

# **Genetics and Epidemiology of Celiac Disease**

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## **Introduction**

Celiac disease (CD) is an immune-mediated enteropathy triggered by the ingestion of gluten in genetically susceptible individuals. Gluten is a protein component in wheat, a staple food for most populations in the world, and other cereals (rye and barley). The major predisposing genes are located on the HLA system, namely the HLA-DQ2 and/or DQ8 genotypes found in at least 95 % of patients.

CD is one of the most common lifelong disorders in Europe and in the US. This condition can manifest with a previously unsuspected range of clinical presentations. These include the typical malabsorption syndrome (chronic diarrhea, weight loss, abdominal distention) and a spectrum of symptoms potentially affecting any organ or body system (Tab. 1). Since CD is often atypical or even silent on clinical ground, many cases remain undiagnosed and exposed to the risk of long term complications, such as osteoporosis, infertility or cancer (1). There is a growing interest on the social dimension of CD, since the burden of illness related to this condition is doubtless higher than previously thought. This is highlighted in a recently published position statement of the American Gastroenterology Association on CD (2).

## **The global village of CD**

In countries where individuals are mostly of European origin, the prevalence of CD ranges between 0.25 and 1 % in the general population (3-5). The initial mass studies were performed in Europe, but recently this finding has been confirmed also in the U.S. (5), South America (Brazil, Argentina) (6-7), and Australia (8).

It is also increasingly clear that CD is a common disorder in many areas of the developing world, such as North Africa, Middle East and India (9). The highest frequency of CD in the world has actually been reported among the Saharawi refugees, an inbred population of berber-arabic origin (10). A large serological screening performed on 989 children found a mean prevalence of 5.6 %, almost ten fold higher than in Europe, in the Saharawi people (10). The reasons for such a

high frequency of CD are likely to be related to both genetical (strong association of the DR3, DQB1\*0201-DQA1\*0501 positive haplotypes) and environmental factors (high consumption of wheat flour). The clinical picture of CD in developing countries is usually typical, with chronic diarrhea, stunting, and anemia as prominent features. In younger children there is an increased mortality, especially during the summer months, due to severe diarrhea and dehydration (11).

The treatment of CD is based on the lifelong exclusion of gluten-containing cereals from the diet. In most developed countries this is easily accomplished by using both cereals that do not contain gluten (e.g. rice and maize) and palatable gluten-free, commercially available, products which are specifically manufactured for celiac patients. In contrast, treating CD in a poor context of life appears to be an exceptionally hard task. The situation is more and more complex, since the consumption of wheat is increasing in many developing countries that tend to adopt the “western” dietary style. An international cooperation is required to implement the possibility of diagnosing and treating CD in the developing world.

### **The genetics of CD**

The role of both genetic and environmental factors in the pathophysiology of CD has been recently reviewed (12).

In identical twins the concordance for CD is about 70 %. First-degree relatives of a celiac patient carry a tenfold risk of having CD compared to the general population. The major component of the genetic predisposition to CD resides in the HLA region of chromosome 6. CD is strongly associated with HLA class II antigens, and approximately 90% of cases show a particular DQ2 alpha/beta heterodimer encoded by DQA1\*0501 and DQB1\*0201 alleles inherited in *cis* with DR3 or in *trans* with DR5/7 haplotypes. Almost all DQ2-negative patients have either DR4-DQ8 haplotype, or either the DQA1\*0501 or DQB1\*0201 part of the DQ2 heterodimer (13). It should be noted that HLA alleles explain only part of the genetic susceptibility to CD. In most European populations the frequency of DQ2 is high (15-30 %), but only a minority of DQ2 positive subjects

develop CD. In the absence of strong functional candidate genes, several genome-wide scans in families with affected sib pairs have been conducted. Although no additional susceptibility loci have been clearly identified so far, there is some evidence of a genetic risk factor on chromosomes 5q (14) and 11p11 (15).

The celiac enteropathy is most likely the result of an immune-mediated damage to the small intestinal mucosa. The cascade of pathophysiological events could start with an alteration in the barrier function of the small intestinal mucosa. The up-regulation of zonulin, a recently described intestinal peptide involved in tight junctions regulation (16), seems to be responsible, at least in part, for the increased gut permeability to gliadin peptides (17). In the lamina propria the tTG, an ubiquitous enzyme that catalyzes the crosslinking of proteins, deamidates gliadin peptides, strongly increasing their affinity for the HLA molecules located on the membrane of antigen-presenting cells (APC), e.g. the macrophages. The HLA molecule forms a “groove” where short peptides (e.g. a product of gliadin digestion) can be specifically linked. The interaction between gliadin peptides and HLA molecules activates intestinal T cells. The release of pro-inflammatory cytokines (e.g. IFN-gamma) by activated T cells could determine damage to the enterocyte, increased proliferation in the intestinal crypts and finally, severe damage to the intestinal mucosa architecture (18) (Fig. 1).

There is currently a strong interest in the identification of gluten peptides that trigger the loss of tolerance in CD patients, since this could open the way to immunotherapies alternative to the gluten-free diet (GFD). Unfortunately gluten contains several epitopes that are recognised by small intestinal T cells of CD patients. Recent results indicate that there may be more than ten distinct DQ2 restricted epitopes. In the case of the three DQ2-specific gliadin epitopes identified thus far, T cell recognition is completely dependent on tTG transformation (19). In contrast, the two known DQ8-specific epitopes, one gliadin- and one glutenin-derived, induce T cell proliferation as native peptides (20). It has been hypothesized that in children there is a more “selective” response towards some of the epitopes generated during the early phases of disease development. The wider response observed in adults could be the consequence of epitope spreading (12).

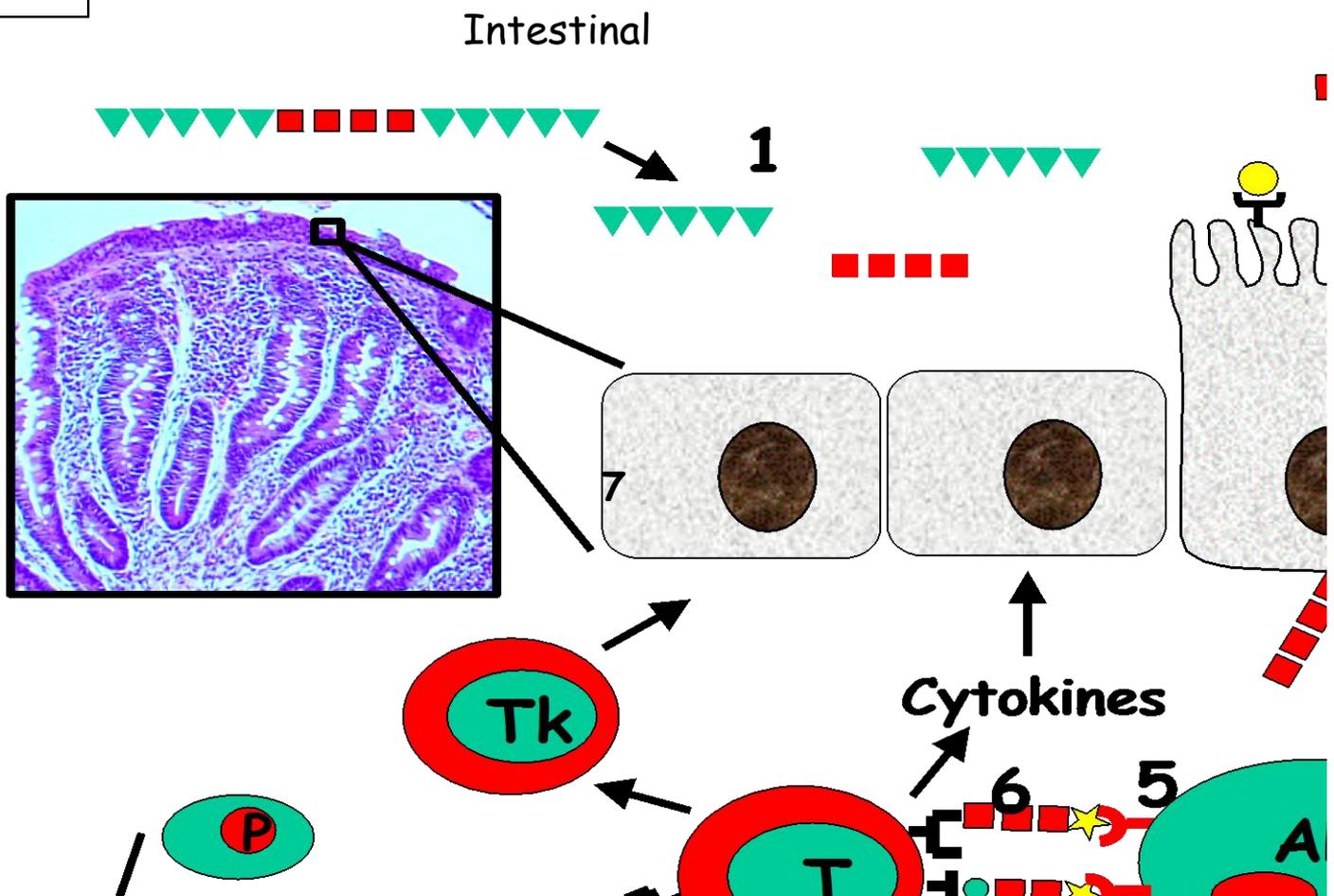
## **Conclusions**

CD is a common disorder in children as well in adults. At any age, the spectrum of clinical presentations is wide, and currently extra-intestinal manifestations (e.g. anemia or short stature) are more common than the classical malabsorption symptoms. A high degree of awareness among health care professionals and a “liberal” use of serological CD tests can help to identify many of the atypical cases. The primary care physician has therefore a central role in this process of case-finding, as elegantly shown by two recent studies, one in adults (20) and in children (21). Although the GFD currently remains the cornerstone of the CD treatment, new perspectives are at the horizon that could disclose a better future for all the individuals affected with this condition.

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**Figure 1.** Proposed cascade of events leading to the intestinal damage typical of celiac disease. 1. Intraluminal digestion of gliadin peptides and liberation of toxic epitopes (squares); 2. Gliadin-dependent intraluminal release of zonulin (circles); 3. Opening of intercellular tight junctions secondary to zonulin action, followed by passage of toxic gliadin fragments into the submucosa; 4. Tissue transglutaminase-mediated gliadin deamidation (star), followed by engagement to DQ2/DQ8 HLA located on the surface of antigen presenting cells (APC); 5. Antigen presentation to lymphocyte T; 6. Presentation to lymphocyte B followed by generation of plasmacells producing anti-gliadin (AGA) and anti-endomysium/anti tissue transglutaminase (AEA/tTG) antibodies; 7. Activation of lymphocyte T killer and increased production of cytokines, leading to intestinal mucosa damage.