

HLA-DQ2 And HLA-DQ8 Haplotypes Influence Circulating Levels of Anti-Tissue Transglutaminase and Anti-Gliadin Antibodies in Celiac Disease: A Review

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Abstract

Celiac disease indicates symptoms like damage to small intestinal mucosa, and challenges with nutrient absorption when gluten is consumed by individuals who are genetically predisposed. Genetic, immunological, and environmental factors play important roles in the pathogenesis of the diseases. Here, we briefly reviewed how specific haplotypes linked with genetic risk of celiac disease influence the levels of serological markers associated with the disease. By understanding this link, personalised medicine methods based on genetic risk could be created, thereby potentially improving early disease diagnosis, accuracy of diagnosis, patient care and treatment methods.

تأثير الأنماط المتعددة من HLA-DQ2 و HLA-DQ8 على مستويات الأجسام المضادة للجلوتاميناز النسيجي والأجسام المضادة للجليادين لدى مرضى السيلياك: مراجعة

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الخلاصة

يشير مرض السيلياك إلى أعراض تشمل تلف بطانة الأمعاء الدقيقة وصعوبات في امتصاص المغذيات عند تناول الغلوتين من قبل أشخاص لديهم استعداد وراثي. تلعب العوامل الوراثية والمناعية والبيئية أدوارًا مهمة في تطور هذا المرض. في هذه المراجعة الموجزة، قمنا بتسليط الضوء على كيفية تأثير أنماط معينة من الجينات المرتبطة بالمخاطر الوراثية لمرض السيلياك على مستويات المؤشرات المصلية المرتبطة بالمرض. ومن خلال فهم هذا الارتباط، يمكن تطوير أساليب الطب الشخصي المعتمدة على الخطر الوراثي، مما قد يسهم في تحسين تشخيص المرض المبكر، ودقة التشخيص، ورعاية المرضى وطرق العلاج.

1. Introduction

Gluten sensitivity in individuals with a genetic predisposition, results in a kind of enteropathy commonly known as celiac disease. It is typified by an overreactive immune response brought on by gluten consumption, cystic hyperplasia and small intestinal lesions resulting from villi atrophy (Rubin and Crowe, 2020). Growing awareness of the clinical manifestations of celiac disease as well as its increasing occurrence have led to the understanding of the global epidemiology of the disease. Although exact statistics may vary depending on genetic and geographic variables, celiac diseases is estimated to affect 1% of people worldwide (Lebwohl and Rubio-Tapia, 2021). Epidemiological studies conducted in four regions: Oceania, the Middle East, East Asia and South Asia showed that South Asia has the highest incidence of celiac disease i.e. 0.8% and 7% among low- and high-risk populations respectively. However, Middle Eastern countries have the highest seroprevalence of celiac disease i.e. 1.4% (Ashtari et al., 2021). It is estimated that the prevalence rate in Africa is 1.1% while it is noteworthy that since North Africa consumes more wheat relative to sub-Saharan Africa, and its population has a greater frequency of the HLA-DQ2 haplotype, the sub-region have a high prevalence of the disease (Rajput et al., 2021). Sub-Saharan Africa, on the other hand, has lower incidence rates; nevertheless, this data may be impacted by underdiagnosis and lack of awareness (Lebwohl and Rubio-Tapia, 2021). While individuals can be affected by celiac disease at any age, adult diagnosis are increasingly occurring, although many individuals learn about their diagnosis at a relatively young age (Raiteri et al., 2022). This tendency is due to increased awareness of the disease and its symptoms, extra intestinal abnormalities such as dermatitis herpetiformis, malabsorption and gastrointestinal difficulties. Since its symptom might be mistaken for those of other diseases, celiac disease is still underdiagnosed worldwide. Improving screening procedures and raising public and professional awareness are crucial for prompt diagnosis, disease management and treatment (Besser and Khosla, 2023).

Celiac disease presents a wide range of symptoms which vary significantly among different individuals and since the disease primarily affects the small intestine, leading to malabsorption of nutrients, it can also have systemic effects (Laurikka et al., 2022). The symptoms can be gastrointestinal (chronic diarrhea, abdominal pain, bloating and gas, loss of weight, constipation, and exhaustion), extra-intestinal (dermatitis herpetiformis, as skin condition marked by itchy, blistering rashes, often found on the elbows, knees and buttocks), neurological (headaches, migraines, peripheral neuropathy and cognitive impairment), bone and joint (osteoporosis, osteopenia and joint pain) as a result of calcium and vitamin D malabsorption, reproductive (irregular menstruations, infertility and pregnancy complications), and enamel hypoplasia. Interestingly however, some individuals with celiac disease may be asymptomatic, meaning they do not exhibit any noticeable symptoms despite intestinal damage (de Graaf et al., 2024, Durazzo et al., 2022, Lupianez-Merly et al., 2022). This can lead to delayed diagnosis and increased risk of complications, such as intestinal lymphoma or other autoimmune disorders (Mulder et al., 2023, Khorsheed et al., 2022). According to available data, gliadin peptides present in dietary gluten have the ability to interact with tissue transaminase (tTG) and cause damage to the mucosa of the intestine. This may stimulate CD4+ T cells to respond immunologically, which may lead to immunological hyperactivity. The major histocompatibility complex (MHC) gene present in all vertebrates, may play a role in immunity in some circumstances. The human equivalent of MHC is called Human Leukocyte Antigen (HLA) system. The human MHC antigens are encoded by the DNA surrounding the centromere on the short arm of chromosome 6 (Espino and Núñez, 2021, AL-Ghuraby et al., 2022). The HLA antigens are categorised into three groups as class I, class II, and class III according to their structures and functions. Regarding the celiac disease, the basic determinants of the genetic susceptibility for

celiac disease are the MHC class II HLA-DQA and DQB genes (these genes are encoded by the histocompatibility region on the short arm of chromosome 6) (Aboulaghras et al., 2023, Espino and Núñez, 2021). Individuals are genetically predisposed to celiac disease if they possess particular haplotypes of the HLA, most notably HLA-DQ2 and HLA-DQ8. These haplotypes are essential in the pathophysiology of the disease because they help T lymphocytes present gluten-derived peptides, which cause the intestinal mucosa to become inflamed. In addition to being essential for the diagnosis of celiac disease, the existence of the HLA-DQ2 and HLA-DQ8 haplotypes affects the levels of circulating antibodies, particularly anti-gliadin (AGA) and anti-tissue transglutaminase (tTG) antibodies (Losurdo et al., 2021). Elevated levels of these antibodies are frequently employed as serological indicators for celiac disease, facilitating the diagnosis and continual monitoring of the disease. These haplotypes have different impacts on how the immune system reacts to gluten, hence, as reported in previous studies, individuals with the HLA-DQ2 haplotype generally, have higher levels of these antibodies than those with the HLA-DQ8 haplotype (Mansouri et al., 2021). This review briefly examines the current understanding of the influence of HLA-DQ2 and HLA-DQ8 haplotypes on the levels of anti-tTG and AGA in circulation with the objective to highlight the importance of genetic predisposition in the clinical presentation of celiac disease. To better understand the pathogenesis of celiac disease and possibly improve individualized treatment options, it is essential to decipher the connection between HLA haplotypes that confer genetic susceptibility to celiac disease, and serological levels of antibodies associated with the disease.

1.1. Genetic Basis of Celiac Disease

One of the most extensively studied regions of the human genome is the MHC region, which has polymorphic HLA genes. The MHC proteins are linked to a variety of complicated diseases and are essential for antigen-specific immunity (Espino and Núñez, 2021). Its genetic and genomic variability is still challenging to characterize and interpret, despite decades of research and numerous advancements in the field. This region is extremely gene rich and contains many additional protein-coding genes, some of which are immune-related and others unrelated, in addition to the MHC genes found in the majority of the species that have been investigated to date. Immune effector cells, such as cytotoxic T cells, are presented with short peptides by MHC proteins, which are produced on the surface of cells. They contribute significantly to the antigen-specific immune response by presenting potentially antigenic peptides that can originate from both self-tissue and infectious sources. The coding sequence of an MHC gene corresponds to the repertoire of peptides that a particular MHC protein can bind. Within the MHC region, the HLA genes are typically present in several gene copies that are located adjacent to one another. Depending on whether they encode for MHC class I or class II proteins, they are categorized into MHC class I and class II genes (Rubin and Crowe, 2020, Medrano et al., 2012). The MHC class I proteins consist of a monomorphic β 2-microglobulin and an alpha chain, which are encoded by a single MHC class I gene. All nucleated cells have MHC class I proteins, which primarily present peptides from the intracellular matrix. MHC class II alpha chain gene (HLA-DRA) and MHC class II beta chain gene (HLA-DRB1) encode heterodimers of an alpha and a beta chain, which make up MHC class II proteins (e.g., HLA-DR). They primarily present peptides generated from the extracellular matrix and are only expressed on antigen-presenting cells, like macrophages (Del Pozzo et al., 2021). There are two other categories of MHC genes: classical and non-classical MHC genes. These genes are located inside the MHC region of a particular genome. Non-classical MHC genes are often limited in their expression and have low genetic variability, whereas classical MHC genes, such as the HLA-DRB1 and HLA-B, encode a functional MHC protein sequence, show important allelic variations within a specific

species, and are likely to be ubiquitously expressed (Matern et al., 2020, Dehghani et al., 2021). Over the course of the year, a considerable number of enlightening reviews have been published on multiple features of the MHC and its function in immunity. The HLA-DQ2 and HLA-DQ8 haplotypes are significant in the development of celiac disease. These haplotypes are particular HLA gene variations that are linked to the disease condition's pathological immune response. About 90% of individuals with celiac disease have HLA-DQ2, which is made up of two subunits: DQB1*02:01 as well as DQA1*05:01. DQA1*03:01 and DQB1*03:02 make up HLA-DQ8 (Matern et al., 2020). The presence of specific HLA haplotypes significantly influence susceptibility to celiac disease (presented in Table1), as they are responsible for presenting gluten-derived peptides to the immune system.

Table1: HLA Haplotypes and Level of Celiac Disease Risk

Samples#	HLA Haplotypes	Level of Disease Risk
1	DQ2.5/DQ2.2	Extremely high
2	DQ2.5 and DQ8	Extremely high
3	DQ2.5 & DQB1*02 (double dose)	Extremely high
4	DQ2.2 & DQB1*02 (double dose)	Moderately high
5	DQ2.5 & DQB1*02 (single dose)	Moderately high
6	DQ8 homozygous	Moderately high
7	DQ8/DQ2.2	Moderately high
8	DQ2/DQ7	Moderately high
9	DQ8/DQ7	Moderately low
10	DQ2.2 & DQB1*02 (single dose)	Moderately low
11	DQ8 heterozygous	Moderately low
12	DQX.5	Extremely low
13	DOX.x	Extremely low
14	DQ2.x	Extremely low
15	DQ7/DQX	Extremely low
16	DQX homozygous	Extremely low
17	DQ7 homozygous	Extremely low

Since celiac disease does not always emerge in individuals who carry HLA-DQ2 or HLA-DQ8, environmental factors may also play a role in the pathogenesis of the disease. According to a systematic review and meta-analysis by Aboulaghras et al., the homozygous and heterozygous status of HLA-DQ2 is present with increased frequency in the majority of adult patients, confirming that the DQ2 allele is the primary one associated with celiac disease due to its high frequency in adult patients in all studies (Aboulaghras et al., 2023). There is a close association between HLA haplotypes and celiac disease, which can be attributed to the pathogenic processes of gluten peptide presentation via DQ2 and strong immunodominance. A small percentage of celiac disease cases develop without having any predisposing HLA haplotypes, despite the fact that the traditional DQ2/DQ8 connections with celiac disease were validated in many meta-analyses (Aboulaghras et al., 2022). In clinical settings, genetic testing for HLA-DQ2 and HLA-DQ8 is typically used to help diagnose celiac disease. It is extremely unlikely that celiac disease will be diagnosed if these haplotypes test negative. On the other hand, the existence of these haplotypes, particularly in a person exhibiting symptoms indicative of celiac disease, justifies additional diagnostic

assessment, such as serological testing for particular antibodies against gliadin and transglutaminase (Gualandris et al., 2021).

1.2. Pathophysiology of Celiac Disease

The immune system, especially T and B cells, environmental variables, and genetic predisposition all play intricate roles in the pathophysiology of celiac disease. Celiac disease is largely influenced by T lymphocytes, more especially CD4+ T helper cells. Genetic markers, specifically the HLA-DQ2 or HLA-DQ8 haplotypes, are frequently present in individuals with celiac disease (Aboulaghras et al., 2022). These haplotypes encode molecules that present T lymphocytes with peptides produced from gluten. After consumption, gluten undergoes partial digestion in the digestive system, which produces immunogenic peptides. These peptides are delivered to CD4+ T lymphocytes on the surface of antigen-presenting cells (APCs) by HLA-DQ2 or HLA-DQ8 molecules in genetically susceptible individuals (Aboulaghras et al., 2022, Núñez and Rubio, 2021). After becoming activated, these T cells proliferate and release cytokines that promote inflammation, like TNF- α and interferon-gamma (IFN- γ). These cytokines support the intestinal mucosa's inflammatory response, which damages enterocytes, or intestinal epithelial cells, and results in the distinct villous atrophy linked to celiac disease. The recruitment of additional immune cells is encouraged by the activation of T cells, which intensifies the inflammatory response and also degrades the intestinal lining (Ge and Chen, 2024, Silvester et al., 2021, Kagnoff, 2005). Fig.1 shows a flowchart that summarizes the pathogenesis of celiac disease.

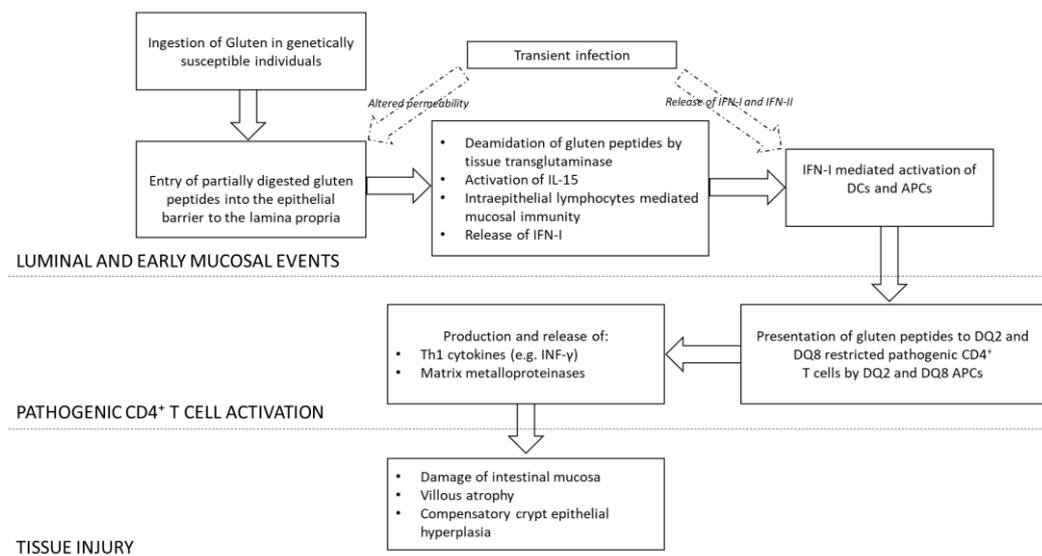


Figure1: Pathogenesis of Celiac Disease

Celiac disease pathogenesis involves three key events: luminal/mucosal processes, CD4+ T cell activation, and tissue injury. Initially, genetically predisposed individuals consume gluten, leading to the production of large, undigested gluten peptides. Tissue transglutaminase modifies these peptides, which are then presented by dendritic cells and antigen-presenting cells expressing DQ2 or DQ8. When these peptides cross the epithelial barrier into the lamina propria, they activate CD4+ T cells. Subsequently, these activated T cells release mediators that cause tissue damage, contributing to the symptoms of celiac disease.

Additionally, B cells are essential to the development of celiac disease, mainly through the generation of antibodies. B cells have the ability to develop into plasma cells in response to the gluten peptides that T cells present, and they are also able to generate particular antibodies against gluten, which include immunoglobulin A (IgA) and immunoglobulin G (IgG) antibodies (Kagnoff, 2005, du Pré and Sollid, 2015). One diagnostic criterion for celiac disease is the presence of these antibodies in the serum, which is a characteristic of the condition. Anti-endomysial and anti-tissue transglutaminase (tTG) antibodies are the most often tested types of antibodies (EMA). Antibodies generated by B cells have dual roles in celiac disease i.e. as a disease marker as well as an effector of its pathophysiology (Kagnoff, 2005, Lindeman et al., 2024). For instance, anti-tTG antibodies bind to tissue transglutaminase that modifies gluten peptides, further triggering inflammation and immunological activation. This interaction may perpetuate the cycle of intestinal tissue damage and immune activation (Majeed et al., 2022). Moreover, the dysregulation of B cell responses may worsen the autoimmune component of celiac disease by causing the production of antibodies that may attack the tissues of the body (du Pré and Sollid, 2015, Lindeman et al., 2024). This aberrant immune response is likely to be influenced by a variety of factors, including the gut microbiome, which can modify immune response and possibly affect the severity of the disease (Ge and Chen, 2024).

1.3.Serological Markers in Celiac Disease

Antibodies are central to the diagnosis of celiac diseases. The most important of these antibodies is the anti-tTG antibodies which target gluten peptides by altering them post-translationally through the action of an immunoglobulin enzyme (Ribes-Koninckx et al., 2022). Gluten proteins are altered by the tTG when ingested, into peptides that are more immunogenic and hence stimulates the body to make antibodies against them. Since anti-tTG antibodies exhibit symptoms of the autoimmune response to gluten, they are a useful biomarker for celiac disease (Khan et al., 2020). An intestinal biopsy, the presence of specific symptoms, and a positive serological test can all lead to a definitive diagnosis. Anti-tTG antibodies are typically assessed in conjunction with anti-endomysial antibodies (EMA) and deamidated gliadin peptides (DGP) to increase diagnostic accuracy (Anbardar et al., 2022). Measuring anti-tTG antibody levels is also helpful for monitoring disease activity because they drop dramatically when gluten is eliminated from the diet. Moreover, persistently elevated levels may indicate ongoing gluten use or possible health challenges. Anti-tTG antibodies, which represent the autoimmune mechanism behind gluten ingestion and provide therapeutic possibilities, are the basis for both diagnosis and treatment of celiac disease (Volta et al., 2024). Routine screening and monitoring of serological levels of these antibodies are crucial for individuals who are at risk or have been diagnosed with celiac disease. Antigliadin antibodies (AGA) are specific immunoglobulins that target gliadin. AGAs can be evaluated as IgA and IgG subclasses and were one of the first serological indicators used to diagnose celiac disease (Green et al., 2022). Elevated levels of these antibodies can indicate abnormal immune response to gluten, even though they are less specific relative to other serological indicators such as anti-tTG and EMA (Volta et al., 2024). The emergence of more sensitive and specific tests, like as anti-tTG antibodies, has reduced the diagnostic value of AGA testing, while it can still yield additional proof for celiac disease. Moreover, AGAs are more frequently found in those with various gastrointestinal diseases including non-celiac gluten sensitivity. Furthermore, individuals with celiac disease may not always test positive for AGAs, especially if they currently follow a gluten-free diet (Green et al., 2022, Anbardar et al., 2022). The existence of AGAs can nevertheless be helpful in clinical practice, despite its limitations, especially when screening for celiac disease or in individuals whose test results are unclear. Overall,

more trustworthy serological tests have essentially replaced anti-gliadin antibodies in the final diagnosis of celiac disease, despite the fact that these antibodies offer insight into gluten sensitivity and immune response. Frequent AGA monitoring may still be helpful in determining how each patient reacts to gluten exposure (Green et al., 2022).

Influence of HLA-DQ2 and HLA-DQ8 on Antibody Levels

One significant field of research in the understanding of autoimmune diseases, like celiac disease in this case, is the comparative measurement of antibody levels in individuals with different haplotypes. According to many studies, individuals with the HLA-DQ2 haplotype often have higher levels of anti-tTG antibodies than those with the HLA-DQ8 haplotype (Khudher et al., 2020, Kadhum et al., 2022). This variation could be explained by the different ways that these haplotypes expose T cells to gluten-derived peptides, which produce different immunological reactions. In general, gluten peptides bind to HLA-DQ2 more strongly than they do HLA-DQ8, which enhances antibody formation and immune system activation (Aboulaghras et al., 2022). People with different haplotypes have varying amounts of AGA in addition to different anti-tTG antibodies. Moreover, previous studies have reported that individuals with HLA-DQ2 may have higher levels of IgA and IgG AGA, while those who have HLA-DQ8 would react more inconsistently (Taşkın and Anlaş, 2023). AGA is often associated with early stages of gluten exposure and may serve as a sign of gluten sensitivity before more specialized antibodies such as tTG are produced. Haplotypes also influence the timing of antibody production. While HLA-DQ8 carriers may react more slowly, HLA-DQ2 carrier may develop antibodies earlier in life, often when gluten is added to the diet (Taşkın and Anlaş, 2023, Khudher et al., 2020). Genetic studies have also identified additional factors that may influence serological responses in individuals with different HLA haplotypes. Antibody levels may be affected by differences in immune regulatory genes, such as IL-15, which have been connected to an increased risk and severity of celiac disease (Kara et al., 2021). D'Avino et al clarified the intricate relationship between genes and serological responses by highlighting the part that these genetic differences play in regulating the immune response to gluten (D'Avino et al., 2021).

1.4. Clinical Implications of HLA Typing in Celiac Disease

HLA typing has extensive and multifaceted clinical significance as a vital diagnostic, therapeutic, and management tool for celiac disease (Kadhum et al., 2022). Conventional diagnostic techniques, such as serological testing for particular antibodies like AGA and anti-tTG, might result in false negative results, especially in patients who have already begun a gluten-free diet (Deja et al., 2020). Since the development of celiac disease requires the presence of HLA-DQ2 or HLA-DQ8, HLA typing offers a genetic basis for diagnosis. More so, studies indicate that at least one of these haplotypes is present in more than 95% of individuals with celiac disease (Aboulaghras et al., 2023, Espino and Núñez, 2021). Thus, negative HLA typing essentially rules out celiac disease, which in some situations eliminates the need for invasive tests like intestinal biopsies. HLA typing can also be used to identify individuals who are at risk, especially first-degree relatives of patients who have been diagnosed. Whether these people have the HLA-DQ2 or HLA-DQ8 haplotypes can be ascertained through genetic testing, enabling early surveillance and intervention (Del Pozzo et al., 2021). This proactive approach is essential because long-term consequences such as nutritional deficits, osteoporosis, and an increased risk of certain cancers can be avoided with early diagnosis and management of the disease. Fundamentally, strict adherence to a gluten-free diet is the main treatment strategy for celiac disease. However, patient education and dietary recommendations may be influenced by information derived from HLA typing. Healthcare practitioners can stress

the significance of avoiding gluten-containing foods and offer resources for managing dietary adjustments to individuals who test positive for HLA-DQ2 or HLA-DQ8 (Del Pozzo et al., 2021, Dieli-Crimi et al., 2015). Furthermore, by helping patients and their families realize that the disease is lifelong, knowledge of the genetic predisposition might promote adherence to dietary restrictions. Also, HLA typing can help with managing celiac disease in relation to other comorbidities, such as autoimmune diseases, which may also have genetic components, and are common among individuals with celiac disease (Martina et al., 2018).

1.5. Current Research and Future Directions

Recent studies have attempted to decipher the exact mechanisms by which HLA haplotypes influence the immune response. For example, it has been reported that the specific pattern of T cell activation exhibited by individuals with HLA-DQ2 in response to gluten peptides was connected with the extent of intestinal injury (Risnes et al., 2024, Voisine and Abadie, 2021). The new trajectory emphasizes the importance of HLA typing in predicting the severity of the disease and its repercussions. Additionally, the relationship between specific antibody production and HLA haplotypes has been the subject of recent research. According to recent studies, individuals with HLA-DQ2 are more likely to develop anti-tTG antibodies, but those with HLA-DQ8 may exhibit a different antibody profile (Poddighe and Capittini, 2021, Ramakrishna et al., 2021, Lee et al., 2020). The potential to tailor therapy and diagnostic methods based on the unique HLA haplotype of the patient is highlighted by this variance in immune response. For example, patients with HLA-DQ2 may benefit from more regular monitoring for repercussions due to their increased possibility of developing serious illness. Recent studies have examined the potential of adjunct therapy, such as immunomodulation or enzyme supplementation, which may be more advantageous in particular genetic backgrounds (Valvano et al., 2023, Discepolo et al., 2024). Using personalized medicine can boost effectiveness and lower side effects, thereby achieving enhanced therapeutic outcomes. Additionally, studies are being conducted to find additional genetic factors that influence the immune response in celiac disease. For instance, susceptibility to and severity of celiac disease have been associated with variations in immune-related genes such as CTLA-4 and IL-15 (Gaba et al., 2024). Improved understanding of these genetic relationships can aid in the creation of personalized treatment programs and provide more profound understanding of the pathophysiology of celiac disease. Recent studies have shown that, in addition to genetic predisposition, environmental factors like timing of gluten introduction and the composition of the gut flora also affect the immune response. These factors can interact to significantly impact the onset and progression of the disease (Catassi et al., 2024, Galipeau et al., 2024). For this reason, personalized medical approaches that take into account the environmental and genetic factors may lead to more effective treatments and preventative measures.

2. Conclusion

In conclusion, the pathophysiology of celiac disease can be better understood by comparing the antibody levels among individuals with various haplotypes. The HLA-DQ2 and HLA-DQ8 haplotypes have a significant impact on the immune response to gluten, leading to variations in antibody production. Additionally, the application of HLA typing in clinical settings paves the way for tailored medical approaches based on genetic predisposition, which could enhance patient outcomes, boost diagnostic accuracy and direct treatment strategies. Future studies should concentrate on elucidating the molecular processes that underlie these immune reactions and investigating how other environmental and genetic variables influence antibody levels in celiac disease.

3. Conflict of Interest

The authors declare there is no conflict of interests

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