Open Access

Original Article

Human Leukocyte Antigen (HLA) DQ2 and DQ8 Haplotypes in Children with Celiac Disease

Ifnan Shamraiz, Shaista Naz*, Saba Idrees, Farooq Ikram, Husna Khan, Samina Khan

Department of Paediatric Gastroenterology & Hepatology, Combined Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan, *Department of Paediatric Oncology, Combined Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan,

ABSTRACT

Objective: To determine the frequency of human leukocyte antigen-DQ2 and -DQ8 haplotypes in children with celiac disease in a tertiary care hospital.

Study Design: Comparative cross-sectional study.

Place and Duration of Study: Paediatric Gastroenterology and Hepatology Departments Combined Military Hospital, Rawalpindi Pakistan, from Feb 2022 to Feb 2023.

Methodology: Diagnosed cases of celiac disease, from 1 to 15 years old, were selected as Cases (n=50), and an equal group of normal children of the same age as Control (n=50), were selected. Polymerase chain reaction for Human Leukocyte antigen (Human leukocyte antigen -DQ) genotyping was performed on all children.

Results: The most frequently observed haplotype was DQ2, followed by DQ8. Among celiac patients, 94% tested positive for human leukocyte antigen-DQ, with 82% DQ2, 10% DQ8, and 2% DQ2/DQ8 positive. 6% were negative for any HLA-DQ allele, while only 8% were DQ2 positive in the control group. The frequency of human leukocyte antigen -DQ between the two groups was statistically significant (p-value<0.05). The association between anti-tissue transglutaminase antibody levels and human leukocyte antigen -DQ was also statistically significant (p-value<0.05). Biopsy findings and gender had no statistically significant association with human leukocyte antigen -DQ (p-value>0.05).

Conclusion: Celiac disease has a varied spectrum of presentation, which often goes unrecognized by physicians. Therefore, genetic testing can be used as an additional diagnostic tool to reduce ambiguity and improve the accuracy of celiac disease diagnosis.

Keywords: Celiac disease, Gluten, Human leukocyte antigen (HLA).

How to Cite This Article: *Shamraiz I, Naz S, Idrees S, Ikram F, Khan H, Khan S. Human Leukocyte Antigen (HLA) DQ2 and DQ8 Haplotypes in Children with Celiac Disease. Pak Armed Forces Med J 2025; 75(1): 199-204. DOI: https://doi.org/10.51253/pafmj.v75i1.10651*

INTRODUCTION

Numerous diseases are linked to the human leukocyte antigen (HLA) gene family, which predisposes to various diseases, including celiac disease (CD), an autoimmune enteropathy due to a hypersensitivity reaction to Gluten. When ingested, Gluten is a protein present in wheat, rye, and barley, damaging the small intestine, especially the duodenum.[1] Gluten is broken down into smaller peptides, particularly gliadin. Gliadin is harmful to individuals with genetic susceptibility. This activates the innate and adaptive response of the immune system. Individuals with celiac disease have major histocompatibility complex (MHC) class II genes found on chromosome-6, which encode specific heterodimers called HLA-DQ2 or HLA-DQ8. These HLA molecules get activated by gliadin. A B-cell response is initiated by this interaction, which leads to the production of three types of antibodies: anti-gliadin, immunoglobulin A (IgA) anti-tissue transglutaminase (IgA-tTG), and anti-endomysium (IgA-EMA). Additionally, cytokines are also released by the T-cells. Enterocytes are damaged by these combined inflammatory reactions, which ultimately lead to villous atrophy.[2,3]

Villous atrophy causes malabsorption with a range of symptoms such as diarrhoea, anaemia, growth retardation, lethargy, constipation, abdominal pain and in chronic cases, potential complications such as osteoporosis, dental enamel defects, reproductive disorders, short stature and dermatitis herpetiformis may occur.[3,4] Celiac disease is usually diagnosed by detecting anti-gliadin, anti-endomyseal, and more commonly, anti-tissue transglutaminase antibodies in the blood samples by enzyme-linked immunosorbent assay (ELISA).[5] Intestinal biopsy is done for further confirmation of the diagnosis, as recommended by the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN).[6]

The genetic predisposition to celiac disease involves the HLA class II genes that encode the MHC-II heterodimers, HLA-DQ2 and HLA-DQ8, consisting of alpha and beta chains encoded by the HLA-

Correspondence: Dr Ifnan Shamraiz, Department of Paediatric Gastroenterology, Combined Military Hospital, Rawalpindi Pakistans

Received: 19 Jul 2023; revision received: 26 Oct 2023; accepted: 01 Nov 2023

DQA1∗05–DQB1∗02 (DQ2) and DQA1∗03–DQB1∗03:02 (DQ8) genes, respectively. HLA-DQA1 and HLA-DQB1 genes are the main determinants encoding for HLA-DQ2 and HLA-DQ8 molecules.[5,6]

HLA-DQ2 or HLA-DQ8 haplotypes occur in more than 90% of the patients with celiac disease. Therefore, it is instrumental in decreasing the burden of further diagnostic workups because of its high negative precadability.[7]

HLA-DQ genotyping is very helpful for the early and precise diagnosis of celiac disease. It can identify atypical or latent CD and celiac disease forms in patients with IgA deficiency. It can also prove beneficial in assessing the genetic predisposition to the disease. It can also differentiate between celiac disease and other childhood gastrointestinal disorders with similar presentation. It is also helpful for individuals with coexisting autoimmune and non-autoimmune conditions, such as Down syndrome and Turner syndrome, which are known to have associations with CD.[8,9]

Although most patients carry either HLA-DQ2 or -DQ8, data regarding its exact prevalence and distribution is lacking in our region. Very few studies have been done in this field in our country. This study focused on documenting the prevalence of HLA-DQ genotypes and distribution of specific alleles associated with celiac disease (namely HLA-DQA1∗05, -DQB1∗02, and -DQB1∗02:03) in paediatric patients.

METHODOLOGY

The comparative cross-sectional study was conducted at the Paediatric Gastroenterology and Hepatology Departments, Combined Military Hospital, Rawalpindi, Pakistan where all paediatric patients diagnosed with celiac disease, were enrolled from February 2022 to February 2023. Approval for the study was obtained from the Institutional Review Board/ ERC (Serial No. 323).

Inclusion Criteria: Diagnosed (through serological and intestinal biopsy) patients of celiac disease, from 1 year to 15 years, were included in the Celiac Group, while participants in the Control Group were normal children of the same age with negative anti-tissue transglutaminase antibodies.

Exclusion criteria: Celiac patients with celiac crises, patients with IgA deficiency, celiac patients with diabetes mellitus, patients with positive anti-endomysial antibodies (EMA) or anti-gliadin antibodies (AGA) but negative anti-tissue transglutaminase antibodies and biopsy were excluded.

Participants were divided into Cases and Control Groups. The sample size was calculated using the WHO calculator, taking the worldwide prevalence of celiac disease as 1%.[9] Each group had an equal number (n=50) of participants. All patients were enrolled consecutively after giving informed consent. The data was obtained during indoor stays and scheduled outpatient visits.

Fresh blood (3mL) was drawn from all the individuals in ethylenediamine tetra-acetic acid tubes and sent for polymerase chain reaction by sequence-specific primers (PCR-SSP). PCR amplification of celiac disease susceptible alleles was used to rapidly type the HLADQA1∗05, DQB1∗02, and DQB∗03:02 alleles, the known celiac-specific HLA-DQ variants.

Statistical analysis and data interpretation were done using Statistical Package for the Social Sciences (SPSS) version 21.0. Quantitative variables with normal distribution were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages. The association between different categories was measured using the Chi-square test. The *p*-value of 0.05 or less was taken as significant.

RESULTS

Fifty known cases of celiac disease were included in the celiac group; 24(48%) were males, and 26(52%) were females. In the non-Celiac Group, males were 22(44%), and females were 28 with a mean of 6.69±3.829 years.

All of the celiac patients were diagnosed by anti-TTGs (more than 10 IU was taken as positive), and intestinal (duodenal) biopsies were performed on all celiac patients. Biopsy findings were categorized according to the Modified Marsh classification. Controls having anti-TTGs less than 10 IU/ml were labelled as negative. The most common documented levels of the anti-TTGs were > 200 IU/ml and < 300 IU/ml, accounting for 20 % of the total, followed by 17% of >300 IU/ml and < 400 IU/ml. Marsh Type-3a was the most common histological finding on biopsy reported in 46% of cases, as shown in Table-I.

All the positive celiac patients and normal children were tested for HLA-DQ genotypes. The results of HLA typing are summarized in Table-II. The individuals were termed according to the presence of HLA alleles. Subjects carrying both HLADQA1∗05, HLA-DQB1∗02 were: DQ2, Subjects carrying only

HLA-DQB1∗03:02 were: DQ8. The presence of HLA-DQB1∗03:02 was sufficient to tell that a celiac patient was positive for DQ8 molecule). Subjects carrying all three alleles HLA-DQA1∗05, HLADQB1∗02, and HLA-DQB1∗03:02 were DQ2/DQ8 (heterozygous for beta chain). The overall percentage of HLA-DQ in celiac patients was 94%. Dissemination of DQA1∗05, DQB1∗02, and DQB1∗03:02 alleles within the celiac patients was as follows: DQ2 was the most common observed type in 42(82%), followed by DQ8 in 5(10%) and DQ2/DQ8 in 1(2%). HLA-DQ genotyping was negative in 3 (6%). Only HLA-DQ2 was observed in 4 (8%) children in the controls. The prevalence of HLA-DQ between the two groups (94% vs 8%) was statistically significant (p-value<0.05) (Table-II). The association of gender and type of Modified Marsh classification with HLA-DQ was statistically insignificant (p-value>0.05), while the association between the serum levels of anti-tissue transglutaminase antibodies with HLA-DQ was statistically significant (p-value <0.05) as shown in the Table-III.

Table-I: Laboratory Findings: Intestinal Biopsy and Anti-Tissue Transglutaminase Antibodies and (n=100)

Clinical Parameters	Categories	n (%)
Anti-tissue transglutaminase Antibodies (n=100)	<10 IU/ml	50(50)
	>10 IU/ml <100 IU/ml	7(7)
	>100 IU/ml <200 IU/ml	4(4)
	>200 IU/ml <300IU/ml	20(20)
	>300 IU/ml <400 IU/ml	17(17)
	>400 IU/ml	2(2)
	Total	100(100)
Biopsy Findings (Modified Marsh Classification) (n=50)	Type-2	3(6)
	Type-3a	12(24)
	Type-3b	12(24)
	Type-3c	23(46)
	Total	50 (100)

DISCUSSION

In the local population of Pakistan, gastrointestinal diseases are widespread, mainly due to unhygienic and poor nutritional status. A common autoimmune celiac disease involving the gastrointestinal tract often goes undiagnosed by healthcare professionals.[7] The prevalence of celiac disease in the general population is estimated to be 1% in the world.[8-10] The seroprevalence of celiac disease and a biopsy-proven prevalence of celiac disease in the world is 1.4% and 0.7%, respectively. It is very important to diagnose the disease at early stages, which is critical for timely treatment and management. In Pakistan, it is typically diagnosed by serological testing for anti-tissue transglutaminase (anti-TTG) antibodies, followed by confirmation through intestinal biopsy.[11] However, new guidelines proposed by reputable organizations such as the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN), the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), and the British Society of Gastroenterology (BSG) have introduced updated recommendations in this regard. HLA-DQ genotyping-based diagnosis is highly valuable. If both HLA-DQ2 and HLA-DQ8 haplotypes are absent in the patients, they are unlikely to have celiac disease. It may eliminate the need for further workup.[7]

Table-II: Distribution of Human Leukocyte Antigen (HLA-DQ) in Celiac (n=50) and Non-Celiac Groups (n=50)

Human Leukocyte Antigen HLA-DQ TYPE	Cases, N=50	Control, N=50	p-value
DQ-2	41(82)	4(8)	<0.001
DQ-8	5(10)	0(0)	
DQ-2/8	1(2)	0(0)	
Negative	3(6)	46(92)	
Total	50(100)	50(100)	

In certain situations where chances of false negative results are high, like patients with IgA deficiency, HLA-DQ typing may help to clear the diagnostic ambiguity. Some studies have even reported instances of incorrect diagnosis, where celiac disease was confirmed through intestinal biopsy despite the absence of DQ2/DQ8 alleles. In order to enhance the accuracy of diagnosis, genetic testing should be applied along with serology to enhance the diagnostic accuracy further.[12]

According to our research findings, many individuals exhibited HLA-DQ positivity. This outcome was closely aligned with the outcomes observed in a previous study conducted in Pakistan by Siddiqui *et al.*, on a cohort of individuals from the Sindh region, where 85.7% exhibited the HLA-DQ2 allele,11.4% HLA-DQ8 allele with a minor subset 2.8% displaying the DQ2/DQ8 allele similar to our study where HLA-DQ2 was present in 82%, HLA-DQ8 in 10% and HLA-DQ2/8 was present in 2% in celiac patients. A subset of patients, 5.7%, tested negative

Table-III: Association of Human Leukocyte Antigen with Gender, Anti-Tissue Trans-Glutaminase Antibodies and Marsh Classification type in Celiac Patients (n=50)

Clinical Parameters	Categories	Human Leukocyte Antigen HLA-DQ Types				*p*-value
		HLA DQ-2, N=41	HLA DQ-8, N= 5	HLA DQ-2/8, N=1	Negative, N=3	
Gender	Male	21(51.2)	1(20)	1(100)	1(33.3)	0.257
	Female	20(48.8)	4(80)	0(0)	2(66.7)	
	Total	41(100)	5(100)	1(100)	3(100)	
Modified Marsh Classification	Type-2	3(7.3)	0(0)	0(0)	0(0)	0.512
	Type-3a	8(19.5)	1(20)	1(100)	2(66.7)	
	Type-3b	10(24.4)	1(20)	0(0)	1(33.3)	
	Type-3c	20(48.8)	3(60)	0(0)	0(0)	
	Total	41(100)	5(100)	1(100)	3(100)	
Anti-Tissue Trans-Glutaminase Antibodies	> 10 IU/ml < 100 IU/ml	6(14.6)	0(0)	0(0)	1(33.3)	< 0.001
	> 100 IU/ml < 200 IU/ml	3(7.3)	0(0)	1(100)	0(0)	
	>200 IU/ml <300 IU/ml	15(36.6)	3(60)	0(0)	2(66.7)	
	>300IU/ml < 400 IU/ml	15(36.6)	2(40)	0(0)	0(0)	
	> 400 IU/ml	2(4.9)	0(0)	0(0)	0(0)	
	Total	41(100)	5(100)	1(100)	3(100)	

for all three alleles, mirroring the 6% negative HLA-DQ status observed in our study. The research revealed 8.5% positivity for HLA-DQ2 in normal children, similar to our findings of 8% in normal children, while HLA-DQ8 and DQ2/8 were absent in normal children.[7]

Another Pakistani study by Alam et al., reported that the occurrence of HLA-DQ2 was higher among celiac disease (93%) patients as compared to healthy patients (20%). The frequency of HLA-DQ8 was 4% in celiac disease patients compared to 2% in healthy subjects. This study included both adults and children, contrary to our study, which was conducted on children only.[13] Similarly, in the European paediatric population with celiac disease, Krini *et al*., reported that the allele frequency for HLA-DQ2 stands at 84.75%, whereas approximately 11.02% of individuals are negative for any HLA-DQ2 or DQ-8 allele.[14]

A study conducted at the University Children's Hospital in Belgrade, Serbia, by Stanković *et al*., l revealed that 94.5% harboured alleles responsible for encoding the DQ2 protein variant. In contrast, a smaller proportion, 2.7%, possessed alleles associated with the DQ8 protein variant and 25.8% HLA-DQ2 positivity in normal children.[15]

A similar case-control study conducted in Iran by Rostami-Nejad *et al*., demonstrated that 97% of individuals diagnosed with celiac disease were carriers of HLA-DQ2 and/or HLA-DQ8 heterodimers, either in the homozygous or heterozygous state as compared to our study where 94% celiac patients were positive for HLA-DQ. However, 3% diagnosed with celiac disease tested negative for both DQ2 and DQ8 alleles in the aforementioned study, with a 25.4% prevalence of HLA-DQ 2 in the control group, which is relatively high as compared to our study (8%).[16] Similarly Megiorni *et al*., reported HLA- DQ2 in 90-95% of individuals diagnosed with celiac disease.[17]

In contrast, studies conducted in Northern India (Rajasthan) by Pareek *et al*., and in Turkey by Sahin *et al*., reported a higher prevalence of HLA DQ2/DQ8 genotypes in 100% and 98.2%, respectively, with a 23.1% positivity in controls in an Indian study.[18,19]

On the other hand, contrary to our research, Selleski *et al*., conducted a case-control study among a cohort of Brazilian children diagnosed with celiac disease, found that out of the 100 participants, 78(78%) tested positive for the DQ2 allele. In contrast, 13(13%) exhibited the DQ2/DQ8 composite allele, and 6(6%) displayed positivity for the DQ8 allele while the HLA-DQ pattern in the 110 non-celiac children was as follows: DQ2 was positive in 33(29.9%), DQ2/8 was positive in (1.8%), and DQ8 was positive in15 (13.6%).[20] In contrary to above findings a low prevalence of HLA-DQ2 was reported as 77.6%,72%, 68%, in different studies.[21,22,23]

The association of gender with HLA-typing was insignificant (*p*-value >0.05), which was in accordance with the previous studies.[22,23] The association of anti-TTGs with HLA-DQ typing was significant in a study performed in India by Pareek *et al*., and in Brazil by Selleski *et al*.[18,20] These findings were similar to the

significant association found in our study (p-value<0.001). We did not find any significant association of Marsh classification with HLA-DQ typing (p-value=0.512) in contrast to the findings by Salarian *et al.*, in Iran.[24]

Castillejo *et al*., in Spain, revealed that HLA-DQ typing can eliminate the need for intestinal biopsy without compromising diagnostic accuracy in suspected celiac patients. HLA-DQ genotyping combined with serological evaluation can have a high negative predictive value.[25] The significant differences in the frequency of HLA-DQ2 and HLA-DQ8 alleles in Syrian patients compared with controls highlight the possibility of using HLA-DQ typing to confirm the disease.[21]

This approach can be helpful for histological and immunological uncertainties. Furthermore, negative genetic testing using this method can effectively exclude unnecessary treatment and follow-up procedures.

CONCLUSION

There is insufficient data regarding the overall prevalence of celiac disease in the Pakistani population. The prevalence of HLA-DQ genetic markers varies across geographical locations, emphasising the importance of comprehensive data specific to our region. Consequently, to enhance diagnostic accuracy, including HLA genotyping for children suspecting celiac disease and serology or intestinal biopsy is advisable.

Conflict of Interest: None.

Funding Source: None.

Authors' Contribution

The following authors have made substantial contributions to the manuscript as under:

IS & SN: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

SI & FI: Data acquisition, data analysis, approval of the final version to be published.

HK & SK: Critical review, concept, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Aziz DA, Kahlid M, Memon F, Sadiq K. Spectrum of celiac disease in paediatric population: Experience of tertiary care center from Pakistan. Pak J Med Sci 2017; 33(6): 1301-1306. https://doi.org/10.12669/pjms.336.13489
2. Al-Toma A, Volta U, Auricchio R, Castillejo G, Sanders DS, Cellier C, et al. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. United European Gastroenterol J 2019; 7(5): 583-613. https://doi.org/10.1177/2050640619844125
3. Lodhi M, Saleem Z, Ayub A, Munir T, Hassan S. Epidemiology of celiac disease in the children presenting at the tertiary care hospital of Pakistan. Pak Armed Forces Med J 2022; 72(1): 299-302. https://doi.org/10.51253/pafmj.v72i1.8293
4. Javed F, Sattar F, Gill A, Lodhi Y, Iqbal K, Nazir A, et al. Clinical Spectrum of Celiac Disease in Children: Experience from A Public Hospital in Pakistan. Ann Punjab Med Coll 13(3): 192-196. https://doi.org/10.29054/apmc/2019.145
5. Sciurti M, Fornaroli F, Gaiani F, Bonaguri C, Leandro G, Di Mario F, et al. Genetic susceptibilty and celiac disease: what role do HLA haplotypes play? Acta Biomed 2018; 89(9-S): 17-21. https://doi.org/10.23750/abm.v89i9-S.7953
6. Jamila, Kiani AR, Ahmed I, Yousafzai JK, Mehmood W, Khan SA, et al. Celiac disease in different age groups and gender in Pakistan. J Rawalpindi Med Coll 2018; 22(3): 244-247.
7. 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 2021; 100(11): e24954. https://doi.org/10.1097/MD.0000000000024954
8. Aboulaghras S, Piancatelli D, Oumhani K, Balahbib A, Bouyahya A, Taghzouti K, et al. Pathophysiology and immunogenetics of celiac disease. Clin Chim Acta 2022; 528: 74-83. https://doi.org/10.1016/j.cca.2022.01.022
9. Catassi C, Verdu EF, Bai JC, Lionetti E. Coeliac disease. Lancet 2022; 399(10344): 2413-2426. https://doi.org/10.1016/S0140-6736(22)00794-2
10. Lindfors K, Ciacci C, Kurppa K, Lundin KEA, Makharia GK, Mearin ML, et al. Coeliac disease. Nat Rev Dis Primers 2019; 5(1): 3. https://doi.org/10.1038/s41572-018-0054-z
11. Saleem N, Ali S, Ahmed TA, Iqbal M, Bashir M. HLA-DR alleles among Pakistani patients of coeliac disease. J Pak Med Assoc. 2013; 63(10): 1271-1274.
12. Poddighe D, Capittini C. The role of HLA in the association between IgA deficiency and celiac Disease. Dis Markers 2021; 2021: 8632861. https://doi.org/10.1155/2021/8632861
13. Alam M, Tipu HN, Ahmad D, Hussain M, Khalid UB, Ijaz N, et al. HLA-DQ2 and HLA-DQ8 Alleles in celiac disease patients and healthy controls. J Coll Physicians Surg Pak 2022; 32(2): 157-160. https://doi.org/10.29271/jcpsp.2022.02.157
14. Krini M, Chouliaras G, Kanariou M, Varela I, Spanou K, Panayiotou J, et al. HLA class II high-resolution genotyping in Greek children with celiac disease and impact on disease susceptibility. Pediatr Res 2012; 625–630. https://doi.org/10.1038/pr.2012.133
15. Stanković B, Radlović N, Leković Z, Ristić D, Radlović V, Nikčević G, et al. HLA genotyping in pediatric celiac disease patients. Bosn J Basic Med Sci 2014; 14(3): 171-6. https://doi.org/10.17305/bjbms.2014.3.28
16. 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 patients. World J Gastroenterol 2014; 20(20): 6302-6308. https://doi.org/10.3748/wjg.v20.i20.6302

17. 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(1): 88. https://doi.org/10.1186/1423-0127-19-88
18. Pareek S, Gupta RK, Sharma A, Gulati S. Human leukocyte antigen-DQ genotyping in pediatric celiac disease. Pediatr Gastroenterol Hepatol Nutr 2023; 26(1): 50-57. https://doi.org/10.5223/pghn.2023.26.1.50
19. Sahin Y, Mermer S. Frequency of celiac disease and distribution of HLA-DQ2/DQ8 haplotypes among siblings of children with celiac disease. World J Clin Pediatr 2022; 11(4): 351-359. https://doi.org/10.5409/wjcp. v11.i4.351
20. Selleski n, Almeida IM, Almeida FC de, Pratesi CB, Nóbrega YK de M, Gandolfi I, et al. prevalence of celiac disease predisposing genotypes, including hla-dq2.2 variant, in Brazilian children. Arq Gastroenterol 2018; 55(1): 82–85. https://doi.org/10.1590/s0004-2803.201800000-16
21. Murad H, Jazairi B, Khansaa I, Olabi D, Khouri L. HLA-DQ2 and -DQ8 genotype frequency in Syrian celiac disease children: HLA-DQ relative risks evaluation. BMC Gastroenterol 2018; 18: 70. https://doi.org/10.1186/s12876-018-0802-2
22. Jafari SA, Chaichi Z, Hammoud M, Kianifar H, Mir F. HLADQ2 and HLADQ8 alleles are associated with celiac disease in children. Int J Pediatr 2022; 10(8): 16498-16504. https://doi.org/10.22038/ijp.2022.64904.4908
23. Tian S, Weidong L, Ting L, Huan L, Wenjia H, Qiang L, et al. HLA-DQ genotype distribution and risk evaluation of celiac disease in Northwest China. Scand J Gastroenterol 2023; 58: 5, 471-476. https://doi.org/10.1080/00365521.2022.2147801
24. Salarian L, Khavaran M, Dehghani SM, Mashhadiagha A, Moosavi SA, Rezaeianzadeh S, et al. Extra-intestinal manifestations of Celiac disease in children: their prevalence and association with human leukocyte antigens and pathological and laboratory evaluations. BMC Pediatr 2023; 23(1): 8. https://doi.org/10.1186/s12887-022-03826-w
25. Castillejo G, Ochoa-Sangrador C, Pérez-Solís D, Cilleruelo ML, Donat E, García-Burriel JI, et al. Coeliac Disease Case–Control Study: Has the time come to explore beyond patients at risk? Nutrients 2023; 15(5): 1267. https://doi.org/10.3390/nu15051267