The Role of Genetics in Celiac Disease: A Review of the Genes Involved and Their Effects

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ABSTRACT

Background:
Celiac disease (CD) is an enteropathy associated with a genetic disorder and several constitutive genes. This study examines the genes and factors affecting CD.

Materials and Methods:
This review was conducted on structured findings up to September 2023 regardless of language published according to the protocol of systematic review articles (PRISMA). To identify relevant studies, online searches were generally conducted in PubMed, Google Scholar, MEDLINE, and SCOPUS databases.

Results:
Many studies have been conducted on CD genes, and researchers have achieved good results. So far, 60 genomic loci related to CD have been discovered, which is the most important genetic loci of CD related to HLA(Human Leukocyte Antigen). Most of the gene loci identified in autoimmune diseases have pleiotropic effects and cause disruption of the immune system, which in turn causes CD.

Conclusion:
According to the linkage studies conducted on genetic regions, the most important genetic positions identified in CD are HLA-DQ2 and HLA-DQ8. Due to the progress of genetic science and the uncertainty of the genomic position of this disease, they have not been able to use genetic science to prevent this disease. Considering the common genes that this disease has with other gastrointestinal diseases as well as thalassemia, there may be newer and more effective genetic approaches to treat this disease in the future.

Keywords: Celiac disease; HLA; DQ2; DQ8; Genetics

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INTRODUCTION

Autoimmune diseases are increasing worldwide. This causes society to bear a heavy economic and social burden (1). One of these autoimmune diseases is known as celiac disease (CD). One out of every 10 people suffers from this disease (2). This disease is one of the most common diseases that cause malnutrition. This chronic disease causes the villi of the small intestine to atrophy (3). According to many studies, the exact and complete mechanism of CD still remains unknown (1). Although environmental and genetic factors are known to be the main factors, a complex genetic disorder with several contributing genes causes CD (4,5). This disease causes a chronic inflammatory reaction in the intestines of people who are prone to CD when consuming gluten (6). In fact, gluten proteins can provoke pathogenic immune responses and sensitive reactions in people prone to CD (7). Gluten is obtained from grains, and grains are an essential food item in the daily diet of most people worldwide (6,8). Gluten is one of the main components of wheat protein, which consists of glutenin (on chromosome 1) and gliadin (on chromosomes 1 and 6), encoded in about one hundred genes in wheat (7). Triticum aestivum L has a genetically complex genome that is divided into three sub-genomes, and each of these sub-genomes contains seven pairs of chromosomes (9,10). Currently, eliminating gluten from the diet is the only effective treatment for patients with CD, and studies are being conducted for appropriate and alternative treatment approaches (7). Researchers are also looking for genetic changes in gluten-containing compounds such as wheat and barley.

Most of the research conducted worldwide to silence genes such as omega-9 gliadin, regardless of the role of short double-stranded RNA, has made RNAi cassettes of arbitrary sequences, which led to the deletion of off-target gene sequences (11). Recent genomic studies can give us more information about diseases (12). Also, investigations of autophagy in different levels of CD are promising. Examining the expression level of key autophagy genes in peripheral blood and intestinal samples can fairly differentiate between patients with CD and control subjects (13). However, it is still too early to use genetics in clinical practice to predict individual risk. The main challenge for the future is to translate genetic findings into a better understanding of the underlying disease mechanism and to develop new ways to treat and prevent CD (14). Also, CD is an excellent model for studying the role of genetic factors in immune-related disorders since this disease has a higher prevalence rate in both family members and other members of society compared with other autoimmune diseases, and it has also become an environmental trigger (It is actually gluten). Also, both innate and adaptive immune responses play a role among patients with CD, and similar to other autoimmune diseases, HLA genes are strongly involved in this disease, and there are even non-HLA disease-sensitive sites, many of which are shared with other autoimmune diseases (15). Considering the unique characteristics of CD, we may be able to better understand its pathogenesis and contributing factors and identify the effective factors in other autoimmune diseases whose external triggers and genetic backgrounds are unknown. Considering the fact that in recent decades, this disease has been increasing, more investigations are required in this field.

MATERIALS AND METHODS

Presenting a thorough analysis based on PRISMA (16) guidelines. The following search technique was used between 14.4.1997 and 1/10/2023 to find the eligible studies. Two independent researchers (MT, MA) searched for the pertinent papers published between 1/1/2005 and the end of 1/10/2022. We searched for published literature in the English language in MEDLINE via PubMed and EMBASETM via Ovid, The Cochrane Library, and Trip database. Our search for material written in different languages included national databases (Magiran, SID), KoreaMed, and LILACS. For literature saturation (MT), the list of included references or relevant reviews was examined. The Health Sciences Librarian website was used to develop unique search techniques focused on systematic review searches using MESH terms and open phrases in compliance with the PRESS criteria. Results from searches in other databases were contrasted with those from the MEDLINE approach after it had been finalized (MT, MA). Similarly, PROSPERO was looked up to locate recent or active systematic reviews. The terms Celiac disease OR HLA OR Genetics OR DQ2 OR DQ8 OR Systematic review were used in the search approach. The database of earlier study materials and systematic reviews was also explored to find the published research (MT, MA). A search for unpublished data and abstracts (MT) was also conducted on all papers that met the inclusion criteria.

Eligibility Criteria

The addition of cross-sectional, case-control, cohort, case report, and review publications were the articles that met the criteria for the systematic review. Non-random sample size, lack of relevance, and inadequate data were among the exclusion criteria. Two researchers independently carried out each of the stages mentioned above to prevent bias in the study. Finally, the consistency of the third researcher's findings was checked.

Study Selection and data extraction

All pertinent publications were initially gathered, and a

list of abstracts was created to help special investigations. The complete text of the publications was given to the researchers after the specifics, such as the name of the magazine and the author, were concealed. Two researchers independently examined each publication; the reason was stated if the article was rejected. In the event of a controversy between the two researchers, a third researcher evaluated the paper.

RESULTS

Based on the above description, 106 articles related to the topic were obtained in the initial search. The titles and abstracts of the articles were examined according to the main objectives. If the title or abstract was related to the present research, the full text was prepared for review. Finally, by examining the full text of 26 related studies, 19 studies were excluded due to not having the necessary criteria. Finally, seven eligible studies entered the qualitative evaluation stage (figure 1). If needed, information about authors, general information (first author, country, and year of publication), study information (number of participants, studied genes, and studied population), and HLA-type laboratory (HLA-DQA1 and HLA-DQB1) were collected. The output scales collected by HLA are listed in table 1.

Table 1. Summary of included studies

Author	Year	Country	Study period	Study design	Number	Incidence of HLA DQ2, DQ8	Overall quality
Dehghani SM (4)	2021	Iran	Prospectively	2021	285	72/6%	Good
Amani Mubarak (28)	2013	Netherlands	Retrospective	2009-2012	116	61.8%	Good
Verma AK (38)	2022	Indian	Retrospective	2022	211	42%	Good
Sahin Y (39)	2022	Turkey	Retrospective	2017-2020	169	98/2%	Good
Shi T (40)	2023	China	Prospectively	2022	375	68%	Good
Petronzelli F (41)	1997	Italy	Prospectively	1995	447	36%	Good
Van Belzen MJ (42)	2004	Netherlands	Retrospective	2002	289	40%	Good

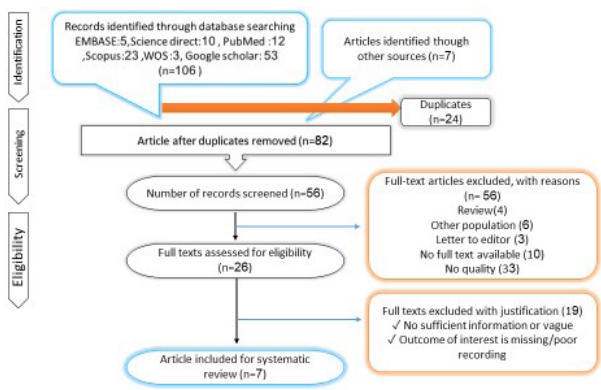

Figure 1. The qualitative evaluation stage of studies

CD is a genetic disorder, and several genes contribute to its development (17). The prevalence of these genes varies among different regions of the world (4). Although searching for the genes responsible for a multifactorial disease, such as CD, is not an easy task, identifying them is necessary to diagnose, prevent, and improve the quality of life in affected patients (18). As the increasing prevalence of this disease indicates that non-genetic factors and gluten consumption play a role in the severity of CD, more studies are required. Therefore, recent new experimental tools have been proposed to deeply investigate the different stages of celiac pathogenesis. One tool is genome-wide association studies (GWAS) and RNAseq analysis, which has increased the science of identifying genetic factors influencing the onset of CD, improving the understanding of the disease and discovering more information about it (1). The first GWAS performed for CD was conducted in 2007 in a relatively small cohort in England (19). Therefore, researchers have identified several genomic regions with the help of GWAS that contain CD-sensitive genes. Hunt and colleagues examined seven genetic regions for CD. They found that six regions, including CCR3, IL12A, IL18RAP, RGS1, SH2B3 (nsSNP rs3184504), and TAGAP. Also, mRNA expression of the IL18RAP gene contains immune response-controlling genes. IL18RAP genotype is completely related to blood (20). In a Yeager study, about 300,000 genetic variants in the human genome (so-called single nucleotide polymorphisms) were examined to find genes related to CD. The results showed that in addition to HLA, there are 13 other genetic loci related to CD. Interestingly, most of the identified regions contained genes that control immune responses, such as the IL2-IL21 locus at 4q27, thus revealing, for the first time, the potential role of IL2, an important cytokine for T cell homeostasis and function (21,22,23). However, in the past few years, many advances have been made in the genetic diagnosis of CD. Until 2014, apart from HLA association with this disease, 40 other genomic locations that are related to CD have been identified (14). In 2017, with the help of mapping and GWAS, aside from HLA, up to 57 genomic locations have been identified that are sensitive to CD. However, most are non-coding variants and do not have any functional annotation (24). Currently, 60 non-HLA genes have been identified for CD, which, in association with HLA genes, explain about 55% of the heritability of the disease (table 2) (12). Most of these loci show pleiotropic effects in many autoimmune diseases and highlight the importance of a dysregulated immune system in the context of CD (14).

Table 2. The number of gene loci discovered for CD (except HLA)

Name	Year	Gene location
Van Heel (19)	2007	13
Wijmenga C (14)	2014	40
Kumar V (25)	2017	57
Bhagavatula S (12)	2021	60

DISCUSSION

Although genes other than HLA play a role in the pathogenesis of CD, HLA genes contribute the most to the development of this disease, and the effectiveness of other predisposing genes in CD is low (17). About 20 years ago, researchers reported the presence of HLA alleles in patients with CD, and recently, it has been proven that a specific heterodimer by HLA-DQ genes causes initial sensitivity and then contributes to the development of the disease (2). The HLA complex on chromosome 6p21 spans 3.6 Mb (26). Researchers have stated that the pathogenesis of CD is the interaction between the gene products of the HLA class II D region on chromosome 6 and gliadin proteins, which is probably an intestinal viral protein (27). Amani Mubarak, in his study on children with CD, found that their tTGA ≥ 100 U/mL is high and also found that they have high heterodimers of HLA-DQ (28). In 2021, Dehghani and others, in a study on children under 18 years of age with CD, found that the prevalence of HLA DQ2 and HLA DQ8 among these people was 72.6% and 53%, respectively, and it is higher than the percentage in the normal population (4). Therefore, based on the studies, it can be concluded that the most important genetic factors identified in CD are HLA DQ2 and HLA DQ8 (17). Indeed, most patients have a form of HLA DQ that is necessary, but not sufficient, to predispose to CD (4). As other genes for CD have been discovered in the studies, Matt and colleagues in 2022 compared the genetic, clinical, serological, histopathological, and immunophenotypic parameters between USCD(Ultra-short celiac disease) patients and normal celiac disease. They found that HLADQ2 was present in these patients (29). Khalkhal stated in a study that the expression of IL15, IL17A, IL23A, GZMB, TBX21, and TNFAIP3 genes in peripheral blood mononuclear cells of patients with CD showed a significant increase compared with the control group. Their results showed that TNFAIP3, IL23A, and GZMB can be useful and reasonable markers in differentiating patients with CD from healthy individuals. However, the diagnostic relevance of other genes identified

by pathway analysis should be further investigated (30). In a Van Heel study, risk variants were identified in the region containing IL2 and IL21. They showed that the diversity of the genetic region in this location was predisposed to CD (31). Also, GWAS showed that HLA carrier genotypes, in addition to being involved in CD, also increase the risk of type 1 diabetes (32). In their study, Hunt and colleagues have found common genetic regions with diabetes with the help of metabolic pathways (33). In this context, linkage studies helped to discover that several genomic regions such as human leukocyte antigens DQ-2 and DQ-8 may also help in the diagnosis of silent CD in children with T1D (Type 1 diabetes). The most important shared genetic source between CD and T1D (other than HLA) includes CTLA-4, TAGAP, IL-18RAP, PTPN2, RGS1, SH2B3, CCR5. The interaction between these loci could be important in susceptibility to CD in T1D. Although other researchers have mentioned some other diseases, including beta-thalassemia and cancers of digestive origin, there are common genes between these diseases, which are listed in table 3 (15,34). Therefore, it can be said that although HLA is one of the most important and effective genes in CD, determining the HLA genotype is almost worthless for predicting CD because its abundance can be the cause of other diseases.

Therefore, it is suggested that people who are prone to CD in their family, in addition to underlying diseases, perform genetic screening (especially for babies, even newborns), before the symptoms and severity of the disease appear, to prevent complications caused by the disease with timely diagnosis and early treatment (35,6). Of course, CD is an important and common immune-mediated disorder, which means that in addition to genetic factors, it could also be affected by environmental factors. The best-characterized agent is α-gliadin found in wheat gluten peptides (36,37).

Table 3. Common genes between celiac disease and several other diseases

Type 1 diabetes and celiac disease in risk areas(21)	HLA-DQ، IL2-IL21، CCR3 و SH2B3
1 T1D, CD, RA, UC, MS, and lupus erythematosus (20,27)	IL2-21
Beta thalassemia major and CD (28)	HLADQA1 and DQB1 alleles

CONCLUSION

Experts in chemistry, molecular biology, and immunogenetics have conducted many studies on the role of genetic, environmental, and immunological factors in CD. So far, 60 genomic loci have been found for CD, and the most important identified genetic factors are HLA-DQ2 and HLA-DQ8. Researchers have found that CD has genes in common with some other diseases, such as diabetes, thalassemia, and digestive diseases. Therefore, we conclude that different diseases can have common genes. Also, genetic variation changes gene expression levels. Therefore, appropriate studies should be conducted on the types of damaged cells to determine how they affect protein-coding genes and non-RNA-coding genes. As a result, researchers need to conduct more genetic studies to obtain more complete information about this disease to find out why the immune system gets disturbed and causes CD, so that alternative ways to treat this disease can be provided. Since one of the ways to control CD is to follow a gluten-free diet, it is possible to produce bread-making cereals without the T-cell epitope by breeding programs or transgenic technology. It is also possible to block the binding sites of HLA molecules DQ2 and DQ8 to prevent the presentation of disease-causing gluten peptides and, thus, the activation of T cells. This treatment method has few side effects that can be predicted. It is also hoped that in the future, with the help of genetic science, models can be found for better prediction, development, and progress of CD treatment.

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