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**Research Article**

# Genetic Hints of Celiac Disease: Current Researches

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***Abstract:*** *Celiac disease is an autoimmune disease that is characterized corruption of small bowel's absorption due to food intolerance against gluten protein in cereals as wheat, rye, oats and barley and can be seen at any age. One in every hundred individuals throughout Turkey and world is celiac patient. Immunologic peptides in gluten protein received via foods trigger activation of T lymphocytes and stimulation of inflammatory mechanisms together immune response. T lymphocytes activated by gluten cause inflammation in small bowel and corruption of absorption. Many genetic and molecular studies for achieving clues to the treatment of celiac disease have been performed. These studies have been focused on genes, metabolic pathways and molecules which have been proposed to be related with celiac disease. Main studies are on genotyping of HLA molecules interrelated with the disease and polymorphism research. In addition there are studies on biomarkers for diagnosis and gene expressions. We reviewed recent data that hints genetic clues of celiac disease.*

***Keywords:*** *Celiac Disease; Genetics; HLA; Immunology.*

## 1. Genetic Basis of Celiac Disease

Celiac disease is a common complex disease of the small intestine induced by dietary proteins as gluten (gliadin) in wheat, barley and rye. Gliadin is a major component of wheat gluten and important for the development of celiac disease [1-4]. Different wheat strains have genes for more than 50 and maybe as many as 150 different gliadins that are classified as α/β-, γ- and ω- gliadins based on their amino acid sequence. Two groups (DQ2 and DQ8) have published sequences of gliadin fragments recognized by small intestinal T cells. DQ2 restricted peptide epitope was isolated from purified gliadins. Their characterized epitope was derived from a γ-gliadin with the sequence "QPQQSFPEQQ". The second restricted peptide epitope isolated from an α-gliadin is DQ8. DQ8 has the sequence "SGQGSFQPSQQ" [1]. Deamidated gluten peptides bind strongly to the specific human leukocyte antigen (HLA) molecules [5].

In 1972, the first genetic consensus about celiac disease was occurred with the identification of an association among the HLA serotypes (HLAB8 and HLA-DR3) and celiac disease development [2-3, 5]. Celiac mostly develops in HLA-DQ2-positive individuals, whereas most of the remaining cases are HLA-DQ8-positive [4]. The HLA region is a 4Mb region on chromosome 6p21 and contains some 200 genes of which over half are known to have immunological function [2-3]. HLA-DQ2 is encoded by the HLA-DQA1*05 all ele (α chain) and HLA-DQB1*02 allele (β chain). The two alleles are often present in the cis conformation on the DR3 haplotype, which is also common to many other autoimmune disorders. The small proportion of patients with celiac disease who do not express HLA-DQ2 molecules are HLA-DQ8-positive, where the α and β chains of the HLA-DQ8 molecule are encoded by HLA-DQA1*03 and HLA-DQB1*0302, respectively [5-6]. The DQ2 and DQ8 α/β heterodimers in wheat gluten mediate the activation of gluten-reactive CD4+T cells in the bowel [4]. HLA-DQ molecules as key steps leading to the intestinal inflammatory response on antigen-presenting cells specifically bind gluten-derived peptides, modified by the enzyme tissue transglutaminase (tTG) [2, 7-9], and present them to intestinal T cells [2, 4, 10]. Therefore, celiac disease is generally characterized by the production of anti-tissue transglutaminase (anti-tTG) [9] and anti-endomysial (EmA) antibodies [4, 10].

CD4+ T cells recognize the HLA–gluten complex and produce pro-inflammatory cytokines, mainly interferon (IFN)-γ [5]. IFN-γ induces interleukin (IL-21) secretion from activated T cells. IL-21 is secreted upon CD3 stimulation of T cells and by natural killer cells (NK) cells [3]. Gluten peptides also trigger an innate immune response characterized by the elevated expression of IL-15 by intestinal enterocytes [5]. The cytokine itself is similar in structure to both IL-2 and IL-15. Although some works on rats have suggested that IL-21 may be a TH2 inducing factor in humans. Treatment of CD4 T cells with IL-21 lead to a significant increase in T-bet (a critical transcription factor for T helper 1 cell differentiation) and IFNγ production as well as IL-2Rα, IL-12Rβ2 [11], IL-18R and MyD88 [3]. The inflammatory response in T cells leads to the production of celiac diseases specific antibodies and to the secretion of pro-inflammatory cytokines with consequent mucosa atrophy and clinical manifestations [4].

Recently, statistical studies related celiac have demonstrated the population prevalence of celiac disease at about 1%. Despite this estimated prevalence of 1%, only approximately 0.14% of the

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population is diagnosed with celiac disease [3]. These statistical studies also suggest a stronger genetic component to celiac disease than many other complex diseases [2]. The concordance of celiac disease between monozygotic twins is very high, 75%, while the concordance rate between dizygotic twins is still high at 11%. This strong heritability is also evident in family studies where the risk of celiac disease is approximately 10% for a sibling of an affected individual [3].

Environmental and genetic factors determine susceptibility to celiac disease in every person [3]. It is seen that gene expression analysis, polymorphism and genome wide association studies will advance understanding of genetic susceptibility of celiac disease [2].

## 2. HLA Genotyping and Genome Studies

Genetic studies have confirmed strong association to HLA and identified 39 nonHLA risk genes, mostly immune-related [5]. Susceptibility to celiac disease is essentially restricted to carriers of specific HLA DQA1 and DQB1 alleles [12]. Main studies have been also showed in table 1.

**Table 1.** Main studies about the genetic clues of celiac disease.

| First author & year | Alleles | Population | Method |
|---|---|---|---|
| Sacchetti, 2001[20] | DQA1*0501, DQB1*0201 and DRB1*04 | European | PCR-based method |
| Neuhausen, 2002[23] | *DQA1**03 *DQB1**0302 and *DQA1**05 *DQB1**02 | Northern and Southern Europeans | PCR-based method |
| Karell, 2003[18] | DQA1*01-DQB*05, DQB1*06 DRB1*04 or DRB1*07 | European | Microsatellite Markers |
| Cintado, 2006[19] | HLA DQA1*0501 and DQB1*02 alleles | Cuban | PCR-based method with Sequence Specific Primers |
| Reinton, 2006[24] | DQB1*05, DQB1*02 and DQB1*0302 | European | Real-Time PCR assay with Sequence-Specific Primers |
| Megiorni, 2009[4] | DQB1*02, DQB1*0302 and DQB1*02/*02 | Italian | PCR-based method with Sequence Specific Primers |
| Alarida, 2010[9] | DQ2 and DQ8 | Libyan | PCR-based method |
| Lavant, 2011[12] | DQA1, DQB1 and DRB1 | Sweden | PCR-based method with Semi-Automated Sequence Specific Primers |
| Vatta, 2011[25] | DQ2.5, DQ8, DQ2.2, and DQ7 | North Eastern Italy | Real-Time PCR assay with Tag–Single Nucleotide Polymorphism |

Greco et al. (1998) confirmed implication of HLA as a risk factor for celiac disease. They deduced that there was not heterogeneity between the symptomatic form samples and silent form samples. This result shows that the HLA component is not a factor that differentiates the symptomatic and silent forms of celiac disease. Beyond the well-known factor in the HLA region (6p21), they suggested that a risk factor in the terminal portion of chromosome 5 (5qter) is involved in both symptomatic and silent forms of celiac disease [13]. Zhong et al. (1996) found some evidence for linkage for five new chromosome locations apart from HLA: 6p23, 7q31, 11p11, 15q26, and 22cen [13-14]. Finally, results of Zhong et al. (1996) for the same region provided an additional evidence for verity of Greco et al. about a risk factor in this region [13]. Mustalahti et al. (2002) aimed to investigate whether differences in HLA DR-DQ genes explain the variation in the exact clinical outcome of celiac disease. But they could not observe differences in the distribution of HLA DR-DQ haplotypes [15]. The other genome study is an α-gliadin cDNA screen of human cDNA and genomic libraries and an approach in keeping with positive human Northern and Southern analyses with the same probe. Kumar et al. (2000) obtained four distinct cDNA clones. The most stringent of these clones (3.2 and 5.1 kb) were novel and featured potential open reading frames with high gliadin domain II and domain IV homologies. Both were also homologous to ESTs. An additional 50 gliadin oligonucleotide screen identified the widely distributed cytoplasmic protein acyl coA hydrolase whose homology was restricted to the oligonucleotide probe; and achaete-scute homologous protein, which displays particularly high gliadin domain II homology. ALR gene that is one of genomic screening uncovered 16 positives was remarkably similar to three of gliadin's five domains (I, II and IV). Novel genomic clone 2 derived by Kumar et al. was more extensive, with fragments hybridizing to cDNA probes approximating gliadin domains I, II, IV, V and the gliadin 50 untranslated region, and mapping by FISH to 19q13.11-13.12 [16]. In 2002, Kumar et al. identified only 11 gut-expressed proteins with high T-cell epitope homology, particularly to the DQ2-γ-I-gliadin epitope, using database searching of the entire human genome. Others were similar to DQ2-α-I-gliadin or DQ2-α-II-gliadin (PHLDA1, known in mice as the T-cell death-associated gene) epitopes. Among proteins previously screened for gliadin homology, noteworthy was achaete-scute homologous protein (DQ2-α-I-gliadin) [17]. Karell et al (2003) identified 61 patients who neither carry the DQ2 nor DQ8 heterodimers among 1008 European celiacs. They found that 57 of these patients encoded half of the DQ2 heterodimer. The remaining 4 patients had a variety of clinical presentations and 3 of them carried the DQA1*01-DQB*05 haplotype as did 20/61 of those carrying neither DQ2 nor DQ8. This may implicate a role of the DQA1*01-DQB*05 haplotype. They found that none of these 4 patients carried the DQB1*06 allele. Owing to 16 DQ2 heterodimer negative patients without DRB1*04 or DRB1*07 haplotypes, they inferred that none encoded the previously implicated DRB4 gene as none had a DRB1*09 haplotype [18].

Cintado et al. (2006) looked the distribution of HLA DQA1*0501 and DQB1*02 alleles (DQ2) for the first time in a group of Cuban celiac patients. They evaluated 22 patients with celiac disease, 54 first-degree relatives and 60 controls for detection of anti-tissue transglutaminase (tTG)-specific antibodies in serum. Both in patients and relatives, a significant over-representation of DQ2 heterodimer was observed. In patients, rate of positive for DQA1*0501 was 86.3%, rate of positive for DQB1*02 was 90.2%, and rate of positive for both alleles was 86.3%. The frequencies in relatives and controls were as follows: 70%, 90%, and 70%; and 56.6%, 45%, and 20%, respectively [19].

Sacchetti et al., (2001) described a PCR-based methodology for the typing of alleles DQA1*0501, DQB1*0201 and DRB1*04 and an improvement of the methodology by which the three alleles can be detected in a single PCR reaction [20]. Leuka et al. (2003) focused on the DR3-DQ2 risk haplotype in European consortium and identified 109 families with a parent homozygous

 

for DQA1*05-DQB1*02. They typed ten microsatellites in the extended HLA complex, and applied the homozygous-parent transmission disequilibrium test (HPTDT) and extended-TDT to transmissions from homozygous parents [21].

Megiorni et al. (2009) typed DR-DQ genes in 437 Italian children with celiac disease, 834 first-degree relatives, and 551 controls. Of these celiac patients, 91% carried DQ2 and/or DQ8 heterodimers, 6% only had β2 chain, 2% was α5 positive, and four were DQ2/DQ8/β2/α5 negative. Whereas effect of the β half of DQ2 dimer on celiac disease predisposition was confirmed, only the presence of α5 resulted was negatively associated to disease. Considering 1:100 celiac disease prevalence (CDP), they obtained a risk gradient ranging from 1:7 for DQ2 and DQ8 individuals down to 1:2518 for subjects lacking all predisposing factors. The DQB1*02 and DQB1*0302 concurrence, besides the DQB1*02/*02 homozygosity, had an additional role in disease genetic determination. The subjects carrying high-risk HLA molecules were 57% in sisters (CDP: 17.6%), 71% in brothers (CDP: 10.8%), and 58% in parents (CDP: 3.4%); among them, 29%, 15%, and 6% respectively had celiac disease [4]. Alarida et al. (2010) tested 31 Libyan children with celiac disease and 156 Libyan controls. They found that HLA-DQ2 and -DQ8 in celiac patients are as common in Libya as in Italy, but the frequency of "high-risk" genotypes is higher in Libyan than Italian patients. The prevalence of HLA-DQ2 and -DQ8 genes in the Libyan general population is higher than in Italy, indicating a strong genetic predisposition to celiac disease [22].

Neuhausen et al. (2002) genotyped DNA samples at HLA DQA1 and DQB1 in a set of nine Bedouin multiplex celiac disease families and one simplex, using transmission disequilibrium testing. They observed a significant over-representation in affecteds of the DQA1*05 DQB1*02 genotype, as well as over-representation of the DQA1*03 DQB1*0302 genotype. The HLA DQA1 DQB1 high-risk genotypes associated with celiac disease are similar in these Bedouin families with celiac disease to what is observed in Northern and Southern Europeans [23]. In 2006, Reinton et al. developed a new real-time PCR assay, using sequence-specific primers (PCR–SSP) and TaqMan® probes, for detection of DQB1*05, DQB1*02 (coding for DQ2) and DQB1*0302 (coding for DQ8). PCR amplification for detection of DQ2 and DQ8 was accurately and clearly performed from genomic DNA isolated from cell lines and human DNA. Amplification was scored digitally, without laboratory manipulation of amplified PCR products and with a higher accuracy than PCR–SSP. They asserted that should increase accuracy and throughput, and reduce risks of contamination in laboratories where testing for HLA DQ2 and DQ8 is performed as part of diagnosis of celiac disease [24]. Lavant et al. (2011) developed a semi-automated sequence specific primer (SSP) PCR method for clinical HLA typing and compared the test results with those from a commercial method. The risk assessment of two methods was derived 100% concordant. They obtained that distinction of celiac disease associated alleles and their homo/heterozygous status by use of three PCR reactions and a single electrophoretic step for DQA1, DQB1 and DRB1 typing. Lavant et al. asserted that this multiplex analysis reduces reagent costs, personnel and instrument time, while enabling improved allelic assignment through HLA-DR-DQ haplotype association [12]. Similarly, Vatta et al. (2011) genotyped celiac disease–associated haplotypes DQ2.5, DQ8, DQ2.2, and DQ7 in 1005 CD patients from North Eastern Italy using a Tag–single nucleotide polymorphism (SNPs) approach and real time PCR platform, checking the accuracy and reliability of the method and comparing it to traditional PCR-SSP [25]. In other study, Sherrill et al. (2011) genotyped a cohort of 272 eosinophilic esophagitis patients and 450 normal controls for polymorphisms previously linked with celiac disease [26].

### 2.1. Polymorphism Studies

Celiac disease's etiology is still unknown despite it is a common cause of morbidity in the developed world. Considering that Celiac Disease was first documented in Scandinavian Europe, a population exposed to a high fat diet, perhaps the polymorphic genetics of the disease provides balanced polymorphism against this environmental stimulus [27].

Ramos-Arroyo et al. (2001) studied the polymorphisms in the 59 regulatory region of the HSP70-1 gene and performed genomic HLA-DQ and -DR typing in 128 CD patients and 94 healthy controls from Navarra (Spain). They characterized frequency of the C allele of HSP70-1 by using the intermediate electrophoretic mobility of DNA, and it was significantly increased among celiac disease patients (64.5% vs 37.2%. p<1 3 10-7). When subjects were stratified by the HLA II genotype, differences were statistically significant between DR3-negative or DR3-DQB1*02-negative celiac disease patients and matched controls. Homozygosity for the DQB1*02 allele was present in 48.4% of celiac disease patients and 12.8% of controls. They observed similar increased risk for DQB1*02/*02, DRB1*03/-, or DRB1*03/07 patients. Furthermore, those individuals expressing the classical HLA alleles in celiac disease (DQB1*02/*02, DRB1*03/*07) who also carried the HSP70-1 CC genotype were twelve times more likely to develop the disease than the matched controls. Finally, they conclude that although HSP70-1 gene does not see to be primarily associated with celiac disease, it might be a component of the high risk haplotype, playing a role as an additional predisposing gene for the disease [28].

Vidales et al. (2004) examined the polymorphism of HLA-DQA1 and HLA-DQB1 genes in a sample of patients with celiac disease residing in the Basque Country, in order to contribute new data on the association between HLA and celiac disease in a southern European population. 136 unrelated children diagnosed with celiac disease were typed at the DNA level for HLA-DQA1 and -DQB1 loci. HLA class II typing was performed by PCR–sequence specific primer procedures. Conspicuous frequencies of the alleles associated with susceptibility to celiac disease were observed (DQA1*0501: 0.592, DQB1*0201: 0.471). When compared with the Spanish general population, the haplotypes DQA1*0501-DQB1*0201 and DQA1*0201-DQB1*0202 revealed a strong linkage disequilibrium (18.84% and 18.75%, respectively). They found that carriers of DQ2 heterodimer were 93.4% of the total sample, either in homozygosis or in heterozygosis. This percentage coincides with figures reported in previous studies, implying the effect of other genes in the development of celiac disease [6]. Rueda et al. (2005) aimed to assess the role of the PTPN22 1858C→T polymorphism in the genetic predisposition to celiac disease. They analyzed a case-control cohort composed by 534 patients with celiac disease and 653 healthy controls and additionally a panel of 271 celiac families. The PTPN22 1858C→T genotyping was performed by TaqMan 5' allelic discrimination assay. But they did not observe any statistically significant deviation after comparing allele and genotypic frequencies of PTPN22 1858C→T between patients with celiac disease and controls [29].

Over 50% of the disease-associated single nucleotide polymorphisms are correlated with gene expression [5].

### 2.2. Gene Expression Studies

Lately, many gene expression studies have been made for different aims with celiac disease patients. In these studies, researchers have used different methods as cDNA microarray, semi-quantitative RT (reverse transcription)-PCR, quantitative real-time PCR, immuno-fluorescence analyses and western blotting.

Juuti-Uusitalo et al. (2004) studied gene expression in duodenal biopsy samples from untreated celiac patients, patients on gluten-free diet and healthy controls by using cDNA microarray analysis. Compared to healthy controls, the expression of 156 and 60 genes was changed in untreated and treated celiac disease, respectively. They found that 98 genes had altered expression between treated and untreated celiac disease. Of the 5184 genes or expressed sequence tags, altogether 263 were affected. It was detected that many of these genes was directly or indirectly connected to T-cell activation, B-cell maturation or epithelial cell differentiation [30]. Daniels et al. (2005) investigated the role of nitric oxide synthase (NOS) in the pathophysiology of celiac disease via mRNA (reverse transcription multiplex polymerase chain reaction) and protein expression (Western blotting) of i,e and nNOS (NOS I) in enterocytes isolated from the duodenum of patients with untreated celiac disease and iron deficiency anaemia (IDA)., They also studied expression of IL1β and TNFα, two pivotal "NOS-controlling" cytokines. Whereas nNOS gene expression was not statistically different between groups, iNOS (NOS II) expression was higher in patients with celiac disease when compared to patients with IDA. They suggested that iNOS could be an important mediator in celiac disease and expression of this regulatory protein may be under the control of IL1β [31].

Wapenaar et al. (2004) aimed at further ascertaining the role of interferon gamma (IFN-γ), either as a genetic factor in the etiology, or as a facilitator of celiac disease initiation/progression. Their material was duodenal biopsies from celiac disease patients. These duodenal biopsies were used to determine IFN-γ gene expression by real-time RT-PCR. IFN-γ gene expression correlated with the extent of tissue restructuring, reaching a 240-fold higher expression in total villous atrophy compared to healthy tissue. But they declared that there was no evidence for IFNG as a predisposing gene in celiac disease, despite its enhanced expression in patients in complete remission [32]. Pizzuti et al. (2004) investigated the expression and localization of a tight junction protein ZO-1 (Zonula occludens-1) in the intestinal mucosa of celiac disease patients. Localization and expression levels of ZO-1 protein were detected by immunofluorescence followed by confocal microscopy analysis and immunoblotting. ZO-1 mRNA expression was assessed by RT-PCR. They found that both ZO-1 protein levels and mRNA were clearly reduced in patients with active celiac disease [33].

Fernandez-Jimenez et al. (2011) determined qualitative expression of Killer cell immunoglobulin-like receptors (KIR) genes in biopsies from celiac disease patients at diagnosis and after >2 years on a gluten-free diet. They performed quantitative expression analysis of KIR2DL4, KIR3DL1, KIR3DL3, and KLRC2 (a marker of an NK-reprogrammed T-cell subpopulation augmented in CD) in celiac disease biopsy pairs and non- celiac disease control biopsies. No specific KIR expression profile was observed in celiac disease. KIR3DL1 was more frequently expressed in active celiac disease compared with gluten-free diet and controls, with slightly increased levels in active disease. KLRC2 was over-expressed in active and gluten-free diet patients compared with non- celiac disease controls and co-expressed with KIR3DL1. Their results suggested that the participation of KIR3DL1 over-expression in the overall immune activation seen in mucosa, which could be partly explained by the natural killer-like T-cell subpopulation increase [34].

### 2.3. Biomarker Studies

Recently, the new biomarkers for diagnosis of celiac disease have been described by researchers. Although a biopsy of the patient's small intestine is the only way to confirm a diagnosis of celiac disease, these new biomarkers allow a better preliminary diagnosis.

Maki et al. (1991) claimed several antibody (gliadin, reticulin and endomysium antibodies) tests as markers for diagnosis of celiac disease but they did not compare with available tests. Celiac disease patients and their healthy first-degree relatives were studied. Gliadin-antibody-positive relatives with normal mucosa were genetically different from patients. IgA reticulin and endomysium antibodies detected 92·3% of subjects with silent celiac disease. Gliadin antibodies detected only half of the cases. Their study showed that irrespective of the state of the jejunal mucosa, healthy reticulin-antibody-positive first-degree relatives of celiac disease patients were genetically similar to celiac disease patients. In addition, they found that reticulin-antibody positivity was an indicator of both silent and latent celiac disease [35]. Celestino et al. (2011) aimed to evaluate in a group of celiac patients, the role of DQA and DQB alleles in determining the severity of the clinical manifestations at the diagnosis. They tested 122 patients (44 children) with celiac disease. Their data showed a statistical association between genetic risk and the clinical manifestations of celiac disease. Indeed these patients carrying two copies of DQB1*02 or one copy of DQ2 in trans-presented clinical features more suggestive of celiac disease (typical and atypical). They claimed that both HLA alleles DQ2 and DQ8 have an important role in determining celiac disease but there are probably other factors that contribute to express different symptoms, like environmental factors [36].

Planas et al. (2011) aimed to determine whether the serum regenerating gen I α (REG Iα) concentration reflects the destructive/regenerative process in the small intestine in celiac disease. REG Iα was determined by enzyme-linked immunosorbent assay (ELISA) in 40 patients with active celiac disease, and in 19 of them, REG Iα was assessed after following a gluten free diet. They also measured auto-antibodies to transglutaminase, gliadin, and endomisium. They founded a significant increase in REG Iα in the sera of celiac disease patients when compared with controls. REG Iα levels decreased after a gluten-free diet together with a significant reduction in antitransglutaminase antibodies. Finally, they suggested that REG Iα protein levels can be used as a biomarker for the diagnosis and monitoring of celiac disease [37].

Rossi et al. (2012) studied the Cannabinoid Receptor type 2 gene (CNR2) as a novel molecular biomarker for diagnosis of celiac disease. They used both an TaqMan assay toward a CNR2 common missense variant Q63R (CNR2 rs35761398: CAA/CGG→ Glutamine/Arginine in codon 63) and an immunohistochemical assay toward cannabinoid Receptor type 2 (CB2) receptor and CD4+ cells in small intestine biopsies from South Italian celiac children They observed that CB2 is up-regulated in celiac disease small bowel biopsies and CNR2 rs35761398 is significantly associated with celiac disease. They suggested that there was a role of CB2 in celiac disease and the Q63R variant, increasing more than six-fold the risk for CD susceptibility, might eventually represent a novel molecular biomarker for CD risk stratification [38].

 

### 2.4. Other Studies Related Celiac

There are many reasons why coeliac disease attracts our attention. The disease is common and represents a clinical challenge [1]. Coeliac disease is an inflammatory disorder with an autoimmune component [5], but its etiology is still unknown [27]. Therefore, researches related to celiac disease have been still performed. The some studies about possible genes and proteins related to celiac disease are presented below.

Polvi et al. (1998) studied whether celiac disease patients without DQ2 share other MHC (major histocompatibility complex) class II or TNF (tumor necrosis factor) alleles and screened DQ2-negative patients in Finland and Spain. 14% of Finnish patients and 6% of Spanish patients were negative for DQ2. They observed that all but two of altogether DQ2-negative patients had the DR4 DQ8 haplotype, or either DQA1*0501 or DQB1*02 alone. Results of their study showed that none of the TNF, TAP, or DPB1 alleles was found to be significantly associated with celiac disease [39].

Costantini et al. (2005) modeled the three-dimensional structure of the DQ2 dimer protein that is the most frequent in celiac patients, by using a homology modeling strategy. They simulated the interactions of DQ2 with different gluten peptides and the deamidation of specific peptide glutamines. By analysing the peptide–DQ2 complex at the atom level, they observed that these glutamate side chains can interact with specific positively charged amino acids of DQ2, absent in other HLA alleles not relate to celiac disease [40].

Bodd et al., (2012) described the gluten T-cell response of a DR7DQ2/DR9DQ9 heterozygous celiac disease patient. Interestingly, this patient had T cells recognizing gluten in the context of HLA molecules of both haplotypes. They identified DQ9 for the DR9DQ9 haplotype as the antigen-presenting molecule. As DQ9 carries aspartate at DQβ57, but it is otherwise identical to DQ8 and not consider associated with celiac disease. They aimed to characterize this DQ9-restricted T-cell response in detail and identified an epitope stimulatory for several T-cell clones. This epitope was identical to an epitope (DQ8-glut-1) previously identified in DQ8 patients. Their findings correlated with peptide binding data demonstrating that this epitope bound better to DQ9 than the two other DQ8-restricted epitopes. They suggested that DQ9 is a susceptibility factor for celiac disease [41].

Bakker et al. (2013) aimed to investigate clinical and genetic characteristics of patients with both diagnoses so as to lead to better detection of celiac disease in adult patients with type 1 diabetes mellitus (T1DM). They studied 118 patients with both T1DM and celiac disease identified in The Netherlands and frequently found a delay of celiac disease diagnosis in adult T1DM patients. In addition, two peaks in the age of celiac disease diagnosis are present in T1DM patients [42].

Francavilla et al. (2010) aimed the two-step strategy based on selection of potential celiac disease children via HLA-DQ typing. They declared that it is a cost-effective strategy in the setting of a tertiary referral centre for pediatric gastroenterology [43].

Tucci et al. (2010) performed expression studies on RNA extracted from intestinal biopsies, isolated from healthy control, celiac, potential and celiac on GFD (gluten free diet patients), analyzing the genes located on 4q27 locus (KIAA1109, IL2, IL21). They analyzed tree markers (KIAA1109, IL2, IL21) in monocytes isolated from peripheral blood of controls, celiac, potential and GFD celiac patients in order to show a possible different expression of selected genes in this cell type compared to cells from intestinal biopsies. Their analyses detected that the comparison between KIAA1109 gene in monocytes of controls and potentials celiac disease patients showed the same trend presented in intestinal biopsies. They suggested that this important result may indicate a similar role in both cell types (monocytes and biopsies) within potential celiac disease patients [44].

De la Concha et al. (2000) used DNA-based methods to screen for HLA-DRB1, -DQA1, and -DQB1 alleles, TNFα promoter polymorphism and TNFα and β microsatellites. The guanine-to-adenine polymorphism at position -308 of the TNFa gene promoter region was found associated with celiac disease as the TNF-308A allele appeared significantly increased in frequency in celiac disease haplotypes, and this was shown to be independent of the association between celiac disease and the DRB1*0301,DQA1*0501,DQB1*0201 alleles [45]. Chernavsky et al. (2008) aimed to assess the joint contribution of interleukin 1 beta (IL-1B) and tumor necrosis factor alpha (TNFα) to the genetic risk of developing celiac disease and analyzed four biallelic polymorphisms of TNFα and IL-1B genes in 228 patients and 244 healthy controls. The individual contribution of TNFα -308A and IL-1B -511C alleles was weak and was null for TNFα-238 A/G and IL-1B +3953 C/T single nucleotide polymorphisms (SNPs). They first defined two-position risk haplotypes by the combined presence of -511C and +3953T alleles for IL-1B or -308A and -238A alleles for TNFα. Their data suggested that the coexistence of both risk haplotypes seems to work synergistically, which enhances the risk of developing celiac disease [46]. Guariso et al. (2012) deduced that whether five SNPs in the TNFα promoter are associated singly or as haplotypes with celiac disease and whether their effect is HLA-DQA1/-DQB1 dependent or independent. They founded that TNFα promoter haplotypes CCAG, TCGA and CCGA was shown to increase celiac disease risk independently from HLA-DQ alleles suggesting the pivotal role of TNFα in the disease pathogenesis [47].

Hüe et al. (2004) investigated the participation of the MICA/NKG2D pathway in the destruction of intestinal epithelium by intraepithelial T lymphocytes (IEL) in Celiac disease and its premalignant complication, refractory sprue. MICA molecules interact with the NKG2D-activating receptor on human natural killer and CD8 T cells. They showed that MICA is strongly expressed at epithelial cell surface in patients with active disease and is induced by gliadin or its p31-49 derived peptide upon in vitro challenge, an effect relayed by IL-15 [48].

Kolkowski et al. (2006) aimed to compare the cytokine profile and the cytotoxicity pattern from CD8+ intraepithelial lymphocytes clones isolated from celiac and non-celiac biopsies. The role of intraepithelial lymphocytes population in the pathology is unknown. They reported that the number of IL-10 producing celiac clones was significantly lower than that obtained from the non-celiac sample, whereas IL-2 was produced by more celiac than non-celiac clones [49]. Dema et al. (2009) aimed to study the role of IL6 and IL6R polymorphisms in celiac disease (CD) susceptibility. They suggested that functional -174G/C IL6 polymorphism seems to influence CD susceptibility in girls [50].

Amundsen et al. (2006) studied association analysis of MYO9B gene polymorphisms with celiac disease in a Swedish/Norwegian cohort [51]. Kaur et al. (2006) studied polymorphism in L-selectin, E-selectin and ICAM-1 genes in Asian Indian pediatric patients with celiac disease [52]. Bjørnvold et al. (2006) studied FOXP3 polymorphisms in type 1 diabetes and celiac disease [53]. Tolone et al. (2009) aimed to investigate the possible influences of the cytotoxic-T-lymphocyte-associated protein 4 (CTLA4)

CT60 A/G polymorphism in the susceptibility of Italian children to celiac disease and in the predisposition to develop autoimmune thyroid disease (AITD) in children with celiac disease. Their data showed a significant effect of the CTLA4 CT60G allele at the homozygous state on the risk of developing AITD in children with celiac disease and suggest that the reported association of the CTLA4 CT60 A/G polymorphism with celiac disease is limited to the subgroup of patients who are or will be complicated with AITD [54]. Fernandez-Jimenez et al. (2010) studied analysis of β-defensin and Toll-like receptor gene copy number variation in celiac disease [55].

## 3. Conclusion

Understanding of molecular and genetic mechanisms of celiac disease will be the origin of the studies that will focus on diagnose and treatment. In this review we have discussed the results of recent molecular research on celiac disease. With different materials – methods and approach these studies form a huge perspective. We thought that information organized under different titles wil provide basic contribution to researchers for studies focused on diagnose and treatment of celiac disease.

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