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Genetic variants in the HLA-DQ2 and HLA-DQ8 genes and their involvement in the predisposition to celiac disease

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Abstract

Celiac disease is a multisystem disorder that is triggered by the consumption of gluten in genetically predisposed people, particularly those who carry the HLA-DQ2 and HLA-DQ8 alleles. Environmental factors and certain epigenetic mechanisms play a fundamental role in the manifestation of the disease. It has been shown that the gut microbiome can influence disease progression to some extent. Celiac disease presents with gastrointestinal and extraintestinal symptoms that complicate the diagnosis. Classic symptoms include digestive disorders, while non-classic symptoms include anemia, osteoporosis, and unexplained fatigue. Serological antibody tests and duodenal biopsy are key to a diagnosis, especially in atypical cases. At present, the only treatment is a strict gluten-free diet, although this presents certain problems due to the high cost and nutritional deficiencies. New research is looking for alternatives such as gluten-breaking enzymes as well as immunomodulatory treatments in hopes of more comprehensive options in the future.

Keywords: Celiac disease; Genetic predisposition; Environmental and epigenetic factors; Serological diagnosis and biopsy

1. Introduction

Celiac disease (CD) is an autoimmune condition that is triggered by the ingestion of gluten. The main characteristic is the series of damages it causes to the small intestine, all this due to the presence of specific antibodies and human leukocyte antigens (HLA)-DQ2 or HLA-DQ8 [1]. From a histological point of view, celiac disease is distinguished by the flattening of the villi of the proximal intestine and hyperplasia of the crypts, which causes a decrease in the absorption surface [2]. Gluten, the main storage protein in wheat grains, is a complex mixture of hundreds of related proteins, mainly gliadin and glutenin. In addition, it is one of the few digestive-resistant proteins consumed in significant amounts, and its presence in the human diet is relatively recent [3-4].

The prevalence of celiac disease has increased significantly in the last three decades. This increase is not only due to increased awareness and knowledge on the part of specialists of this disease, but also to the increasingly frequent use of highly sensitive and specific diagnostic tests. However, despite advances in diagnosis and growing awareness, up to 95% of patients with celiac disease still do not receive a proper diagnosis [1].

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2. Distribution of HLA-DQ2 and HLA-DQ8

Consuming gluten is the main trigger for celiac disease in only a small part of population who are carriers of the specific variants of the HLA alleles, such as DQA1 0501-DQB1 02 and DQA1 0301-DQB1 0302, which are responsible for encoding the MHC class II heterodimers DQ2 and DQ8 respectively. This condition is associated with HLA-DQ2 gene antigens in 90% of HLA-DQ81 and Cases in the remaining 10% [5].

Despite this environmental exposure and other epigenetic mechanisms are likely to play a crucial role in determining which individuals will develop disease in a population that is genetically predisposed [6].

As has been seen in other autoimmune diseases, celiac disease has a hereditary role, as it is in familial recurrence (around 10-15%) as well as its high concordance between monozygous twins (75-80%). In this case, class II heterodimers, DQ2 and DQ8 being more exact, play an important role in the heritability of the disease, if homozygous for HLA-DQ2 it increases the risk (25-30%) of developing early-onset celiac disease in infants with first-degree relatives who have the disease. Both HLA-DQ2 and HLA-DQ8 are common in the general population (25-35%), only 3% of these people develop celiac disease [7].

3. Prevalence

In recent times the prevalence of celiac disease in the world is around 1%, and it is known that this percentage has been increasing even in areas where there were minimal cases [6].

Was once thought that celiac disease only occurred in Europeans or their descendants, information that now understood to be inaccurate, current global seroprevalence is 1.4% data that was already confirmed through a biopsy study that resulted in 0.7%. In Cameroon, Congo, and Gabon, there is a lower prevalence of the DQ2 and DQ8 genes, making the disease less common in these populations, compared to countries like Morocco and Algeria, where the statistics are similar to global averages [8].

The highest prevalence is observed in both the young and adult demographic groups; however, it is more frequently diagnosed at older ages compared to children, which could lead to an increase in the reported information [9].

Among high-risk groups, the condition of celiac disease tends to manifest in higher proportions. Iron-deficiency anemia occurs in 3-15%, type 1 diabetes in 1-12%, autoimmune hepatitis in 3-7%, autoimmune thyroid disease around 2-6%, and osteoporosis in 1-3% [10].

In the United States of America, the prevalence within the first-degree relatives of patients with celiac disease was found to be 4.5%, and 2.5% amid second-degree relatives, statistics that are notably high. Therefore, some institutes used biopsy studies to confirm this information, showing that the prevalence among first-degree relatives actually ranges from 4% to 12% [11].

A study conducted in the Gaza Strip looked at the distribution of DQ2 and DQ8 haplotypes in patients with celiac disease and in a control group. The results showed that the DQ2 haplotype is more common in patients with celiac disease (70.8%) compared to the control group (17.5%), with a statistically significant difference ($P = 0.000$). On the other hand, the DQ8 haplotype was more frequent in controls (27.8%) than in patients with celiac disease (15.4%), although this difference was statistically significant ($P = 0.064$). In addition, the coexistence of the DQ2 and DQ8 haplotypes did not present a significant difference between both groups ($P = 0.615$) [12].

4. The microbiome

Research suggests that microbiota may influence the development of celiac disease. For instance, patients with celiac disease were found to have elevated concentrations of *Bifidobacterium bifidum* compared to healthy adults, with children showing higher levels of gram-negative and pro-inflammatory bacteria than control groups [13].

5. Symptomatology

People with seemingly unrelated ailments should be checked and a proper diagnosis should be obtained because celiac disease manifests as extraintestinal protein symptoms. An attempt to unify the nomenclature for the clinical stages of celiac disease has been underway over the past ten years. Celiac disease was originally thought to be a juvenile ailment

and was typified by the typical malabsorption signs of poor growth, weight loss, and persistent diarrhea. Nonetheless, it is now understood that celiac disease can strike at any age, including old age and adulthood. Despite the fact that symptoms like weight loss and steatorrhea were once thought to be typical signs, recent global research shows that the majority of patients now exhibit atypical symptoms [14].

Gluten-induced damage is a hallmark of celiac disease in its classic to the intestines, resulting in symptoms and indicators associated with malabsorption. Chronic diarrhea, steatorrhea, stomach pain, abdominal distension, poor weight gain, and weight loss are typical symptoms [13].

Unrelated symptoms are: fatigue, anorexia, delayed puberty, short stature, decreased bone density, unusual rashes, iron deficiency serology positive, it is considered the diagnostic gold standard for diagnosing celiac disease [14]. The phenotypic expression of CD is variable from an asymptomatic case to one with very severe symptoms.

The clinical manifestations of Celiac Disease can be related to the gastrointestinal tract, called "classic ECe", which is seen in 50%-60% of all cases, or with non-gastrointestinal symptoms called "non-classic ECe", which represent 40%-50% of cases. Non-classic symptoms, such as anemia of short stature, dyspepsia, infertility, or hypertransaminemia, may be the only manifestations of ECe, making clinical diagnosis more difficult to achieve. In addition, ECe can coexist with type 1 diabetes or other autoimmune diseases [15]. There is a strong link between CD and autoimmunity, with 5% to 10% of T1D patients developing CD, while 15% to 20% of CD patients have or will develop autoimmune diseases [16].

6. Pathogeny

Celiac disease is considered a multisystem disorder. It is likely that the human leukocyte antigen (HLA)-DQ2, restricted by gliadin peptide, induce T cells that originate in the small intestine, circulate in the peripheral blood, and make their way to other organs, leading to organ-specific cellular injury [15]. Exposure to gliadin, a protein rich in proline and glutamine, causes recognition by specific T cells in the context of specific HLA, DQ2 and DQ8 alleles. Once the tissue transglutaminase enzyme tTG2 modifies glutamine into glutamic acid, the gliadin molecule can attach firmly to HLA lymphocytes. It's not clear how autoantibodies against tTG2 are actually formed. Gluten peptides activate both the innate and adaptive branches of the immune system, including CD4+ and CD8 cells [14]. Figure 1

It is important to have a timely diagnosis of celiac disease, to avoid possible risks and even death. Chronic inflammation of the small intestine, an established risk factor for cancer, is a hallmark of untreated or poorly controlled celiac disease. Therefore, the non-compliance to follow a gluten-free diet can increase the risk of cancer and mortality [17].

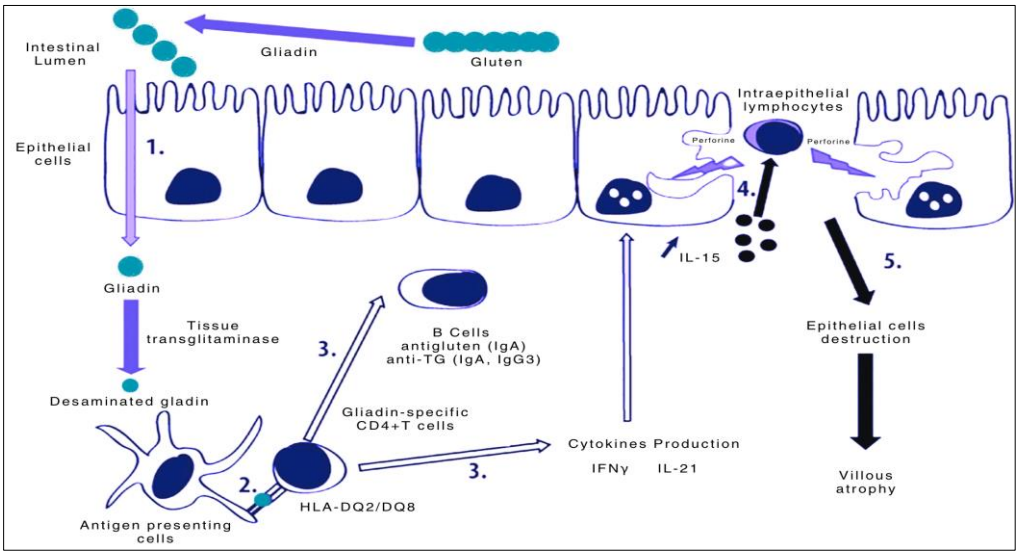

Figure 1 Immunopathological mechanism of celiac disease adapted from Celiac disease: Understandings in diagnostic, nutritional, and medicinal aspects [10]

7. Diagnosis

The lack of typical manifestations combined with the lack of familiarity with the disease reduces the rate of suspicion of CD in such clinical settings. This results in the misdiagnosis of CD and about 85%-90% of CD patients remain undiagnosed [15]. Improper diagnosis and failure to follow appropriate treatment increases significant morbidity and even mortality in these patients. There are currently specific tests for the detection of celiac disease. Serologic antibody testing is important in the diagnosis of CD and depends on dietary gluten intake. Positive TTG-IgA/IgG and IgA-EMA tests, accompanied by a small bowel biopsy, will define genetic testing for the evaluation of patients on a gluten-free diet [18]. The most commonly used diagnostic method today consists of duodenal biopsies that show villous atrophy, crypt hyperplasia, and an increase in intraepithelial lymphocytes with a gluten-containing diet, which remain the "gold standard" for patients with celiac disease [15].

8. Treatment

Currently, there is no drug treatment for celiac disease, so for newly diagnosed patients, the only effective treatment is a lifelong gluten-free diet, with strict attention to avoiding foods such as wheat, barley, and rye [19]. However, relying solely on gluten restriction as the only measure for managing this disease has several disadvantages, including the high cost of such a diet and nutrient and mineral deficiencies. As a result, patients with gluten restriction are advised to incorporate other nutritious food sources, such as fruits, vegetables, fish, meat, etc [20].

A recent study from 2021 demonstrated that a gluten-free diet can restore the histology of small intestine architecture in 95% of children within two years, and 34% of people experience recovery of this architecture between two and five years [19].

Considering the above, ongoing research aims to develop drugs that complement the current treatment. However, there has been limited success as these drugs must meet specific requirements, such as being stable in the acidic environment of the stomach and the nearly neutral pH of the duodenum [21].

One of the most promising proposals is the therapeutic use of enzymes that degrade gluten. Bacterial or cereal-derived enzymes with this property have been described, which degrade gluten to the point of eliminating its immunogenicity before the gluten-containing food reaches the intestines [2]. This through the use or technologies such as ELISPort, mainly used as a useful tool to monitor pharmacological therapies in modulating the response of T cells to gluten, in the same way, the HLA-DQ: gluten tetramer has been o great importance in being able to identify the repertoire of T cell in the disease, becoming a target for research for future therapies [22].

Another focus of interest in the search for treatment for celiac disease is the loss of tolerance to gluten peptides that triggers the pathogenesis in this disease. In this way, an agent has been investigated that can restore gluten tolerance and this allows patients to consume gluten in their diet. The Nexvax2 study attempted to induce this tolerance by dermal vaccination of three immunodominant gluten peptides dissolved in the saline solution. Although the initial results showed indicative signs of tolerance during an interim analysis, NexVax2 failed to prevent the development of villous atrophy and associated symptoms following a gluten tolerance test [21].

9. Conclusion

Celiac disease is a complex autoimmune disorder primarily associated with genetic susceptibility, particularly involving the HLA-DQ2 and HLA-DQ8 alleles. Although environmental and epigenetic factors play a role in triggering the disease, only a fraction of those genetically predisposed will develop it. Despite progress in diagnostic methods and growing awareness worldwide, celiac disease is frequently undiagnosed, leading to risks such as chronic inflammation and an increased likelihood of cancer. Presently, the only treatment is adherence to a lifelong gluten-free diet, which can pose nutritional and financial challenges. However, ongoing research into gluten-degrading enzymes and immunomodulatory therapies offers hope for more comprehensive treatments that could enhance disease management and patient well-being

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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