We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

The Association of HLA-DQ2 with Celiac Disease

Federica Gualandris, Laura Castellani and Anna Falanga

Abstract

DQ2 is a surface receptor of class II MHC exposed on APC immune-competent cells. Its function is to recognize non-self-antigens and present them to CD4⁺ T-helper lymphocytes, which activate cytokine production and control antibody production and cell response. The activation of T lymphocytes by peptides derived from gluten proteins and the production of antibodies directed against tTG in tissues where it is localized is the basis of the etiopathogenesis of celiac disease (CD). CD is frequently associated with the presence of specific HLA system genes encoding heterodimers DQ2 and DQ8, identifiable by the DQA1*0501/DQB1*0201 or DQA1*0501/DQB1*0202 and DQB1*0302 alleles. DQ2 is also associated with genetic, endocrinological and neurological diseases such as: type 1 diabetes, thyroiditis, pancreatitis and multiple sclerosis. Interactions between DQ2 and T lymphoma have also been demonstrated. The correlation between autoimmune diseases in patients with CD and therefore DQ2 is much more frequent than in healthy subjects.

Keywords: HLA-DQ2, DQ2 isoforms, DQ2 and celiac disease, DQ2 and diseases, T helper lymphocytes

1. Introduction to HLA-DQ2 structure and localization

HLA-DQ2 antigen is a surface receptor of antigen-presenting cells (APC), it is composed of two polypeptide subunits: the α chain (of 32–34 kD) and the β chain (of 29–32 kD) [1]. Each one presents a peptide-binding domain, an Ig-like domain, and a transmembrane region with a cytoplasmic tail (**Figure 1**). These structures are bound by non-covalent association. Unlike Major Histocompatibility Complex (MHC) class I molecules, both polypeptide chains are encoded by genes in the HLA-DQ regions strictly located on chromosome 6 (**Figure 2**). The pocket for the bond with the peptide is constituted for half by one chain and half by the other; each one contributes with an α -helix and 4 filaments of the β sheet.

In the extracellular portion, each chain has an Ig domain ($\alpha 2$ and $\beta 2$) of which, $\beta 2$ contains the binding site for lymphocyte helper CD4⁺. In HLA-DQ2 both the α -chains and the β -chains are polymorphic, as a result, unique DQ molecules can be formed, with α - and β -chains encoded on the same chromosome (encoded in cis) or on opposite chromosomes (encoded in trans). However, evidence suggests that not every α - and β -chain pairing will form a stable heterodimer. It is generally considered that alleles of DQ α - and DQ β -chains pair up predominantly in cis rather than in trans. However, the occurrence of trans-encoded HLA class II molecules is well

Figure 1.
Label: The structure of the MHC-II molecule [2].

Figure 2.
Label: Chromosomal origin of HLA class I and class II [3].

documented in the literature, such as in the case of type 1 diabetes (T1D), where the trans encoded HLA molecules may play a role in pathogenesis [4].

Each MHC molecule has only one antigen pocket that can bind one peptide at once, but different peptides at different times. Peptides that can bind to MHC-II molecules reach 30 or more, while class I MHC molecules can accommodate peptides with 8–11 amino acids. The peptide–MHC binding is created during its

assembly and is used to stabilize the complex to allow its expression on the cell surface and for this reason, the dissociation rate is very slow. This naturally provides a very long half-life that allows T lymphocytes to meet the antigen. Between MHC and peptide, a non-covalent connection is formed among the residues in the pocket. Once the binding has occurred, the peptide and the water molecules that solubilize it fill the pocket, making contact with the walls and the floor that make it up.

T cells activated by class II molecules are CD4⁺ helper cells that: activate cytokine production, control antibody synthesis, and regulate cellular response. DQ is also involved in the common recognition of auto-antigens; the presentation of these antigens to the immune system provides tolerance at a young age. When this tolerance is lost DQ can be involved in autoimmune diseases such as celiac disease (CD), type 1 diabetes, and many others as we will see more details afterward [5].

2. HLA-DQ2 isoforms

As mentioned before, there are many potential DQ isoforms, as a result of the combination of cis- and trans haplotypes and those with cis-pairing are more common. Typically individuals can produce 4 isoforms, but only HLA-DQ2.5 and HLA-DQ2.2 tend to be predominantly represented.

HLA-DQ2.5 is composed of the allele HLA-DQA1*0501 (or DQA1*0505) encoding the alpha chain and the allele HLA-DQB1*0201 (or DQB1*0202) encoding the beta chain. HLA-DQ2.2 consists of the HLA-DQA1*02 alpha chain allele and the HLA-DQB1*0202 beta chain allele [6].

Very important concerning isoforms is that different subunit matches can cause the binding of different foreign or self-antigens. Generally, MHC molecules have slots at the pocket level that can interact with specific amino acids or be complementary to certain amino acid side chains. The importance of polymorphism is detected here: only the ability of MHC to bind specifically to a peptide permits it to be recognized by lymphocytes and to trigger the immune response to it.

The molecule HLA-DQ2 has a peculiar ligation system with three binding sites, preferably for negatively charged residues and different peptide-binding motifs. The binding motifs associated with HLA-DQ2 consist of truncated variants of eight different peptides with a length of 9–19 amino acids.

Data from the pooled sequencing and the biochemical binding analyses of synthetic variants of a ligand indicate that the side chains of amino acid residues at relative position P1 (bulky hydrophobic), P4 (negatively charged or aliphatic), P6 (Pro or negatively charged), P7 (negatively charged) and P9 (bulky hydrophobic) are important for binding of peptides to DQ2 (**Figure 3**).

Computer modeling of the DQ2 with variants of the ligand in the groove suggests that peptides bind to DQ2 through the primary anchors P1, P7, and P9 and making additional advantageous interactions using the P4 and P6 positions [8].

2.1 HLA-DQ2.5

DQ2.5 refers to both a protein isoform and a genetic haplotype. DQ2.5 isoform or heterodimer is shorthand for the cell surface receptor HLA-DQ $\alpha 5\beta 2$ (**Figure 4**).

DQ2.5 and the linked DR3 are associated with probably the greatest frequency of autoimmune occurrence relative to any other haplotypes. A genome-wide survey of markers linked to celiac disease, reveals that the highest linkage is for a marker within the DQA1*0501 allele of the DQ2.5 haplotype. The association of DQB1*0201 is almost as high. Greatly elevating risk is the ability of the DQ2.5 haplotype encoded isoforms to increase abundance on the cell surface in DQ2.5 double

Figure 3.
Label: Analysis of the HLA-DQ2 protein: (A) the 3D structure; (B) the binding sites; (C) the amino acids residues and the α helix and the β sheet domains [7].

homozygote. While the frequency of DQ2.5 haplotype is only 4 times higher than the general population, the number of DQ2.5 homozygotes is 10 to 20 times higher than the general population. Of the approximately 90% of celiacs that bear the DQ2.5 isoform, only 4% produce DQ2.5trans and differs slightly, one amino acid, from DQ2.5cis.

Multiple copies of the DQ2.5 haplotype do not cause apparent increases of severity in celiac disease, but the 25% of celiac patients homozygous DQ2 (DQ2.5/DQ2) tend to show increases risk of life-threatening complications and more severe histological findings. The HLA-DQ2.5 molecule preferentially binds peptides with negatively charged amino acids at anchor positions [10, 11]. Whereas gluten peptides contain few negative charges, these charges can be introduced by

Figure 4.
 Label: The crystal structure of HLA-DQ2.5-CLIP1 [9].

the enzyme tissue transglutaminase (tTG) that selectively deamidates glutamine residues in gluten peptides [12–14]. DQ2.5cis is the major factor in adaptive immunity by frequency and efficiency in alpha-gliadin presentation and its responses can be differentiated from other DQ isoforms. Specifically, this DQ2 heterodimer is responsible for presenting the α 2-gliadin that most effectively stimulates pathogenic T-cells.

As mentioned before, the DQ2.5 haplotype is linked to DR3, which is not linked to DQ2.2. Using either serotyping or genotyping DQ2.5 can be distinguished from DQ2.2 or DQ2.3 [5].

2.2 HLA-DQ2.2

HLA-DQ2.2 is shorthand for the DQ α 2 β 2 heterodimeric isoform (**Figure 5**). DQ2.2 homozygotes represent about 1.1% of the celiac population. While HLA-DQ2.5 is strongly associated with the disease, HLA-DQ2.2 is not [5].

Whereas the molecular surfaces of the antigen-binding clefts of HLA-DQ2.5 and HLA-DQ2.2 are very similar, there are important differences in the nature of the peptides presented. These peculiarities in peptide motif binding cause differences in responding to T cell repertoires and in the disease penetrance [16].

DQ2.2 individuals can mount an antigluten response but bear a lower risk of celiac disease. The reason is fewer gluten peptides would bind stably to this HLA molecule. The results give insight into processes important for the establishment of T-cell responses to antigen in HLA-associated diseases. Patients with celiac disease with DQ2.2 have gluten-reactive T cells in their small intestine [17].

Figure 5.
 Label: The crystal structure of HLA-DQ2.2 [15].

2.3 HLA-DQ2.3

DQ2.3 is the shorthand for the heterodimeric DQ $\alpha 3\beta 2$ isoform and is encoded by the DQA1*03:DQB1*02 haplotype (**Figure 6**). The receptor coded for the haplotype is a DQ2.3cis isoform, which is genetically linked to DR7 [5]. The gluten epitope, which is the only known HLA-DQ2.3-restricted epitope, is preferentially recognized in the context of the DQ2.3 molecule by the T-cell clones of a DQ8/DQ2.5 heterozygous celiac patient.

The DQ2.3 molecule combines the peptide binding signatures of the DQ2.5 and DQ8 molecules. This results in a binding motif with a preference for negatively charged anchor residues at both the P1 and the P4 positions. In this way, some epitopes can be presented even more effectively in the context of the trans-encoded

Figure 6.
Label: The crystal structure of HLA-DQ2.3 [18].

DQ2.3 molecule. This has relevance for understanding how the trans-encoded DQ2.3 molecule is predisposing to type 1 diabetes [4].

The analysis of the structure of DQ2.3 together with all other available DQ crystals shows that the P1 pocket in DQ2.3 is significantly different from that of DQ2.5 due to the polymorphic MHC residues found in this region. Additionally, DQ2.3 presents a gluten epitope to T-cells much more efficiently than DQ2.5 [4].

3. Other isoforms

DQ2 beta chains can combine with trans chains to other alpha chains. However, there is no preference in cis isoforms for DQ2 alpha chains, 4, 7, 8, or 9 bindings

to DQ1 alpha chains (DQA1*01). The DQA1*03, *05 chains process nearly identical alpha chains. The *04 chain can potentially combine with DQ2 to form DQ2.4. There is the possibility of DQ2.6 resulting from coupling with DQA1*0601 [5].

4. HLA-DQ2 and celiac disease

Celiac disease is a genetically determined immune-mediated disorder in which individuals carrying HLA DQ2 and/or DQ8 haplotypes develop an immunologic response to gluten ingestion that leads to a wide range of clinical signs and symptoms.

The Humoral nature, the hereditary and the polygenic CD have great influence in triggering the disease. The assessment of HLA-DQ2/DQ8 is relevant from a diagnostic aspect to detect celiac disease; in fact, about 95% of patients with CD present the HLA-DQ2 genotype [19].

In celiac patient inflammatory T cell responses to HLA-DQ2-bound gluten peptides are thought to cause disease. Gluten-reactive T cells can be isolated from small intestinal biopsies of celiac patients. T cells derived from the lesion mainly recognize gluten deamidate peptides. There are several distinct T cell epitopes within gluten. DQ2 and DQ8 bind the epitopes so that the glutamic acid residues created by deamidification are placed in compartments that have a preference for negatively charged side chains. Evidence indicates that in vivo deamidation is mediated by the enzyme tissue transglutaminase (tTG) that can also cross-link glutamine residues of peptides with lysine residues in other proteins, including tTG itself. This can lead to the formation of gluten-tTG complexes. These complexes may allow gluten-reactive T-cells to provide aid to tTG-specific B-cells through an intramolecular aid mechanism, thus explaining the presence of gluten-dependent tTG autoantibodies which is a characteristic feature of active CDs.

5. HLA-DQ2 and celiac disease class risk

Ideally, all patients with CD carry alleles encoding for the DQ2 and/or DQ8 molecules or at least one chain of the DQ2 heterodimer. The presence of CD in the absence of these DQ risk factors is extremely rare. The presence of these molecules does not accurately predict that CD will develop, as they are present in 25–50% of the general population, although the fact that the vast majority of these individuals will never develop the disease. About 90% of individuals with CD carry HLA-DQ2.5, while individuals with CD who do not express these haplotype usually express either HLA-DQ2.2 or HLA-DQ8; very few coding for HLA DQ7.5 (DQA1*05:05–DQB1*03:01), DQ2.3 or DQ8.5 (DQA1*05–DQB1*03:02).

Differences in CD risk between haplotypes are related to gluten peptide binding and subsequent T-cell response. The effect of gene dose is related to the level of peptide binding to homozygous and heterozygous HLA-DQ2 and its subsequent presentation to T cells. Individuals homozygous for DQ2.5 and DQ8 have an increased risk of the disease. Gluten presentation by HLA-DQ2 homozygous was superior to HLA-DQ2/non-DQ2 in terms of T cell proliferation and cytokine secretion (**Figure 7**).

HLA-DQ2.5 predisposes to celiac disease respect to DQ2.2, because the first one presents a large repertoire of gluten peptides, whereas the second one presents only a subset of these. HLA-DQ2.2 does not predispose to CD unless it is expressed in combination with HLA-DQ2.5. Gluten presentation by HLA-DQ2.5/2.2 induces intermediate T-cell stimulation. However, individuals homozygous for HLA-DQ2.5

Figure 7.
Label: Haplotypes and different class risk for celiac disease [20].

Figure 8.
Label: Genotypes and celiac disease prevalence [21].

or heterozygous HLA-DQ2.2/2.5 have the highest risk of developing CD. In HLA-DQ2.5/2.2 heterozygous individuals have properties identical with HLA-DQ2.5 dimers. In contrast, HLA-DQ2.5/non-DQ2.2 heterozygous individuals have an only slightly increased risk (**Figure 8**).

Considering even more in detail, it has been demonstrated that differences in conferred risk associated with CD are the result of the polymorphism in the α chain between HLA-DQ2.5 and HLA-DQ2.2.

HLA-DQ2.2 is virtually identical to the peptide-binding properties of HLA-DQ2.5. Both are highly homologous except for a single polymorphic residue (HLA-DQ2.5-Tyr22 α and HLA-DQ2.2-Phe22 α). The role of the Phe22 α variant in HLA-DQ2.2 is to influence peptide binding preferences and to decide how DQ2.2 TCRs engage the DQ2.2-gluten complex.

Crystal structure studies revealed a docking strategy, where the TCR HLA-DQ2.5 gliadin epitopes complexes were notably distinct from the HLA-DQ2.2-glut TCR complex [22].

HLA-DQ2.5 and HLA-DQ2.2 binds and presents gluten peptides with glutamate residues at anchor positions P4, P6, or P7). Three HLA-DQ2.2 epitopes (DQ2.2-glut-L1, DQ2.2-glia- α 1, and DQ2.2-glia- α 2) have sequences similar to HLADQ2.5 binding peptides, with the exception that they all carry serine at P3. As seen for HLA-DQ2.5 epitopes, the HLA-DQ2.2 ones display a hierarchy with DQ2.2-glut-L1 being the epitopes recognized by most T cells [23].

6. HLA-DQ2 and interaction with HLA-DM

HLA-DQ2 is influenced by interaction with Ag presentation cofactors, invariant chain (Ii), HLA-DM (DM), a peptide exchange catalyst for MHC class II (**Figure 9**).

DM can enhance or suppress the presentation of specific MHCII peptide complexes. In general, MHCII-peptide complexes with lower intrinsic stability are DM susceptible, but not all high-stability complexes are DM resistant. HLA-DQ2 is relatively resistant to DM because DQ2 has a natural deletion in the region involved in the interaction with DM, compared with most other alleles.

The role of DQ2/DM concerns interaction in the DQ2-restricted gliadin epitopes, relevant to celiac disease, or DQ2-restricted viral epitopes, relevant to host defense. DM activity has different consequences on DQ2 presentation of epitopes to T cell clones, with suppression of gliadin presentation and enhancement of viral peptide presentation. These results imply key differences in DQ2 Ag presentation pathways.

DM-resistant feature of DQ2 likely contributes to the escape of gliadin peptides from extensive DM editing. Also, DQ2 has the special ability to stably bind proline-rich gliadin peptides that use TG2-deamidated residues as DQ2-binding anchors.

Figure 9.
Label: Localization of HLA-DM on the MHC class II region [24].

Together, these unique features of DQ2 may allow gliadin presentation to disease-driving CD4⁺ T cells and contribute to the uniquely selective DQ2 presentation of DM-sensitive gliadin epitopes.

In contrast, the presentation of DM-resistant epitopes that form more-stable complexes with DQ2 likely relies less on the above mechanisms, as DM editing positively affects the presentation of these epitopes. The elevation of DM expression in peripheral APC (particularly during infection) may benefit self-tolerance by attenuating the presentation of DM-sensitive epitopes while boosting the presentation of DM-resistant pathogen-derived epitopes and aiding in host defense [25].

7. HLA-DQ2 refractory celiac disease (RCD) and enteropathy-associated T-cell lymphoma (EATL)

Refractory celiac disease (RCD) is defined by persistent mal-absorptive symptoms and villous atrophy despite strict adherence to a GFD for at least 6–12 months in the absence of other causes of non-responsive treated celiac disease.

The pathology can be classified as type 1 (normal intraepithelial lymphocyte phenotype), or type 2 (defined by the presence of abnormal [clonal] intraepithelial lymphocyte phenotype). RCD 1 usually improves after treatment with a combination of aggressive nutritional support, adherence to GFD, and alternative pharmacologic therapies. By contrast, clinical response to alternative therapies in RCD 2 is less certain and the prognosis is poor. Severe complications such as ulcerative jejunitis and Enteropathy T-cell lymphoma (ETL) may occur in a subgroup of patients with RCD [26].

ETL is a T-cell non-Hodgkin lymphoma arising in the gastrointestinal tract that shows a differentiation of tumor cells toward the phenotype of intestinal intraepithelial T cells. The clinical course of ETL is highly aggressive, with most patients dying from the disease within months of diagnosis. Enteropathy T-cell lymphoma comprises two morphologically, clinically, and genetically distinct lymphoma entities: the ETL type 1 and 2.

ETL arises in individuals with the DQA1*0501, DQB1*02 CD-predisposing genotype. The HLA typing found in these patients revealed that more than 95% have an HLA-DQ2/-DQ8 genotype [27]. Comparing studies of HLA-DQB1 genotyping in celiac disease and ETL have detected that the overall HLA-DQB1 genotype pattern observed in type 1 ETL closely resembled those for ETL, whereas those of type 2 ETL are not significantly different from that of normal Caucasian controls.

ETL1 patients show significantly more frequent expression of HLA-DQB1*02 than the type 2 ones [28]. Lymphoma type 1 may arise and be pathogenetically linked to refractory celiac disease by a stepwise acquisition of genetic alterations. Contrary given the genetic alterations and HLA-DQB1 genotype patterns, celiac disease may not be causal to type 2 ETL. At least 47% of patients with type 2 ETL are very likely to never have had celiac disease [29].

The highly significant correlation between HLA-DQ2 homozygosity and the development of RCD II and ETL, suggests that the strength of the gluten-specific T-cell response in the lamina propria directly or indirectly influences the likelihood of RCD II and lymphoma development. As already mentioned in the chapter, also in this case, the higher T-cell proliferation and cytokine secretion induced by HLA-DQ2 homozygous APC, than HLA-DQ2 heterozygous APC, may explain the strongly increased risk for disease development in HLA-DQ2/DQ2 individuals [30]. This would indicate that adherence to a gluten-free diet is particularly important for CD patients who are HLA-DQ2 homozygous.

These observations suggest that specific tests, such as those for lymphocyte typing for T cells, should be indicated in all patients with CD who are not responding to a gluten-free diet. The availability of a simple and reliable immune histochemical method can make the distinction between CD and RCD feasible. HLA-DQ typing is doable and it may be an efficient test to recognize individuals at risk for these conditions with a poor prognosis, particularly now that some evidence has been given to support the hypothesis that autologous hematopoietic stem-cell transplantation can alter disease progression in severe [29].

8. HLA-DQ2 and liver/gastrointestinal (GI) disease

Liver and gastrointestinal diseases have many etiologies that are poorly understood. Whether due to genetic abnormalities, psychological factors, or other environmental variables, functional disorders can be complex and difficult cases to resolve. A strongest evidence of an association with *DQ2/8* was found in patients with functional upper GI disorders [31]. There are several reasons why it may be prudent to study *DQ2/8* alleles in GI disease outside of celiac disease in fact, evidence suggests that celiac disease may alter the risk of developing irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), eosinophilic esophagitis, or certain liver diseases. Several studies have directly compared the prevalence of the *DQ2/8* haplotype in GI disease. These haplotypes may play a role in liver/digestive disease through pathological mechanisms different from those of celiac disease. *DQ2/8* contains myriad genes involved in inflammatory processes, such as tumor necrosis factor- α , causal mechanisms between these genes, and GI disease may exist.

Known immunological associations between IBD and *DR7*, which is linked to both *DQ2* and *DQ8* haplotype have been established. The relation between *DQ2/8* and IBD/IBS was analyzed in particular in two studies from an Italian and a Danish group and both demonstrated that the proportion of IBS was lower among HLA *DQ2/8* positive individuals. However the Italian group also found that IBD and liver diseases were more prevalent among *HLADQ2/8* subjects, but it is not confirmed in the Danish study. Prior prevalence data though suggest that IBD, particularly Crohn's disease, is lower in individuals with the *DQ2/8* linked celiac disease.

IBS has also been linked to HLA *DQ2/8* haplotypes and intestinal transit rates [31]. Approximately 46% of patients with diarrhea-predominant IBS (IBS-D) have accelerated colonic transit. Some patients with IBS report an association of symptoms with specific foods, suggesting a role for food hypersensitivity. One such food is gluten in the absence of overt celiac disease. The spectrum of gluten sensitivity ranges from minimal histological changes such as increased intraepithelial lymphocytes without villous atrophy, increased immunoglobulin A (IgA) deposits in intestinal villi, gluten-sensitive diarrhea, and immunological mucosal response to gluten exclusion in patients with celiac disease. Typically, one or more of these findings are seen in individuals who are positive for HLA-*DQ2* or HLA-*DQ8*. Wahnschaffe et al. demonstrated that, among patients with IBS-D, response of diarrhea to a gluten-free diet was influenced by HLA-*DQ2* positivity and the presence of IgG tissue transglutaminase (TTG) antibody in duodenal aspirates. Symptom response to gluten withdrawal occurred in 62% of patients positive for both HLA-*DQ2* and IgG-TTG; in contrast, only 12% of patients negative for HLA-*DQ2* and TTG-IgG responded; suggesting that symptom generation in this subset of patients is immune-mediated. Is demonstrated that patients with IBS-D, positive for either HLA-*DQ8* or both HLA-*DQ2/DQ8* genotypes that are associated with gluten sensitivity, have an accelerated colonic transit time [32].

The HLA DQ2 in association with HLA-DR3 is also associated with another GI disease; in fact, this combination is linked with a more rapid progression of primary sclerosing cholangitis (PSC) [33].

9. HLA-DQ2 and diabetes

Type 1 diabetes (T1D) is an autoimmune disease attacking pancreatic Langerhans islets. The islets are composed of several types of cells: α , β , δ , ϵ , and pancreatic polypeptide (PP). Each type plays a different role in the secretory function of the pancreas and, among others, α and β cells produce glucagon and insulin, respectively. The interplay between these two compounds provides proper glucose level administration in blood.

It has been already shown that auto aggression in T1D starts in mutations in the MHC system. HLA-DQ molecules have the role to bind and present beta-cell auto-antigen derived peptides in T1D. The combinations of DR4-DQ8 and DR3-DQ2 antigens occur in 90% of people with diabetes. However, the homozygous state for an allele does not further increase the risk. Indeed it is well established that individuals heterozygous for HLA-DQ2 and HLA-DQ8 have almost 5 fold higher risk than homozygous to development of T1D [1, 13, 14]. This has been linked to the formation of trans dimers between the HLA-DQ2 α chain and the HLA-DQ8 β chain (HLA-DQ8 trans) [19, 22, 26, 34]. In particular, the HLA DQ8 trans heterodimer confers the highest risk for the development of T1D. This indicates that such HLA-DQ trans dimers can bind and present a unique autoantigen derived peptide that leads to beta-cell destruction in the pancreas and the development of T1D [35].

Juvenile diabetes has a high association with DQ2.5. A combination of DQ2.5 and DQ8 significantly increases the risk of type 1 onset of adult diabetes, while the presence of DQ2 with DR3 reduces the age of onset and severity of the autoimmune disease.

The formation of trans encoded molecules DQ8.5 (DQA1*05:01/DQB1*03:02) and DQ2.3 (DQA1*03:01/DQB1*02:01), which could present one or a few specific diabetogenic epitopes to CD4+ T-cells, possibly inducing an immune response that leads to the destruction of insulin-producing pancreatic β islet cells [12]. A strong argument for the involvement of the DQ2.3 heterodimer in type 1 diabetes comes from trans racial gene mapping studies that have found that this heterodimer, which is typically found in the trans configuration among Caucasian subjects, exists and is over-represented in the cis configuration among type 1 diabetes patients of African origin [16, 17]. The increased diabetes risk of the African DQ2.3 (DQA1*03:01/DQB1*02) carrying DR7 haplotype is contrasted by a protecting effect of the DQ2.2 (DQA1*03:01/DQB1*02) carrying DR7 haplotype of European origin [17].

Patients with homozygous type 1 DQ2 diabetes have a marked prevalence of IgA anti-transglutaminase autoantibodies. The great excess of positive transglutaminase autoantibodies among homozygous DQ2 diabetics is related to both the presence of DQ2 and its addition to all genetic or environmental factors associated with type 1 diabetes. These additional factors may be related to abnormalities in mucosal immunity that increases the risk of both type 1 diabetes and celiac disease.

Type 1 diabetes is an autoimmune disease attacking pancreatic Langerhan's islet. The islet is composed of several types of cells: α , β , δ , ϵ , and pancreatic polypeptide (PP). Each type plays a different role in the secretory function of the pancreas and, among others, α and β cells produce glucagon and insulin, respectively [36]. Interplay between these two compounds provides proper glucose level administration in blood.

It has been already shown that auto aggression in T1D starts in mutation in the MHC system. HLA-DQ molecules have the role to bind and present beta cell auto-antigens derived peptides in T1D. The combinations of DR4-DQ8 and DR3-DQ2 antigens occur in 90% of people with diabetes. However, the homozygous state for an allele does not further increase the risk. It is well established that individuals heterozygous for HLA-DQ2 and HLA-DQ8 have an almost 5 fold higher risk than those who are homozygous for either of the DQ variants for the development of T1D, and this has been linked to the formation of trans dimers between the HLA-DQ2 α chain and the HLA-DQ8 β chain (HLA-DQ8 trans). This indicates that such HLA-DQ trans dimers can bind and present a unique auto antigen-derived peptide that leads to beta-cell destruction in the pancreas and the development of T1D. In particular, HLA DQ8 trans heterodimer confers the highest risk for the development of T1D.

Indeed diabetes has a high association with DQ2.5. A combination of DQ 2.5 and DQ8 significantly increases the risk of type 1 onset of adult diabetes, while the presence of DQ2 with DR3 reduces the age of onset and severity of the autoimmune disease.

The formation of trans encoded molecules DQ8.5 (DQA1*05:01/ DQB1*03:02) and DQ2.3 (DQA1*03:01/DQB1*02:01), which could present one or a few specific diabetogenic epitopes to CD4+ T cells, possibly inducing an immune response that leads to the destruction of insulin-producing pancreatic β islet cells. Moreover, a strong argument for the involvement of DQ2.3 heterodimer in type 1 diabetes comes from transracial gene mapping studies that have found that this heterodimer, which is typically found in the trans-configuration among Caucasian subject, exists and is over-represented in the cis configuration among type 1 diabetes patients of African origin. The increased diabetes risk of the Africans DQ2.3 carrying DR7 haplotype is contrasted by a protecting effect of the DQ2.2 carrying DR7 haplotype of European origin, speaking to the functional importance of α chain in the DQ2.3 molecule.

Patients with homozygous type 1 DQ2 diabetes have a marked prevalence of IgA anti-transglutaminase autoantibodies. The great excess of positive transglutaminase autoantibodies among homozygous DQ2 diabetics is related to both the presence of DQ2 and its addition to all genetic or environmental factors associated with type 1 diabetes. These additional factors may be related to abnormalities in mucosal immunity that increases the risk of both type 1 diabetes and celiac disease. In T1D the risk associates with the HLA-DQ2/8 heterozygous haplotype was found to be increased compared with homozygous HLA-DQ2 or HLA-DQ8 individuals, suggesting an epistatic or synergic effect [37].

10. HLA-DQ2 and thyroid disease

The term autoimmune thyroid disease (AITDs) encompasses several different entities characterized by varying degrees of thyroid dysfunction and the presence of serum auto-antibodies against thyroid tissue-specific components, such as thyroglobulin (TG) and thyroid peroxidase (TPO) [34].

Hashimoto's thyroiditis (HT) and Graves' disease (GD) are AITDs with different physiopathology, being traditionally regarded as two different disease entities. More recent views, in contrast, have considered the hypothesis that there might be a continuum between HT and GD.

Genes of, or closely associated with, the HLA complex are assumed to contribute to the genetic predisposition to AITDs. Genetics plays a prominent role in both the determination of thyroid hormone and thyrotropin (TSH) concentrations and susceptibility to autoimmune thyroid disease. Heritability studies have suggested

that up to 67% of circulating thyroid hormone and TSH concentrations are genetically determined, suggesting a genetic basis for narrow intra-individual variation in levels [34]. Until today the mechanisms leading to thyroid autoimmunity are largely unknown.

In 30%–40% of healthy individuals, DQ2, and DQ8 are associated with diseases such as Hashimoto's Thyroiditis. In patients with a CD instead, autoimmune thyroid disease was observed in 14% and 30.3% in adults, while thyroid abnormalities were described in 37.6% and 41.1% in pediatric age.

Noteworthy was the presence of high titers of serum TPO antibodies [11] and serum TG antibodies [12] in the celiac pediatric patients without a gluten-free diet (GFD), these values were reported to return to normal after 2 or 3 years on a GFD. This finding suggests that these antibodies are gluten dependent.

Furthermore has been analyzed the association between Hashimoto's thyroiditis and celiac disease in the Dutch population and it has been demonstrated that HLA DQ2.5 was associated with higher TSH levels. This correlation is not been found for the other thyroid markers (TPO, FT4). A reason could be that TSH is a more sensitive marker for hypothyroidism, as well as the fact that TSH is a quantitative parameter measured in all participants of that study, giving more power to detect differences.

More than doubled GD rates are correlated to the genetic association to the DR3-DQ2 haplotype [38]. A study of Asian Indian patients with Graves' disease revealed a significant increase in the frequency of HLA-DQW2 as compared to the control population [37]. HLA-DQA1*0501 was also shown to be associated with GD in a Caucasian family study [37] but, the primary susceptibility allele in GD is indeed HLA-DR3 [37]. Further analyses have shown that these variants are almost always inherited together in Caucasian populations, so they act as a single genetic factor. These haplotypes are among the crucial genetic factors of celiac disease in European descendants, confirming a strong connection between gluten intolerance and autoimmune thyroid conditions. This theory is confirmed by studies on a large UK Caucasian case–control population, which have shown that the contribution of the HLA class II region to the genetic susceptibility of Graves' disease is due to the haplotype DRB1*0304-DQB1*02-DQA1*0501, with no independent association of any individual allele. However, as a result of strong linkage disequilibrium within the MHC region, it is difficult to assess which loci are acting as primary etiological determinants. The same HLA haplotype is associated with the large multifunctional proteasome 2 loci (LMP-2). The LMP molecules are overexpressed in thyrocytes, the target cells of Graves' disease and the LMP genes are found within the MHC class II region. The LMP genes may therefore play a role in susceptibility to Graves' disease [39].

11. HLA-DQ2 and dermatitis herpetiformis

Dermatitis herpetiformis (DH) is a chronic, pruritic, papulovesicular skin disease of unknown origin. The characteristic rash is symmetrically distributed over the extensor surfaces and buttocks and, also, most patients with DH have asymptomatic gluten-sensitive Enteropathy [40].

All patients with DH had typical clinical and histologic features, as well as granular deposits of IgA at the dermal-epidermal junction. The gastrointestinal lesions are essentially identical to those seen in patients with ordinary CD, although less severe and more patchy. A pathophysiologic link between CD and DH has been suggested by the observation that the skin lesions of DH as well as the abnormalities of the jejunal mucosa regress on a gluten-free diet.

DH is associated with a markedly increased frequency of the HLA class II antigens DR3 and DQ2. The primary HLA association is HLA-DQ2 (expressed in 100% of DH patients), whereas the HLA-DR3 is code in 95% of cases [41]. HLA-DQ8 may therefore be a second HLA susceptibility molecule in DH; all the DH patients carrying DQ2 plus a DR4 haplotype also carried DQ8.

An increased frequency of DR3, DQ2 homozygosity, and a slightly increased frequency of DR3, DQ2 heterozygosity were found among the DH patients. It is, therefore, possible that a gene dosage effect of DQB1*02 may be present also in DH patients.

DH and CD both are primarily associated with the same DQ ($\alpha 1^*0501$, $\beta 1^*02$) heterodimers, and in both diseases most of the few remaining patients not carrying this heterodimer instead carry the DQ ($\alpha 1^*03$, $\beta 1^*0302$) heterodimers.

In patients where a jejunal biopsy has been performed have been detected abnormal biopsies both among the DQ ($\alpha 1^*0501$, $\beta 1^*02$) positive and negative patients. No significant differences in the frequency of abnormal biopsies were observed between the two groups of patients.

CD and DH have different HLA associations; CD being primarily associated with genes in the DQ/DR region, while DH was more strongly associated with genes in the complement region. Anyway, the very similar associations in CD and DH to the same cis or trans associated DQ2 heterodimer, or the DQ8 heterodimer, can be taken as an argument against differences in primary HLA associations in these two diseases [41].

12. HLA DQ2 in recurrent pregnancy loss women

Recurrent pregnancy loss (RPL) is diagnosed when three or more consecutive spontaneous abortions occur. RPL occurs in about 2–3% of clinically diagnosed pregnancies of reproductive-aged women.

At present, accepted etiologies for RPL include parental chromosomal abnormalities, untreated hypothyroidism, uncontrolled diabetes mellitus, certain uterine anatomic abnormalities, antiphospholipid antibody syndrome, thrombophilias, infections, and environmental factors [42].

In RPL women, an increased risk of immune abnormalities, such as increased antinuclear antibodies (ANA) and thyroid antibody is been observed [43].

However, in 40% of cases, the cause is unknown.

A significant association between RPL and celiac disease is been demonstrated. Various pathogenic mechanisms underlying the pregnancy failure in CD have been suggested: among them the ability of anti-transglutaminase antibodies to impair the trophoblast invasiveness and endometrial endothelial cells differentiation and disrupt early placentation. A higher proportion of individuals HLA DQ2/DQ8 positive in women with RPL compared to controls is found, (52.6% vs. 23.6%), with 3.6 times higher odds of DQ2/DQ8 positivity.

Whether a similar mechanism to that of CD can be linked to this obstetric complication needs to be investigated. This model might appear a simplification of all the complex mechanisms underlying RPL.

The HLA-DQ2/DQ8 alleles by themselves, outside of CD, are found more frequently in RPL women. A possible pathogenic link of HLA-DQ2/DQ8 positivity, in presence of exogenous still unknown stimuli, may favor an immune condition with detrimental effects during the early stages of pregnancy.

A statistically significant association between HLA-DQ2/DQ8 and ANA positivity in RPL women is demonstrated. There is a significantly higher prevalence of ANA positivity in RPL women compared to control (~ 50% vs. 8.3%–27%).

ANA are a group of autoantibodies found both in the serum of patients with autoimmune and rheumatic diseases and in the general population.

As serological markers, ANA show diagnostic and prognostic significance, while their clinical utility in normal individuals is still unclear. Even if many serologically positive individuals will never develop an autoimmune disease, others may be in a pre-autoimmune state.

Further studies are needed to better understand the possible pathogenic mechanism to this observation; the clinical and therapeutic implications of our observation to provide a new approach to RPL couples [44].

13. HLA-DQ2 and allergy

HLA class-II alleles are associated with some allergies indicating that these alleles might confer susceptibility to the respective allergens. HLA plays a role in antigen/allergen presentation and IgE deregulations.

Few studies have associated HLA DQ2/DQ8 with allergy and other ones have analyzed the association between HLA class II antigens and the specific IgE response to purified allergens. One of these studies found an association between DQ8 and have in specific IgE immune response in individuals with a latex allergy, while others found DQ2 to be associated with olive pollen. However, the association of HLA DQ2/8 with allergy remains unclear.

There is a significant difference between HLA DQ2/8-positive and -negative individuals for dust mite allergy.

A significant association between the IgE antibody response to a highly purified allergen from olive tree pollen and HLA class II antigens DR7 and DQ2 in Spanish patients with seasonal allergic pollenosis is reported. The HLA-DQ2 phenotypic frequency is greater in patients with IgE antibodies olive tree pollen compared with the control group.

The combined involvement of DR and DQ in the allergen response has only been described in the study of reactive T-cell repertoire in a mite sensitized patient. It's identified HLA-DR and DQ restricted T-cell epitopes, one of which can bind to both DR and DQ molecules.

These results empathize the importance of genetic factors in the allergic response. As described in several reports, antigen-specific and non-specific factors are involved in genetic restriction.

Until now none of these factors can be considered as the exclusive determinant of the restriction. It is necessary to perform more studies with T-cell lines and peptides of this protein to determine which is the main region implicated in this response, and clarify this complex response [45].

14. HLA-DQ2 and HIV

Infection with human immunodeficiency virus type 1 (HIV-1) and progression to acquired immune deficiency syndrome (AIDS) are controlled by both host genetic factors and viral factors.

The HLA region controls immune response functions and tissue rejection and influences susceptibility to infectious diseases including HIV. There are HLA class II alleles associated with susceptibility to and protection from HIV-1 infection and that these differences between ethnic groups.

In the HIV+ Caucasian group, a poor prognosis was associated with HLA-DQ2 and a preferable prognosis was associated with HLA-DQ3.

The HLA-DQ3 association appears to be linked with the development of Toxoplasmic Encephalitis (TE) in AIDS. An association of HLA-DQ2 with the occurrence of opportunistic infections in AIDS patients is been confirmed [46]. Of interest was the absence of difference in the frequencies of the HLA-DQ2 antigen between TE patients and controls.

The development of TE in HIV infected patients is regulated by genes in or near the HLA complex and suggests that HLA-DQ typing may help in decisions regarding TE prophylaxis.

An immune response gene in the DQ region may control the progression of HIV infection in adults. The rapidly progressive DQ-associated peptide might block the progression of HIV if given as a novel vaccine [47].

15. HLA-DQ2 and vaccines

Although DQ2 is associated with vigorous antiglutten T cell responses, DQ2 also is associated with poor responses to several vaccines and failure to control hepatitis virus C and hepatitis virus B.

Studies analyses the association between HLA class II alleles and haplotypes with antibody response to recombinant HBsAg vaccination in Iranian healthy adult individuals. The results, in parallel with other reports, confirm the association of certain HLA class-II alleles with a lack of antibody response to HBsAg vaccine [48].

Discordant HLA/peptide binding and cytokine production patterns observed in genetically identical monozygotic twins vaccinated with HBsAg suggest the involvement of post genetic and environmental factors influencing the T cell repertoire.

However, APC from non-responders can present HBsAg to HLA class II-matched T-cells of responders. This indicates that defective HBsAg-specific T-cell repertoire rather than APC dysfunction could be involved in vaccination failure [49].

Several studies have established significant associations between DQ2, primary sclerosing cholangitis, and hepatitis C virus recurrence after transplant. A significant relationship between the individual scores of HLA mismatches HLA-DQ2 and the recurrence of HCV was observed.

The large proportion of DQ2/8 positive viral hepatitis patients agrees with the hypothesis that these haplotypes may be involved in certain liver disease pathogenesis. DR3-DQ2 haplotype is the principal risk factor for the disease [50].

Analyses by restriction fragment length polymorphism do not implicate a single susceptibility gene at the DQ locus. The unique factor that allows patients with autoimmune hepatitis to be distinguished from normal subjects or those with viral hepatitis is the DR3-DQ2 haplotype.

The association of DQ2 with suboptimal responses to some viruses raised the possibility that its reduced interaction with DM might also lead to the presentation of moderate-affinity viral peptides, whose unstable binding to DQ2 would reduce the surface of the DQ2/peptide complex and compromise CD4+ T cell responses [51].

16. HLA-DQ2 and autism

HLA genes also play a role in reproduction, pregnancy maintenance, in parental recognition and have been associated with over 100 diseases and disorders including autism.

Autism remained a poorly understood pathology for several decades. It is important to note that the diagnostic criteria have been modified over the years to include a broader category of symptoms, thus increasing the number of children diagnosed with the disorder, now referred to as Autism Spectrum Disorder (ASD) [52].

It has been reported that ASD subjects often have associations with HLA genes or haplotypes, suggesting underlying deregulation of the immune system mediated by HLA genes.

A significant number of autistic children have serum levels of IgA antibodies against the enzyme tissue transglutaminase II (TG2) above normal, and the expression of these antibodies is linked to the HLA-DR3, DQ2, and DR7, DQ2 haplotypes [53].

TG2 is expressed in the brain, where it is important in cell adhesion and synaptic stabilization.

These children constitute a subpopulation of autistic children who fall within the autism disease spectrum, and for whom autoimmunity may represent a significant etiological component of their autism.

17. HLA-DQ2 and multiple sclerosis

Multiple sclerosis is a chronic disease in young adults. It is caused by the demyelination of the central nervous system cells. It is considered a T-cell-mediated autoimmune disease that is likely caused by exogenous events, such as infectious agents, in susceptible individuals [54].

Population, family, and twin studies indicate that genetic factors and most likely several genes are associated with the disease, but genetic backgrounds as well as exogenous or somatic events are required to develop the disease. The strongest genetic association with disease among the many candidate genes that were analyzed was demonstrated for HLA-DR15, HLA-DQ2, and HLA-DQ6 [55]. HLA-class II haplotypes such as DR2/DQ6, DR3/DQ2, and DR4/DQ8 show the strongest linkage with the disease.

A positive connection of primary progressive MS with DR4-DQ8 and DR1-DQ5 and an association of “bout onset” MS with DR17-DQ2 is be found, while an HLA association with disease severity was not found [56].

It is currently unclear how the expression of a particular HLA class II gene would result in susceptibility to develop an organ-specific autoimmune disease.

18. HLA-DQ2 and world frequencies

The HLADQ2 associated disease risk is known to be modified across individuals or populations varying in ethnic background, geography, or gender.

The presence of genes coding for DQ2 and DQ8 molecules explains up to 40% of the occurrence of celiac disease in European populations. DQ2 is most common in Western Europe; higher frequencies are observed in parts of Spain and Ireland. In European celiac patients, the frequency of the HLA DQ2 is up by 90% e the HLA DQ8 is between five and 10% like was described in Dutch, UK, and Irish cases.

Differences in the frequencies of the HLA genotypes DQ2 and DQ8 in non-European populations have already been described. Patients of Indian origin had a lower frequency of HLA DQ2 than those of British origin. Lower frequencies of HLA DQ2 and higher frequency of HLA DQ8 than Europe have also been described among CD patients in the United States (82% DQ2 and 16% DQ8 only) and in Cuba (86% DQ2) In Chilean celiac patients the genotype DQ8 predominates. The genotypes

DQ2 and DQ8 were present in 93.2% of patients with CD in the Northeast of Brazil. The HLA DQ2 was present in 75.6% and DQ8 in 17.8% of these patients.

Another finding from this group is that 79% of the unaffected control families carried genotype DQ2 and/or DQ8, which is one of the highest frequencies so far described among first-degree relatives. Most studies on HLA among first-degree relatives found that no more than 59.5% of first-degree relatives in Europe presented HLA DQ2 and DQ8. Since the frequencies of genetic markers among populations of first-degree relatives reflect and amplify those among the general population of which they form part, in this region, a large proportion of the general population may carry these markers.

The frequencies of the different isoforms of DQ2 were also analyzed. The Eurasian geographic distribution of DQ2.2 is slightly greater than DQ2.5. Compared to DQ2.5, the frequency in Sardinia is low, but in Iberia, it is high reaching a maximum frequency of ~30% in Northern Iberia, and half that in the British.

Cases of DQ2.2 patients with CD without DQ2.5 are in some populations, particularly in the south of Europe. It extends along the Mediterranean and Africa at relatively high frequency and is found in high frequencies in some Central Asian, Mongolians, and Han Chinese. It does not appear to have an indigenous presence in the West Pacific Rim and DQ2.2 presence in South-east Asia and Indonesia is likely the result of gene flow from India and China in the past. The haplotype shows considerable diversity in Africa. The expansion of DQ2.2 into Europe appears to have been slightly later. DQ2.5 is generally highest in northern, Icelandic Europe, and Basque in northern Spain. Phenotype frequency exceeds 50% in parts of Ireland, which overlaps one of three global nodes of the DQ2.5 haplotype in Western Europe [57].

19. Conclusion

This work is designed to provide a quick overview of the HLA-DQ2 molecule, analyzing the main points such as molecular structure, gene variants, and the role played by the molecule in the clinical context; dealing not only with the most known autoimmune diseases to which it is linked but also with less known areas of development.

This work aimed to offer a new point of view on the subject, although aware of having only skimmed the topic, we hope to have offered a starting point for any new analysis of the molecule.

This chapter allowed us to analyze HLA in a different context from the most known of compatibility in hematopoietic stem cell transplantation, confirming once again the enormous complexity of the HLA system and its many facets and applications.

IntechOpen

Author details

Federica Gualandris^{1*}, Laura Castellani² and Anna Falanga³

1 ASST Papa Giovanni XXIII UOC Immunoematologia e Medicina Trasfusionale (SIMT), Laboratorio di Immunogenetica, Bergamo, Italy

2 ASST Papa Giovanni XXIII UOC Immunoematologia e Medicina Trasfusionale (SIMT), Laboratorio di Immunogenetica Director, Bergamo, Italy

3 Università Milano Bicocca, Dipartimento di Medicina e Chirurgia; ASST Papa Giovanni XXIII UOC Immunoematologia e Medicina Trasfusionale (SIMT) Director, Bergamo, Italy

*Address all correspondence to: federicagualandris.fg@gmail.com

IntechOpen

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

References

- [1] <https://www.immunopaedia.org.za/immunology/basics/4-mhc-antigen-presentation/>
- [2] Bellanti, JA (Ed). Immunology IV: Clinical Applications in Health and Disease. I Care Press, Bethesda, MD, 2012
- [3] Bellanti, JA (Ed). Immunology IV: Clinical Applications in Health and Disease. I Care Press, Bethesda, MD, 2012
- [4] Structural and functional studies of trans encoded HLA-DQ2.3. Stig Tollefsen, Kinya Hotta, Xi Chen, Bjørg Simonsen, Kunchithapadam Swaminathan, Irimpan I. Mathews, Ludvig M. Sollid, and Chu-Young Kim, J Biol Chem. 2012 Apr 20; 287(17): 13611-13619. Published online 2012 Feb 23. doi: 10.1074/jbc.M111.320374
- [5] Wikipedia: HLA-DQ2
- [6] HLA types in celiac disease patients not carrying the DQA1*05-DQB1*02 (DQ2) heterodimer: results from the European Genetics Cluster on Celiac Disease; Kati Karell 1, Andrew S Louka, Simon J Moodie, Henry Ascher, Fabienne Clot, Luigi Greco, Paul J Ciclitira, Ludvig M Sollid, Jukka Partanen, European Genetics Cluster on Celiac Disease; May 2003 Human Immunology 64(4):469-77 DOI: 10.1016/S0198-8859(03)00027-2
- [7] What-when-how In Depth Tutorials and Information The Major Histocompatibility Complex (The Immune System in Health and Disease) (Rheumatology) Part 2
- [8] The peptide-binding motif of the disease-associated HLA-DQ (alpha 1* 0501, beta 1* 0201) molecule F Vartdal 1, B H Johansen, T Friede, C J Thorpe, S Stevanović, J E Eriksen, K Sletten, E Thorsby, HG Rammensee, L M Solid; Eur J Immunol 1996 Nov;26(11):2764-72. doi:10.1002/eji.1830261132.
- [9] Crystal structure of HLA-DQ2.5-CLIP1 at 2.73 resolutions DOI: 10.2210/pdb5KSU/PDB
- [10] Peptide binding characteristics of the coeliac disease-associated DQ (alpha1*0501, beta1*0201) molecule. van de Wal Y, Kooy YM, Drijfhout JW, Amons R, Koning F Immunogenetics. 1996; 44(4):246-53.
- [11] The peptide-binding motif of the disease-associated HLA-DQ (alpha 1* 0501, beta 1* 0201) molecule. Vartdal F, Johansen BH, Friede T, Thorpe CJ, Stevanović S, Eriksen JE, Sletten K, Thorsby E, Rammensee HG, Solid LM Eur J Immunol. 1996 Nov; 26(11):2764-72.
- [12] Tissue transglutaminase selectively modifies gliadin peptides that are recognized by gut-derived T cells in celiac disease. Molberg O, Mcadam SN, Körner R, Quarsten H, Kristiansen C, Madsen L, Fugger L, Scott H, Norén O, Roepstorff P, Lundin KE, Sjöström H, Solid LM Nat Med. 1998 Jun; 4(6):713-7.
- [13] Different binding motifs of the celiac disease-associated HLA molecules DQ2.5, DQ2.2, and DQ7.5 revealed by relative quantitative proteomics of endogenous peptide repertoires Elin Bergseng 1, Siri Dørum, Magnus Ø Arntzen, Morten Nielsen, Ståle Nygård, Søren Buus, Gustavo A de Souza, Ludvig M Solid Immunogenetics 2015 Feb;67(2):73-84. doi: 10.1007/s00251-014-0819-9. Epub 2014 Dec 12.
- [14] Specificity of tissue transglutaminase explains cereal toxicity in celiac disease. Vader LW, de Ru A, van der Wal Y, Kooy YM, Benckhuijsen W, Mearin ML, Drijfhout JW, van Veelen P, Koning F J Exp Med. 2002 Mar 4; 195(5):643-9.
- [15] Crystal structure of HLA-DQ2.2-glut-L1 (protein) resolutions DOI: 10.2210/pdb5KSU/PDB

- [16] A molecular basis for the T cell response in HLA-DQ2.2 mediated celiac disease Yi Tian Ting, View ORCID Profile Shiva Dahal-Koirala, Hui Shi Keshia Kim, Shuo-Wang Qiao, Ralf S. Neumann, Knut E. A. Lundin, Jan Petersen, Hugh H. Reid, Ve Ludvig M. Sollid, and Jamie Rossjohn PNAS February 11, 2020, 117 (6) 3063-3073; first published January 23, 2020; <https://doi.org/10.1073/pnas.191430811>
- [17] T-Cell Response to Gluten in Patients With HLA-DQ2.2 Reveals Requirement of Peptide-MHC Stability in Celiac Disease Michael BoddChu-Young Kim Knut E. A. Lundin Ludvig M. Sollid Gastroenterology 2012 Mar;142(3):552-61. doi: 10.1053/j.gastro.2011.11.021. Epub 2011 Nov 19
- [18] Structural and functional studies of the trans-encoded HLA-DQ2.3 (DQA1*03:01/DQB1*02:01) molecule DOI: 10.2210/pdb4D8P/pdb
- [19] <https://www.euroimmun.it/prodotti/biologia-molecolare/hla-dq2-dq8/>
- [20] Celiac Disease Ludvig M. Sollid, Knut E. A. Lundin, in *The Autoimmune Diseases* (Fifth Edition), 2014
- [21] Genotype DQ2.5/DQ2.2 ($\beta\beta 2/\beta\beta 2$) and High Celiac Disease Risk Development; Yanna Karla de Medeiros Nóbrega; November 30th 2018; DOI: 10.5772/intechopen.80578
- [22] T cell sensing of antigen dose governs interactive behavior with dendritic cells and sets a threshold for T cell activation. Henrickson S.E. Mempel T.R. Mazo I.B. et al. 9 Fallang L.E. Bergseng E. Hotta K. et al. Nat Immunol. 2008; 9: 282-291
- [23] A molecular basis for the T cell response in HLA-DQ2.2 mediated celiac disease Yi Tian Ting, Shiva Dahal-Koirala, Hui Shi Keshia Kim, Shuo-Wang Qiao, Ralf S. Neumann, Knut E. A. Lundin, Jan Petersen, Hugh H. Reid, Ludvig M. Sollid, and Jamie Rossjohn PNAS February 11, 2020, 117 (6) 3063-3073; first published January 23, 2020; <https://doi.org/10.1073/pnas.191430811>
- [24] Cellular and Molecular Immunology; Abbas & Lichman; Elsevier 2005. 5e www.studentconsult.com
- [25] Epitope Selection for HLA-DQ2 Presentation: Implications for Celiac Disease and Viral Defense; Shu-Chen Hung, Tieying Hou, Wei Jiang, Nan Wang, Shuo-Wang Qiao, I-Ting Chow, Xiaodan Liu, Sjoerd H. van der Burg, David M. Koelle, William W. Kwok, Ludvig M. Sollid and Elizabeth D. Mellins, J Immunol May 1, 2019, 202 (9) 2558-2569; DOI: <https://doi.org/10.4049/jimmunol.1801454>
- [26] Classification and Management of Refractory Celiac Disease Alberto Rubio-Tapia, MD and Joseph A Murray, MD PMC 2011 Apr 1. Gut. 2010 Apr; 59(4): 547-557. doi: 10.1136/gut.2009.195131
- [27] HLA genotyping in pediatric celiac disease patients Biljana Stanković, Nedeljko Radlović, Zoran Leković, Dragana Ristić, Vladimir Radlović, Gordana Nikčević, Nikola Kotur, Ksenija Vučićević, Tatjana Kostić, Sonja Pavlović, and Branka Zukić, Bosn J Basic Med Sci. 2014 Aug; 14(3): 171-176. doi: 10.17305/bjbm.2014.3.28
- [28] Whole-Genome Analysis and HLA Genotyping of Enteropathy-Type T-Cell Lymphoma Reveals 2 Distinct Lymphoma Subtypes; Ronald J Deleeuw, Andreas Zettl, Erdwine Klinker, Eugenia Haralambieva, Magan Trottier, Raj Chari, Yong Ge, Randy D Gascoyne, Andreas Chott, Hans-Konrad Müller-Hermelink, Wan L Lam Gastroenterology 2007

May;132(5):1902-11. doi: 10.1053/j.gastro.2007.03.036. Epub 2007 Mar 24.

[29] Human Leukocyte Antigen-DQ2 Homozygosity and the Development of Refractory Celiac Disease and Enteropathy-Associated T-Cell Lymphoma Abdulbaqi Al Toma, Marije S. Goerres, Jos W. R. Meijer, A. Salvador Peña, J. Bart, A. Crusius, and Chris J. J. Mulder; Clin Gastroenterol Hepatol 2006 Mar;4(3):315-9. doi: 10.1016/j.cgh.2005.12.011.

[30] The HLA-DQ2 gene dose effect in celiac disease is directly related to the magnitude and breadth of gluten-specific T cell responses Willemijn Vader, Dariusz Stepniak, Yvonne Kooy, Luisa Mearin, Allan Thompson, Jon J van Rood, Liesbeth Spaenij, Frits Koning Proc Natl Acad Sci U S A 2003 Oct 14;100(21):12390-5. doi: 10.1073/pnas.2135229100. Epub 2003 Oct 6.

[31] Human leukocyte antigen DQ2/8 prevalence in non-celiac patients with gastrointestinal diseases Daniel DiGiacomo, Antonella Santonicola, Fabiana Zingone, Edoardo Troncone, Maria Cristina Caria, Patrizia Borgheresi, Gianpaolo Parrilli, and Carolina Ciacci; World J Gastroenterol 2013 Apr 28;19(16):2507-13. doi: 10.3748/wjg.v19.i16.2507.

[32] HLA-DQ Genotype Is Associated with Accelerated Small Bowel Transit in Patients with Diarrhea-Predominant Irritable Bowel Syndrome; Maria I Vazquez-Roque 1, Michael Camilleri, Paula Carlson, Sanna McKinzie, Joseph A Murray, Tricia L Brantner, Duane D Burton, Alan R Zinsmeister Eur J Gastroenterol Hepatol 2011 Jun;23(6):481-7. doi: 10.1097/MEG.0b013e328346a56e.

[33] The HLA-DR3, DQ2 heterozygous genotype is associated with an accelerated progression of primary sclerosing cholangitis; K M Boberg, A Spurland, G Rocca, T Egeland, S

Saarinen, S Mitchell, U Broomé, R Chapman, O Olerup, A Pares, F Rosina, E Schrupf; Scand J Gastroenterol 2001 Aug;36(8):886-90. doi: 10.1080/003655201750313441.

[34] Thyroid Autoimmunity: Role of Anti-thyroid Antibodies in Thyroid and Extra-Thyroidal Diseases Eleonore Fröhlich^{1,2} and Richard Wahl; Front Immunol 2017 May 9;8:521. doi: 10.3389/fimmu.2017.00521. eCollection 2017.

[35] Differences in the risk of celiac disease associated with HLA-DQ2.5 or HLA-DQ2.2 are related to sustained gluten antigen presentation. Nat Immunol. 2009; 10: 1096-1101

[36] Etiology of Type 1 Diabetes; John A Todd; April 2010, Immunity 32(4):457-67. DOI: 10.1016/j.immuni.2010.04.001

[37] Genetics of thyroid function and disease Vijay Panicker 1; Clin Biochem Rev 2011 Nov;32(4):165-75.

[38] HLA antigens in Asian Indian patients with Graves' disease; N Tandon 1, N K Mehra, V Taneja, M C Vaidya, N Kochupillai; Clin Endocrinol (Oxf) 1990 Jul;33(1):21-6. doi: 10.1111/j.1365-2265.1990.tb00461.x.

[39] Association of the large multifunctional proteasome (LMP2) gene with Graves' disease is a result of linkage disequilibrium with the HLA haplotype DRB1*0304-DQB1*02-DQA1*0501; J M Heward 1, A Allahabadia, M C Sheppard, A H Barnett, J A Franklyn, S C Gough; Clin Endocrinol (Oxf) 1999 Jul;51(1):115-8. doi: 10.1046/j.1365-2265.1999.00755.x.

[40] Dermatitis herpetiformis and celiac disease are both primarily associated with the HLA-DQ (alpha 1*0501, beta 1*02) or the HLA-DQ (alpha 1*03, beta 1*0302) heterodimers; A. Spurland, G. Ingvarsson, E. S. Falk, I. Knutsen, L. M.

- Sollid, E. Thorsby. *Tissue Antigens* 1997; 49: 29-34. 0 Munksgaard, 1997
- [41] Alterations in HLA-DP and HLA-DQ Antigen Frequency in Patients with Dermatitis Herpetiformis; Russell Martin Rene J. Duquesnoy M.D. Stephen I. Katz M.D., Ph.D. *J Invest Dermatol* 1989 Oct;93(4):501-5. doi: 10.1111/1523-1747.ep12284056.
- [42] Recurrent Pregnancy Loss: Etiology, Diagnosis, and Therapy; Holly B Ford, MD* and Danny J Schust, MD; *Rev Obstet Gynecol Spring* 2009;2(2):76-83.
- [43] Antiphospholipid Syndrome during pregnancy: the state of the art; Fosca A. F. Di Prima, Oriana Valenti, Entela Hyseni, Elsa Giorgio, Marianna Faraci, Eliana Renda, Roberta De Domenico, and Santo Monte; *Journal of Prenatal Medicine*; 2011 Apr-Jun; 5(2): 41-53.
- [44] Human leukocyte antigen (HLA) DQ2/DQ8 prevalence in recurrent pregnancy loss women; Silvia D'Ippolito, Antonio Gasbarrini, Roberta Castellani, Sandro Rocchetti, Leuconoe Grazia Sisti, Giovanni Scambia, Nicoletta Di Simone; *Autoimmun Rev* 2016 Jul;15(7):638-43. doi:10.1016/j.autrev.2016.02.009. Epub 2016 Feb 13.
- [45] Identification of HLA-DR and -DQ alleles conferring susceptibility to pollen allergy and pollen associated food allergy; Boehncke WH1, Loeliger C, Kuehn P, Kalbacher H, Böhm BO, Gall H; *Clinical and Experimental Allergy: Journal of the British Society for Allergy and Clinical Immunology*, 01 Apr 1998, 28(4):434-441; DOI: 10.1046/j.1365-2222.1998.00246.x
- [46] Prevalence of toxoplasma encephalitis in AIDS patients treated with Didanosine hospitalised in a French infectious service; Marie-Elisabeth Sarciron, Arnaud Ghérardi, Chantal Delorme, Dominique Peyramond, Anne-Françoise Pétavy; *Curr HIV Res* 2004 Oct;2(4):301-7. doi: 10.2174/1570162043351101.
- [47] Evidence for Genetic Regulation of Susceptibility to Toxoplasmic Encephalitis in AIDS Patients Yasuhiro Suzuki, Sin-Yew Wong, F. Carl Grumet, Jeffrey Fessel, Jose G. Montoya, Andrew R. Zolopa, Amy Portmore, Francolse Schumacher-Perdreau, Matthias Schrappe, Stefan Koppen,* Bernhard Ruf, Byron William Brown, and Jack S. Remington; *J Infect Dis* 1996 Jan;173(1):265-8. doi: 10.1093/infdis/173.1.265.
- [48] HLA-DRB1, DQA1, and DQB1 alleles and haplotypes frequencies in Iranian healthy adult responders and non-responders to recombinant hepatitis B vaccine; Ali Akbar Amirzargar 1, Nilufar Mohseni, Mohammad Ali Shokrgozar, Zohreh Arjang, Nahid Ahmadi, Manijeh Yousefi Behzadi, Amir Amanzadeh, Fazel Shokri; *Iran J Immunol* 2008 Jun;5(2):92-9.
- [49] Humoral response to recombinant hepatitis B virus vaccine at birth: role of HLA and beyond Martinetti, M., A. De Silvestri, C. Belloni, A. Pasi, C. Tinelli, A. Pistorio, L. Salvaneschi, G. Rondini, and M. A. Avanzini. 2000. *Clin. Immunol.* 97: 234-240.
- [50] HLA-DRB1, DQA1, and DQB1 alleles and haplotypes frequencies in Iranian healthy adult responders and non-responders to recombinant hepatitis B vaccine; Amirzargar, A. A., N. Mohseni, M. A. Shokrgozar, Z. Arjang, N. Ahmadi, M. Yousefi Behzadi, A. Amanzadeh, and F. Shokri. 2008. *Iran. J. Immunol.* 5: 92
- [51] Role of HLA allele polymorphism in chronic hepatitis B virus infection and HBV vaccine sensitivity in patients from eastern Turkey; Albayrak, A., M. Ertek, M. A. Tasyaran, and I. Pirim. 2011. *Biochem. Genet.* 49: 258-269

[52] Advances in Autism;
Daniel H. Geschwind; *Annu Rev Med*
2009;60:367-80. doi: 10.1146/annurev.
med.60.053107.121225.

[53] Autism spectrum disorders
are associated with an elevated
autoantibody response to tissue
transglutaminase-2; Allen Rosenspire,
Wonsuk Yoo, Sherri Menard,
Anthony R Torres; *Autism Res* 2011
Aug;4(4):242-9. doi: 10.1002/aur.194.
Epub 2011 Apr 19.

[54] The immunopathogenesis of
multiple sclerosis; Elisabetta Prat,
Roland Martin; *J Rehabil Res Dev* Mar-
Apr 2002;39(2):187-99.

[55] Genetics of multiple sclerosis-how
could disease-associated HLA-types
contribute to pathogenesis?; Martin R;
J Neural Transm Suppl 1997;49:177-94.
doi: 10.1007/978-3-7091-6844-8_19.

[56] HLA-DRB1*1501, -DQB1*0301,
-DQB1*0302, -DQB1*0602, and
-DQB1*0603 alleles are associated with
more severe disease outcome on Mri
in patients with multiple sclerosis;
Robert Zivadinov 1, Laura Uxa, Alessio
Bratina, Antonio Bosco, Bhooma
Srinivasaraghavan, Alireza Minagar,
Maja Ukmar, Su yen Benedetto, Marino
Zorzon; *February 2007 International
Review of Neurobiology* 79:521-35 DOI:
10.1016/S0074-7742(07)79023-2

[57] Frequency distribution of HLA DQ2
and DQ8 in celiac patients and first-
degree relatives in Recife, northeastern
Brazil Margarida Maria Castro-Antunes,
Sergio Crovella, Lucas André Cavalcanti
Brandão, Rafael Lima Guimarães, Maria
Eugênia Farias Almeida Motta, and
Giselia Alves Pontes da Silva; *Clinics*
(Sao Paulo) 2011;66(2):227-31.doi:
10.1590/s1807-59322011000200008.