



The Genotype-phenotype Correlation of HLA-DQ2 and HLA-DQ8 Haplotypes in Pediatric Celiac Disease: A Single Center Experience

Çocuk Çölyak Hastalarında HLA-DQ2 ve HLA-DQ8 Haplotiplerinin Genetik ve Fenotip ile Korelasyonu: Tek Merkez Deneyimi

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Abstract

Objective: Celiac disease (CD) is a multifactorial disease caused by the interaction of HLA-DQA1 and HLA-DQB1 alleles, which are known to be associated with disease susceptibility in addition to gliadin and other environmental factors. The aim of this study was to determine the incidence of genetic alleles in pediatric CD at our center.

Materials and Methods: This study was designed as a retrospective evaluation of the clinical and genetic findings of patients followed up with a diagnosis of CD in the Pediatric Gastroenterology Outpatient Clinic. According to the study; the data of age, compliance with the diet, family history of disease, genetic testing outcomes, and Marsh classification were compared.

Results: A total of 138 CD patients (94 female, 44 male) were included in our study. The most frequent genetic allele was HLA-DQ2 (69.6%). There was no significant relationship between genetic results and gender, age at diagnosis, body mass index, monthly growth rate, and compliance with diet. In addition, no relationship was found between the genetic structure of the patients and their positive family history with CD. In our study, type 1 diabetes mellitus (DM) was the most frequent disease accompanying CD. Remarkably, higher concomitant positivity of DQ2(+) and DQ8(+) was found in patients presenting with CD and type 1 DM co-existence.

Conclusion: Genetic tests are used for the exclusion of CD disease, rather than diagnosis of. The importance of genetic testing to reduce interventional procedures for CD must be acknowledged.

Keywords: Pediatric, celiac disease, genetic mutations, HLA-DQ2, HLA-DQ8

Öz

Amaç: Çölyak hastalığı (ÇH), gliadin ve diğer çevresel faktörlere ek olarak hastalık duyarlılığı ile ilişkili olduğu bilinen HLA-DQA1 ve HLA-DQB1 alellerinin etkileşimi ile ortaya çıkan multifaktöriyel bir hastalıktır. Bu çalışmanın amacı, merkezimizde pediatrik ÇH'de genetik allel insidansını ortaya koymaktır.

Gereç ve Yöntemler: Bu çalışma Pediatrik Gastroenteroloji Polikliniği'nde ÇH tanısı ile takip edilen hastaların dosyalarının değerlendirilmesi şeklinde retrospektif olarak tasarlanmıştır. Hastaların yaş, diyet uyumları, ailede hastalık hikayesi, genetik testleri ve Marsh sınıflamaları istatistiksel olarak karşılaştırılmıştır.

Bulgular: Çalışmaya toplam 138 ÇH tanılı çocuk (94 kız, 44 erkek) dahil edilmiştir. HLA-DQ2 haplotipi hastalarda en sık (%69,9) saptadığımız genetik alleldir. Saptadığımız genetik haplotip ile hastaların cinsiyet, tanı yaşı, vücut kitle indeksi, aylık büyüme oranları ve diyet uyumu arasında anlamlı bir ilişki bulunamamıştır. Aile öyküsünde ÇH varlığı ile genetik mutasyon arasında da bir ilişki

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bulunamamıştır. Çalışmamızda, ÇH'ye en sık tip 1 diabetes mellitus (DM) varlığının eşlik ettiği saptandı. HLA DQ2 ve HLA DQ8 allellerinin birlikte pozitifliği, özellikle ÇH ve tip 1 DM hastalığı birlikte olan çocuklarda belirgin olarak yüksek saptanmıştır.

Sonuç: Genetik testler, ÇH tanısından ziyade hastalığın dışlanması için kullanılır. Genetik testlerin yapılması, gereksiz yere yapılan girişimsel işlemleri azaltmak açısından önemlidir.

Anahtar Kelimeler: Çocuk, çölyak hastalığı, genetik mutasyonlar, HLA-DQ2, HLA-DQ8

Introduction

Celiac disease (CD) is a systemic autoimmune disease that may be presented with gastrointestinal findings causes malabsorption. A wide variety of non-gastrointestinal findings are also seen in most of the patients (1). Its frequency is thought to be around 1% while differences may be seen between countries depending on socioeconomic, cultural, and environmental factors (2). CD is a multifactorial disease that occurs with the interaction of HLA-DQA1 and HLA-DQB1 allelic variants, which are known to be associated with disease susceptibility, and lesser known non-HLA genes, gliadin and other environmental factors (3). HLA-DQ2 and HLA-DQ8 haplotypes, determined by molecular genetic analysis of HLA-DQA1 and HLA-DQB1 allelic variants, are the most important genetic risk factors associated with susceptibility to CD (4). HLA-DQ2 and HLA-DQ8 haplotypes are transcribed from major histocompatibility complex class II genes, localized on chromosome 6. DQ2 and DQ8 α/β heterodimers mediate the activation of gluten-reactive CD4 T cells in the gut. As a result of this, a T-cell response occurs and produce disease specific antibodies, resulting to secretion of pro-inflammatory cytokines that may cause the mucosal atrophy and clinical findings (5). The prevalence of these haplotypes in the general population is about 30-40%, whereas only approximately 1% of the population have CD. So, this means genetic haplotype positivity is necessary, but not sufficient, to cause CD (6-8). While the presence of HLA structure and gluten contact is strictly required, it is not sufficient in the development of CD (9).

Material and Methods

This study was designed as a retrospective evaluation of the clinical and genetic findings of the patients followed up with the diagnosis of CD between 1-18 years of age in the Pediatric Gastroenterology Outpatient Clinic in University of Health Sciences Turkey, Adana City Training and Research Hospital between 15.10.2017-01.11.2020. Ethics approval was obtained from Adana City Training and Research Hospital Ethics Committee (decision number: 1123, date: 04.11.2020).

According to the study; the age of diagnosis, growth rate calculations in the follow up visits (3, 6, and 12 months), presence of presenting symptoms, compliance with the diet, family history of disease, and genetic testing outcomes were compared with Marsh classification. The growth rate measurements of the patients was calculated using <https://cedd.saglik-network.org> software program. We aimed to analysed the genetic HLA-DQ2 and HLA-DQ8 gene positivity

rates and allele distribution in CD and the relationship with different parameters of the patients.

DNA Extraction and Genetic Analysis

Patients' genomic DNA was extracted from peripheral blood sample using QIAGEN QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany) according to the protocol of the isolation kit. The Qubit® 3.0 Fluorometer (Thermo Fisher Scientific, US) was used to verified DNA integrity. Analysis of HLA-DQA1 and HLA-DQB1 alleles were performed with Genvinset® HLA Celiac Real-Time PCR Assay. According to this, samples which had both DQA1*05 and DQB1*02 alleles were considered as DQ2 positive. If there is only DQA1*05 or DQB1*02 allele, these samples had named half DQ2 positive. Samples which had both the DQA1*03 and DQB1*03:02 alleles, they were considered as DQ8 positive.

Statistical Analysis

All the statistical analyses were carried out using IBM SPSS Statistics Version 20.0 statistical software package. Numbers and percentages were used to express categorical variables. At the same time continuous variables were expressed as mean and standard. Fisher's exact test was used to compare categorical variables between the genetic groups. The Shapiro-Wilk test was carried out to confirm the normality of distribution of continuous variables. One-way ANOVA was used to compare genetic groups. To appraise the change of the growth rate in time, the Repeated Measurements Analysis was applied. While evaluating the results, values less than 0.05 were considered statistically significant.

Results

A total of 138 patients with diagnosis of CD were included in the study. Ninety-four of the patients were female and 44 were male. All of subjects enrolled in the study had received the diagnosis of CD according to the the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition 2012 guideline through the pathologic examination of gastroscopic biopsy performed based on clinical findings or laboratory test positivity (10). Patients' demographic characteristics are summarized in Table 1. HLA DQ2 genetic was the most frequent genetic positivity (69.6%) in patients diagnosed with CD. HLA DQ8 genetic positivity was seen in 11 patients diagnosed with CD (8%). HLA DQ2 and HLA DQ8 genetic tests were negative in 4 patients. The distribution of HLA genetic of the patients was shown in Table 2. No significant relationship was found when genetic

Table 1. General features of the subjects	
Gender, n (%)	
Male	44 (32%)
Female	94 (68%)
Age (years), mean \pm SD	12.3 \pm 4.0
Min-max	4.3-20.8
Age of diagnosis (years), mean \pm SD	7.5 \pm 4.1
Min-max	0.8-17.7
Compliance to diet n (%)	103 (75%)
Presence of admission complaint n (%)	118 (86%)
Those with a family history = 2 n (%)	72 (52%)
Concomitant disease n (%)	
None	108 (78%)
Type 1 diabetes	14 (10%)
Thyroiditis	3 (2%)
Cystic fibrosis	3 (2%)
Down syndrome	2 (2%)
Other	8 (6%)
3-month growth rate, mean \pm SD	1.54 \pm 0.66
6-month growth rate, mean \pm SD	3.04 \pm 1.37
12-month growth rate, mean \pm SD	6.20 \pm 2.65
BMI, mean \pm SD	17.6 \pm 3.8
Marsh (Histopathological analysis)	
1	2 (1%)
2	1 (1%)
3a	46 (34%)
3b	58 (43%)
3c	28 (21%)
SD: Standard deviation, BMI: Body mass index	

Table 2. The distribution of subjects according to HLA-DQ2 and HLA-DQ8 genetic positivity		
Genetic	Number	Percentage (%)
DQ2 (+)	96	69.6
DQ2 (+) DQ8 (+)	10	7.2
DQ8 (+)	11	8.0
Half DQ2 (+)	7	5.1
Half DQ2 (+) DQ8 (+)	10	7.2
Normal	4	2.9

features were compared to gender, age of diagnosis, body mass index (BMI), monthly growth rate, and compliance to diet. No correlation was found between genetic features and the patients complaints on admission. No relationship was found between the genetic distribution of the patient and the presence of CD in the family. Table 3 summarizes the comparison of some parameters with the genetic distribution. Type 1 diabetes mellitus (DM) is the most frequent disease accompanying with CD. According to our results, the attendant positivity of HLA-DQ2 and HLA-DQ8 alleles together are significantly higher in patients with CD and type-1 DM co-existence. But this is not statistically significant due to the limited number of patients. A review of genetic features at the allele level is summarized in Table 4. No correlation was found between alleles in patients with respect to the age of diagnosis, gender, monthly growth rates, BMI, compliance to diet, presence of complaints at admission, family history, and Marsh classification. However, the rates of complaints at admission in patients with A1*03 - B1*03:02 combination (DQ2) (64%) and in those with A1*05 - B1*02 - A1*03 - B1*03:02 combination (DQ2 and DQ8 together) (67%) were much lower compared to the other groups despite not being statistically significant. Assessment of the patients for presence of concomitant diseases between alleles showed that type 1 DM was higher in patients with A1*05 - B1*02 - A1*03 - B1*03:02 combination (DQ2 and DQ8 together) compared to others. However, due to the small number of patients, it was not considered statistically significant. Therefore, further studies according larger number of patients are required.

Although an increase was observed ($p < 0.001$) over time in growth rates at 3, 6, and 12 months for all groups as evaluated during outpatient follow-up, this difference was not associated with the alleles carried ($p = 0.101$). A more detailed evaluation of the results actually suggests that it may be a distinctive feature for this allele based on the fact that the growth rate at 3 months is the lowest with the A1*05 allele and the growth rate was still low at 12 months. This conclusion cannot be extrapolated while only 4 patients are found here, and studies are needed with a larger number of patients (Figure 1). No significant association was found between the genetic structures and the growth rates of the patients. The annual growth rate was higher in patients (4 patients) with negative HLA-DQ2 and DQ8 (Figure 2).

Discussion

The most frequent genetic structure in CD was complete positivity of HLA DQ2 (69.6%) and it is similar to the literature followed by HLA DQ8 genetics (8%). In the literature the most frequent allele in CD was HLA-DQ2 (90%) (3). In the subject group in this study, however, genetic distributions were different from the literature. The genetic distribution may vary according to the regional and ethnic aspects of the country. A different study that was conducted in our region (11) showed that the rates of HLA-DQ2 with HLA-DQ8 positivity, HLA-DQ2 positivity, and HLA-DQ8 positivity were

76%, 67% and 25%, respectively. The proportion of patients with HLA-DQ2 positivity in our study (69.6%) was similar to the proportion of patients with HLA-DQ2 positivity in that study (67%). The proportion of HLA-DQ8 positivity (8%), however, was different from the proportion of patients in the same study with HLA-DQ8 positivity (25%). There are also studies in the literature where HLA-DQ8 positivity in CD is consistent with our study (2% in Italy, 2.3% in Hungary,

and 6.4% in Finland) (12). HLA-DQ2 and HLA-DQ8 genetic tests were negative in 2.9% of the subjects. Consistent with the rates given in the literature, the rates of negativity with HLA-DQ2 and HLA-DQ8 in CD were 0% and 10% (13). Some studies in the literature are supportive of our result; patients with CD are found to be negative for DQ2 and DQ8 at a rate of 3.4% (1). Although DQ variants are not sufficient for the development of the disease. The negative predictive value

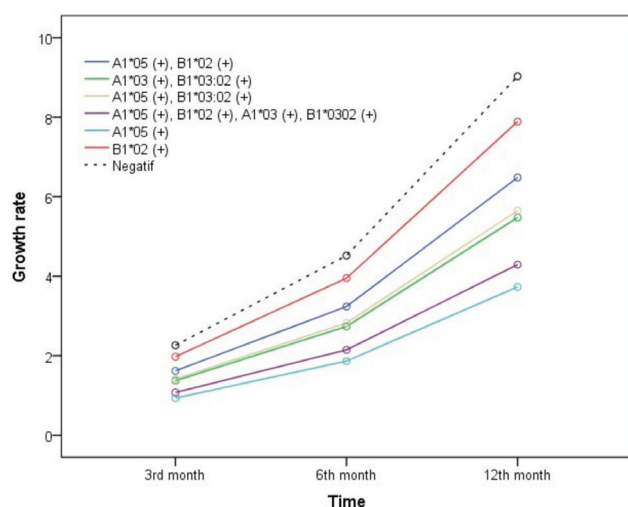


Figure 1. Growth rates comparison of the patients based on the HLA genetic allele structure

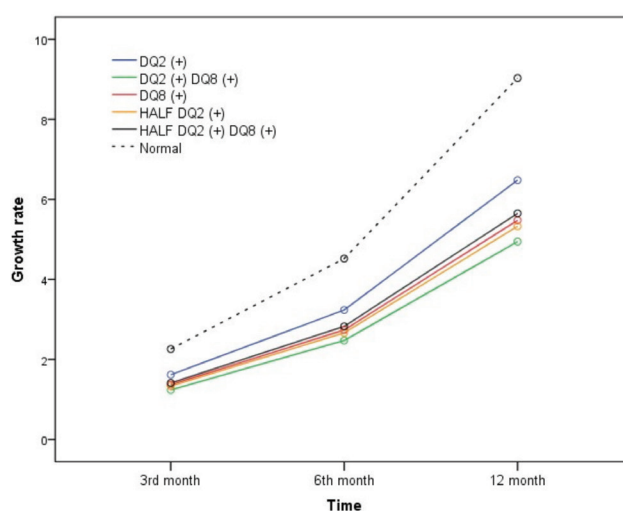


Figure 2. Comparison of growth rates in patients based on the HLA-DQ2 and DQ8 characteristics

Table 3. Genetic features compared with some parameters of the patients							
	DQ2 (+)	DQ2 (+) DQ8 (+)	DQ8 (+)	HALF-DQ2 (+)	HALF-DQ2 (+) DQ8 (+)	Normal	p-value
n	96	10	11	7	10	4	
Age	12.5±4	12.1±3.9	12±3.7	12.6±4.5	11.2±4	11.1±5.7	0.930
Age of diagnosis	7.7±4.1	7.8±4.5	6.4±3.3	7.4±4.6	6.4±4	7.3±5.5	0.868
12-month growth rate	6.48±2.7	4.94±2.8	5.48±1.26	5.33±2.93	5.65±2.47	9.0±0	0.345
BMI	17.8±3.8	16.3±2.3	17.5±3.6	19.6±6.8	16.4±2.6	17.8±5.2	0.687
Compliance to diet	73 (76%)	5 (50%)	9 (82%)	6 (86%)	7 (70%)	3 (75%)	0.533
Female gender	67 (70%)	6 (60%)	7 (64%)	6 (86%)	6 (60%)	2 (50%)	0.758
Presentation	84 (88%)	7 (70%)	7 (64%)	7 (100%)	9 (90%)	4 (100%)	0.146
Those with a family history = 2	52 (54%)	6 (60%)	3 (27%)	4 (57%)	6 (60%)	1 (25%)	0.108
Concomitant disease							
None	80 (83%)	4 (40%)	8 (73%)	5 (71%)	9 (90%)	2 (50%)	0.005
DM	7 (7%)	6 (60%)	1 (9%)	0 (0%)	0 (0%)	0 (0%)	
Thyroiditis	3 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
CF	2 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (25%)	
Down	1 (1%)	0 (0%)	1 (9%)	0 (0%)	0 (0%)	0 (0%)	
Other	3 (3%)	0 (0%)	1 (9%)	2 (29%)	1 (10%)	1 (25%)	

n: Number, BMI: Body mass index, DM: Diabetes mellitus, CF: Cystic fibrosis

Table 4. Distribution of genetic alleles in patients and associated parameters

	A1*05 (+), B1*02 (+)	A1*03 (+), B1*03:02 (+)	A1*05 (+), B1*03:02 (+)	A1*05 (+), B1*02 (+), A1*03 (+), B1*03:02 (+)	A1*05 (+)	B1*02 (+)	All Negative	p-value
n	95	11	10	9	4	2	4	
Presence of complaints at admission	83 (87%)	7 (64%)	9 (90%)	6 (67%)	4 (100%)	2 (100%)	4 (100%)	0.219
Concomitant disease								
None	79 (83%)	8 (73%)	9 (90%)	4 (44%)	2 (50%)	2 (100%)	2 (50%)	0.015*
DM	7 (7%)	1 (9%)	0 (0%)	5 (56%)	0 (0%)	0 (0%)	0 (0%)	
Thyroiditis	3 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
CF	2 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (25%)	
Down	1 (1%)	1 (9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Other	3 (3%)	1 (9%)	1 (10%)	0 (0%)	2 (50%)	0 (0%)	1 (25%)	
n: Number, BMI: Body mass index, DM: Diabetes mellitus, CF: Cystic fibrosis								

of not harboring DQ gene is considered to be 100% (14). Routine use is not recommended since genetic analyses are costly and difficult to work with and unable to establish the diagnosis. Megiorni et al. (15) found in their study associating HLA groups with gender, that DQ2 and/or DQ8 carrying was higher in females and DQ2/DQ8 negativity was more frequent in males. In our study, no relationship was found between the genetic features of the patients and gender. As stated in the literature, the HLA-DQ2 haplotype positivity was associated with early onset disease, while the presence of the HLA-DQ8 haplotype was associated with adult-onset disease rather than child-onset (16). However, the association between the age of diagnosis and genetic features was not statistically significant in our study ($p=0.868$). No significant relationship was found between the body mass index, monthly growth rate and compliance to diet. Some studies (3,5) have shown that there is a positive relationship between the DQ2 allele and mucosal damage. However, no relationship was found between the patient's genetic structure and Marsh classification and the presence of CD in the family. Despite being conducted with a small number of patients (17,18) some studies did not find a significant relationship between carrying HLA-DQ2 and DQ8 and the age of diagnosis or the clinical presentation. Although the complaints were shown to be lower in patients with negative HLA-DQ2 and HLA-DQ8, no relationship was found in our study for the presence of complaints at admission or diagnosis by chance in terms of genetic features (11).

Type 1 DM is the most frequent disease accompanying with CD. In particular higher concomitant positivity of DQ2 (+) DQ8 (+) in patients presenting with CD and type 1 DM co-existence is remarkable despite not being statistically significant due to the limited number of patients.

No correlation was found between alleles in patients with respect to the age of diagnosis, gender, monthly growth rates, BMI, compliance to diet, presence of complaints at admission, family history, and Marsh classification. However, the rates of complaints at admission in patients with A1*03-B1*03:02 combination (DQ2) (64%) and in those with A1*05, B1*02, A1*03, B1*03:02 combination (DQ2 and DQ8 together) (67%) were much lower compared to the other groups. Assessment of the patients for presence of concomitant diseases between alleles showed that type 1 DM was higher in patients with A1*05 - B1*02 - A1*03 - B1*03:02 combination (DQ2 and DQ8 together) compared to others. However, this was not statistically significant due to the small number of patients. However, further studies with a larger number of patients are required. Although an increase was observed ($p<0.001$) over time in growth rate at 3, 6, and 12 months for all groups as evaluated during outpatient follow-up, this difference was not associated with the alleles carried ($p=0.101$). A more detailed evaluation of the results actually suggests that it may be a distinctive feature for this allele based on the fact that the growth rate at 3 months is the lowest with the A1*05 allele and the growth rate was still low at 12 months. This conclusion cannot be extrapolated while only 4 patients are found here, and studies are needed with a larger number of patients. The limitations of our study is the number of the patients.

Conclusion

In the guidelines that are updated in time through cumulative knowledge and experience, HLA genetic studies were included in the diagnostic algorithm in some cases to support the diagnosis of CD. Genetic tests are used for exclusion of CD disease, rather than diagnosis of. The presence of HLA-DQ2 or HLA-DQ8 has a negative predictive value of

near 100% and may be used to exclude the diagnosis of CD but it is still not sufficient for diagnosis. The importance of genetic testing to reduce interventional procedures for CD must be acknowledged.

Ethics

Ethics Committee Approval: Ethics approval was obtained from University of Health Sciences Turkey, Adana City Training and Research Hospital Ethics Committee (decision number: 1123, date: 04.11.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.G.T., Ö.A., Concept: D.G.T., Design: D.G.T., Ö.A., Data Collection or Processing: D.G.T., Ö.A., Analysis or Interpretation: Ö.A., Literature Search: D.G.T., Ö.A., Writing: D.G.T., Ö.A.

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References

- Rostami-Nejad M, Romanos J, Rostami K, Ganji A, Ehsani-Ardakani MJ, Bakhshipour AR, et al. Allele and haplotype frequencies for HLA-DQ in Iranian celiac disease patient. *World J Gastroenterol* 2014; 20: 6302-8.
- Dieli-Crimi R, Cénit MC, Núñez C. The genetics of celiac disease: A comprehensive review of clinical implications. *J Autoimmun* 2015; 64: 26-41.
- Megiorni F, Pizzuti A. HLA-DQA1 and HLA-DQB1 in Celiac disease predisposition: practical implications of the HLA molecular typing. *J Biomed Sci* 2012; 19: 88.
- Taylor AK, Lebowhl B, Snyder CL, Green PHR. Celiac Disease. 2008 Jul 3 [updated 2019 Jan 31]. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Taylor AK, Lebowhl B, Snyder CL, Green PHR. Celiac Disease. 2008 Jul 3 [updated 2019 Jan 31]. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023.
- Megiorni F, Mora B, Bonamico M, Barbato M, Nenna R, Maiella G, et al. HLA-DQ and risk gradient for celiac disease. *Hum Immunol* 2009; 70: 55-9.
- Siddiqui K, Uqaili AA, Rafiq M, Bhutto MA. Human leukocyte antigen (HLA)-DQ2 and -DQ8 haplotypes in celiac, celiac with type 1 diabetic, and celiac suspected pediatric cases. *Medicine (Baltimore)* 2021; 100: 24954.
- Gnodi E, Meneveri R, Barisani D. Celiac disease: From genetics to epigenetics. *World J Gastroenterol* 2022; 28: 449-63.
- Brown NK, Guandalini S, Semrad C, Kupfer SS. A Clinician's Guide to Celiac Disease HLA Genetics. *Am J Gastroenterol* 2019; 114: 1587-92.
- Lindfors K, Ciacci C, Kurppa K, Lundin KEA, Makharia GK, Mearin ML, et al. Coeliac disease. *Nat Rev Dis Primers* 2019; 5: 3.
- Husby S, Koletzko S, Korponay-Szabó IR, Mearin ML, Phillips A, Shamir R, et al. European society for pediatric gastroenterology, hepatology, and nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr* 2012; 54: 136-60.
- Basturk A, Artan R, Yilmaz A. The incidence of HLA-DQ2/DQ8 in Turkish children with celiac disease and a comparison of the geographical distribution of HLA-DQ. *Prz Gastroenterol* 2017; 12: 256-61.
- Koskinen L, Romanos J, Kaukinen K, Mustalahti K, Korponay-Szabó I, Barisani D, et al. Cost-effective HLA typing with tagging SNPs predicts celiac disease risk haplotypes in the Finnish, Hungarian, and Italian populations. *Immunogenetics* 2009; 61: 247-56.
- Vidales MC, Zubillaga P, Zubillaga I, Alfonso-Sánchez MA. Allele and haplotype frequencies for HLA class II (DQA1 and DQB1) loci in patients with celiac disease from Spain. *Hum Immunol* 2004; 65: 352-8.
- Wolters VM, Wijmenga C. Genetic background of celiac disease and its clinical implications. *Am J Gastroenterol* 2008; 103: 190-5.
- Megiorni F, Mora B, Bonamico M, Barbato M, Montuori M, Viola F, et al. HLA-DQ and susceptibility to celiac disease: evidence for gender differences and parent-of-origin effects. *Am J Gastroenterol* 2008; 103: 997-1003.
- Schirru E, Jores RD, Cicotto L, Frau F, De Virgiliis S, Rossino R, et al. High frequency of low-risk human leukocyte antigen class II genotypes in latent celiac disease. *Hum Immunol* 2011; 72: 179-82.
- Martínez-Ojinaga E, Fernández-Prieto M, Molina M, Polanco I, Urcelay E, Núñez C. Influence of HLA on clinical and analytical features of pediatric celiac disease. *BMC Gastroenterol* 2019; 19: 91.
- Tolone C, Piccirillo M, Dolce P, Alfiero S, Arenella M, Sarnataro M, et al. Celiac disease in pediatric patients according to HLA genetic risk classes: a retrospective observational study. *Ital J Pediatr* 2021; 47: 107.