

Dear Editor,

Thank you very much for your kind response and worthy comments on our manuscript. We tried to make corrections according to your suggestions. All corrections were made and indicated in red text in the manuscript according to your suggestions.

Yours faithfully,

Associate Professor Yasin Sahin

Reviewers' Comments:

Reviewer #1:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Revision required First: findings need to be put in correct perspective Second: Highlight your new findings, if any Third: Chart out new approaches based on your findings correctly

Comments: First: findings need to be put in correct perspective

Response:

First, findings are put in correctly at the Result section of the manuscript according to your suggestions.

...

A total of 57 celiac patients, 57.9% of them had HLA-DQ2, 29.8% had HLA-DQ2/8 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). Tissue transglutaminase antibody 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 four of

16 siblings because of parental refusal. Out of 100 cases not diagnosed with CD, 59 had HLA-DQ2 positivity, 16 had HLA-DQ2/8 positivity, 14 had DQ8 positivity, and 11 had both negativity of HLA-DQ2 and 8....

Comments:

Second: Highlight your new findings, if any

Response: We have found little new findings. But the findings we found support the literature and are parallel to the literature. We highlighted our findings in the Result and Conclusion section of the manuscript as the following.

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 was shown to be associated with HLA-DQ2 and DQ8 genotypes. In addition, one of the two 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 developing risk of CD is much higher in asymptomatic siblings, we recommend that siblings should be screened for CD even if they are asymptomatic.

Comments:

Third: Chart out new approaches based on your findings correctly

Response: We highlighted our findings and approaches in the Conclusion section of the manuscript as the following.

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 was shown to be associated with HLA-DQ2 and DQ8 genotypes. In addition, one of the two 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 developing risk of CD is much higher in asymptomatic siblings, we recommend that siblings should be screened for CD even if they are asymptomatic.

Reviewer #2:

Scientific Quality: Grade D (Fair)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Specific Comments to Authors: This is a retrospective study evaluating prevalence of HLA haplotype of siblings with patients with CD. Methodology: needs more elaboration and details on type of laboratory kits, biopsy procedure, handling of biopsies, pathology reports, etc Results: poorly presented and needs major revision

Comments: Methodology: needs more elaboration and details on type of laboratory kits, biopsy procedure, handling of biopsies, pathology reports, etc

Response: According to your suggestion, the Method section of manuscript is corrected as the following.

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CD was diagnosed according to the ESPGHAN 2012 guidelines (2). 57 celiac patients and their 112 siblings were included in the study. Three patients who do 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 immunosorbent assay method (Diametra, Spello PG, Italy). The cut-off 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 duodenum and at least one biopsy from bulb were obtained. All intestinal biopsy specimens are evaluated according to modified Marsh-Oberhuber classification (16). 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....

Comments: Results: poorly presented and needs major revision

Response: According to your suggestion, the Result section of manuscript is corrected as the following.

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A total of 57 celiac patients, 57.9% of them had HLA-DQ2, 29.8% had HLA-DQ2/8 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). Tissue transglutaminase antibody 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 four of 16 siblings because of parental refusal. Out of 100 cases not diagnosed with CD, 59 had HLA-DQ2 positivity, 16 had HLA-DQ2/8 positivity, 14 had DQ8 positivity, and 11 had both negativity of HLA-DQ2 and 8.....