

## Human Leukocyte Antigen and its Association with Celiac Disease and Associated Autoimmune Diseases

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### ABSTRACT

**INTRODUCTION:** Human Leukocyte Antigen (HLA) is a crucial component for the regulation of human immune systems. Celiac disease (CeD) is a gluten dependent multifactorial disorder with a strong association with HLA-DQ alleles. HLA-DQ alleles also have a role in Non-Celiac Gluten Sensitivity (NCGS), Dermatitis herpetiformis (DH), and CeD associated autoimmune diseases like Type 1 diabetes (T1D), Rheumatoid arthritis (RA), Multiple sclerosis (MS). However, contribution of HLA in all these diseases is not fully understood. We aimed to provide a concise information about the HLA status in these autoimmune diseases.

**METHODOLOGY:** We explored already published articles having information about HLA in autoimmune diseases in relation to CeD from different scientific platforms. We filtered the HLA data from them. We included original and review articles and excluded articles

which had only clinical information, and case reports.

**RESULTS:** We found that HLA alleles have strong association in the development of CeD and other autoimmune diseases. HLA-B1\*02 is the most critical allele associated with the susceptibility to CeD and also have major role in other gluten related disorders (GRD).

**CONCLUSIONS:** We concluded that although HLA has a major role in the autoimmune disease development, multiple unknown non-HLA genes are also critically involved and must be explored frantically.

**Key words:** Celiac disease; HLA; GRD; Dermatitis herpetiformis; Type 1 diabetes; Rheumatoid arthritis; Multiple sclerosis

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### INTRODUCTION

Human Leukocyte Antigen (HLA) heterodimer is a membrane-bound glycoprotein having a major role in the regulation of the immune system<sup>[1,2]</sup>. HLA gene complex is located on the short arm of chromosome 6p21 and is known to be the most polymorphic genetic system in humans<sup>[1]</sup>. HLA is associated with the development of various infectious and autoimmune diseases<sup>[3]</sup>.

Wheat is worldwide staple food but ingestion of wheat specifically 'gluten' (a storage protein of wheat) in some individuals causes several gluten-dependent diseases. These conditions are collectively known as gluten-related disorders (GRD)<sup>[4]</sup>. GRD includes Celiac disease (CeD), Non-Celiac Gluten Sensitivity (NCGS), Dermatitis herpetiformis (DH), Gluten ataxia (GA), Wheat allergy (WA), and among these disorders, CeD is the most studied disorder and its pathophysiology is comprehensively explained<sup>[5]</sup>. HLA has a major role in the development of CeD<sup>[6]</sup>, its role in the development of other GRD is also studied but not fully explained<sup>[7]</sup>.

CeD is an autoimmune, chronic enteropathy which gets triggered on exposure to dietary gluten in genetically predisposed individuals who carry HLA-DQ alleles. CeD is also a multi-systemic disease.

HLA has a major role in the development of other autoimmune diseases like Type 1 diabetes (T1D), Rheumatoid arthritis (RA), Multiple sclerosis (MS)<sup>[8]</sup> and oral manifestations such as dental enamel defects (DED)<sup>[9]</sup> and recurrent aphthous stomatitis (RAS)<sup>[10]</sup> and other gluten sensitive patients<sup>[11]</sup>. Pathophysiology of CeD is similar to T1D and RA, so the role of HLA in these diseases shares similar pathophysiology. In the last decades, multiple studies have shown an association of CeD with RA, T1D, and thyroid<sup>[12]</sup>. In this article, we explored the role of HLA class II molecules in disease development of GRD including CeD and its associated diseases and the status of HLA in these diseases.

## METHODOLOGY

We explored already published articles having information about HLA in autoimmune diseases in relation to CeD from different scientific platforms like PubMed, and google scholar with the key words, 'celiac disease and other autoimmune disease', 'Gluten related disorders', role of HLA in 'Dermatitis herpetiformis', 'type 1 diabetes', 'rheumatoid arthritis', 'multiple sclerosis', 'dental enamel defects' and 'recurrent aphthous stomatitis'. We filtered the HLA data from them. We included original and review articles and excluded articles which had only clinical information, and case reports.

### HLA gene complex

The HLA molecule recognizes the processed exogenous/endogenous peptide antigens and present them to the T-cell ( $T_C/T_H$ ) for appropriate immunological action. Based on immunological action HLAs have three classes.

**HLA class I (A, B, and C) molecules:** Class I HLA molecule, also referred as classical class I molecule, is a 45 kilo Dalton (KD) heavy chain glycopeptide with three domains ( $\alpha 1$ ,  $\alpha 2$ , and  $\alpha 3$ ) that non-covalently associates with  $\beta 2$ -microglobulin which provides structural support to the heavy chain. Among HLA-A, B, and C loci, HLA-B is the most significant and highly polymorphic locus. HLA class I molecules expressed on nucleated cells and its  $\alpha$ -chain anchors itself into the plasma membrane through its cytoplasmic tail. HLA class I molecules are associated in the development of several infectious diseases (Hepatitis B and C viral infection, HIV/AIDS, mycobacterial, protozoan infections, etc)<sup>[13]</sup>. Primary function of HLA class I molecules is to recognize the endogenous antigen (antigenic peptides that are produced inside the host cell. e.g. viral proteins) and present these processed peptides to the cell surface by linking them to the T-cytotoxic (TC-cells)/CD8+ T cells that ultimately impose a killing action to these peptides and neutralize the cells from viral infection<sup>[14]</sup>.

**HLA class II (DQ, DR, and DP) molecules:** This class of HLA molecule is highly polymorphic that expresses itself on antigen-presenting cells (APCs) (B-cells, dendritic cells, and macrophages). HLA class II molecules are associated in the development of autoimmune diseases. Primary function of HLA class II molecules is to present the exogenous antigen (antigenic peptides that are produced outside the body and enter the cells by phagocytosis) to the T helper (CD4+) cells. The HLA class II elicits a general immune response (humoral response) so it remains present on APCs only and not on every cell. HLA Class II molecules contain two polypeptide chains, a 33KD  $\alpha$  chain (with two domains  $\alpha 1$  and  $\alpha 2$ ) that are non-covalently associated with a 28 KD  $\beta$  chain (with two domains  $\beta 1$  and  $\beta 2$ ). HLA class II molecule has a transmembrane segment that remains attached to the lipid bilayer of the cell membrane<sup>[13]</sup>.

HLA class I and Class II genes are highly polymorphic in nature

and remain in a strong linkage disequilibrium i.e. there is a high possibility of combinations of alleles that are not expected often. DRB locus (HLA class I genes) alone encodes for 18 different alleles. Protein products of HLA Class I genes are also highly polymorphic e.g. there are at least 8 different alleles for the DQA1 gene and 19 different alleles for the DPB1 gene<sup>[15,16]</sup>. Additionally, multiple DRB gene loci (DRB1, DRB3, and DRB4) code to form DR  $\beta$  chains<sup>[15]</sup>.

**HLA class III molecules:** HLA class III molecule participates in the specific immunological machinery that is why HLA Class III molecules do not have a crucial role. It is associated with hormones, complement system (C4A, C4B, Bf, and C2), and molecules involve inflammation<sup>[17]</sup>.

## RESULTS AND DISCUSSION

### HLA and its association with celiac disease susceptibility

Celiac disease (CeD) globally has serological prevalence of 1.4% and biopsy proven prevalence of 0.7%<sup>[18]</sup>. During the early development of HLA characterization, on the basis of serological findings, B locus (B8) of HLA Class I molecules were associated with the CeD<sup>[19]</sup>. However, later D locus (DR3) of HLA Class II molecules were found strongly associated with CeD<sup>[20]</sup>. Association of CeD with B locus was primarily suggested due to strong linkage disequilibrium between the alleles that encode for HLA-B8 and HLA-DR3. However, the latest knowledge confirms that HLA-DQ2 heterodimer from HLA class II genes is closely associated with CeD susceptibility<sup>[14]</sup>.

The HLA heterodimer plays a crucial role in CeD development, it remains present on the surface of APC, it attaches with the deamidated gluten peptide by tissue transglutaminase enzyme, and present this gluten to the T-cells that finally caused villous atrophy in CeD patients<sup>[21-23]</sup> HLA (HLA-DQ2 and/or HLA-DQ8) heterodimers explain about 40% of the CeD heritability, while 60% of genetic susceptibility of CeD by non-HLA genes<sup>[24,25]</sup>. Other than HLA DQ2/ DQ8, more than 40 candidate genes have been discovered to be associated with CeD<sup>[26,27]</sup>. Hence, HLA typing is used to clarify the uncertain diagnosis, considering its high negative predictive value<sup>[28]</sup>.

About 90%-95% patients with CeD from the western population express HLA-DQ2 heterodimer also known as HLA-DQ2.5 heterodimer that is encoded by DQ A1\*0501 and DQB1\*0201 alleles. Remaining 5%-10% of HLA-DQ2.5 negative CeD individuals express DQ8 heterodimer that is encoded by DQA1\*03 and DQB1\*0302 alleles<sup>[29]</sup>. HLA-DQ alleles (A1 and B1) could be present in *cis* (both genes inherited together on the same chromosome) or in *trans* configuration (both genes separately inherited on two homologous chromosomes). DQA1\*05 and DQB1\*02 alleles are present at the DR3 haplotype in the *cis* form (DRB1\*03:01-DQA1\*05:01-DQB1\*02:01) and on *trans* form on DR5/DR7 haplotype (DRB1\*11/12-DQA1\*05:05-DQB1\*03:01; DRB1\*07DQA1\*02:01-DQB1\*02:02).

Likewise, HLA-DQ8 alleles present in *cis* form on the DR4 haplotype (DRB104\*-DQA1\*03:01-DQB1\*03:02). The DQB1\*02 alleles are considered as the at-risk allele to CeD and DQB1\*02 homozygosity is associated with the increased risk and more aggressive form of CeD<sup>[2]</sup>. CeD cases negative with HLA-DQ2.5/ DQ8 alleles (which is a rare case) express HLA-DQB1\*02 at-risk allele in absence of the DQA1\*05 variant, also known as HLA-DQ2.x<sup>[30,31]</sup>. However, there are about 25%-30% of individuals who carry HLA-DQ7 and/or DQ8 alleles but only a small number of such individuals develop CeD<sup>[2]</sup>.

Highly polymorphic HLA class II molecules are closely related to CeD with DQB1\*02 as a prime at-risk allele for CeD. While 100% CeD Caucasian carry HLA-DQ2/-DQ8 alleles<sup>[2,29]</sup>. However, there are several other similar conditions where HLA class II plays major role in the disease development. A quick view of critical HLA gene associated with respective disease is given in table 1.

**HLA and its association with Non-celiac gluten sensitivity (NCGS):** The global prevalence of NCGS is unknown however, it's prevalence in the United States is considered about 6%<sup>[32]</sup>. NCGS is diagnosed in individuals who do not have CeD or wheat allergy (WA) but who have intestinal symptoms, extraintestinal symptoms, or both, related to ingestion of gluten-containing grains, with symptomatic improvement on obtaining gluten-free diet (GFD). Study shows that there is a genetic risk for hydrolyzed wheat protein allergy and this genetic risk is mainly represented by multiple combinations of HLA variants<sup>[33]</sup>. Half of the patients with NCGS were HLA-DQ2 or HLA-DQ8 positive, which was slightly higher than in the general population (40%)<sup>[7,34]</sup>. It is known that HLA has a major role in the development of NCGS however, so far its specific mechanism is not fully known<sup>[34]</sup>. Nevertheless, few studies have reported an increased permeability in a subgroup of HLA-DQ2/DQ8-positive adult patients having NCGS<sup>[35-37]</sup>. The genotype combination A1-3/B2-6 has been found in gluten-sensitive patients. Allele A5 (DQA1:05) and allele B2 (DQB1:02) were found to be higher in gluten-sensitive patients when compared to controls<sup>[11]</sup>.

**HLA and its association with Dermatitis herpetiformis (DH):** Dermatitis herpetiformis (DH) is a chronic skin inflammatory condition due to the ingestion of gluten that results in skin rashes, blisters filled with watery fluid. Global prevalence of DH has been reported as 10 in 100,000 people<sup>[38]</sup>. Elbows and upper forearms are the most affected body parts (almost 90% DH patients)<sup>[39]</sup>. DH is strongly associated with the HLA-A1 (74% of patients with DH), -B8 (88%), -DR3 (95%), and -DQw2 (100%). It is rarely seen in American blacks which might be due to the decreased frequency of HLA-A1 and -B8 in them compared with Caucasians (American blacks: HLA-A1 = 15.3%, HLA-B8 = 10.7%; Caucasian: HLA-A1 = 26.4%, HLA-B8 = 18.3%)<sup>[40]</sup>. Two American blacks with DH reportedly had results of HLA typing for HLA-A, -B, -C, -DR, and -DQ antigens. It was also revealed that neither patient expressed HLA-A1 or -B8; however, both patients did express the class II antigens which is mostly seen in DH, HLA-DR3 and -DQw2<sup>[40]</sup>. A comparison of HLA class II antigen frequency in normal American blacks and Caucasians revealed a similar frequency of HLA-DR3 and -DQw2 (American blacks: HLA-DR3 = 27.6%, HLA-DQw2 = 40.9%; Caucasian: HLA-DR3 = 22.6%, HLA-DQw2 = 32.9%)<sup>[40]</sup>. All this has the importance of the HLA class II region in the pathogenesis of DH. It was also stated that the occurrence of DH in American blacks is rare, not due to the decreased frequency of the HLA class I antigens -A1 and/or -B8 but instead was related to differences in the HLA class II region not detected by routine HLA typing<sup>[40]</sup>.

MA Hall *et al* in 1991 performed HLA-DR, DQ, and DP restriction fragment genotyping in 23 DH patients and 53 healthy controls. They had shown that all 23 patients were positive for HLA-DQw2 versus 40% of control subjects (21 of 53)<sup>[41]</sup>. Secondary associations with HLA-DR3 (91% of patients versus 28% of control subjects) and DPw1 (39% of patients versus 11% of control subjects) were also significant<sup>[41]</sup>. Thus DH and CeD share an identical HLA class II association. It can thus be hypothesized that HLA class II for disease susceptibility to DH other than DR3 and DPw1<sup>[42]</sup>, DQ alpha/DQ beta

**Table 1** Worldwide prevalence and associated HLA gene with different diseases.

SNo.	Disease Name	Worldwide Prevalence (%)	Critical HLA allele
1.	Celiac Disease	0.7 <sup>[14]</sup>	HLA-DQB1*02 <sup>[10]</sup>
2.	Non-Celiac Gluten Sensitivity	6% <sup>[24]</sup>	HLA-DQ2, HLA-DQ8 <sup>[7,26]</sup>
3.	Dermatitis herpetiformis	0.01 <sup>[31]</sup>	HLA-A1, -B8, DR3, -DQw2 <sup>[33]</sup>
4.	Type 1 diabetes	2-5 <sup>[36]</sup>	DRB1*03/DQB1*02:01 /B1*04/DQB1*03:02 <sup>[38]</sup>
5.	Rheumatoid arthritis	1% <sup>[42]</sup>	DRB1-0401, 0404, 0405, 0101 <sup>[46]</sup>
6.	Multiple sclerosis	10.4 <sup>[48]</sup>	HLA-DRB1*15:01 <sup>[35]</sup>

heterodimer is the HLA molecule that is most likely to be involved in CeD. It is encoded in the cis arrangement in DR3 haplotypes or in trans arrangement in a DR5, 7 genotypes<sup>[41]</sup>. DH and CeD shared identical HLA class II association. HLA class II genes less likely influence the immune responses which lead to mucosal damage in both diseases<sup>[41]</sup>.

**HLA and its association with Type I diabetes (T1D):** Type I diabetes (T1D) is an autoimmune disease, with a global prevalence ranging from 2-5%<sup>[43]</sup> in which  $\beta$ -cells are destroyed. Specific HLA regions have been identified to precede the development of T1D. Genes from the HLA complex have a major contribution in T1D. High incidence may be the result of the HLA-DR3-DQ2 and DR4-DQ8 haplotypes, and the DQB1\*06:02 alleles are common because they protected people from succumbing to T1D<sup>[44]</sup>. Of particular importance in this regard are the HLA-DR, -DP and -DQ loci. Ninety percent of T1D patients carry HLA-DRB1\*03/DQB1\*02:01 or HLA-DRB1\*04/DQB1\*03:02 genes<sup>[45]</sup>. Methylation changes in the HLA region have been found to occur before the development of T1D. For T1D, apart from HLA genes, more than 50 non-HLA loci have been assessed to explain more than 75% of the disease heritability<sup>[46]</sup>, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the beta-cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action (American Diabetes Association, 2011) Patients with T1D carry HLA-DRB1\*03/DQB1\*02:01 or HLA-DRB1\*04/DQB1\*03:02 genes which are responsible for the disease development and on the other hand HLA -DQB\*0602 and HLA-DRB1\*0402 have conferred a strong safeguard against T1D.<sup>[45,47]</sup> HLA class II gene 'HLA-DQB1', is known to be the strongest known genetic risk factor for T1D<sup>[48]</sup>.

**HLA and its association with Rheumatoid Arthritis (RA):** Rheumatoid Arthritis (RA) a chronic autoimmune disease that primarily targets the joints where it affects about 1% population globally and tend to increase with age<sup>[49]</sup>. The inheritance of susceptibility to RA has shown to be associated with DRB1 genes that encode HLA-DR4 and HLA-DR1 molecules<sup>[50]</sup>. Linkage and association studies have shown that HLA-DRB1 gene is the foremost genetic susceptibility locus for RA. In 1976. it was found that patients with RA tend to share the similar HLA genes to CeD, which clearly explains the lack of reactivity in mixed cultures<sup>[15,51]</sup>. Stastny P showed that an increased proportion of patients with RA were positive for the HLA allele (HLA-DRw4), in comparison with healthy controls proving the HLA region as a genetic contributor to

RA susceptibility<sup>[52]</sup>. A decade later, Gregersen PK. *et al.* identifies multiple HLA locus with RA risk alleles within HLA-DRB1 and documented that the molecules that they encoded, shared a conserved amino acid sequence; which led to the 'shared epitope' hypothesis<sup>[50]</sup>. In progressive RA, 90% cases display either HLA-DR4 and/or -DR1 genes and the most common alleles that associated with RA susceptibility are DRB1-0401, DRB1 DRB1-0404, DRB1-0405, and DRB1-0101<sup>[53]</sup>. However, in 1998 Cope AP. *et al.* have confirmed that another variant of DR gene i.e. DRB1\*0402 allele is associated with the protection against the RA<sup>[54]</sup>.

**HLA and its association with Multiple sclerosis (MS):** Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system and is a common cause of non-traumatic neurological disability affecting young adults<sup>[42]</sup>. Its prevalence has been reported to be 10.4% in 2016 which is reportedly increasing<sup>[55]</sup>. More than 100 loci have been reported to be strongly associated with susceptibility, whereas class II HLA gene cluster has 10.5% of the genetic variance underlying risk. HLA-DRB1\*15:01 has the strongest effect with an average odds ratio of 3.08<sup>[42]</sup>. CeD is associated with different autoimmune and neurological disorders. It has been found that there is an increased prevalence about 11.1% of CeD in MS and 32% in first-degree relatives<sup>[56]</sup>. Studies also demonstrate that patients diagnosed with MS have an increased chance of RA independent of age, gender and history of smoking<sup>[57]</sup>. In Caucasian populations, DRB1\*1501-DQA1\*0102-DQB1\*0602 has been reported to be the primary HLA genetic susceptibility factor for MS. Schmidt H. *et al.* showed that DR15 haplotype and/or its component alleles has a higher frequency in MS patients than controls<sup>[58]</sup>.

**HLA and its association with infectious oral diseases:** Several studies have investigated the contribution of HLA types (class I and Class II molecules) for the development of infectious oral diseases. A study done by Mauramo M. *et al.* in Swiss adults found a significant association of HLA B-15, HLA B-51, and DRB1\*12 for periodontal disease manifestations and HLA-A32 for temporomandibular dysfunction (TMD)<sup>[59]</sup>. Another study, conducted by Valarini N, *et al.* in 164 Brazilian adolescents (age 15-19 years) showed HLA-DQ group influencing the susceptibility to dental caries<sup>[60]</sup>. In a large cohort of genetically predisposed Italian general pediatric population, authors investigated the role of HLA -DQ2 in the disease protection and development of dental caries. However, they did not find a significant role of HLA-DQ alleles in the development of enamel defects, oral aphthosis, and dental caries<sup>[61]</sup>. Mariani P. *et al* reported that patients with HLA-DR3 genotype have a higher risk of enamel lesions, pointing to a genetic contribution<sup>[62]</sup>. Erriu M. *et al.* have gave proof that there is a significant relation between dental enamel defects (DED) and allele expression while it was impossible to find a similar correlation with RAS. The authors of the study also found an increase in correlation with HLA-DQB1\*02 expression in oral signs<sup>[9]</sup>. The statistical analysis evidenced that the absence of the HLA-DQB1\*02 allele predisposes to oral manifestations such as RAS<sup>[10]</sup>. HLA genes have diversity in their associated alleles<sup>[63]</sup>. A particular HLA-A and/or HLA B allele may be associated with a specific disease development whereas, another allele from the same gene may act as a protective allele to the same disease<sup>[64]</sup>.

## CONCLUSIONS

This review gives proof that HLA genes have strong association in the development of CeD and other autoimmune diseases. HLA-B1\*02 is the most critical allele for the development of CeD and it is also critically associated for the development of other GRD.

However, HLA cannot be the sole gene responsible for these diseases possibly there could be non-HLA genes also be involved.

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