

## Retrospective Study

## Frequency of celiac disease and distribution of HLA-DQ2/DQ8 haplotypes among siblings of children with celiac disease

Yasin Sahin, Serdar Mermer

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## Abstract

## BACKGROUND

Celiac disease (CD) is a multifactorial disease, but genetic factors play a major role in its etiology. It has been known that human leucocyte antigen (HLA)-DQ2/DQ8 haplotypes are one of the most important predisposing genetic factors. The risk of developing CD in first-degree relatives and especially siblings of celiac patients is quite high because of having the same HLA haplotypes.

## AIM

To evaluate the frequency of CD and the distribution of the HLA-DQ2/DQ8 haplotypes in siblings of celiac patients.

## METHODS

Patients with biopsy-proven CD and their siblings were included in the study; those who did not have HLA genotyping were excluded from the study. All siblings were on a gluten-containing diet. The HLA genotyping, tissue transglutaminase antibody IgA antibody test, and total IgA test were performed in all participants.

## RESULTS

A total of 57 celiac patients and their 112 siblings were included in the study. The mean age of celiac patients and siblings were  $10.30 \pm 3.87$  years and  $9.90 \pm 6.11$  years, respectively. HLA-DQ2/DQ8 alleles were detected in 98.2% of patients with CD and 90.2% of siblings of celiac patients. HLA-DQ genotypes were present in all siblings diagnosed with CD. Tissue transglutaminase antibody IgA test was found to be positive in 16 siblings. CD was diagnosed in 12 siblings (10.7%) by intestinal biopsy.

## CONCLUSION

The prevalence of CD was found to be 10.7% in siblings of celiac patients in our study. One-third of the siblings diagnosed with CD were asymptomatic. We detected HLA-DQ alleles in 98.2% of celiac patients and 100% in siblings diagnosed with CD. In addition, 1 of the 2 siblings was diagnosed with CD 1 year later and the other 4 years later. Therefore, we suggest that siblings of celiac patients should be followed up with clinical findings as well as HLA analysis and serological examination. Since the risk of developing CD is much higher in asymptomatic siblings, we recommend that siblings should be screened for CD even if they are asymptomatic.

**Key Words:** Celiac disease; Frequency; Genetic; HLA haplotypes; Intestinal biopsy; Siblings

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**Core Tip:** Celiac disease (CD) is a multifactorial disease, but genetic factors play a major role in its etiology. Human leucocyte antigen-DQ2/DQ8 haplotypes are one of the most important predisposing genetic factors. We detected human leucocyte antigen-DQ alleles in 98.2% of celiac patients and 100% in siblings diagnosed with CD. Also, 1 of the 2 siblings was diagnosed with CD 1 year later and the other 4 years later. Siblings of celiac patients should be followed up with clinical findings and human leucocyte antigen analysis and serological examination. We recommend that siblings should be screened for CD even if they are asymptomatic.

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## INTRODUCTION

Celiac disease (CD) is a systemic autoimmune disease triggered by gluten intake in genetically susceptible individuals characterized by various degrees of small intestinal damage[1]. It is a multifactorial disease, but genetic factors play a major role in its etiology. It has been known that human leucocyte antigen (HLA)-DQ2/DQ8 genotypes are one of the most important predisposing genetic factors[2-4].

The risk of developing CD in first-degree relatives and especially siblings of celiac patients is quite high due to having the same HLA genotypes and environmental triggers such as gut microbiome[5-8]. It has been reported that the risk of developing CD is higher in siblings of celiac patients compared to other first-degree relatives[9-11]. CD may be asymptomatic for years or even be diagnosed 10 years after the first symptom appears[12]. It has been reported that approximately half of the first-degree relatives of celiac patients newly diagnosed with CD are completely asymptomatic[2,8,10]. Early diagnosis of CD is very important for the prevention of long-term complications of CD such as osteoporosis, growth retardation, infertility, and malignancy.

Although there are many studies on the frequency of CD in first-degree relatives of celiac patients, the number of studies investigating the frequency of CD and the distribution of HLA-DQ2/DQ8 in siblings of celiac patients is rare[8,10,13,14]. The aim of our study was to evaluate the frequency of CD and the distribution of HLA-DQ2/DQ8 haplotypes in siblings of celiac patients.

## MATERIALS AND METHODS

This study was carried out between February 2017 and June 2020. Patients with biopsy-proven CD and their siblings were included in the study; those who did not have HLA genotyping were excluded from the study. All siblings were on a gluten-containing diet. The current study was approved by the Local Ethics Committee (Toros University, Mersin, Turkey, 17.06.2020/41). The patient who was first diagnosed with CD was defined as an index case.

CD was diagnosed according to the European Society for Paediatric Gastroenterology, Hepatology and Nutrition 2012 guidelines[2]. In total, 57 celiac patients and their 112 siblings were included in the study. Three patients who did not have any siblings were not included in the study. The HLA genotyping, tissue transglutaminase antibody (tTG) IgA antibody test, and total IgA test were performed in all participants. tTG IgA antibody levels were measured by enzyme-linked immuno-

sorbent assay method (Diametra, Spello PG, Italy). The cutoff value for tTG IgA was 20 U/mL. Total IgA levels were measured by nephelometric method (Siemens Diagnostics, Marburg, Germany).

Gastroduodenoscopy and small intestinal biopsy were performed in all patients with tTG positivity. Four biopsies from the duodenum and at least one biopsy from the bulb were obtained. All intestinal biopsy specimens were evaluated according to the modified Marsh-Oberhuber classification[15] as follows: Marsh stage 0: normal mucosa; Marsh stage 1: increased intraepithelial lymphocytosis (> 40 lymphocytes per 100 epithelial cells); Marsh stage 2: increased intraepithelial lymphocytosis with crypt hyperplasia; Marsh stage 3a: increased intraepithelial lymphocytosis with crypt hyperplasia and partial villous atrophy; Marsh stage 3b: increased intraepithelial lymphocytosis with crypt hyperplasia and subtotal villous atrophy; and Marsh stage 3c: increased intraepithelial lymphocytosis with crypt hyperplasia and total villous atrophy. If the pathology result was compatible with Marsh stage 2 or stage 3, the patient was diagnosed with CD.

### Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences software version 22.0 (SPSS Inc; Chicago, IL, United States). Frequency, percentage, and mean  $\pm$  standard deviation were used as descriptive statistics. Independent sample *t*-test was used for nominal data. The Mann-Whitney *U* test was used to compare groups of numerical variables.  $\chi^2$  test was used for comparison of categorical variables.

## RESULTS

A total of 57 celiac patients and their 112 siblings were included in the study. Of 112 siblings, 54 (48.20%) were female; 33 (57.89%) of the 57 celiac patients were female. The mean age of celiac patients and siblings were  $10.30 \pm 3.87$  years and  $9.90 \pm 6.11$  years, respectively (Table 1).

HLA-DQ2/DQ8 alleles were detected in 98.2% of patients with CD and 90.2% of siblings of celiac patients (Table 2). A total of 57 celiac patients (57.9%) had HLA-DQ2, 29.8% had HLA-DQ2/DQ8, and 10.5% had HLA-DQ8. Both alleles were found to be negative in 1.8% of them. HLA-DQ genotypes were present in all siblings diagnosed with CD (Table 3). tTG IgA test was found to be positive in 16 siblings. CD was diagnosed in 12 siblings by intestinal biopsy (Table 3). The pathology result of 10 siblings was compatible with Marsh stage 3. The prevalence of CD was found to be 10.7% in siblings of celiac patients in our study, and this rate was 22.7 times higher than the general population. Gastroduodenoscopy could not be performed in 4 of 16 siblings because of parental refusal. Out of 100 cases not diagnosed with CD, 59 had HLA-DQ2 positivity, 16 had HLA-DQ2/DQ8 positivity, 14 had HLA-DQ8 positivity, and 11 were negative for HLA-DQ2 and HLA-DQ8.

Seven of those twelve celiac patients had anemia, six of them had growth retardation, and four of them had no symptoms. HLA-DQ alleles were also positive in all 4 patients who refused to undergo gastroduodenoscopy. No IgA deficiency was detected in either group. Two siblings of three index cases were diagnosed with CD. The first sibling of the first index case was diagnosed 2 mo later, and the second sibling 1 year later (when looking at the second serology). The first sibling of the second index case was diagnosed with CD 4 years later (in the second serology examined with an interval of 2 years), and the second sibling was diagnosed with CD 4 mo after the first. The two siblings of the other index case were also diagnosed with CD within 3 mo.

## DISCUSSION

The estimated prevalence of CD is 1% in the world, and this rate varies in different geographical regions [2,16]. The reason of that may be due to differences in genetic susceptibility and changes in dietary gluten intake.

With the identification of the major role of HLA-DQ2/DQ8 in genetically susceptible individuals, it has been reported that the negative detection of both HLA-DQ2 and HLA-DQ8 in first-degree relatives of celiac patients does not require further investigation for CD[17,18]. On the contrary, it has been reported that the risk of CD is higher in individuals with homozygous HLA-DQ2[19].

In the European Society for Paediatric Gastroenterology, Hepatology and Nutrition 2012 guidelines, HLA genotyping is recommended as the initial screening test for CD especially in risk groups such as first-degree relatives of celiac patients[2]. It has been shown that HLA-DQ analysis is helpful in predicting CD especially in first-degree relatives of celiac patients[20-22]. The absence of HLA-DQ2 and HLA-DQ8 most likely excludes CD, but celiac specific antibody tests are required to diagnose CD in the presence of those alleles[20]. While some authors have suggested that HLA analysis can be used in the diagnosis of CD, others have suggested that it is a good alternative for determining genetic predisposition[23,24].

**Table 1 The demographic and laboratory characteristics of celiac patients and their siblings**

	Celiac patients, <i>n</i> = 57	Siblings, <i>n</i> = 112	<i>P</i> value
Age (yr)	10.30 ± 3.87	9.90 ± 6.11	0.648
Sex (female/male)	33/24	54/58	0.234
Height (cm)	132.71 ± 20.29	130.27 ± 31.37	0.594
Weight (kg)	30.44 ± 12.82	33.22 ± 19.18	0.325
Hb (g/dL)	11.65 ± 3.87	12.71 ± 1.56	< 0.001
tTG IgA (U/mL)	108.65 ± 60.61	17.24 ± 41.14	< 0.001
Total IgA (mg/dL)	155.43 ± 78.44	124.33 ± 71.47	0.014

Hb: Hemoglobin; tTG: Tissue transglutaminase antibody.

**Table 2 The distribution of human leucocyte antigen genotypes of celiac patients and their siblings**

HLA genotypes	Celiac patients, <i>n</i> = 57 (100%)	Siblings, <i>n</i> = 112 (100%)
HLA-DQ2	33 (57.9)	68 (60.7)
HLA-DQ2/DQ8	17 (29.8)	18 (16.1)
HLA-DQ8	6 (10.5)	15 (13.4)
Both negative	1 (1.8)	11 (9.8)

HLA: Human leucocyte antigen.

**Table 3 The laboratory and clinical data of siblings of celiac patients diagnosed with celiac disease**

	Patient age at diagnosis (yr)	Symptoms	Hb (g/dL)	tTG (U/mL)	IgA (mg/dL)	HLA	Pathology
1	6	Failure to thrive, anemia	10.9	140	206	DQ2	Marsh 3a
2	8.5	-	13.4	94	87	DQ8	Marsh 3a
3	18	-	13.5	105	99	DQ2	Marsh 3a
4	4.3	Failure to thrive, anemia	10.4	46	33	DQ2	Marsh 3b
5	13.5	Failure to thrive, anemia	7.7	135	254	DQ2	Marsh 3b
6	5.5	Failure to thrive, anemia	11.7	35	66	DQ2	Marsh 3b
7	16.5	Anemia	11.7	41	86	DQ2	Marsh 3b
8	16	-	13.3	187	190	DQ2	Marsh 3b
9	14.5	-	14.3	37	179	DQ2/DQ8	Marsh 2
10	12	Anemia	11.9	46	122	DQ2/DQ8	Marsh 2
11	11.5	Failure to thrive	13.1	127	148	DQ2	Marsh 3a
12	10.5	Failure to thrive, anemia	10.9	34	70	DQ2	Marsh 3b

HLA: Human leucocyte antigen; Hb: Hemoglobin; tTG: Tissue transglutaminase antibody.

The prevalence of CD in siblings of celiac patients is 5.9%-18.3%[8,10,13,14,25]. As consistent with the literature, the prevalence of CD was found to be 10.7% in siblings of celiac patients in our study. Twelve siblings were diagnosed with CD by intestinal biopsy. Four siblings (25%) with positive tTG refused gastroduodenoscopy. In another study, the rate of those who did not accept biopsy (22.2%) was similar to our study[10]. The real prevalence of CD could not be estimated, as there were cases who refused the biopsy.

In a systematic review, it has been reported that the prevalence of CD in sisters of celiac patients is approximately two times higher than in brothers[25]. Contrary to this, the prevalence of CD was equal

in males and females in our study. The reason of that may be the study was cross-sectional, and 4 cases with positive serology did not accept endoscopy. For this reason, we may not have been able to fully determine the risk of CD. The other reason is that our study had a short follow-up period. Some seronegative individuals may be seropositive in the future and be diagnosed with CD.

In a multicenter study conducted in Europe, it was reported that 90% of celiac patients had the HLA-DQ2 genotype, and 5% to 10% of them had HLA-DQ8[26]. Those genotypes were found in 40%-65% of first-degree relatives of celiac patients and 18%-30% of the general population[10,11,27]. HLA-DQ8 positivity is higher in America, Asia, Chile, and Cuba compared to Europe[28-31]. In our study, 57.9% of celiac patients had HLA-DQ2, 29.8% had HLA-DQ2/DQ8, and 10.5% had HLA-DQ8. Both alleles were found to be negative in 1.8% of patients. HLA-DQ2/DQ8 ratios vary from region to region[26,28-31].

HLA analysis was performed on all siblings of celiac patients in the current study. HLA antigens were positive in 90.2% of siblings of celiac patients. As consistent with our study, HLA antigens were found to be positive in all siblings of celiac patients (100%) in another study conducted in our country [14].

In our study, out of 100 cases not diagnosed with CD, 59 had HLA-DQ2 positivity, 16 had HLA-DQ2/DQ8 positivity, 14 had HLA-DQ8 positivity, and 11 were negative for both HLA-DQ2 and HLA-DQ8. In a study with the same number of cases, 49 of 100 cases whose siblings of celiac patients were not diagnosed with CD had HLA-DQ2 positivity, 6 had HLA-DQ8 positivity, 2 had HLA-DQ2/DQ8 positivity, and 43 were negative for both HLA-DQ2 and HLA-DQ8[10]. The reason may be due to the HLA-DQ2/DQ8 ratios varying from region to region[26,28-31].

In the study by Bonamico *et al*[10], it was shown that the use of HLA genotyping as a first step can be used to exclude one-third of first-degree relatives, but it has been reported that patients negative for HLA-DQ2 and HLA-DQ8 can be overlooked. Also, it has been suggested that it may be more useful to evaluate the first-degree relatives of celiac patients together with tTG antibody test and HLA typing.

HLA antigens were detected in 94.7%-100% of siblings of celiac patients diagnosed with CD[10,14]. In parallel with the literature, HLA antigens were detected in all 12 siblings of celiac patients diagnosed with CD in our study.

It has been known that HLA-DQ alleles have a high prevalence among celiac patients[2,14,20,32,33]. Those alleles may determine susceptibility to CD in risk groups such as first-degree relatives of celiac patients[19]. It has been reported that the frequency of HLA-DQ2/DQ8 is high in risk groups such as first-degree relatives of celiac patients[2,34]. We found a high rate of positive HLA-DQ alleles in celiac patients and their siblings as compatible with the literature.

It has been reported that 30.0%-78.9% of siblings of celiac patients diagnosed with CD are asymptomatic[8,13,14,34]. As consistent with the literature, one-third of our patients were found to be asymptomatic. Since patients diagnosed with silent CD have a high prevalence, asymptomatic siblings of celiac patients should be screened for CD.

It has been suggested that HLA genotyping can be used to exclude 25%-33% of first-degree relatives from serological follow-up[10,23,35-37]. The absence of HLA-DQ alleles has a high negative predictive value for CD; positive results indicate only a genetic predisposition[38].

CD can occur at any age. A negative serological test once does not mean that there will be no CD in the future. Many studies have been conducted on serologically negative celiac patients[39-42]. In the study by Pittschieler *et al*[39], serological positivity was detected in 3 cases with HLA-DQ2 positivity after more than 10 years of follow-up, and then CD was diagnosed. In parallel with that study, CD was diagnosed in 1 of 2 cases with HLA-DQ2 positive 1 year later and the other 4 years later in our study. CD may be seen in any period of life. Since the follow-up period was short in our study, we think that other cases with positive HLA antigens may be diagnosed with CD in the future. Therefore, we recommend that cases in a high-risk group should be followed clinically and serologically.

In a Western cohort, only 0.5% of celiac patients were found to have HLA-DQ negativity[18]. In a recent study, it has been reported that HLA-DQ typing is insufficient to identify individuals susceptible to CD and could not be used to diagnose CD[43]. In another study conducted in Iran, HLA-DQ negativity was found to be 3.9%[44]. HLA-DQ2 and HLA-DQ8 were found to be negative in 5% of cases in another study[10]. In parallel with those studies, HLA-DQ antigens were found to be negative in 1.8% of celiac patients in our study. In those studies, it has been reported that the risk of developing CD is very low in cases with negative HLA-DQ. It has been suggested that cases negative for HLA-DQ2/DQ8 negative should be followed clinically and serologically every 2 years or 3 years[10]. For this reason, it has been suggested that HLA analysis would be more appropriate in cases where it is difficult to diagnose.

In a study conducted in healthy school children in our country, the prevalence of CD was found to be 0.47%[45]. In the current study, the prevalence of CD in siblings of celiac patients was found to be 10.7%. That is, we found that the prevalence was 22.7 times higher than in the general population.

One of the limitations of the study was that 15 celiac patients and their 28 siblings refused to participate in the study. If they did, the results would have been different, and the power of study would have been better. Another limitation was the short follow-up period. CD may develop over time in our serologically negative cases. For these reasons, we think that we were unable to estimate the real prevalence of CD.



## CONCLUSION

In conclusion, the prevalence of CD was found to be 10.7% in siblings of celiac patients in our study, and this rate was 22.7 times higher than the general population. One-third of the siblings diagnosed with CD were asymptomatic. We detected HLA-DQ alleles in 98.2% of celiac patients and 100% in siblings diagnosed with CD. Thus, CD has been shown to be associated with HLA-DQ2 and HLA-DQ8 genotypes. In addition, 1 of the 2 siblings was diagnosed with CD 1 year later and the other 4 years later. Therefore, we suggest that siblings of celiac patients should be followed up with clinical findings as well as HLA analysis and serological examination. Since the risk of developing CD is much higher in asymptomatic siblings, we recommend that siblings should be screened for CD even if they are asymptomatic.

## ARTICLE HIGHLIGHTS

### Research background

Celiac disease (CD) is a systemic autoimmune disease triggered by gluten intake in genetically susceptible individuals. It is a multifactorial disease, but genetic factors play a major role in its etiology. It has been known that human leucocyte antigen (HLA)-DQ2/DQ8 genotypes are one of the most important predisposing genetic factors. The risk of developing CD in siblings of celiac patients is quite high because of having the same HLA genotypes and environmental triggers such as gut microbiome.

### Research motivation

Although there are many studies on the frequency of CD in first-degree relatives of celiac patients, the number of studies investigating the frequency of CD and the distribution of HLA-DQ2/DQ8 in siblings of celiac patients is rare. Because of that, we aimed to evaluate the frequency of CD and the distribution of HLA-DQ2/DQ8 haplotypes in siblings of celiac patients.

### Research objectives

To investigate the frequency of CD and the distribution of HLA-DQ2/DQ8 haplotypes in siblings of celiac patients.

### Research methods

The current study was carried out between February 2017 and June 2020. Biopsy-proven celiac patients and their siblings were included in the study. CD was diagnosed according to the European Society for Paediatric Gastroenterology, Hepatology and Nutrition 2012 guidelines. In total, 57 celiac patients and their 112 siblings were included in the study. All siblings were on a gluten-containing diet. The HLA genotyping, tissue transglutaminase antibody IgA antibody test, and total IgA test were performed in all participants. Gastroduodenoscopy was performed in all patients with tissue transglutaminase antibody positivity. Four biopsies from the duodenum and at least one biopsy from the bulb were obtained. All intestinal biopsy specimens were evaluated according to the modified Marsh-Oberhuber classification.

### Research results

HLA-DQ2/DQ8 alleles were detected in 98.2% of patients with CD and 90.2% of siblings of celiac patients. Tissue transglutaminase antibody IgA test was found to be positive in 16 siblings. CD was diagnosed in 12 siblings by intestinal biopsy. Seven of those twelve celiac patients had anemia, six of them had growth retardation, and four of them had no symptoms.

### Research conclusions

The prevalence of CD was found to be 10.7% in siblings of celiac patients in our study, and this rate was 22.7 times higher than the general population. One-third of the siblings diagnosed with CD was asymptomatic. We detected HLA-DQ alleles in 98.2% of celiac patients and 100% in siblings diagnosed with CD. Thus, CD has been shown to be associated with HLA-DQ2 and HLA-DQ8 genotypes. In addition, 1 of the 2 siblings was diagnosed with CD 1 year later and the other 4 years later.

### Research perspectives

According to the current study, we suggest that the siblings of celiac patients should be followed up with clinical findings as well as HLA analysis and serological examination. Since the risk of developing CD is much higher in asymptomatic siblings, we recommend that siblings should be screened for CD even if they are asymptomatic.

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## FOOTNOTES

**Author contributions:** Sahin Y designed the study, analyzed the data, interpreted the data and wrote the manuscript; Mermer S designed the study and collected and analyzed the data; All authors had read and approved the final manuscript.

**Institutional review board statement:** The current study was approved by the Local Ethics Committee (Toros University, Mersin, Turkey, 17.06.2020/41).

**Informed consent statement:** Written informed consent was not obtained as the study is retrospective. However, the Local Ethics Committee approved the current study.

**Conflict-of-interest statement:** All the authors declare that they have no conflict of interest.

**Data sharing statement:** No additional data are available.

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**Country/Territory of origin:** Turkey

**ORCID number:** Yasin Sahin 0000-0002-7394-4884; Serdar Mermer 0000-0002-7810-258X.

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**L-Editor:** Filipodia

**P-Editor:** Liu JH

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