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Review Article

Association between Celiac Disease and Human Leukocyte Antigen

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Abstract: Coeliac disease is an immunologically mediated disease of the small intestinal mucosa, characterized by flattening of the small intestinal villi, increased numbers of intra-epithelial lymphocytes and inflammatory cell infiltrates in the lamina propria, resulting in gut damage and nonspecific malabsorption of nutrients. The disease is elicited by ingestion of gluten, a protein found in several cereals, principally wheat, but also barley and to a lesser extent, oats. Successful treatment is avoidance of dietary gluten. Long-standing evidence suggests a T-cell-mediated response to peptides derived from the gliadin fraction of wheat gluten, leading to immunologically mediated intestinal injury in genetically susceptible individuals. The strength of this genetic susceptibility is indicated by 80% disease concordance in monozygotic twins and 11% concordance in dizygotic twins, and HLA has long been implicated as strongly associated with susceptibility to CD. Various studies in the late 1980s and early 1990s, including those under the auspices of the International Histocompatibility Workshops, lead to definition of the DQA1*05:01, DQB1*02:01 heterodimer, encoded in *cis* or *trans*, as being the principal HLA association.

Keywords: Celiac disease, genetic predisposition, HLA typing.

INTRODUCTION

Coeliac disease or celiac disease is a long term autoimmune disorder, primarily affecting the small intestine, where individuals develop intolerance to gluten, present in foods such as wheat, rye and barley [1, 2]. Classic symptoms include gastrointestinal problems such as chronic diarrhoea, abdominal distention, malabsorption, loss of appetite, and among children failure to grow normally [3]. This often begins between six months and two years of age [3]. Non-classic symptoms are more common, especially in people older than two years [4]. There may be mild or absent gastrointestinal symptoms, a wide number of symptoms involving any part of the body, or no obvious symptoms [3]. Coeliac disease was first described in childhood; however, it may develop at any age. It is associated with other autoimmune diseases, such as Type 1 diabetes mellitus and Hashimoto's thyroiditis, among others [5].

According to recent epidemiological studies, the prevalence in the Western countries has been estimated to be around 1%. More than 600.000 celiac patients live in Italy and around 500 new diagnoses are made every year, although it seems that for every diagnosed celiac patient another 5 patients are undiagnosed.

Celiac disease has a multifactorial etiology, linked to the contribution of both the genetic predisposition and various environmental factors, including gluten and the timing of its introduction in infant diet. Other possible environmental factors are under study as possible concurring element in etiology, such as an alteration in the intestinal microbiota, an alteration in the intestinal mucosa permeability, and infections [6]. Nowadays, CD is more common between the ages of 19 and 40, with a male-female ratio of 1:2 [7].

CD development depends on the presence of key genes that orchestrate the immunological response to dietary gluten. Genetic risk genes are searched with the help of two complementary methods: genetic linkage and genetic association studies. Genetic linkage studies identify common chromosomal regions shared by affected siblings using Single Nucleotide Polymorphisms (SNPs) as genetic markers. After linkage has been identified, association studies are used to

identify the disease-specific gene from the candidate gene locus. This type of study compares frequencies of genetic variants in patients with those in controls [6].

CD is a complex disorder of the small intestine caused by an inappropriate immune response to ingested wheat gluten. CD has a strong genetic component as illustrated by a monozygotic twin concordance of nearly 90% compared to 10% in first-degree relatives [8].A significant proportion of the genetic predisposition comes from HLA genes. HLA-DQ2 (encoded by HLA-DQA1*05:01-DQB1*02:01) [9], or HLA-DQ8 (encoded by DQA1*03:01-DQB1*03:02) is expressed in 30%–35% of the populations where CD is prevalent with only 2%–5% of gene carriers developing CD. This implicates other genetic as well as environmental factors as contributors to the manifestation of CD [6].

The principal disease triggering component of wheat gluten belongs to a family of closely related proline-rich and glutamine-rich proteins called gliadins. When genetically predisposed individuals who express HLA-DQ2 or DQ8 are exposed to certain gliadin epitopes, these epitopes are presented on the surface of antigen presenting cells (APC) in the lamina propria. These, in turn stimulate proliferation of gliadin-specific CD4 T cells in the mucosa. A 33-mer peptide of α2-gliadin, in particular, which is extremely resistant to gastrointestinal digestion because of its rich proline content, is the most powerful immunodominantgliadin peptide. In CD patients, undigested gliadin fragments present in the intestinal lumen can be transported and released intact in the mucosa thereby triggering an immune response and perpetuating intestinal inflammation [10].

DQ2 and DQ8 molecules can only bind gliadin peptides if they have been enzymatically modified by tissue transglutaminase (TG2). This pleiotropic enzyme, which is present in many organs including the small intestine, catalyzes a deamination of certain glutamine residues, the most abundant amino acid in gluten, by converting them into glutamate residues. When deamidated, most of the resultant negatively charged gluten peptides bind more strongly to HLA-DQ2 (or HLA-DQ8), which leads to a more rigorous gluten-specific $CD4^+$ Th1 T Cell activation [11].

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