A Clinician's Guide to Celiac Disease HLA Genetics

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Celiac disease is a common inflammatory disease triggered by dietary gluten in genetically susceptible individuals. The strongest and best-characterized genetic susceptibilities in celiac disease are class II human leukocyte antigen (HLA) genes known as *HLA-DQ2* and *DQ8*. HLA genetic testing is available through a number of commercial and academic laboratories and is used in the evaluation of celiac disease and to identify at-risk family members. Importantly, HLA genetic testing has a high negative predictive value for celiac disease, but a low positive predictive value. Therefore, for a practicing clinician, it is important to understand when to order HLA genetic testing, what test to order, and how to interpret the result. This review provides a practical primer on HLA genetics in celiac disease.

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INTRODUCTION

Celiac disease is a multiorgan inflammatory disorder that results in intestinal damage. Celiac disease is triggered by dietary gluten in genetically susceptible individuals (1). The disease prevalence is estimated between 1% and 2% in individuals of European descent (2,3). Gastrointestinal mucosal injury occurs after ingestion of gluten, proteins found in wheat, barley, and rye. Clinical presentation encompasses a wide spectrum from gastrointestinal symptoms of diarrhea and weight loss to extraintestinal manifestations, including iron deficiency anemia, bone loss, and neurological symptoms, or no symptoms (4). The diagnosis of celiac disease relies on specific serological testing, histological evaluation of duodenal biopsies, and improvement after the introduction of a gluten-free diet (5,6). Increasingly, genetic testing for human leukocyte antigen (HLA) susceptibility is included in the workup of celiac disease and to determine risk in family members.

Celiac disease has a strong hereditary component. Epidemiological studies show that 7.5%–15% of first-degree relatives are affected by the disease (7,8), with concordance rates of 50%–80% in monozygotic twins and 10% in dizygotic twins (9,10). Unlike classical Mendelian hereditary syndromes such as cystic fibrosis, celiac disease is a complex genetic disorder with genetic and nongenetic factors that likely contribute to disease. The strongest and best-characterized genetic susceptibilities in celiac disease are HLA class II genes known as *HLA-DQ2* and *DQ8*. Importantly, the *HLA-DQ2/DQ8* genes are encoded by approximately 30% of the general population, whereas only approximately 1% of the population have celiac disease (11,12), indicating that other factors besides these genes are involved in disease progression. In this review, we provide a practical approach to understanding HLA genetics, when to order the test, and how to interpret the results for the management of celiac disease.

GENERAL HLA FEATURES AND NOMENCLATURE

In this section, a basic primer on important concepts related to HLA genetics is provided to enable practitioners to understand the results of their clinical genetic test. Whenever possible, illustrations are included to help clarify these concepts. A list of definitions used in this review can be found in Table 1.

The HLA complex is found on the short arm of chromosome 6 and consists of multiple genes (loci; Figure 1). The HLA loci are notable for their extreme polymorphism, meaning that each locus has many known variants (alleles), with new alleles continuously being characterized (13). HLA loci involved in celiac disease are found in a region known as class II at the DQ locus. *HLA-DQA1* and *DQB1* loci code for α- and β-chain proteins, respectively, that associate as heterodimers on the surface of antigen-presenting cells. The protein heterodimers formed by these chains are known simply as HLA-DQ molecules.

There are 2 parallel HLA nomenclature systems that are based on denoting either the genetic information or the expressed proteins of HLA loci; determining which alleles or proteins are present in an individual is referred to as "HLA typing." In the molecular nomenclature, HLA is followed by letters for the locus, an asterisk denoting molecular nomenclature, and sets of numbers arranged in colon-separated fields (e.g., *HLA-DQA1*05:01*). To determine a class II HLA heterodimer, both loci encoding for that heterodimer (*DQA1* and *DQB1* for the DQ protein) need to typed. On the other hand, in the serological nomenclature, which is based on detecting expressed HLA molecules using antibodies specific for different heterodimers, the class II HLA proteins are named based on the whole heterodimer (e.g., HLA-DQ2), with the DQB1 allele generally providing the number for the serological name, although exceptions exist (e.g., the HLA-DQ8 protein is encoded by the DQB1*03:02 allele). Most laboratories use molecular techniques to type HLA, and so use molecular nomenclature, although it is possible to "translate" the results of molecular typing to serological nomenclature (14), so a sample typed by molecular methods may be reported in both molecular and serologic nomenclature.

As every person encodes 2 alleles of each of the *DQA1* and *DQB1* loci, up to 4 different heterodimers are possible in an

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Table 1. Definitions

Allele	A particular genetic sequence; polymorphic genes have more than 1 allele
Cis	Located on the same chromosome
Trans	Located on opposite chromosomes
Haplotype	Genes that are inherited together on a chromosomal segment
Heterodimer	Protein complex formed by 2 different proteins
Heterozygote	Encoding 2 different alleles
Homozygote	Encoding 2 identical alleles
Locus	The chromosomal location of a protein-coding region; a gene
Polymorphism	Variation in the sequence of a locus between individuals

individual. A heterodimer encoded by *DQA1* and *DQB1* alleles on the same chromosome (hence inherited from 1 parent) is said to be encoded in *cis* (Figure 2). Conversely, a heterodimer formed from alleles on different chromosomes (1 from each parent) is said to be encoded in *trans*. Importantly, if compatible heterodimers are encoded either in *cis* or in *trans*, functional molecules will be expressed (15). For this reason, celiac disease does not follow simple Mendelian inheritance, as one half of a heterodimer permissive for celiac disease can be inherited from each parent, without either parent encoding the full heterodimer.

Across human populations, there is variability in the frequencies of HLA alleles. Specific sets of alleles are often inherited together in blocks known as haplotypes (the *DQA1-DQB1* alleles encoded in *cis* above is an example of a haplotype). In the past, when serological methods were used, HLA typing for celiac disease was often reported as an extended haplotype with HLA-DR, the classical HLA locus that is most closely linked to the DQ loci (Figure 1). For example, a result of DR3 and DQ2 indicated that the *DRB1*03:01-DQA1*05-DQB1*02* haplotype, which is permissive for celiac disease, was likely present. Contemporary testing usually omits typing of DR, as it is not linked to celiac disease, and instead directly types the *DQA1* and *DQB1* loci.

HLA-DQ2 AND DQ8 IN CELIAC DISEASE PATHOGENESIS

HLA-DQ2 and DQ8 play crucial roles in celiac disease pathogenesis (Figure 3). For in-depth reviews, readers are directed to references (16,17). HLA-DQ molecules are responsible for presentation of peptide antigens to $CD4^+$ T cells. Peptides presented by class II HLA molecules are derived from degraded proteins found in the microenvironment and range in size from 12 to 25 amino acids (18). Each HLA type presents a different set of peptide antigens, based on the amino acid sequence present at the peptide-binding region of the heterodimer. HLA-DQ2 and DQ8 are uniquely able to present specific gluten-derived peptides, whereas other HLA types cannot (19–22). Before binding to DQ2 or DQ8, though, native gluten peptides are converted to negatively charged particles in the intestine. Tissue transglutaminase 2 (TTG2) is responsible for this modification, which is termed deamidation (23,24). Antigen-presenting cells then present deamidated

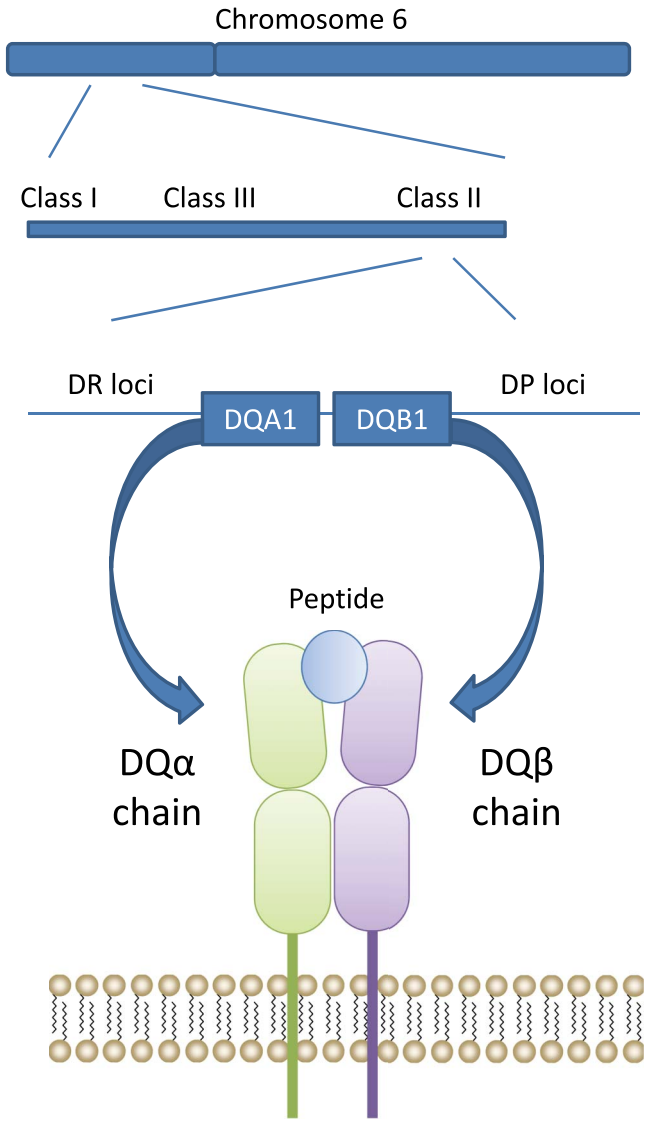

Figure 1. *HLA-DQ* genetic and protein structure. The genes encoding HLA molecules are found in the MHC complex on chromosome 6. HLA molecules involved in celiac disease are encoded in a region known as class II at the *DQ* loci (other class II genes include *DR* and *DP*). *HLA-DQA1* and *DQB1* loci encode for α- and β-chains, respectively, that associate as heterodimers on the surface of APC, forming a cleft that binds peptide antigens. APC, antigen-presenting cell; HLA, human leukocyte antigen; MHC, major histocompatibility complex.

gluten bound to HLA-DQ2 or DQ8 to elicit a gluten-specific $CD4^+$ T-cell response, initiating inflammation (16). It must be acknowledged, however, that this pathogenic process is not active in most individuals encoding DQ2 or DQ8, as only approximately 3% of DQ2- or DQ8-positive individuals develop celiac disease (11,12).

GENETICS OF HLA ALLELES PERMISSIVE FOR CELIAC DISEASE

The genetics of the various HLA types that support celiac disease are complex, as the number and configuration of the *DQA1* and *DQB1* alleles determine risk for celiac disease. We will attempt to simplify this complexity by highlighting the component parts of

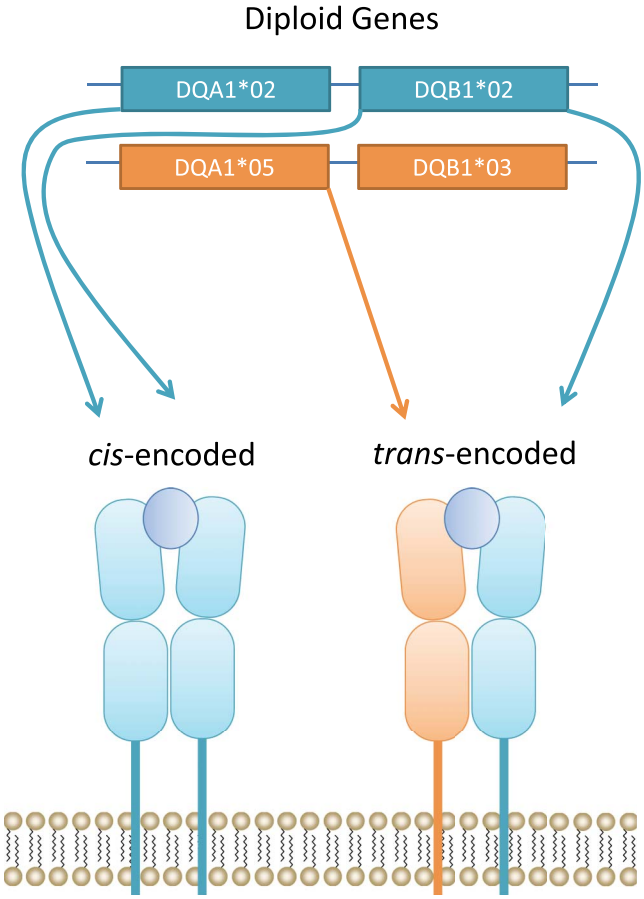

Figure 2. DQ molecules encoded in *cis* and *trans*. DQ molecules encoded in *cis* form from alleles on the same chromosome, whereas those in *trans* form from alleles on opposite chromosomes. Once a gene is translated to a protein, a cell cannot determine which chromosome the protein came from, so any compatible DQ chains will form functional heterodimers.

the HLA genetics and how they combine to increase susceptibility to celiac disease. Table 2 highlights HLA configurations associated with celiac disease, as discussed below.

HLA-DQ2.5

The HLA-DQ2.5 heterodimer, one variant of the DQ2 molecule, is most permissive heterodimer for celiac disease, encoded by approximately 90% of patients with CD (12,25). HLA-DQ2.5 is encoded by the *DQB1*02* and *DQA1*05* alleles (the "2" and "5," respectively, in "DQ2.5"). The DQ2.5 heterodimer can be encoded in either *cis* or *trans*, and these genetic configurations are similarly associated with celiac disease (12,26).

HLA-DQ8

The HLA-DQ8 heterodimer is encoded by the *DQB1*03:02* and *DQA1*03* alleles. Note that "8" is not apparent in either of these alleles. The reason is that there are several DQ3 variants, which are recognized differently by serology. Therefore, the DQ3 group was "split" into DQ7, DQ8, and DQ9 proteins, encoded by *DQB1*03:01*, *03:02*, and *03:03* alleles, respectively. Importantly, only the DQ8 protein, encoded by the *DQB1*03:02* allele, is permissive for celiac disease and is present in approximately 20% of patients with CD (12,25).

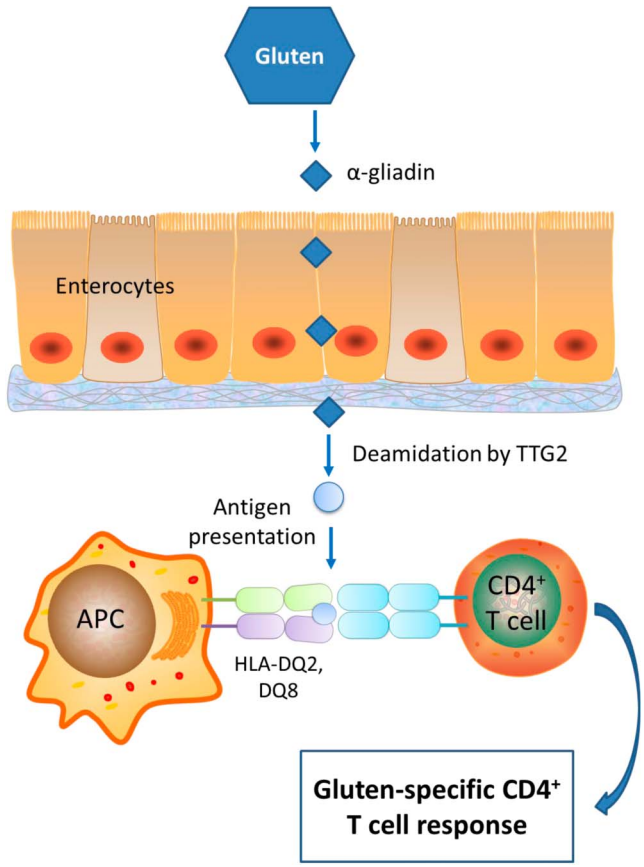

Figure 3. HLA in celiac disease pathogenesis. Gluten is digested into α-gliadin, which can mediate both adaptive (shown here) and innate (not shown) immune responses. Gliadin traverses enterocytes and is deamidated to a negatively charged particle by TTG2. Deamidated gliadin preferentially binds to HLA-DQ2 or DQ8 on APC and is presented to $CD4^+$ T cells. This, in turn, leads to a gluten-specific $CD4^+$ T-cell response. APC, antigen-presenting cell; HLA, human leukocyte antigen; TTG2, tissue transglutaminase 2.

HLA-DQ2.2

The HLA-DQ2.2 heterodimer is similar to the DQ2.5 heterodimer, except that the DQα chain is encoded by a *DQA1*02* allele, instead of a *DQA1*05* allele. The resulting "2.2" heterodimer is significantly less capable of presenting gluten-derived peptides compared with the 2.5 heterodimer (27,28), although this HLA type is still capable of supporting celiac disease, illustrated by the fact that most celiac patients without DQ2.5 or DQ8 (approximately 5%) encode the DQ2.2 heterodimer (26,29). However, this heterodimer is often found in patients also encoding either DQ2.5 or DQ8, bringing its total prevalence to 35% of patients with CD (12).

Other HLA types in celiac disease

Rarely, patients diagnosed with celiac disease encode neither DQ2 nor DQ8 heterodimers. In a large European collaborative study, 20 of 1,008 patients (2.0%) fulfilled the criteria for celiac disease but did not carry DQ2 or DQ8 (29). Two additional studies in the United States and Italy found the prevalence of DQ2/DQ8 negativity in celiac disease to range from 0.16% to 0.9% (11,30). A study published in 2003 concluded that encoding half of the DQ2.5 haplotype, either the *DQB1*02* or *DQA1*05* alleles, can explain these results (29). However, contemporary analysis of

Table 2. Human leukocyte antigen types permissive for celiac disease, listed in order of decreasing association with diagnosis

	*DQA1**	*DQB1**
DQ2.5	05:XX[a]	02:XX[b]
DQ8	03:XX[c]	03:02
DQ2.2	02:XX[d]	02:XX[b]

DQA1 encodes the alpha-chain protein, and *DQB1* encodes the beta-chain protein of the DQ molecule.
[a]Refers to any allele in the *DQA1*05* family; *DQA1*05:01*, *DQA1*05:03*, and *DQA1*05:05* are the most common in the general population.
[b]Refers to any allele in the *DQB1*02* family; *DQB1*02:01* and *DQB1*02:02* are the most common in the general population.
[c]Refers to any allele in the *DQA1*03* family; *DQA1*03:01*, *DQA1*03:02*, and *DQA1*03:03* are the most common in the general population.
[d]Refers to any allele in the *DQA1*02* family; *DQA1*02:01* is the only common allele in the general population.

DQ2.5- and DQ8-negative patients indicate that the DQ2.2 heterodimer, discussed above, can best explain these results (12,26), as most DQ2.5- and DQ8-negative patients in the 2003 study encoded DQ2.2 (29), which was not recognized as permissive for celiac disease at the time. The *DQA1*05* allele, when not encoded as part of the *DQB1*02-DQA1*05* haplotype, is often encoded with *DQB1*03:01* (DQ7 in serologic nomenclature), leading to the conclusion that either the half-haplotype of *DQA1*05* or the DQ7 heterodimer may also be permissive for celiac disease, which is supported by a recent study (31). However, Italian and Brazilian studies found the *DQA1*05* half heterodimer at higher frequencies in controls compared with patients, indicating a negative association for the *DQA1*05* half heterodimer (11,12). Taken together, it is clear that the overwhelming majority of patients with celiac disease encode the DQ2.5, DQ8, or DQ2.2 heterodimers. For those rare patients not encoding any of these DQ molecules, there is not a clear association with any other DQ molecule. Therefore, the diagnosis of celiac disease in these patients can be made with supportive serology or pathology results, regardless of which HLA alleles are encoded by the patient.

Patients encoding more than 1 permissive heterodimer

The presence of any of the DQ2.5, DQ8, or DQ2.2 heterodimers puts a patient at risk of developing celiac disease. However, multiple studies have shown that patients who encode 2 of these permissive heterodimers are at an even greater risk (11,12). In a study by Almeida et al. (12), the risk of celiac disease in patients encoding 1 copy of the DQ2.5 heterodimer was 1:30, whereas the risk for patients carrying 2 copies was 1:7. Encoding 2 permissive alleles can come in several combinations: for example, a patient can be "homozygous" for DQ2.5, meaning that they encode the same DQ alleles on both chromosomes, or a patient can encode DQ2.5 on 1 chromosome, and DQ8 on the other, etc. In cases of homozygosity, the HLA typing report may not make this important point clear. For example, a report may only list 1 allele at each locus, instead of the 2 expected of diploid humans, with the understanding that both chromosomes encode that 1 listed allele (see Table 3 for examples of reports with homozygous results). For this reason, it is important to carefully review the HLA typing results and consult the HLA laboratory with any questions.

DQ2.5 homozygosity

In addition to the increased risk of developing celiac disease in patients encoding 2 permissive heterodimers, patients homozygous for DQ2.5, specifically, have also been reported to have more severe disease symptoms (32–35). This "gene dose" effect appears to be due to increased presentation of gluten-derived peptides by DQ2.5-homozygous individuals (32).

CLINICAL APPLICATION OF HLA GENETIC TESTING

When to test

There are several clinical scenarios in which genetic testing should be considered (Table 4). HLA testing can be used to virtually exclude celiac disease in symptomatic patients who have self-started a gluten-free diet (36,37). HLA testing can also be helpful to clarify a diagnosis. For example, in those with equivocal serology or biopsy findings and/or incomplete gluten elimination, HLA testing can be used to rule out celiac disease if HLA-DQ2 or DQ8 is absent and would warrant further testing if DQ2 or DQ8 are found (6,36).

Genetic testing can be used to identify at-risk individuals, particularly first-degree family members of patients with celiac disease. Although the 2013 guidelines from the American College of Gastroenterology do not recommend routine testing of family members, because of the high likelihood (>80%) of these individuals encoding HLA susceptibility (6), the 2012 European Society for Paediatric Gastroenterology, Hepatology and Nutrition guidelines do endorse HLA testing in high-risk groups, including first-degree family members, based on the high negative predictive value (5). Moreover, a Finnish group concluded that because up to 17.6% of first-degree family members tested negative for HLA-DQ2 or DQ8, and thus would not require further follow-up, HLA testing can be clinically useful for these patients (38). If a family member tests negative for DQ2/DQ8, further testing is not needed. On the other hand, genotype positive family members could be considered for future testing, especially if symptoms arise. A recent study of first-degree family members with permissive genotypes recommended repeat serological testing for children younger than 10 years, whereas 1-time evaluation of serologies in first-degree adolescents and adults might be sufficient (7). Although further research is needed to determine optimal serology testing for at-risk individuals, we would recommend that each clinician decide whether the benefits outweigh the costs associated with HLA testing of first-degree

Table 3. Examples of homozygous HLA reports

	*DQA1**	*DQB1**
Example 1:		
One allele listed at each locus[a]	05:01	02:01
Example 2:		
Two alleles listed at each locus[b]	05:01 05:01	02:01 02:01

[a]Because humans are diploid, if only one allele is listed at a locus, it is assumed that both chromosomes encode the same locus.
[b]Listing both loci at a locus makes the presence of homozygosity more obvious, although this typing is equivalent to example 1.
HLA; human leukocyte antigen.

Table 4. When to consider HLA testing in celiac disease

Patient on gluten-free diet to rule out disease (if HLA-DQ2 or DQ8 negative)
Support diagnosis of celiac disease when biopsy or serology equivocal
Identify at-risk individuals (especially first-degree family members)

HLA, human leukocyte antigen.

relatives, given that the guidelines do not agree on this issue at the present time.

What to test

HLA testing is usually performed on blood or cheek swab samples and is available through most commercial and academic laboratories in the United States. Given that the risk gradient depends on *DQA1* and *DQB1* typing, clinicians should ensure that both loci are typed. Cost of the test is variable and individuals need to consult with their health insurance provider to ensure that it will be covered. It should be noted that direct-to-consumer genetic testing companies have begun to report HLA-DQ2/DQ8 and CD risk. Clinicians should keep in mind that these companies use HLA typing methods significantly less robust than dedicated HLA laboratories and should make sure to order full *HLA-DQA1* and *DQB1* typing to workup celiac disease. Last, as HLA typing is a genetic test, patients need only to be tested once in their lifetime, as their genetic status will not change over time and is not affected by gluten ingestion.

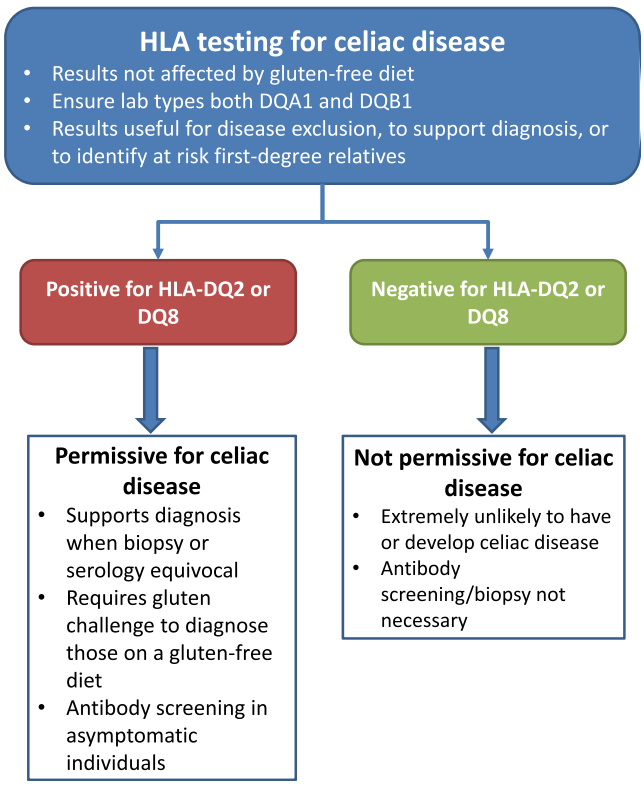

Figure 4. Clinical application of HLA testing. HLA testing should be considered for disease exclusion, to support a diagnosis of celiac disease, and to identify at-risk first-degree relatives. It is not affected by a gluten-free diet. Providers should ensure that both *DQA1* and *DQB1* are typed. A result of HLA-DQ2 and/or DQ8 is permissive for celiac disease, with risk varying based on which DQ heterodimer is encoded; additional workup is necessary to make a diagnosis of celiac disease. If HLA-DQ2 or DQ8 is absent, celiac disease is extremely unlikely, and antibody screening is not necessary. HLA, human leukocyte antigen.

Considerations when testing

Patients sometimes express reluctance to undergo genetic testing for fear of insurance discrimination because a positive result might be interpreted as a preexisting condition. In comparison to genetic testing for hereditary cancer syndromes where lifetime risk of disease development is high, most patients with genetic susceptibility for celiac disease will not be affected by the disease; 30%–40% of individuals encode either HLA-DQ2 or DQ8 (11,12), whereas the prevalence of celiac disease is only 1% in the general population (39). Moreover, the 2009 passage of the "Genetic Nondiscrimination Act of 2008" (or GINA) made it illegal for employers and health insurers to discriminate because of genetic information (www.genome.gov). In contrast to other hereditary diseases, genetic testing for celiac disease is often ordered by a clinician rather than a genetic counselor trained in disclosure of genetic test results. Therefore, clinicians ordering these tests must be informed about the implications of the results and know how to counsel patients and family members.

Interpretation of genetic results

When HLA typing is ordered for a patient, correct interpretation of the results is important. Figure 4 summarizes the considerations involved in, and the interpretation of, HLA typing results. After ensuring that HLA testing is needed, and that both the *DQA1* and *DQB1* loci were typed, the clinician will be presented with results that indicate either the presence or absence of HLA-DQ2/DQ8. In cases in which neither DQ2 nor DQ8 was detected, celiac disease can be all but ruled out, as patients who do not encode either of these alleles are not permissive for celiac disease. In this way, HLA typing for celiac disease can be thought of as having a very high negative predictive value.

On the other hand, for patients who are typed as either DQ2 or DQ8 positive, it is important to note that this means that the patient is only permissive for celiac disease. DQ2/DQ8 positivity indicates that a patient is capable of having or developing celiac disease, but is not diagnostic on its own, giving HLA typing for celiac disease a low positive predictive value. Indeed, in light of this low positive predictive value, there is some controversy about the overall role of HLA testing in celiac disease diagnosis (40). However, we think that the high negative predictive value, discussed above, provides sufficient clinical value to make this test an important part of the celiac disease workup.

Finding that a patient is positive for DQ2 and/or DQ8 gives information as to the risk for celiac disease; DQ2.5 is most highly associated with celiac disease, DQ8 is less so, and DQ2.2 is least, while a patient encoding 2 of any of these molecules is more likely to develop disease. Last, patients with 2 copies of DQ2.5 specifically are associated with more severe symptoms of celiac disease. However, in all cases of DQ2/DQ8 positivity, a diagnosis of celiac disease requires other clinical correlates: a positive serology (e.g., IgA TTG or endomysial antibodies) with or without an abnormal duodenal biopsy, as described in the American College of Gastroenterology and European Society for Paediatric Gastroenterology, Hepatology and Nutrition guidelines, respectively (5,6). Importantly, serology and biopsy studies must be performed while the patient is eating a gluten-containing diet.

CONCLUSION

Genetics play an important role in celiac disease, and HLA is the genetic system with the strongest disease association. However, the HLA system is complex and requires specialized testing and careful interpretation to support or exclude a diagnosis of celiac disease. The most important guidelines for a clinician to follow for HLA testing in celiac disease are the following: (i) ensure the laboratory types and reports both the *DQA1* and *DQB1* loci in molecular nomenclature, (ii) look for a positive result of DQ2 (either DQ2.5 or DQ2.2) or DQ8, and (iii) understand that in the absence of both DQ2 and DQ8, celiac disease can be ruled out, whereas the presence of DQ2 and/or DQ8 only infers risk, but cannot be used by itself to make a diagnosis of celiac disease. HLA testing is a powerful and accurate test for celiac disease permissiveness, and correct interpretation will assure proper use to support clinical decision making.

CONFLICTS OF INTEREST

Guarantor of the article: Sonia S. Kupfer, MD.
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