Interleukin-6 and Interleukin-17 gene polymorphisms and celiac disease susceptibility

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Received: October 8, 2017 Accepted: October 15, 2017 Available Online Date: October 30, 2017
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Cite this article as: Ecevit ÇÖ. Interleukin-6 and Interleukin-17 gene polymorphisms and celiac disease susceptibility. Turk J Gastroenterol 2017; 28: 432-3.

See “Interleukin-6 and interleukin-17 gene polymorphism association with celiac disease in children” on page: 471.

Celiac disease (CD) is an autoimmune disease characterized by intestinal inflammation caused by a reaction to dietary gluten in genetically susceptible individuals (1). The prevalence of CD ranges between 1/100 and 1/500 subjects; CD has a high incidence in females (2). CD may present in its classical infantile form with symptoms of diarrhea, vomiting, nausea, abdominal pain, and growth retardation. Most patients with CD remain undiagnosed because they are asymptomatic, and those who are symptomatic show atypical clinical presentations, which are not correctly diagnosed.

Celiac disease is a complex disorder involving both genetic determinants and environmental factors. Altered processing of gliadin by intraluminal enzymes, intestinal permeability changes, and activation of the innate immune system precede the adaptive immune response observed in established CD. One of the key events in the pathogenesis of CD is the activation of lamina propria T cells by gliadin peptides presented with histocompatibility class II molecules (MHC-II) human leukocyte antigens HLA-DQ2 or HLA-DQ8. Several studies have demonstrated that CD4+ T helper cells that are specific for gluten peptides presented by these HLA-DQ molecules are found in patients with CD. Therefore, T-cell responses play an important role in disease development (3). The pattern of cytokines produced following the activation of T cells has been characterized to be T helper 1 (Th1) dominant (4). Th1 cells produce the proinflammatory cytokine interferon-gamma (IFN-γ) in response to the major Th1-inducing factor interleukin-12 (IL-12) (5).

More recently, another population of CD4+ T cells named T helper 17 (Th17) cells are considered to play a relevant role in several autoimmune or inflammatory diseases (6). This differentiation is controlled upon stimulation with some cytokines, such as transforming growth factor beta (TGF-β), IL-23, IL-1β, and IL-6. IL-6 seems to be important in promoting Th17 differentiation. There are many reports on the role of IL-6 in several inflammatory and immune conditions as well as in CD (7). Increased serum levels of IL-6 were found in patients with CD in some studies (8). Th17 cells secrete some proinflammatory cytokines, namely IL-17A, IL-17F, IL-21, and IL-22; this production shows features different from other Th1 and T helper 2 (Th2) subtypes in T lymphocytes. The major difference is that these cells need transcription factors for the production of interleukins. The production of IL-17A is mainly dependent on the expression of the orphan nuclear receptor transcription factor C (RORC) (9). Other molecules that activate IL-17A and IL-17F are the IL-23 receptor (IL-23R) and C-C chemokine receptor type 6 (CCR6).

The results of these studies indicate that genetic polymorphisms modifying IL-6 and IL-17 levels can contribute to CD susceptibility. Other reports studying how interleukin polymorphisms influence CD in other populations have reported different results (10,11). For this reason, it is necessary to continue searching genetic susceptibility factors in patients with CD.

In this issue of the journal, Akbulut et al. (12) conducted a prospective study with a group of 84 pediatric patients diagnosed with CD. They investigated polymorphisms in the genes responsible for encoding cytokines IL-6 (-572G/C, rs1800796) and IL-17 (-197A/G, rs2275913). They demonstrated a significant difference only for the...
In a study by Medrano et al. (13), the role of genes involved in the Th17 response was examined. Sixteen Th17-related genes including genes for IL-6 and IL-6R were genotyped in a very large group of patients with CD; no association was observed regarding CD susceptibility. In another study of patients with CD in Italy, IL-6 (-174 G>C) single-nucleotide gene polymorphisms were analyzed for an association with CD susceptibility; no association was found between IL-6 gene polymorphism and patients with CD who were positive for HLA-DQ2 and HLA-DQ8 (14). Dema et al. (11) in a study of 374 pediatric patients with CD involving three single-nucleotide polymorphisms with the highest variability in the IL-6 gene (rs2069827, rs1800795, and rs2069840) could not find any association between overall CD and any polymorphism. However, after stratification subjects by sex, they observed that IL-6 (-174 C) increases the risk of developing CD in female patients.

There are three points to note from this body of work. First, it will be useful to plan an extensive genetic study involving many genes coding different cytokines, aiming to determine whether an HLA-stratified association analysis involves HLA-DQ, IL-6, and IL-17 genes in patients with CD. Second, in the inflammatory process, it appears that the cytokine microenvironment and transcription factors influence the immune response of patients with CD. In other words, genetics may not be the major factor because other compensatory mechanisms may exist in disease susceptibility. From this point of view, it will be useful to identify the additional nuclear or cytoplasmic proteins involved in the control of these cytokines other than the effects of gene polymorphisms in patients with CD. Finally, studies involving the Turkish population with groups from different geographic areas of the country are necessary to contribute to the current findings and to possibly add to the confirmation of the observed associations between gene polymorphisms and CD susceptibility. In future studies, it may be possible to reveal the genetic architecture of CD with exome sequencing and next-generation whole-genome sequencing.

**REFERENCES**