

The age of patients was from 8 months to 17 years, of which there were 60 (54.5 %) girls and 50 (45.5 %) boys (average diagnosis age 4.9±0.4 years).

The diagnosis of celiac disease is based on clinical, serological (positive anti-TTG, anti-DGP, EMA of IgA and IgG classes), morphological (stages of atrophy 3A-3C following the classification of Marsh-Oberhuber), and genetic (HLA-DQ2/DQ8 haplotypes) ESPGHAN criteria (1990, 2012).

A typical form of celiac disease with the leading enteric syndrome and signs of impaired intestinal absorption was diagnosed in 85 (77.3 %) patients; in 25 (22.7 %) patients an atypical form was detected, which was monosymptomatic and without a typical enteric syndrome.

Inclusion criterion: HLA typing to identify haplotypes of predisposition to celiac disease.

Centile and sigma tables evaluated indicators of physical development. WHO Anthro and AnthroPlus calculated deviations of anthropometric indicators (body weight, height and BMI Z-scor).

Statistical processing was carried out using the software package «AtteStat», «Statistica 10.0». Descriptive statistics included the calculation of the mean (M) ± standard error of the mean (m). All parametric indicators were checked for normal distribution of characteristics. To assess the intergroup differences, parametric data with a normal distribution of characteristics were evaluated using the Student t-test, and with an anomalous distribution of the characteristics, the Mann – Whitney U-test was used. The relationship assessment of nonparametric indicators was calculated by the Pearson criterion ( $\chi^2$ ). Differences between groups of patients were considered significant at p<0.05.

**Results and Discussion.** HLA-positive haplotypes of predisposition to celiac disease were detected in 108 (98.2 %) patients. In 87 (79.1 %) children, the DQ2 allele was found in 16 (14.6 %) – DQ8, and only in 5 (4.5 %) patients – DQ7. The DQ2 allele was represented

by DQ2.5 in 26 (29.9 %), by the combination of DQ2.5 with DQ2.2 – in 21 (24.1 %), only DQ2.2 – in 7 (8.1 %) patients. The combination of DQ2 with DQ7 was detected in 25 (28.7 %) children, and 8 (9.2 %) children had a combination of DQ2 with DQ8. The DQ8 allele in 5 (31.3 %) cases was in combination with DQ8 and DQ7.

The frequency of HLA-positive haplotypes revealed by us in patients with celiac disease is comparable with the national and world data. So, in the study of Kasatkina E. N., alleles associated with celiac enteropathy were detected in 97.2 % of patients with celiac disease, among whom the DQ2 allele was found in 88.6 % of patients, and DQ8 molecule – in 8.6 %. An independent role of individual alleles of the DQ2 molecule, haplotypes DQ2.2 and DQ7 was established in the development and celiac disease [24]. In children with celiac disease in the Tomsk Region, pathological HLA alleles were detected in 77.6 % of cases (DQ2 genotype in 56.6 % and DQ8 in 21.0 % of patients), in the Krasnodar Region HLA-positive haplotypes were detected only in 48.1 % of patients [30]. In the study of Vokhmyanina N. V. (St. Petersburg), in the group of patients with celiac disease, HLA-positive haplotypes were detected in 92.4 % of cases [31].

In European countries, the HLA-DQ2 haplotype is found in 90–95 % of patients and DQ8 only in 5–10 %. In most cases, the development of the celiac disease is determined by the full DQ2 molecule. Alleles of the DQ2 heterodimer determine the risk of celiac disease, both jointly and separately [28]. In a study of Mubarak A. et al. HLA haplotypes were analyzed in 155 children with celiac disease. 89.7 % of patients were diagnosed with HLA-DQ2.5, 4.5 % – HLA-DQ8, and 5.8 % – HLA-DQ2.2. The authors consider the absence of these genotypes to be a decisive criterion for the exclusion of celiac disease [10].

A group of Brazilian scientists during the HLA typing of 100 children with celiac disease showed that the DQ2 allele (51 % – DQ2.5, 22 % – DQ2.5/DQ2.2 and 5 % – DQ2.2) was identified in 78 % of cases, the association of DQ2/DQ8 – in 13 % (7 % – DQ2.5/DQ8, 6 % – DQ2.2/DQ8) and DQ8 – in 6 % of patients [32].

A comparative analysis of the gender structure of our patients showed that the DQ2 allele is more common in girls – in 53 (88.3 %) cases, which is 1.3 times higher than in boys – in 34 (68.0 %) cases ( $p < 0.01$ ). The DQ8 allele, in contrast, was 3.6 times more likely for boys – 12 (24.0 %) cases than for girls – 4 (6.7 %) cases ( $p < 0.01$ ). The DQ7 allele was detected in 3 (6.0 %) boys and 2 (3.3 %) girls ( $p > 0.05$ ). Among the HLA-negative patients, there was one boy and one girl.

Anamnestic data of patients with celiac disease, depending on their genetic predisposition, are shown in Table 1.

Analyzing the medical history of the disease, it was found that the onset of clinical symptoms in children occurs at different ages. In patients with the DQ2 haplotype, the average age of complaints is 2.0 times higher than in children from the DQ8 group ( $p < 0.01$ ). It is noteworthy that the verification of celiac disease in children with the DQ2 allele occurs somewhat later than with DQ8 and DQ7 ( $p > 0.05$ ), which is due to the relatively large number of patients with an atypical form of the disease in this group, in which not only erased or subclinical symptoms, but also the manifestation of the disease occurs later than in the typical form.

The average latent period of celiac disease (from the onset of the first symptoms of the disease to the diagnosis) did not differ significantly in the patients of the studied groups, amounting to  $2.6 \pm 0.3$  years for DQ2,  $2.8 \pm 0.6$  years for DQ8 and  $3.1 \pm 2.2$  years for DQ7 ( $p > 0.05$ ).

Table 1

**Anamnestic data of patients with celiac disease depending on the HLA allele**

Anamnestic data	Haplotype HLA			p ( $\chi^2$ )		
	DQ2, n – 87	DQ8, n – 16	DQ7, n – 5	p <sub>1</sub>	p <sub>2</sub>	p <sub>3</sub>
Age of complaint						
<1 years	38 (43.7 %)	12 (75.0 %)	2 (40.0 %)	<0.05	>0.05	>0.05
1–3 years	29 (33.3 %)	3 (18.8 %)	3 (60.0 %)	>0.05	>0.05	>0.05
>3 years	20 (23.0 %)	1 (6.2 %)	–	>0.05	–	–
Middle age of complaint, years	2.4±0.3	1.2±0.3	1.6±0.5	<0.01	>0.05	>0.05
Age of diagnosis						
Before 1 years	4 (4.6 %)	3 (18.8 %)	2 (40.0 %)	<0.05	<0.01	>0.05
1–3 years	33 (37.9 %)	4 (25.0 %)	1 (20.0 %)	>0.05	>0.05	>0.05
3–7 years	28 (32.2 %)	8 (50.0 %)	1 (20.0 %)	>0.05	>0.05	>0.05
7–12 years	14 (16.1 %)	1 (6.2 %)	–	>0.05	–	–
12–18 years	8 (9.2 %)	–	1 (20.0 %)	–	>0.05	–
Middle age of diagnosis, years	5.1±0.5	4.0±0.6	4.7±2.6	>0.05	>0.05	>0.05

Note: p<sub>1</sub> – DQ2 vs DQ8; p<sub>2</sub> – DQ2 vs DQ7; p<sub>3</sub> – DQ8 vs DQ7.

Table 2 presents the symptoms of celiac disease in the acute period of the disease.

Table 2

**Symptoms of celiac disease in children depending on the allele HLA**

Symptom of celiac disease	Haplotype HLA			p ( $\chi^2$ )		
	DQ2, n – 87	DQ8, n – 16	DQ7, n – 5	p <sub>1</sub>	p <sub>2</sub>	p <sub>3</sub>
A big symptom of CD						
Diarrhea	50 (57.5 %)	12 (75.0 %)	2 (40.0 %)	>0.05	>0.05	>0.05
Bloating of abdomen	46 (52.9 %)	7 (43.8 %)	2 (40.0 %)	>0.05	>0.05	>0.05
Recurrent abdominal pain	42 (48.3 %)	7 (43.8 %)	2 (40.0 %)	>0.05	>0.05	>0.05
Vomiting	20 (23.0 %)	2 (12.5 %)	–	>0.05	–	–
Violation of appetite	31 (35.6 %)	7 (43.8 %)	1 (20.0 %)	>0.05	>0.05	>0.05
Irritability	26 (29.9 %)	5 (31.3 %)	1 (20.0 %)	>0.05	>0.05	>0.05
Deficiency body weight	52 (59.8 %)	10 (62.5 %)	3 (60.0 %)	>0.05	>0.05	>0.05
Growth retardation	41 (47.1 %)	11 (68.8 %)	1 (20.0 %)	>0.05	>0.05	>0.05
A small symptom of CD						
Bone/leg pain	5 (5.7 %)	1 (6.3 %)	–	>0.05	–	–
Caries	1 (1.1 %)	1 (6.3 %)	–	>0.05	–	–
Headache	9 (10.3 %)	–	–	–	–	–
Restless sleep	13 (14.9 %)	5 (31.3 %)	2 (40.0 %)	>0.05	>0.05	>0.05
Constipations	9 (10.3 %)	2 (12.5 %)	–	>0.05	–	–
Skin rashes	20 (23.0 %)	6 (37.5 %)	–	>0.05	–	–

Note: p<sub>1</sub> – DQ2 vs DQ8; p<sub>2</sub> – DQ2 vs DQ7; p<sub>3</sub> – DQ8 vs DQ7.

A comparative analysis of the clinical picture showed that no significant differences were depending on the presence and type of predisposition allele in children. There were also no patterns between the severity of clinical manifestations of celiac disease and combinations of DQ2 alleles.

In all groups of patients with approximately the same frequency of about 60 %, there was a complaint about a lack of body weight. Gastrointestinal symptoms (diarrhea, increase in the size of the abdomen, recurrent abdominal pain) in patients with the DQ2 allele occurred in 50–60 % of cases. In patients with the DQ8 allele, the main complaint was unstable stool – 75.0 %, the second place was occupied by delay in the rate of physical development, while «minor» symptoms of the disease (skin allergic reactions, restless sleep) were somewhat more conventional.

Anthropometric characteristics of children during the verification of the diagnosis are presented in Table 3.

Table 3

**Deviations of indicators of physical development in children with celiac disease depending on HLA alleles**

Z-score	Haplotype HLA			p ( $\chi^2$ )		
	DQ2, n – 87	DQ8, n – 16	DQ7, n – 5	p <sub>1</sub>	p <sub>2</sub>	p <sub>3</sub>
Weight	-1.15±0.1	-1.73±0.4	-1.55±0.7	<0.05	>0.05	>0.05
Length	-0.86±0.1	-1.83±0.5	0.03±0.6	<0.005	>0.05	<0.05
BMI	-1.01±0.1	-0.76±0.3	-1.77±0.7	>0.05	>0.05	>0.05

Note: p<sub>1</sub> – DQ2 vs DQ8; p<sub>2</sub> – DQ2 vs DQ7; p<sub>3</sub> – DQ8 vs DQ7.

The analysis of anthropometric characteristics demonstrates that children with HLA-DQ8 haplotype have a more pronounced delay in physical development by weight and body length. The average Z-score of body length and body weight in patients with HLA-DQ8 is 2.1 times (p<0.005) and 1.5 times (p<0.05) higher than in children with HLA-DQ2. The number of children with somatogenic nanism (Z-score of body height – 2 sigma deviations or more) among children with DQ8 was 37.5 %, which is 2.3 times higher vs. children with DQ2 allele (p<0.05).

The morphological characteristics of patients with various HLA-DQ variants are presented in the Figure.

The morphological structure of the jejunum mucosa in children with the DQ2 and DQ8 alleles did not differ significantly; in both cases, total villous atrophy was noted in almost 60 % of the patients with celiac disease. In children with DQ7 allele, a moderate degree of atrophy was observed in 100 % of cases. 2 patients with HLA-negative haplotype had Marsh 3A and Marsh 3B atrophy.

E. N. Kasatkina demonstrated similar facts that features of genetic markers depending on the form of the disease and degree of jejunal mucosa damage were not detected, the author put forward a hypothesis about

the role of the DQ8 molecule in the formation of atypical celiac disease [24].

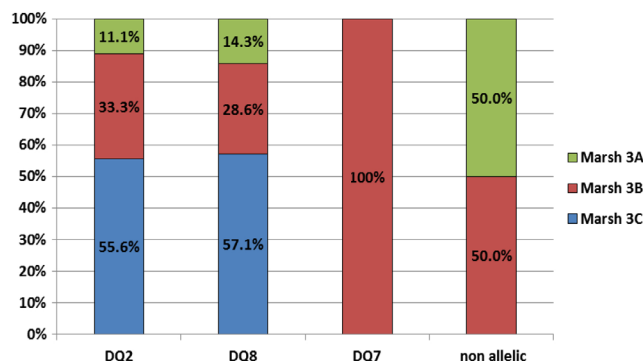


Fig. The stages of atrophy of the jejunum mucosa by Marsh – Oberhuber

When analyzing the level of specific autoantibodies in children with celiac disease depending on the HLA haplotype, it was noted that in patients with HLA-DQ2, the highest levels of anti-TTG IgA, anti-TTG IgG and EMA were observed, amounting to 121.2±8.2 U/ml, 24.1±4.7 U/ml and 759.2±95.0 U/ml. In patients with DQ8 and DQ7 haplotypes, the antibody level was the following: anti-TTG IgA – 60.3±26.5 U/ml and 50.4±13.9 U/ml, anti-TTG IgG – 16.8±5.7 U/ml and 10.9±9.8 U/ml, EMA – 640.0 and 121.7±119.2 U/ml, respectively.

**Conclusions.** The prevalence of HLA-DQ2/DQ8 haplotypes in children and adolescents with celiac disease in the Stavropol Region (southern Russia) does not differ from other regions of Russia, as well as from the structure of the genetic predisposition in populations of children and adolescents in European countries.

In the general group of patients analyzed by us, HLA haplotypes encoding the risk of celiac disease were detected in 98.2 % of cases, which is consistent with Russian and world statistics. At the same time, in the southern regions of Russia, HLA-DQ8 and HLA-DQ7 haplotypes are relatively more common in children and adolescents with celiac disease.

Despite the absence of significant differences in the symptoms of the disease depending on the HLA haplotype, there are similar patterns of delayed rates of physical development, reflecting nutritional deficiencies and hormonal-metabolic disorders caused by malabsorption syndrome.

It is significant that in patients with HLA-DQ2 and HLA-DQ8, the structure of the mucous membrane of the small intestine atrophy stages is very close with the domination of the most severe March 3C stage.

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**Disclosures:**

The authors declare no conflict of interest.

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