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REVIEW ARTICLE

Pathogenic Gene Variants in Celiac Disease

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ABSTRACT: Celiac disease (CD) is an autoimmune disorder with both environmental and genetic risk factors. CD manifests itself when food containing gluten is eaten. It causes malabsorption by damaging the villi in the small intestine. This leads to the question: How do gene variants lead to the pathogenesis of Celiac disease? Other studies include genome-wide association studies to recognize more genetic risk factors associated with CD. This paper reviews how gene variants show a risk for CD and lead to the development of CD. It will show the significance of looking at how certain genes can change our body functions to alter a big part of our digestive system and how it can help us discover other genes possibly related to celiac disease.

KEYWORDS: Biomedical and Health Sciences; Genetics and Molecular Biology of Disease; Celiac Disease; villous atrophy; SNP.

Introduction

Celiac disease (CD), aka coeliac disease and celiac sprue, has been known since ancient Greece but it was not until the 1940s that the disease was linked to wheat consumption.[1] Celiac disease usually follows wherever wheat is produced although originally, it was thought to only affect Europeans. About 10,000 years ago, in the "Fertile Crescent" in the Middle East, wheat and barley grain production began. This production spread to the Mediterranean, Central Europe and Northern Europe and all over the world.[2] CD is manifested when the immune system comes into contact with gluten proteins. It manifests in the mucosa in the small intestine and causes villous atrophy which can result in the absence of villi.[3] This then causes malabsorption which is when the body cannot get enough nutrients.[4] These problems with the digestive system can lead to symptoms such as lactose intolerance, constipation, diarrhea and vomiting but also symptoms that are not associated with the digestive system such as slowed growth, weight loss, and fatigue. It can also affect other parts of the body through mental health problems, joint/bone pain, reproductive issues in women, mouth sores, and dermatitis herpetiformis which is itchy blistery skin rashes. These symptoms mostly appear during childhood but in some cases, they start to appear during adulthood. During adulthood, if CD is not managed it can cause increased mortality.[2] As of right now, there is no cure, but having a gluten-free diet is how the disease can be managed. The aim here is to focus on the major gene variants that cause CD and how they lead to pathogenesis in Celiac Disease. CD affects about 1% of the Western population but according to the Celiac Disease Foundation, the incidence rate has increased about by 7.5% per year over the last several decades.[5] It is important to look at all genes involved to see how they are involved in the development of CD or how they can influence it because it affects such a large part of the population. This paper will talk about what gene variants and how their functional mechanisms have a significant impact on CD in hopes of bringing any other major discoveries about other genes' roles in CD to light. The pathogenesis of Celiac disease will be explained along with how CD is developed and how it affects our bodily functions. Then what genes are associated with CD will be discussed along with data provided through (Table 1). Genome-wide association studies (GWAS) and the NCBI gene database will also be used as secondary data analysis. From there genes that have an actual role in CD will be focused on.

Discussion

Triggers in Celiac Disease:

Celiac disease is an immune disorder that can be caused by environmental factors and genetic factors. Environmental factors include various infections in the small intestine at a young age, different feeding patterns as an infant and exposure to gluten. Genetic factors include the genes that contribute to CD.[6] CD is a systematic disorder (a disorder that affects more than one system) and is strongly associated with the adaptive immune system response to gluten proteins.[1]

Multiple environmental factors need to be discussed. In most people, this disease is triggered through the environmental trigger of gluten: products such as wheat, barley, rye, triticale and in some rare cases, oats. This is because gluten contains gliadin and glutenin which can trigger the immune response in the digestive system. These gluten proteins contain a high proline (amino acid) concentration that renders these proteins exempt from digestion which causes a large increase in peptides. For example, the 33-mer peptide has a large concentration of proline and glutamine and can induce a proinflammatory cytokine response.[7] High numbers can be seen in individuals with CD. These high numbers can be digested by preventing gluten from entering the body.[8] Viral infections such as the rotavirus have shown a risk associated with CD. Feeding patterns can also cause an increased risk of CD: for example, if there was a lack or a difference in the normal milk being fed to an infant. Metals in food could also be a factor but not much is known about

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this topic yet.[6] Factors cannot be limited just to the environment, however.

Two main genes are associated with Celiac disease: HLA-DQ2 and HLA-DQ8. These two genes make up 35% of the genetic risk surrounding CD. HLA-DQ2 affects about 90% of those with CD and the remaining 10% are affected by HLA-DQ8.[6] These genes are found in 89.6% of individuals with a family member.[9] HLA genes are not enough to cause CD; there are many other genes involved in the development of CD.

Pathogenesis in Celiac Disease:

Immune function is first manifested in the small intestine. Gliadin travels to the intestinal epithelial barrier where it is impermeable to gliadin. TTG antibodies are also produced in the small intestine during gluten consumption which can be one sign of CD in a patient. Gliadin interacts with the intestinal cells which triggers the disassembling of the inter-enterocyte tight junctions (TJ) which are responsible for regulating the permeability of ions, molecules and cells in the paracellular pathway.[6,10] The peptide zonulin increases the permeability involved in TJ which allows gliadin peptides to move through the epithelial barrier and activate CD4+ T-lymphocytes in the lamina propria. These lymphocytes then produce proinflammatory cytokines that induce a T-helper 1 (Th1) pattern and a T-helper 2 (Th2) pattern that cause an expansion of B-lymphocytes. This can result in the secretion of antigliadin and anti-tissue transglutaminase antibodies. T-lymphocytes may miss some gliadin peptides and these can activate intestinal epithelial cells, more specifically CD8+ T-lymphocytes which can be seen as a sign of CD.[6] This is why when examining for CD, the levels of TG2, DGP, and cytokines are analyzed.[1]

Toxic peptides, in this case, gliadin, trigger an immune response and lamina propria dendritic cells are produced that are amplified in affected individuals. IL-15, produced by epithelial cells, can increase permeability allowing more gliadin peptides to move through the epithelial barrier. Now more immune adaptive peptides can reach the lamina propria where they are presented to gluten-specific T cells. They bind and that causes proinflammatory cytokines to constantly be stimulated which causes the mucosa to be expanded which then causes the lamina propria to be expanded because of lymphocytes and plasma cells. This causes the villi in the intestinal crypts to be shortened, divided and even possibly absent because of the loss of mature epithelial cells.[2]

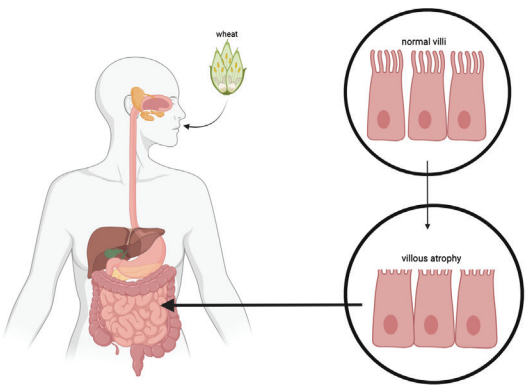

Figure 1: The effects of Celiac disease on individuals.

Wheat is ingested by humans which is a common source of gluten. In someone with Celiac disease, this wheat can have a deadly effect. The wheat travels down to the small intestine and then it causes the normal villi to become shortened as shown in (Figure 1). This is called villous atrophy which is the main effect of Celiac disease. This (Figure 1) was created with BioRender.com.

Many environmental and genetic factors come together to generate a response in the affected individual's immune system that results in the development of CD. Not everything about pathogenesis is known yet. For example, environmental triggers for CD related to certain foods are yet to be known, but fortunately, much is already known about the immune system's function in CD. This raises the question: how many external factors are associated with CD?

Gene Polymorphisms in Celiac Disease:

Over the years, many genome-wide association studies and GRAIL annotations (used to look at relationships between the disease and associated gene loci, aka groups) have been done with CD to recognize new risk factors associated with CD.[11] There have been a multitude of factors recognized such as SNPs, mutations and gene variants, but only some of these cause CD. Genes associated with and the genes causing the pathogenesis of Celiac disease will be differentiated while clearing up the difference in different types of gene variants.

Various types of gene variants exist but the main type are SNPs. SNP stands for single nucleotide polymorphism. According to medlineplus.gov, it is when a nucleotide base (adenine, thymine, guanine or cytosine) in DNA is substituted for another base in a sequence. These are very common in individuals; there have been 600 million identified. SNPs are used by scientists to locate genes that are associated with specific diseases which is why sometimes they can also be used as regions. An example of a SNP region is rs2187668.

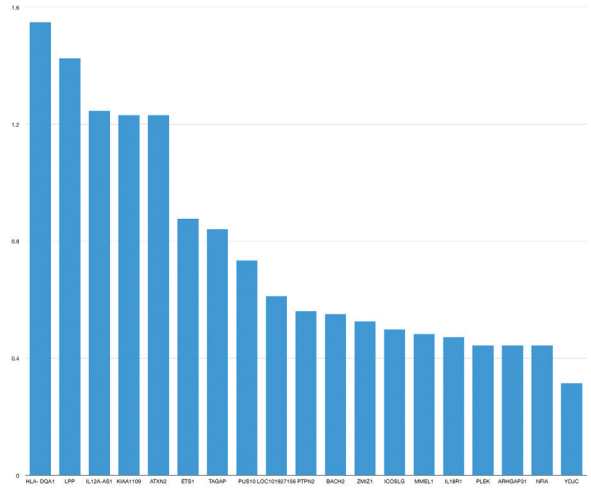

Figure 2: Genes' standardized value in association with celiac disease.

The values in (Figure 2) come from Harmonizome 3.0 and show 19 genes that are associated with CD based on standardized values. Standardized value indicates the strength of association the genes have with the disease. The higher the

value, the more association. These genes were taken from the GWAS catalog SNP- Phenotypes Associations data set.

There are many genes associated with CD but only certain ones are directly related to the development of CD. Through all the GWAS, TEDDY and GRAIL studies, it can be seen that many different SNPs and locations are associated with CD. The genes that have shown clear signals of causing CD are REL, IL12A, HLA-DQ2, HLA-DQ8, HLA-DQA1, HLA-DQB1, ETS1, IRF4, MYO9B, IL15, TAGAP, LPP, IL18RAP, IL18R1, SH2B3 and IL2.

Table 1: Gene locations based on SNP/region in Celiac Disease.

SNP/Region	Genes	Function of bolded genes
rs2187668	**HLA-DQ2, HLA-DQ8, HLA-DQA1, HLA-DQB1**	HLA-DQ Family: Allows the immune system to target agents that might be harmful.
rs13003464	**REL,** AHSA2	REL: Encodes a protein that belongs to the REL RDH (REL homology domain)/IPT (immunoglobulin-like fold plexin) transcription factor family. This family regulates genes involved in the immune response. It helps increase the number of B-cell lymphocytes or helps these cells survive.
rs12990970	CTLA4	
rs917997	**IL1RAP, IL18RI,** IL1RL1, IL1RL2	IL1RAP and IL18RI: These genes encode a protein that is an accessory of IL18 which is a pro inflammatory cytokine involved in cell-mediated immunity.
rs1738074	**TAGAP**	TAGAP: Encodes a member of the RhoGTPase activator family that can function as a RhoGTPase activator.
rs3184504	**SH2B3**	SH2B3: Encodes a protein that is a part of the SH2B adaptor family of proteins that are involved in signaling activities by regulating T-cell receptor growth factors and cytokine receptor mediated signaling implicating leukocyte cell homeostasis.
rs2816316	RSG1	
rs13098911	CCR1, CCR2, CCRL2, CCR3, CCR5, CCR9	
rs17810546	**IL12A**	IL12A: Encodes a unit of cytokines that affect T cells and NK cells.
rs1464510	**LPP**	LPP: Encodes a protein of the LIM domain proteins. This protein localizes to the periphery in focal adhesions which suggests it might be involved in cell-cell adhesion and cell motility. This protein can also act as a transcriptional co-activator.
rs13151961, rs13119723	**IL2, IL15,** IL21	IL15: Encodes a protein that regulates NK cell and T-cell activation and proliferation. IL2: Encodes is a cytokine that is activated by CD4+ and CD8+ lymphocytes.
rs802734	PRPRK, THEMIS	
rs11221332	**ETS1**	ETS1: Is part of the telomerase holoenzyme complex. It enables RNA, single-stranded DNA, and telomeric binding activity. It is involved in the regulation of telomere maintenance and G-quadruplex DNA formation.
rs1033180	**IRF4**	IRF4: Encodes a protein that is in the interferon regulatory factor (IRF) family. This gene is important in the interferons in response to infection by viruses and interferon-inducible genes.
rs17035378	PLEK	
4q27	KIAAQQ09, TENR	
19p13.11	**MYO9B**	MYO9B: Encodes a member of the myosin family of actin-based molecular motor heavy chain proteins. This gene is involved in cell motility.

(Table 1) shows the SNPs or locations that are associated with CD and which genes are in each SNP or location. This information comes from GWAS studies or studies in general done by (Dubois *et al.* 2010), (Sharma *et al.* 2016), (Trier 1991), (Vader *et al.* 2003), (Van Heel *et al.* 2007) and (Monsuur *et al.* 2005). The bolded genes play a role in the pathogenesis of Celiac disease.

Method of Data Collection:

Omim.org was used to get an idea of the genes associated with Celiac Disease. The genes associated with CD were noted down in (Table 1). The reference research articles in omim.org provided a clearer idea of which genes cause CD so data from those was taken for the bolded genes. Additionally, data from GWAS, GRAIL, and TEDDY studies by other scientists were also incorporated into (Table 1) by looking at tables and determining which genes had the most statistically significant p-value/standardized value.

Molecular Mechanisms of Celiac Disease: Immune Signaling:

These genes all result in increased pro-inflammatory cytokines through various types of lymphocytes which would then lead to villous atrophy.

HLA-DQA1 and HLA-DQB1 encode for the HLA-DQ2 and HLA-DQ8 molecules.[17] The SNP rs2187668 near HLA-DQ2 presents gluten peptides to CD4+ cells in the lamina propria and then they bind.[18] This induces inflammatory T-cell responses resulting in CD. HLA-DQ2.2 and HLA-DQ2.5 have also been shown to bind to these gluten peptides but HLA-DQ2.2 has to be expressed with HLA-DQ2.5 or else it will have no effect.[14] HLA-DQ8 promotes the recruitment of T-cell receptors. These T-cells showed a stronger response to deamidated gluten peptides. The SNP rs2187668 near HLA-DQ8 causes HLA-DQ8 to amplify T-cell response when gluten proteins come in contact with the immune system.[19] T-cells activate T-helper 1 cells that produce a high number of pro-inflammatory cells which eventually lead to villous atrophy.[2] The SNP rs17810546 near the IL12A gene also alters the Th1 cell regulation which causes an increase in the simulations of these cytokines.[20] According to the NCBI gene database, STAT4 is a gene that encodes a protein that mediates IL12A-induced lymphocytes so STAT4 could also cause CD.[21]

T-cell lymphocytes and intestinal damage are associated with B-cell lymphocytes. Mutations in the REL gene are usually related to B-cell lymphocytes. The SNP rs13003464 near REL causes B-cell lymphocytes to increase activation in T-lymphocytes and intestinal damage which are key parts of Celiac disease.[22] IL15 and IL2 also deal with T and B cell lymphocytes. The amount of CD8+ memory cells is controlled by a balance between IL15 and IL2.[2] IL2 is important for the proliferation of T and B lymphocytes because when the balance of the memory cells is thrown off, the SNP rs13119723 near IL2 can cause the cytokine storm inflammatory response.

IRF4 is more lymphocyte-specific and it negatively regulates the Toll-like receptor (TLR) which is vital for the activation of the innate and adaptive immune systems. The SNP rs1033180 near IRF4 could cause TLRs to trigger the induction and generation of proinflammatory cytokines and these molecules have been detected on B-cells and certain T-cells.[23] PRAT4A is shown to regulate the distribution of TLRs so there could be a connection between that gene and CD.[24]

T and B cell lymphocytes cause multiple cytokines to generate, including the cytokine interferon-gamma. The SNP RS917997 near IL18RAP and IL18RI enhances the binding activity of both IL18RAP and IL18RI to the IL18 receptor. IL18 binds to targeted cells through IL18RAP and IL18RI which is related to pathogenesis because IL18 induces T-cells to synthesize interferon-gamma which is a key cytokine involved in mucosal inflammation.[25,26]

The polymorphisms rs2857972 and rs1057972 near IL15 cause IL15 to allow more permeability through the epithelial barrier which allows more peptides to flow through.[27] Because of this, these peptides can reach the T-cells which cause proinflammatory cytokines to be stimulated. When connected with the SNP rs11221332 near ETS1, transcription factors in thy-

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mic CD8+ lineage differentiation promote RUNX expression (RUNX promotes CD8+ T lymphocyte development), which can lead to an increase in pro-inflammatory cytokines. The SNPs rs1545620, rs1457092, and rs2305767 near MYO9B also cause increased permeability through the epithelial barrier by disturbing the tight junction gate and fence function which allows immunogenic gluten peptides to enter the mucosa.[16,28]

Mutations in the SH2B3 gene throw off the gene's inhibiting cytokine function but the SNP rs3184504 near SH2B3 can throw this off which would cause an increase in cytokines.[29]

Molecular Mechanisms of Celiac Disease: Immune Signaling:

The cytoskeleton in epithelial cells controls the transport of ions and molecules across the epithelium. Issues with the cytoskeleton could cause the epithelium to become weaker by the disassembling of the inter-enterocyte tight junctions (TJ). This makes the epithelium more susceptible to peptides. Once these peptides and gluten-specific T-cells bind, villous atrophy is caused.

TAGAP and LPP SNPs both disrupt the cytoskeleton. According to Omim.org, this TAGAP is expressed in T-cells and is a protein that is important for our cytoskeleton since it is a Rho-GTPase activator. CD pathogenesis has a lot of changes, mostly including the number of cells and the SNP rs1738074 near TAGAP can cause the cytoskeleton to become unstable and dysfunctional.[30]

LPP is a substrate of protein tyrosine phosphatase 1B (PTP1B). The SNP rs1464510 near LPP can cause PTP1B's activation of extracellular signal-regulated kinase (ERK), which is activated in the mucosa, to be lost. Loss of ERK phosphorylation can cause the proliferation of CD atrophic mucosa and disturb the cytoskeleton.[30]

■ Conclusion

CD can be seen in humans from young childhood to adulthood. If it is developed during childhood and goes undiagnosed into adulthood, it can cause an increased mortality rate in the undiagnosed individual. This is why it is so important to keep looking for symptoms of this gene especially if it is prevalent in families. CD was not the main focus of researchers for the longest time and was kept in the dark but after the 2000s, progress about CD's trigger factors and pathogenesis is being made.

While HLA DQ2 and HLA DQ8 are known as the strongest genetic risk factors of CD, many other genes come into play here. The pathogenesis of CD involves many processes based around the immune adaptive system and a variety of environmental or genetic factors can influence this. There were many gene variants associated with CD, but that is not surprising since that is the case with every disease. However, there are not as many that are directly related to pathogenesis. The genes causing CD were identified and then explained by recognizing their functions and how they can lead to CD.

While new genes are being recognized through many GWAS studies, there are still limitations. Genes such as PTPRK, THEMIS, KIAA1109 and TENR's expression by CD is unknown which is a limitation because finding out can help identify other genes that are possibly risk factors. CTLA4 information about CD is also weak; there are definite signs of susceptibility however significant research has not been done to ensure it causes CD.

There can also be new revelations, however. STAT4 and PRAT4A are genes that could be associated with CD. EST1 is shown to promote RUNX expression which then increases T-cells in CD. EST1, RUNX and THEMIS promote the same function so they may be connected. LPP is also shown to have a connection with PTP1B. LPP is just a substrate of PTP1B which means that PTP1B is more directly related to CD. Ultimately, STAT4, PRAT4A, RUNX and PTP1B can now be found to play a role in the pathogenesis of CD.

It is known that there is no cure for CD but developing a drug that specifically targets the immune system while gluten is in the affected individual's body would be helpful. The main problem in CD is the villous atrophy which is related to the proinflammatory cytokines. If a drug was developed that could reduce the number of these cytokines, villous atrophy would not occur. Research involving various genes (including multiple genes listed in this article), clinical trials and different forms of the drug must be involved which would take a lot of time and effort.

Currently, multiple methods of preventing CD are being researched which include: developing non-immunogenic wheat (this is not an easy task because so many genes are involved), digesting gluten through exogenous peptidases (Latiglutenase, Aspergillus niger, or TAK-62), neutralizing gluten proteins in the intestinal lumen through two therapies (AGY: an oral egg yolk anti-gliadin polyclonal antibody; BL-7010: a non-absorbable high molecular weight copolymer of hydroxyethyl methacrylate and styrene sulfonate), modulation of tight junctions (Larazotide acetate which inhibits zonulin), transglutaminase inhibition (ZED1227 selectively inhibits TG-2), immune modulation (through blocking HLA genes and inhibiting lymphocyte trafficking), and inducing immune tolerance through therapeutics or strategies (TAK-101, KAN 101, Nexvax 2, or Necator Americanus). None of these are effective without side effects which is why a gluten-free diet remains the most popular treatment.[31]

For now, the first step is to continue to make progress about the genes that are thought (but not known for sure) to be causing CD and continue testing drugs that effectively deal with Celiac disease.

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