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GUIDELINES

Clinical settings in which human leukocyte antigen typing is still useful in the diagnosis of celiac disease

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Abstract

Celiac disease (CD) is a systemic autoimmune disorder triggered by gluten ingestion ingenetically predisposed individuals. It is characterized by intestinal histological damage and the production of specific autoantibodies. The latest European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) 2020 guidelines have excluded human leukocyte antigen (HLA) genotyping from the no-biopsy diagnostic approach due to its weak positive predictive value, limited availability, and high cost in some countries. However, HLA genetic testing remains valuable in certain clinical contexts. This study provided practical indications for when to request and how to interpret HLA genotyping, emphasizing its continued relevance for CD diagnosis in specific cases. We also proposed a strategy for monitoring the risk of developing type 1 diabetes (T1D) in patients with CD, based on the risk stratification carried by different HLA genotypes. A retrospective analysis of 746 patients with CD and 627 controls was conducted at our hospital starting in 2012, when HLA geno-

typing became mandatory for the diagnosis of CD. We identified key clinical scenarios where HLA testing remains useful. Several high risk HLA-DQ genotypes strongly associated with CD were highlighted, including HLA-DQ2.5/HLA-DQ2.2 and HLA-DQ2.5/HLA-DQ2.5. Notably, while the HLA-DQ2.5/HLA-DQ2.2 genotype is linked to CD, it appears to confer protection against T1D. To support clinical practice, we presented a table clarifying commonly used HLA terminology, and another summarized the main clinical situations in which HLA genotyping should still be considered. These findings underscore the dual role of HLA testing: Not only can it help rule out CD in selected cases, but it also identifies patients with CD at risk for T1D, guiding personalized monitoring strategies.

Key Words: Human leukocyte antigens; Celiac disease; Type 1 diabetes; Guidelines; Anti tissue transglutaminase type 2

Core Tip: This guide explained how to interpret human leukocyte antigens (HLA) genetics associated with celiac disease (CD) and the different clinical situations where HLA genotyping can be useful in the diagnosis of CD. It also provided a strategy based on HLA genotyping for monitoring patients with CD at risk for the future development of type 1 diabetes (T1D). Only a subset of HLA genotypes linked to CD is associated with the development of T1D. Interestingly, some HLA genotypes that carry a high risk for CD may offer protection against T1D. Therefore, HLA genotyping in patients with CD could help in identifying those at high risk for T1D, enabling proactive interventions and therapies to preserve beta cell function.

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INTRODUCTION

Celiac disease (CD) is a systemic autoimmune disease characterized by a specific serological antibody profile and a peculiar intestinal histological damage. It is triggered and sustained by the ingestion of gluten and related prolamins in genetically predisposed individuals[1]. CD has a strong hereditary component[2]; 7.5%-15.0% of first-degree relatives and dizygotic twins are affected by CD, while CD concordance is estimated to range between 50%-80% in monozygotic twins [3]. CD is polygenic and multifactorial due to the interaction of multiple genes with a series of environmental factors and lifestyles that can vary rapidly depending on the historical periods in which these interactions occur.

A series of data indicated that the prevalence of CD appears to be increasing[4-9] and that this does not seem to be influenced by either the age at which gluten is introduced or the duration of breastfeeding[10,11]. It is likely that the cause of such an increase in prevalence is attributable not to a single factor but to a combination of elements, including the constant increase, starting from the mid-twentieth century, in the consumption of gluten-containing foods[12] and a modification of the intestinal microbiota due to widespread use of antibiotics and a Western-style diet[13]. In the coming years, the real estimates of CD prevalence will probably be more difficult to establish due to the increasingly high number of individuals who undertake a gluten-free diet (GFD) for health reasons without first excluding CD[14]. In this category of individuals, help for the clinician can come from the human leukocyte antigen (HLA) genetic test of susceptibility for CD.

The heritability of CD is due to 56% of genes outside the major histocompatibility complex (MHC) system, and as much as 44% of genes in the MHC family. Numerous genome-wide association studies have identified that 57 non-HLA susceptibility genes for CD would explain only about 6% of heritability, while 50% would consist of multiple common variants as observed in other polygenic diseases[15]. Recently, five susceptibility variants in the MHC that act independently of the *HLA-DQA1* and *HLA-DQB1* loci have been identified and explain 18% of heritability[16]. Finally, 26% of heritability is made up of the strong association with some alleles at the *HLA-DQA1* and *HLA-DQB1* loci that encode for HLA-DQ2 and HLA-DQ8 molecules[17]. Therefore, to date, the strongest single genetic association with CD is carried by the HLA-DQ loci.

It should be immediately noted that by adding up the frequencies of HLA-DQ2 and HLA-DQ8 in Caucasian populations, their positivity reaches 30%-40% or even about 50% in Sardinians[18] and Sahrawis[19], but the disease manifests itself only in a fraction of them. In addition, disease prevalence does not statistically correlate with the frequency of such HLA molecules in different populations[20]. Overall, these observations confirm the polygenic nature and the need for various environmental factors for the development of CD.

OVERVIEW OF HLA GENETICS

In Table 1 the genetic terminology used in the manuscript is explained, allowing a better understanding of the HLA complex located on the short arm of chromosome 6 (occupying about 3 Mbp in 6p21.3). The region contains more than 220 genes, mostly with immunological functions. The loci that compose it in the center-telomeric direction are HLA-DP, HLA-DM, HLA-DQ, and HLA-DR (belonging to class II) and HLA-B, HLA-C, HLA-E, and HLA-A (belonging to class I). The class III, including some genes that encode for complement fractions, is located between class I and class II. The system has a high degree of polymorphism[21], and for this reason numerous alleles exist at the same locus. For example, 10273 alleles have been reported at the *HLA-B* locus of class I and 2782 at the *HLA-DQB1* locus of class II[22]. For updated data, see the Immuno Polymorphism Database central platform (https://www.ebi.ac.uk/ipd/imgt/hla/allele.html).

HLA is characterized by the presence of strong linkage disequilibrium (LD). Two or more loci are in LD when the frequency of association of their different alleles is higher or lower than expected if the loci were independent and therefore randomly associated. The presence of LD and interdependent immunological function genes suggest a possible selective advantage of particular configurations of alleles, sometimes arranged in extended haplotypes from the class I *HLA-A* locus to the class II *HLA-DQB1* locus[23]. Numerous studies, including ours on the Sardinian population[18,24] and their particular genetic makeup, have shown that *HLA* genes involved in CD are located at the *HLA-DQA1* and *HLA-DQB1* loci of class II[24-26]. Among the many alleles encoded by these loci, those most frequently associated with CD are *HLA-DQA1* 05:01 and *HLA-DQB1* 02:01. These two alleles are in strong LD and encode the alpha chain and beta chain of the HLA-DQ heterodimer (DQα1 05:01, DQβ1 02:01) called HLA-DQ2. This heterodimer can be encoded in cis when the two alleles *HLA-DQA1* 05:01 and *HLA-DQB1* 02:01 are located on the same chromosome (almost always in LD with the *HLA-DRB1* 03:01 allele of the *HLA-DRB1* locus to form the *HLA-DRB1* 03:01, *HLA-DQA1* 05:01, *HLA-DQB1* 02:01 haplotype) or in trans in the *HLA-DQA1* 05:05, *HLA-DQB1* 03:01/*HLA-DQA1* 02:01, *HLA-DQB1* 02:02 genotype[25].

The alleles *HLA-DQA1* 02:01 and *HLA-DQB1* 02:02 also encode a molecule that has been named HLA-DQ2, even though it is composed of a different alpha chain (the polymorphism that differentiates the DQβ1 0201 and DQβ1 0202 chains is negligible from a functional point of view). To differentiate these two HLA-DQ2 molecules at the protein level, the HLA-DQ2 molecule encoded by the *HLA-DQA1* 05:01 and *HLA-DQB1* 02:01 alleles is called HLA-DQ2.5, while the HLA-DQ molecule encoded by the *HLA-DQA1* 02:01 and *HLA-DQB1* 02:02 alleles is called HLA-DQ2.2 (Figure 1 and Table 2).

Approximately 90%-95% of patients with CD are positive for alleles that encode for HLA-DQ2 and more specifically for HLA-DQ2.5 in cis or trans (Figure 1 and Table 2). The other HLA molecule associated with CD in about 5%-7% of patients is HLA-DQ8 encoded by the *HLA-DQA1* 03:01 and *HLA-DQB1* 03:02 alleles, while the remaining 3%-5% is composed of HLA-DQ2.2[27] or very rarely of half heterodimers such as in the HLA-DQ2.3molecule[28] or in the HLA-DQ7.5 molecule[29].

HLA-DQ HETERODIMERS PERMISSIVE FOR CD

Table 2 shows the HLA genotypes and heterodimers of susceptibility for CD. HLA genotypes were ordered by decreasing odds ratio (OR) using the cases of patients with CD from our center[30]. These associations are similar to those observed by other authors[31] and by meta-analysis studies[32]. A brief discussion of some of these high-frequency heterodimers with higher OR will allow us to better understand the HLA association and how to interpret the results provided by the genotyping laboratory.

HLA-DQ2.5

The HLA-DQ2.5 heterodimer, a variant of HLA-DQ2, can be defined as the most permissive for CD since it is present in more than 90% of patients with CD[25]. It can be encoded in cis in the *HLA-DRB1* 03:01, *HLA-DQA1* 05:01, *HLA-DRB1* 02:01 haplotype or in trans in the *HLA-DQA1* 05:05, *HLA-DQB1* 03:01/*HLA-DQA1* 02:01, *HLA-DQB1* 02:02 genotype, conferring a very similar disease risk (Figure 1 and Table 2). The beta chains (DQβ1 02:01 and DQβ1 02:02) encoded by *HLA-DQB1* 02:01 and *HLA-DQB1* 02:02 differ by one amino acid residue at position 135, which is distant from the peptide-binding region and therefore functionally irrelevant. Instead, homozygosity for HLA-DQ2.5 confers a high risk for the development of celiac autoimmunity[4,33].

According to some authors this "double dose" of HLA-DQ2.5 allows for the presentation of a broader repertoire of gluten peptides in greater quantities[34] and stability[35] to T cells than other molecules associated with CD, such as HLA-DQ2.2 and HLA-DQ8. This quantitative model of intestinal damage in CD, where HLA-DQ2.5 expression and the number of gluten-specific T cells available represent the main limiting factors, has been indirectly strengthened by several studies conducted on patients with CD[36,37] and a recent meta-analysis[38].

HLA-DQ8

HLA-DQ8 is encoded by the *HLA-DQA1* 03 and *HLA*-DQB1 03:02 alleles. When *HLA-DQA1* 03 is associated with *HLA-DQB1* 03:01, the molecule is called HLA-DQ7.3. When it is associated with *HLA-DQB1* 03:03, it is called HLA-DQ9. Only HLA-DQ8 is permissive for CD (Figure 1 and Table 2). HLA-DQ8, when present in heterozygosity with HLA-DQ2.5, confers a high risk for CD. In addition, it carries a strong risk for the development of autoimmune type 1 diabetes (T1D). One possible explanation may be the formation of HLA trans-dimers between the alpha chain encoded by *HLA-DQA1* 05:01 and the beta chain encoded by *HLA-DQB1* 03:02[39-41]. On the other hand, when HLA-DQ8 is not in combination with HLA-DQ2.5 it confers a low risk for CD.

Table 1 Genetic terminology used in the present manuscript

Terminology	Explanation
Gene	A particular nucleotide DNA sequence at a specific locus
Allele	Polymorphisms in the sequence of a DNA at the same locus. In a diploid individual, at most two different alleles can be present
MHC and HLA	Major histocompatibility complex. A large region of vertebrate DNA containing a set of closely linked polymorphic genes encoding immune cell surface proteins called MHC molecules. In humans the region is called HLA
Center-telomeric	Refers to the known order of the HLA class II (*DP*, *DM*, *DQ*, and *DR* loci), class III (containing the *C4* and *TNF* genes), and class I (*B*, *C*, *E* and *A*) genes, from centromere to telomere along the chromosome. Centromer is the constricted region of chromosome connecting the sister chromatids and creating a short arm (p) and a long arm (q) on the chromatids. The telomere is a region of repetitive nucleotide sequences associated with specialized proteins at the ends of chromosomes
Polymorphism	Variations in the nucleotide sequence of a given locus (determines more than one allele at that locus)
Homozygous	Presence of alleles with the same nucleotide sequence at the same locus on homologous chromosomes (*HLA-DQB1* 02:01/*HLA-DQB1* 02:01)
Heterozygous	Presence of alleles with different nucleotide sequences at the same locus on homologous chromosomes (*HLA-DQB1* 02:01/*HLA-DQB1* 03:02)
Haplotype	Alleles inherited together on a certain chromosomal segment (*HLA-DQA1* 05:01/*HLA-DQB1* 02:01). In the MHC, due to a strong linkage disequilibrium, haplotypes sometimes extending from the *A* locus to the *DQB1* locus are found quite frequently. A1, Cw7, B8, DR3, and DQ2 are present in Northern European populations, and A30, Cw5, B18, DR3, and DQ2 are present in the Sardinian population
Genotype	Genetic constitution of an individual (*e.g.*, of an HLA genotype -A1, Cw7, B8, DR3, DQ2/-A30, Cw5, B18, DR3, DQ2)
Cis	Alleles at different loci located on the same chromosome (*e.g.*, HLA-DQA1 03:01 *HLA-DQB1* 03:02, coding for the molecule HLA-DQ8)
Trans	Alleles located at different loci on opposite chromosomes (*e.g.*, *HLA-DQA1* 05:05 *HLA-DQB1* 03:01/*HLA-DQA1* 02:01 *HLA-DQB1* 02:02; see also Figure 1)
Heterodimer	Protein complex consisting of two different subunits (*e.g.*, α chain and β chain of HLA-DQ2), also named HLA-DQ molecule
Codominance	Both maternal and paternal alleles are expressed. This allows the formation of the HLA-DQ2 heterodimer in trans
Linkage disequilibrium	The nonrandom association of alleles of different loci within a population

HLA: Human leukocyte antigens; MHC: Major histocompatibility complex; TNF: Tumor necrosis factor.

Table 2 Human leukocyte antigen-DQ genotypes associated with celiac disease

HLA (genotype)	HLA (heterodimer)	CD (*n* = 746)	Controls (*n* = 627)	OR	*P* value	CI
HLA-DQA1 05 *HLA-DQB1* 02:01/*HLA-DQA1* 02:01 *HLA-DQB1* 02:02	-DQ2.5/-DQ2.2	111	17	6.3	1.1×10^{-14}	3.7-10.6
HLA-DQA1 05 *HLA-DQB1* 02:01/*HLA-DQA1* 05 *HLA-DQB1* 02:01	-DQ2.5/-DQ2.5	153	33	4.6	2×10^{-16}	3.1-6.9
HLA-DQA1 05 *HLA-DQB1* 02:01/*HLA-DQA1* 03:01 *HLA-DQB1* 03:02	-DQ2.5/-DQ8	57	21	2.4	6.2×10^{-4}	1.4-4.0
HLA-DQA1 05 *HLA-DQB1* 03:01/*HLA-DQA1* 02:01 *HLA-DQB1* 02:02	-DQ2.5 trans	41	20	1.8	3.9×10^{-2}	1.0-3.0
HLA-DQA1 05 *HLA-DQB1* 02:01/*HLA-DQA1* X *HLA-DQB1*X	-DQ2.5 cis	271	165	1.6	7.2×10^{-5}	1.3-2.0
HLA-DQA1 02:01 *HLA-DQB1* 02:02/*HLA-DQA1* X *HLA-DQB1* X	-DQ2.2/X	17	28	0.5	2.3×10^{-2}	0.3-0.9
HLA-DQA1 03:01 *HLA-DQB1* 03:02/*HLA-DQA1* X *HLA-DQB1* X	-DQ8/X	15	38	0.3	1×10^{-4}	0.2-0.6

HLA: Human leukocyte antigens; CD: Celiac disease; OR: Odd ratio; CI: Confidence intervals.

HLA-DQ2.2

The HLA-DQ2.2 heterodimer differs functionally from HLA-DQ2.5 due to the alpha chain encoded by the *HLA-DQA1* 02:01 allele. The differences between the two alpha chains make the HLA-DQ2.2 molecule less suited than HLA-DQ2.5 to present gluten-derived peptides to cluster of differentiation 4 positive T cells[35,42]. However, when in association with the HLA-DQ2.5 haplotype (*i.e.* HLA-DQ2.5/HLA-DQ2.2 genotype) an OR of 6.3 with a frequency of 14.9% was observed [30], which was comparable to that observed in HLA-DQ2.5 homozygotes (Table 2), a finding consistent with other case studies[31]. On the contrary, when it is not associated with the HLA-DQ2.5 haplotype, it confers a low risk for CD

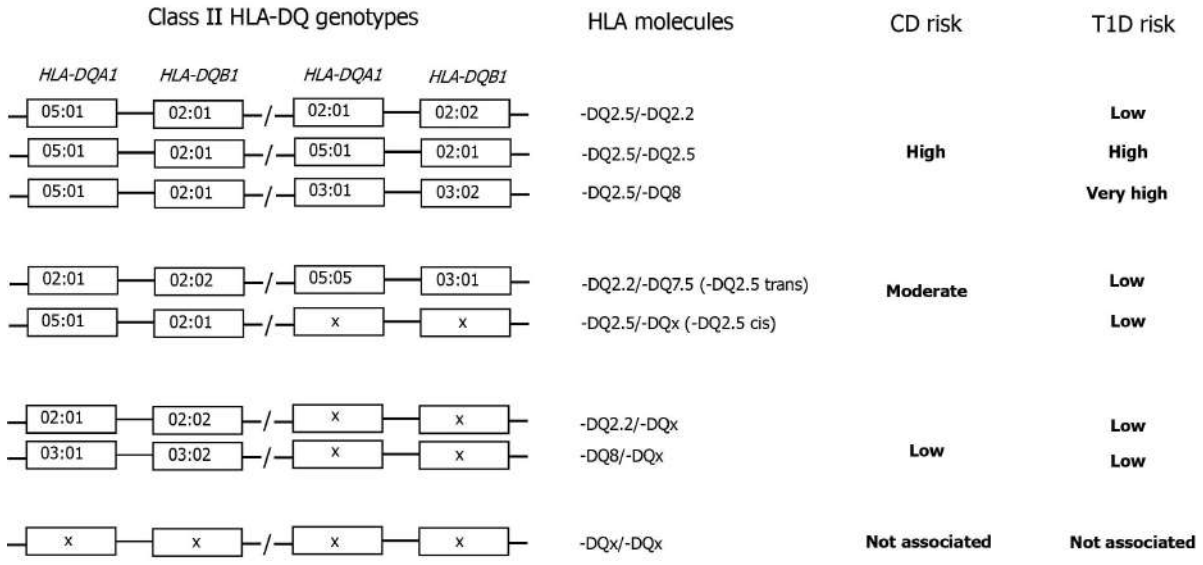

Figure 1 Graphical representation of human leukocyte antigen genotypes grouped according to the current nomenclature of human leukocyte antigen molecules with the associated risk for celiac disease and type 1 diabetes. The symbol x indicates other human leukocyte antigen (HLA)-DQ alleles not associated with celiac disease (CD). The HLA-DQ2.5/HLA-DQ2.2, HLA-DQ2.5/HLA-DQ2.5, and HLA-DQ2.5/HLA-DQ8 molecules confer high risk for CD (see also Table 2). HLA-DQ2.5/HLA-DQ2.5 and HLA-DQ2.5/HLA-DQ8 molecules are also associated with type 1 diabetes (T1D), conferring high risk and very high risk, respectively. Interestingly, the HLA-DQ2.5/HLA-DQ2.2 molecule strongly associated with CD confers a low risk for T1D. The HLA-DQ2.2/HLA-DQ7.5 molecule conferring a moderate risk for CD has a low risk for T1D. The other HLA molecules are similarly associated with both diseases. HLA: Human leukocyte antigen; CD: Celiac disease; T1D: Type 1 diabetes.

(Table 2). When in association with *HLA-DQA1* 05:05 and *HLA-DQB1* 03:01 to form the HLA-DQ2.5 heterodimer in trans, it confers a similar risk of CD to that of HLA-DQ2.5 in cis (Table 2). Therefore, in both cases, HLA-DQ2.2, due to the genetic mechanism of codominance, behaves as a donor of beta chains for the constitution of the HLA-DQ2.5 heterodimer.

Other HLA molecules besides HLA-DQ2 and HLA-DQ8 in CD

Although very rare, HLA genotypes other than HLA-DQ2 and HLA-DQ8 have been reported in CD. In a multicenter European study, such patients were detected in 2% of cases[33]. In another American study, the frequency of endomisial antibody (EMA)-positive individuals but negative for HLA-DQ2 and HLA-DQ8 was even lower (0.16%)[36]. In our case series only 10 patients were non-HLA-DQ2 and non-HLA-DQ8. All 10 of these patients received a diagnosis of CD in the late 1980s, when the anti-tissue transglutaminase type 2-IgA (t-TG2-IgA) and t-TG2-IgG determinations were not yet available. Unfortunately, we were unable to reverify these diagnoses to exclude that mucosal damage was due to other pathologies. On the other hand, none were found to be negative for HLA-DQ2 or HLA-DQ8 when the t-TG2-IgA determination was available. Therefore, we believe that the diagnosis of CD in patients with HLA genotypes other than HLA-DQ2 and HLA-DQ8 or with heterodimeric molecules such as in HLA-DQ2.3[27] or HLA-DQ7.5[28] should be entrusted to reference centers and should be based on unequivocal evidence that mucosal damage is gluten-dependent.

CLINICAL UTILITY OF HLA GENETIC TESTING FOR CD

In the following paragraphs, we outlined the clinical situations for which HLA genetic testing for CD can be proposed to the patient or family. This practical guide should reduce the use of the test to appropriate cases, helping the clinicians make useful decisions for the diagnosis of the disease or the follow-up of individuals at risk (Table 3).

For making new diagnoses of CD

Since the publication of the ESPGHAN guidelines in 2012 for the diagnosis of CD and up to 2020, the main use of HLA genotyping was directed towards formulating new diagnoses of CD in children and adolescents without performing intestinal biopsy[41]. In fact, these guidelines provided the option not to perform intestinal biopsy in case the patient presented with: (1) Symptoms suggestive of CD; (2) A value of t-TG2-IgA greater than 10 times the normal values and, in a second sample, positivity of EMA confirming the positivity of t-TG2-IgA; and (3) HLA genetics compatible with CD, *i.e.* positivity for HLA-DQ2 or HLA-DQ8[43].

These recommendations were revised in the new ESPGHAN 2020 guidelines[44], where neither HLA genotyping for the *HLA-DQA1* and *HLA-DQB1* loci nor the presence of symptoms associated with CD are mandatory to formulate the diagnosis of CD in a pediatric patient with high t-TG2-IgA greater than 10 times normal values confirmed by EMA

Table 3 Clinical settings where it is reasonable to propose human leukocyte antigen genotyping for celiac disease

Condition	HLA-DQ2 and HLA-DQ8 negativity
Before biopsy	
First-degree relatives of a patient affected by CD	Allows the exclusion of serological monitoring in individuals not carrying any genetic risk
Individuals who have started a GFD without performing t-TG2-IgA measurement	Allows the exclusion of CD as the cause of gastrointestinal symptoms regardless of the clinical response to the GFD
Individuals with persistent low t-TG2-IgA titer	Allows unequivocal definition of the false positives, including first-degree relatives of a proband with reduced gluten intake
Individuals affected by IgA deficiency	Allows the exclusion of serological monitoring in individuals not carrying any HLA genetic risk
Patients with chromosomal pathologies associated with increased CD risk (Down syndrome, Turner syndrome, Williams syndrome)	Allows the limit of periodic serological follow-up exclusively to positive patients
Patients affected by Hashimoto's thyroiditis	Allows the limit of the periodic serological follow-up exclusively to positive patients
After biopsy	
Ineffectiveness of GFD in patients with CD	Allows exclusion of CD and suspect other pathologies. Could help in excluding refractory CD type II and enteropathy-associated T cell lymphoma
Dubious CD biopsy performed for other reasons	Allows exclusion of CD and suspect other pathologies

GFD: Gluten free diet; HLA: Human leukocyte antigens; CD: Celiac disease; t-TG2-IgA: Tissue transglutaminase type 2-IgA.

positivity in a second sample. The reasons given in the new guidelines for this change are that HLA testing is not widely available, is expensive, and would not improve the ability of serology to approach diagnosis without biopsy[44]. However, it is important to underscore that the HLA genotyping expenses can be performed at very convenient costs by tagging single nucleotide polymorphisms as shown by Bastos *et al*[45].

Even in a retrospective study conducted on the Sardinian population in subjects attending the ambulatory of the Pediatric Gastroenterological Unit in Cagliari, Italy, between 2005 and 2012, we found that all symptomatic patients with CD with t-TG2-IgA greater than 10 times normal values were positive for HLA-DQ2 or HLA-DQ8, thus confirming the ESPGHAN 2020 recommendations, at least for symptomatic patients[46]. Therefore, it is likely that by adhering to the ESPGHAN 2020 guidelines that HLA genetic testing for diagnosing CD will no longer be used except in selected cases [44].

To exclude CD in the diagnostic process

Table 3 provides a detailed list of scenarios in which HLA genotyping can be proposed as a useful analysis in the diagnostic process of CD to the patient or the patient's parents. The request for the test has been divided into situations where it may be useful before or after performing an intestinal biopsy. It is always necessary to explain rigorously that the test has value only when negative for HLA-DQ2 or HLA-DQ8, while its positivity is of little clinical usefulness. In fact, negativity has a very high negative predictive value, avoiding the need for negative patients to undertake further serological, endoscopic, or possible gluten reintroduction tests[47].

First-degree relatives of a proband with CD

Relatives of patients diagnosed with CD have a higher risk of developing CD over time. A recent retrospective study by the Mayo Clinic found a frequency of 44.4% of CD in first-degree relatives of patients with CD[48], a finding confirmed by other authors[49]. This frequency is much higher than that found in previous studies[50,51]. The awareness that CD can occur at any time in an individual's life often silently (in the Mayo Clinic study, 28% were asymptomatic)[48] seems to indicate a rational choice to exclude from long-term serological screening those first-degree relatives negative for HLA-DQ2 or HLA-DQ8.

Individuals on a GFD who have not undergone t-TG2-IgA determination before starting the diet

This category of individuals is likely to increase in the coming years due to the growing popularity of GFD as a healthier option capable of alleviating chronic gastrointestinal symptoms[52,53]. In addition, gluten-free products are now more abundant, easier to purchase, and less expensive than in the past[54]. Finally, an increasing number of individuals are diagnosed or self-diagnosed with non-celiac gluten sensitivity without following a rigorous clinical path[55,56]. These individuals on GFD, in whom CD has not previously been excluded, may be offered the opportunity of HLA genetic testing for CD, which if negative for HLA-DQ2 or HLA-DQ8 allows the exclusion of CD as the cause of gastrointestinal symptoms.

Low t-TG2-IgA positivity

It is not uncommon in clinical practice, including referral centers, to observe adult and pediatric patients with low t-TG2-IgA positivity who may be affected by CD or may be false positives. A series of clinical conditions are known to be associated with non-specific production of t-TG2-IgA antibodies, such as chronic inflammatory bowel diseases[57], autoimmune diseases[58], simple respiratory and gastrointestinal infections[59], chronic liver diseases[60], HIV infection [61], and other conditions[62]. Even the intestinal production of t-TG2-IgA does not seem to be completely specific for CD [63]. In these particular situations, it seems rational to propose HLA genotyping to identify patients negative for HLA-DQ2 or HLA-DQ8 before undertaking invasive examinations such as esophagogastroduodenoscopy in pediatric patients or in patients with chronic diseases in whom esophagogastroduodenoscopy may be contraindicated.

Selective IgA deficiency

Selective IgA deficiency (IgAD) is a clinical condition that predisposes patients to autoimmune manifestations, the most frequently associated being CD[64]. IgAD also has a strong genetic component that maps to the MHC region[65], and although it tends to be associated with positive HLA-DQ2 haplotypes[66,67], a certain number of haplotypes are HLA-DQ2 negative. In a study of Swedish and Iranian patients with IgAD, about 38% were found to be negative for HLA-DQ2 or HLA-DQ8[68]. The ESPGHAN 2020 guidelines consider intestinal biopsy mandatory in patients with IgAD and positive t-TG2-IgG, as it was not possible to derive a safe t-TG2-IgG cutoff value from the literature capable of predicting CD in IgAD[44]. These guidelines do not mention the possible usefulness of HLA genotyping. We believe that HLA genotyping should be considered in patients with IgAD and positive t-TG2-IgG to spare individuals negative for HLA-DQ2 or HLA-DQ8 from biopsies.

Patients with chromosomal disorders at risk for CD (Down syndrome, Turner syndrome, Williams syndrome)

The 2012 CD diagnostic guidelines clearly indicated HLA genotyping as the initial screening test in such risk groups for CD[43]. Only in individuals positive for HLA-DQ2 or HLA-DQ8 was periodic serological screening recommended using t-TG2-IgA. The 2020 guidelines have been modified, and diagnosis in symptomatic or asymptomatic patients without performing duodenal biopsy can be made with serology alone, even for these conditions[44]. However, in these patients, gastrointestinal symptoms can be frequent but not necessarily related to CD[69]. Furthermore, it is known that CD can run silently in the same patients[69], that some symptoms commonly found in CD can be mistakenly attributed to the syndrome for years[70], and that CD can also occur in adulthood[71]. This implies that such patients, whether symptomatic or asymptomatic, should undergo indefinite serological follow-up over time because they belong to at-risk groups, including those who do not require it. It seems, therefore, more rational to adhere to the ESPGHAN 2012 guidelines in these at-risk groups[43].

CD patients at risk to future development of T1D

HLA genotyping in children with a diagnosis of CD can also establish the risk of future T1D development. The risk may be stratified by high to low risk according to different HLA genotypes. Indeed, we found that CD patients with HLA-DQ2.5/HLA-DQ8, and HLA-DQ2.5/HLA-DQ2.5 genotypes were strongly associated with concomitance of CD and T1D. Conversely, the HLA-DQ2.5/HLA-DQ2.2 genotype appeared to confer protection against T1D development (Table 2) [30]. Therefore, early screening for CD around 2-3 years of age with subsequent CD diagnosis with or without biopsy followed by HLA genotyping could help in identifying those patients at high risk of T1D[30]. This strategy may detect patients with CD at the very early stages of T1D (phase 1) who should undergo periodic pancreatic autoantibody monitoring and further immune, genetic, and metabolic tests to identify those patients susceptible to immunotherapies able to preserve endogenous beta cell function.

Patients with autoimmune thyroiditis

Recent meta-analysis studies have confirmed an increased prevalence of CD in patients with Hashimoto's thyroiditis (HT), recommending screening for CD in such patients[72]. The association with HLA-DQ2 or HLA-DQ8 in HT is not as strong as in CD[73,74]. The HLA-DQ2.2 allele appears to confer protection, while the HLA-DQ2.5 allele has a weak association at the limits of significance and the strongly associated *HLA-DRB1* 04 haplotype is in LD with HLA-DQ7.3 and not with HLA-DQ8[73,74]. Therefore, it is crucial to be able to exclude patients who are negative for HLA-DQ2 or HLA-DQ8 from long-term serological screening. Therefore, we consider it rational to offer this option to pediatric and adult patients in follow-up for HT, as indicated in the 2012 guidelines[43].

An increased prevalence of CD is also observed in Graves' disease[75]. Therefore, serological screening for CD is recommended in this autoimmune thyroid disease as well[75]. Regarding the possible use of genetic testing for CD, it is found that among the alleles most strongly associated with Graves' disease, we find the same ones present in CD, in particular *HLA-DRB1* 03:01 (in LD with HLA-DQ2) and *HLA-DQA1* 05[76]. Therefore, HLA genotyping in patients with Graves' disease will be of limited clinical utility in excluding CD. Therefore, its determination is not recommended to establish the risk of CD in patients with Graves' disease.

Patients diagnosed with CD and not responding to GFD

Approximately 7%-30% of adult patients with CD and 25% of pediatric patients with CD appear to have an unsatisfactory response to a GFD[77-80]. In another retrospective study conducted in a single referral center in patients with different grades of intestinal damage, about 20% who were on a GFD were negative for HLA-DQ2 or HLA-DQ8[47]. Therefore, genetic testing for CD may be useful to identify misdiagnoses related to false positives of t-TG2-IgA and indicate a functional gastrointestinal disorder or other intestinal pathology as responsible for the symptoms.

Refractory celiac disease (RCD) is defined as CD that remains unresponsive to at least 12 months of a strict GFD[81,82]. RCD includes various subtypes with differing characteristics, making diagnosis and management challenging. The overlap between RCD and enteropathy-associated T-cell lymphoma (EATL) adds to this complexity. Genetic factors, such as HLA-DQ2 homozygosity, are strongly linked to RCD-II and EATL, occurring in 44%-65% of RCD-II cases and 53.3% of EATL cases compared with 25.5% in RCD-I and 20.7% in uncomplicated CD[83]. Identifying HLA-DQ2 homozygous patients early could help detect those at higher risk of severe complications. Single-cell analysis highlighted significant variability in abnormal cell populations in RCD-II[84], offering insights that could improve diagnostics and treatments, similar to advances seen in cancer research[85-87].

Patients with inconclusive biopsy performed for other reasons

Sometimes when patients undergo endoscopic investigations and biopsies of the upper gastrointestinal tract for reasons unrelated to the diagnosis of CD, histological lesions may be found that could be part of the initial pathological picture of CD, such as increased intraepithelial T lymphocytes. Since such lesions can also appear in a large group of other pathologies including cases of villous atrophy and negative serology for CD, such as drug-induced mucosal damage[88-90], negativity for HLA-DQ2 or HLA-DQ8 allows CD to be excluded from the differential diagnosis of such pathologies.

FUTURE DIRECTIONS: POSSIBLE UTILITY OF HLA GENOTYPING TEST FOR FUTURE IMMUNOMODULATORY THERAPIES

Recently, a new therapy for autoimmune diseases, including CD, has been proposed. It involves creating nanoparticles coated with MHC-peptide complexes where both the MHC and peptide are disease-specific[91,92]. These nanoparticles are designed to bind specifically to T cell receptors on cluster of differentiation 4-positive cells, triggering the transformation of effector T cells into regulatory T cells. Regulatory T cells in turn could promote antigen-specific immune tolerance while preserving the overall integrity of the immune system[93,94].

Before testing these innovative immunomodulatory therapies in humans, researchers can utilize a mouse model for CD that was recently developed after years of research[95]. It is clear that future patients with CD or other autoimmune diseases, such as multiple sclerosis or T1D, who may benefit from these personalized therapies will need to undergo HLA genotyping for *HLA-DRB1*, *HLA-DQA1*, and *HLA-DQB1*.

CONCLUSION

HLA typing, while deemed non-essential by the 2020 ESPGHAN guidelines for the diagnosis of CD, continues to hold significant diagnostic value in specific clinical contexts. This guide provided clinicians with practical recommendations on when and how to effectively incorporate HLA genetic testing into the diagnostic pathway. In addition, a monitoring strategy in patients with CD for future development of T1D based on the risk stratification conferred by different HLA genotypes is also presented.

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FOOTNOTES

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