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Interleukin-6 and interleukin-17 gene polymorphism association with celiac disease in children

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ABSTRACT

Background/Aims: This study aimed to investigate polymorphisms in the genes responsible for encoding cytokines interleukin-6 (IL-6) (-572G/C) (rs1800796) and IL-17 (-197A/G) (rs2275913) in patients with celiac disease (CD). We further aimed to investigate the relationship between CD symptoms and histopathological findings and the relationship between these polymorphisms.

Materials and Methods: We compared the results with those of healthy control subjects to establish whether any of the polymorphisms are involved in the susceptibility to CD. Eighty-four patients with CD and 83 healthy controls were enrolled in this study. Children with CD were divided into two groups depending on whether their symptoms were typical or atypical. The IL-6 (-572G/C) and IL-17 (-197A/G) polymorphisms were genotyped based on a polymerase chain reaction coupled with restriction fragment length polymorphism.

Results: Significant differences for the IL-6 (-572G/C) polymorphism were observed between patients with CD and controls (p=0.018, odds ratio (OR): 5.47, 95% confidence interval (CI): 1.161-25.800). No statistically significant association was observed between the IL-17 (-197A/G) polymorphism and CD (p>0.05). In addition, the symptoms and histopathological findings of children with CD were not related to either of the polymorphisms.

Conclusion: The results of our study indicate that the IL-6 (-572G/C) polymorphism may play a role in susceptibility to CD.

Keywords: Celiac disease, Interleukin-6, Interleukin-17, single nucleotide polymorphism

Original Article

INTRODUCTION

Celiac disease (CD) is an immune-mediated, chronic inflammatory disease of the small intestine, which is characterized by permanent sensitivity to gluten in genetically predisposed individuals. A natural or acquired immune response is triggered by the intake of the peptide fraction of gluten, known as gliadin, in genetically predisposed individuals, followed by destruction of the intestinal epithelium and mucosa (1). This peptide interacts with grade II molecules of the human leukocyte antigen (HLA) cells on the surface, which produce an antigen through deamination by tissue transglutaminase in the lamina propria, and CD34 is made available to the T cells. Subsequently, proinflammatory cytokines are expressed and the characteristic histopathological changes observed in CD develop (2). Previous studies have shown that CD4 of T cells in the intestinal mucosa of patients with CD is related to HLA-DQ2 and/or HLA-DQ8 molecules, which recognize gluten peptides (3).

When interleukin-6 (IL-6) was stimulated with phytohemaglutinin or antigen for the first time, the B cell was identified as a differentiation factor in a peripheral mononuclear cell culture. In 1985, IL-6 was purified, and the amino acid alignment of IL-6 DNA was revealed in 1986 (4). The chromosomal location of IL-6 and its receptor is 7p21. The fact that a vast majority of IL-6 is expressed from active macrophages, the differentiation in the capacity of B lymphocytes to produce immunoglobulin and the fact that T cells are active are all im-

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portant factors in proliferation and differentiation (5). This cytokine overproduction causes inflammation, and a relationship has been determined with inflammatory and autoimmune diseases (6). Significantly high serum IL-6 levels have been observed in patients with CD compared with healthy controls (5). Genetic polymorphisms modifying IL-6 levels may therefore potentially be involved in susceptibility to CD. Dema et al. (7) determined that IL-6 (-174G/C) polymorphism increased the risk of CD in girls. However, another study determined no relation between this polymorphism and CD (2). IL-6 (-572G/C) (rs1800796) is found adjacent to the IL-6 5′ promoter region (8). Previous studies have determined that this allele is responsible for high serum IL-6 levels and that polymorphism has an effect on the development of allergic rhinitis, osteoarthritis, and ischemic heart disease and on the prognosis of breast cancer (9-11).

IL-17 is a proinflammatory cytokine expressed by T helper (Th) 17 cells, which creates an immune response to extracellular bacterial and fungal pathogens and plays a role in the development of inflammatory and autoimmune diseases (12). The IL-17 cytokine family comprises six members, namely IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F (13). Previous studies have compared treated and potential patients with CD and have reported IL-17 elevation in the mucosa of untreated patients (14,15). However, Ryan et al. (16) examined the relation between IL-17 polymorphisms and CD and showed no relation between IL-17 (762 C/A, 1586 A/G, and 6769 A/G) polymorphisms and CD. Espinoza et al. (17) showed that the IL-17A 197A allele correlates to more efficient IL-17 production. IL-17A (-197A/G) gene polymorphism has been shown to have an effect on the development of ulcerative colitis, gastric carcinogenesis, and acute myeloid leukemia (18-20).

Polymorphisms in gene alignment have been found to have a significant effect on the production and/or functioning of cytokines (21). Genetic polymorphisms have been reported to contribute to CD sensitivity by altering the levels and functions of cytokines (2). This study aimed to evaluate IL-6 (-572G/C) (rs1800796) and IL-17 (-197A/G) (rs2275913) gene polymorphisms in children with CD. Further, we aimed to investigate the relationship between CD symptoms and histopathological findings and the relationship between these polymorphisms.

MATERIALS AND METHODS

Study Population

This prospective study involved patients with a diagnosis of CD for at least 1 year and no other known disease who were being followed-up. The patient group comprised 84 children, and the control group included 83 age- and gender-matched healthy children. The study was conducted in accordance with the principles of the Helsinki Declaration, and the ethics committee of Karadeniz Technical University School of Medicine granted the approval. Informed consent was obtained from patients and/or their parents or legal guardians. After receiving informed consent, 2 mL venous blood was collected from each participant in EDTA tubes. Diagnosis of CD was based on anti-tissue transglutaminase IgA (tTG-IgA) antibody positivity (>200 RU/mL) and typical histopathological findings after the evaluation of clinical symptoms.

Patients with CD were assigned into one of the two groups depending on their symptoms, classic or nonclassic. Classic symptoms were chronic diarrhea and/or abdominal distension and/or weight loss. Nonclassic symptoms included iron deficiency anemia not responding to treatment and of uncertain cause, short stature, dental enamel anomalies, elevated liver enzymes, cutaneous manifestations (dermatitis herpetiformis or recurrent oral aphthous ulcers), neurological manifestations (ataxia or peripheral neuropathy), and metabolic disorders (osteopenia/osteoporosis) (22). The mucosal biopsy sections were subjected to analysis by an experienced histopathologist, and the diagnosis of CD was subsequently confirmed based on the modified Marsh-Oberhuber classification system (23).

DNA Extraction and Genotyping

The presence of tTG-IgA antibody in serum was confirmed using the enzyme-linked immunosorbent assay (Euroimmun, Luebeck, Germany) method. DNA isolation was performed using an automatic Magna Pure Compact DNA isolation Device (Roche Diagnostics, Manheim, Germany). HLA-DQ2 and HLA-DQ8 allele genotyping was performed on Luminex technology (Gen-Probe LIFECODES, Stanford, CA) using the polymerase chain reaction (PCR) and sequence-specific oligonucleotide probe (PCRSSOP) hybridization method. For IL-17 (-197A/G) (rs2275913) polymorphism, F: 5′ TTGACCCATAGCATAGCAGC 3′, R: 5′ GGGCTTTTCTCCTTCTGTGG 3′ and for IL-6 (-572G/C) (rs1800796) polymorphism F: 5′ GGCAATGGGGAGAGCACT 3′, R: 5′ GGGCTTTTCTCCTTCTGTGG 3′ primary pairs were used, and the target areas were multiplied with PCR.

The BstENI enzyme was used for genotypic screening for IL-17A (-197A/G) and the FokI enzyme for IL-6 (-572G>C). PCR products were incubated for 16 h with restriction enzymes in the prepared reaction mixtures at 37°C with FokI enzymes and 37°C with the BstENI enzyme. Following the restriction reaction, the products were visualized with electrophoresis in 2.5% agarose gel.

Agarose gel was prepared following the treatment of PCR products with restriction enzymes. Subsequently, 5 µL was collected from treated products and mixed with 6 µL distilled water and 1 µL loading dye and then loaded into the gel wells. Gel electrophoresis was performed for 15 min at 130 V. The observation of a single 215 bp band was regarded as compatible with the AA genotype for IL-17A (-197A/G) polymorphism; two 108 and 107 bp bands as compatible with GG polymorphism; and three 215, 108, and 107 bp bands as compatible with the AG genotype. For IL-6 (-572G>C) polymorphism, a single 371

bp band was regarded as compatible with the AA genotype; two 225 and 146 bp bands as compatible with the GG genotype; and three 371, 225, and 146 bp bands as compatible with the AG genotype.

Statistical Analysis

Statistical analysis was performed Statistical Package for Social Sciences version 13.0 (SPSS Inc.; Chicago, IL, USA) software. Descriptive statistics were expressed as mean±standard deviation. The chi-square (χ^2) test was used to calculate genotype and allele frequency. Odds ratio (OR) and 95% confidence interval (CI) were calculated between the groups. A value of $p<0.05$ was regarded as statistically significant.

RESULTS

Fifty-five (65%) of the patients with CD were females and 29 (35%) were males, with a mean age of 8.59±3.99 years (range, 4-17 years). According to the histopathological evaluation of the children with CD, 20 (23.8%) were Marsh 3A, 20 (23.8%) were Marsh 3B, and 44 (52.4%) were Marsh 3C. When classified on the basis of symptoms, 16 (19.0%) patients had classic symptoms and 72 (81.0%) had non-classic symptoms.

Analysis of the IL-6 (-572G/C) polymorphism revealed a higher level of the GG genotype in the patients with CD compared with the control group (p=0.018, odds ratio (OR): 5.47, 95% confidence interval (CI): 1.161-25.800). No statistically significant difference was determined between the groups in terms of allele frequency (Table 1). No significant difference was determined between the groups with respect to genotype and allele frequency for IL-17 (-197A/G) polymorphism (Table 2). No difference was determined between patients' histopathological findings and IL-6 (-572G/C) and IL-17 (-197A/G) polymorphisms in terms of genotype and allele frequencies (Table 3). No difference was also determined between patients' symptoms and IL-6 (-572G/C) and IL-17 (-197A/G) polymorphisms in terms of genotype and allele frequencies (Table 4).

In post hoc power analysis, power was calculated as 53.93% between the patients with CD and control group for the IL-6 (-572G/C) polymorphism GG genotype.

DISCUSSION

Genetic factors are known to play a significant role in the development of CD. The most important risk factor for disease development is HLA grade II genes (24). While 40%-90% of patients are HLA-DQ2-positive, fewer are HLA-DQ8 positive. Molecules related to immune system responses that are encoded in the genes have also been found to contribute to the development of CD (24).

Mucosal damage in CD occurs with both a natural and an acquired immune response. Previous studies have shown that intestinal inflammation in CD is due to different cytokines produced by CD4 T cells and that these are responsible for the pathogenesis of the disease (5,25).

Table 1. Genotypic and allelic frequency of the IL-6 (-572G/C) polymorphism in patients with CD and healthy controls

Genotypes	Patients with CD, (n=84) %	Healthy controls, (n=83) %	p	OR (95% CI)
CC	38 (45.2)	52 (62.7)	References	
CG	36 (42.9)	29 (34.9)	p: 0.294	1.39 (0.748-2.609)
GG	10 (11.9)	2 (2.4)	p: 0.018	5.47 (1.161-25,800)
C	112 (66.6)	133 (80.1)	References	
G	56 (33.4)	33 (19.9)	p: 0.070	0.24 (0.050-1.224)

CD: celiac disease; OR: odds ratio; CI: confidence interval

Table 2. Genotypic and allelic frequency of the IL-17 (-197A/G) polymorphism in patients with CD and healthy controls

Genotypes	Patients with CD, (n=84) %	Healthy controls, (n=83) %	p	OR (95% CI)
AA	10 (11.9)	15 (18.1)	References	
AG	28 (33.3)	25 (30.1)	p: 0.656	1.16 (0.604-2.227)
GG	46 (54.8)	43 (51.8)	p: 0.613	1.12 (0.613-2.069)
A	48 (28.5)	55 (32.7)	References	
G	120 (71.5)	113 (67.3)	p: 0.823	0.91 (0.409-2.036)

CD: celiac disease; OR: odds ratio; CI: confidence interval

In addition to cytokines expressed by Th cells in the intestinal mucosa in CD, the production of macrophage-origin IL-6 has been determined to increase and play a role in intestinal inflammation (5,25). Studies have reported a relation between the IL-6 (-572G/C) polymorphism and high serum IL-6 (9). In comparison with the CC genotype, the IL-6 (-572G/C) G allele has been determined to be responsible for greater IL-6 production and higher serum level (26). Fernandes et al. (10) reported that patients with the IL-6 (-572G/C) G allele had higher IL-6 levels than patients with the CC and CG genotypes, and the G allele was identified as a risk factor for the development of osteoarthritis. The relationship of this polymorphism with Type 2 diabetes was examined in a meta-analysis of 10 studies, which concluded that subjects with the GG genotype were at greater risk of developing the disease (27). In the present study, which examined the relationship of the IL-6 (-572G/C) polymorphism with CD, the GG genotype was determined to be a risk factor for disease development. However, we determined no association between the IL-6 (-572G/C) polymorphism and the histopathology (Marsh grade). Although Kapoor et al. (5) reported that IL-6 values were significantly increased in CD and proved to be a reliable marker for disease activity, a poor correlation was noted with the histopathology (Marsh grade).

Table 3. Genotypic and allelic frequency of the IL-6 (-572G/C) and IL-17 (-197A/G) polymorphisms with Marsh stages

Genotypes	Marsh 3A, (n=20) %	Marsh 3B, (n=20) %	Marsh 3C, (n=44) %	p
IL-6 (-572G/C)				
CC	7 (35.0)	11 (55.0)	20 (45.4)	
CG	10 (50.0)	6 (30.0)	20 (45.4)	0.232
GG	3 (15.0)	3 (15.0)	4 (9.2)	
C	24 (66.6)	28 (67.8)	60 (66.3)	0.314
G	16 (33.4)	12 (32.2)	28 (33.7)	
IL-17 (-197A/G)				
AA	3 (15.0)	1 (05.0)	6 (13.6)	
AG	6 (30.0)	9 (45.0)	13 (29.5)	0.575
GG	11 (55.0)	10 (50.0)	25 (56.9)	
A	12 (60.0)	11 (70.0)	25 (68.1)	0.339
G	28 (40.0)	29 (30.0)	63 (31.8)	

Table 4. Genotypic and allelic frequency of the IL-6 (-572G/C) and IL-17 (-197A/G) polymorphisms with symptoms

Genotypes	Classical, (n=16) %	Non-classical, (n=68) %	p
IL-6 (-572G/C)			
CC	6 (37.5)	39 (57.3)	
CG	10 (62.5)	26 (38.2)	0.153
GG	0 (0.0)	3 (4.5)	
C	22 (66.6)	104 (76.5)	0.095
G	10 (33.4)	32 (23.5)	
IL-17 (-197A/G)			
AA	3 (18.7)	6 (9.0)	
AG	6 (37.5)	24 (35.2)	0.623
GG	7 (43.8)	38 (55.8)	
A	12 (37.5)	36 (26.5)	0.645
G	20 (62.5)	100 (73.5)	

In addition to IL-21 and interferon-γ expressed by Th1 cells, the level of IL-17 expressed by Th17 cells has been shown to increase in CD (19,20). The IL-17 (-197A/G) polymorphism in the promoter region of cytokines may be related to higher expression of the IL-17A. In an in vitro study by Espinoza et al. (17), a higher level of IL-17 secretion in stimulated T cells was determined in subjects with IL-17A (-197A/G) A allele compared to those without IL-17A (-197A/G) A allele. We observed no difference between the patients with CD and the control group with regard to IL-17 (-197A/G) polymorphism. Several studies have reported an association between the IL-17A (-197A/G) polymorphism and autoimmune diseases. However, other studies have reported no such relation (18,28). The discrepancy in the results among the various studies may be attributed to the inconsistent effect of IL-17A (-197A/G) gene on serum IL-17A concentrations and the varying frequency of the IL-17A gene among populations. Furthermore, Van Leeuwen et al. (29) reported no increase in IL-17 levels in the intestinal mucosa of patients with CD and determined that IL-21 levels increased independently of IL-17 levels. Bodd et al. (30) determined that while IL-21 is expressed from gliadin-specific T cells, IL-17 is not expressed. Our findings suggested that the increase in IL-17 concentration in CD may occur due to tissue destruction rather than as a result of gluten specific immune response suggested by previous studies.

This study has some limitations. The study population was relatively small, and we cannot generalize our results to other populations with heterogeneous ethnical composition. In addition to the effect of IL-6 (-572G/C) and IL-17A (-197 G/A) polymorphisms on gene transcription were not investigated.

In conclusion, the results of this study show a significant relation between the IL-6 (-572G/C) (rs1800796) polymorphism and CD. The presence of allele G in the IL-6 gene polymorphism (-572G/C) may be regarded as a risk factor for the development of CD. This suggests that the IL-6 (-572G/C) polymorphism should be evaluated as a risk factor in the development of CD. Further studies with higher patient numbers are now needed to confirm the relationship between this polymorphism and CD.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Karadeniz Technical University School of Medicine (Decision Date: 18.04.2016/Decision No: 2015/193).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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