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Chapter

Genotype DQ2.5/DQ2.2 ($\beta2/\beta2$) and High Celiac Disease Risk Development

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Abstract

Celiac disease (CD) is a genetically determined immune-mediated disorder in which gluten immunogenic peptides are presented to CD4 T cells by HLA-DQ2.5, DQ8, DQ2.2, and their combinations. CD is considered one of the most well-characterized autoimmune diseases, having a described environmental factor, a well-established pathogenesis, associated genetic factors, and a well-established laboratory diagnosis, although it is still considered a difficult-to-classify disease. In the last decades, advances in laboratory diagnosis with the emergence of molecular biology techniques have allowed a specific characterization of the CD-associated genotypes and, although clinically the disease management was not modified by this factor, the follow-up of patients at risk of CD development has greatly benefited from the possibility of specifically finding the inherited genotype, and whether it represents a greater or lesser risk for developing the disease. In some populations, it is already possible to calculate the exact risk associated to the inherited genome by each individual, but the genotypes available in several countries sometimes disregard the relevance of searching beyond the genotypes DQ2.5/DQ2.5, DQ2.5/DQ8, and DQ2.5/DQ2.2, which also present a high risk for developing the disease.

Keywords: celiac disease, HLA, disease risk, HLA-DQ2.2, HLA-DQ2, HLA-DQ8

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1. Introduction

1.1 Definition, prevalence, and classification

Celiac disease (CD) is a genetically determined immune-mediated disease, and individuals with CD have specific HLA haplotypes (DQ2 and/or DQ8) that trigger an immune response to gluten intake, leading to intestinal and clinical signs and symptoms [1, 2], besides other autoimmune-associated CD diseases, such as dermatitis herpetiformis [3], type 1 diabetes mellitus, Hashimoto's thyroiditis, and Sjögren syndrome [4]. Also, there are some genetic syndromes that may be CD associated such as Down syndrome [5, 6], Turner syndrome [7], and Williams syndrome [8].

As CD is one of the most well-elicited autoimmune diseases and one of the most common permanent food intolerances among humans [9], its prevalence in the general population from Europe, USA, and countries where the population is

predominantly of European origin is approximately 1% [2]. Prevalence is lower, ranging from 0.15 to 0.84%, in Latin American countries such as Brazil [10–14]. When Brasília city (Brazilian capital and population representation) is considered, since it is a city formed by people from all regions of the country, the prevalence found in the general population is 0.34%, considering 0.21% in adults and 0.54% in children [11].

The CD prevalence can still be related to the cereal consumption that contains gluten (mainly wheat) and to the distribution of predisposing HLA alleles in the population [15, 16]. Besides, the existence of genetic and environmental factors may influence the CD prevalence rate in a region [15]. Last but not least, we highlight the microbiota variability, the existence of intestinal infections, and socioeconomic conditions, which are also factors that may influence the CD development and prevalence [17, 63].

According to clinical signs and symptoms, laboratory and histopathological findings, which together have been called "clinical forms," CD can be classified into five distinct forms (**Table 1**).

1.2 CD pathogenesis and immune response (IR), the HLA importance

CD pathogenesis, which is an inflammatory enteropathy with autoimmune characteristics, is triggered by gluten ingestion [17]. In nonceliac individuals, gluten is cleaved by digestive enzymes into small fragments for eliciting an immunogenic response and is digested by gastrointestinal system without causing damages. In CD patients, the gluten digestion induces gliadin fragments initiating an innate and adaptive immune response resulting in tissue damage of the intestinal mucosa and clinical CD manifestations [24].

Classification	Clinical forms
Classic or typical	Frequently in children, characterized by gastrointestinal manifestations that can arise after the introduction of gluten foods (weeks, months, or even years). Patients have positive serology for CD and HLA compatible; and, in intestinal biopsy, there are usually lesions of variable severity, but they are frequently characterized by hypotrophy or atrophy of intestinal villi and varying degree of intestinal cryptic hyperplasia.
Atypical or nonclassical	Minimal or no gastrointestinal manifestations and recurrent extraintestinal manifestations. It can appear at any age (but commonly in teenagers and adults). It presents positive serology, HLA, and CD-compatible biopsy.
Silent or asymptomatic (subclinical)	Signs and manifestations commonly associated to CD are nonexistent. Patients are diagnosed occasionally in screening programs or because they are in risk CD groups (carriers of autoimmune diseases or celiac relatives), by positive serology, HLA, and CD compatible biopsy.
Potential	Patient may or may not present manifestations, as well as may not develop mucosal lesions in the future. CD-positive serology, CD-compatible HLA typing, normal intestinal mucosa, or with subtle abnormalities (increase of intraepithelial lymphocytes) and absence of significant enteropathy.
Latent (controversy)	Characterized by the presence or absence of antibodies in the normal intestinal mucosa, HLA typing is CD compatible, but for being defined as having CD, there must be a prior diagnosis of at least the presence of an enteropathy associated to gluten consumption.

Adapted from Fasano and Catassi, [18]; Lionetti and Catassi [17]; Admou et al. [19]; Bao, Green and Bhagat [20]; Husby [8]; Kaneepkens and von Blomberg [21]; Ludvigsson et al. [22]; Sapone et al. [23].

Table 1.
Celiac disease classification and clinical forms.

Gluten is the energy storage protein found in wheat, rye, barley, and oat grains, which has a large amount of prolamins (glutamine and proline) in its primary structure. Proline-rich peptides are resistant to gastrointestinal digestion [25].

Specifically in wheat, gluten proteins are divided into gliadins and glutenins [25], according to the solubility of the prolamins present. Gliadin is soluble in alcohol, while glutenin is soluble in acidic and basic dilutions [26]. Gliadin is an alcohol-soluble, 30 kDa protein, particularly rich in glutamine and proline residues, which are contained in polyglutamine sequences, represented as a single chain of polypeptides, which can be divided in four different groups: α-, β-, γ-, and Ω-gliadin [26]. The N-terminal domain of α-gliadin contains the most immunogenic fragment, which has the peptide 31–43 and the 33-mer fragment, which contains six significant epitopes for CD pathogenesis [27, 28].

The presence of gliadin and its peptides is the external factor triggering the immune response in CD, which implies the need for its entry through the mucosa and presence in the lamina propria with consequent obligatory passage through the cells of the intestinal epithelium. This epithelium entry occurs by three mechanisms: (1) through the transcellular route, where gluten is endocytosed in lysosomes, which degrade it in small nonimmunogenic peptides [29]; (2) via the paracellular route, by regulating the TJ junctions responsible for the union of the epithelial cells, promoting a change in cellular permeability and, consequently, the entry of gliadin peptides into the mucosa, such as regulation through zonulin produced by epithelial cells of celiac patients that alter the permeability between epithelial cells [29, 30]; (3) by transepithelial transport in cells of celiac patients, where there is an increase in CD71 (transferrin receptor) expression. This receptor recognizes IgA complexed with gliadin through the Fc portion of the immunoglobulin, and releases this association without processing in the lamina propria [31].

Although these mechanisms of entry and processing by digestive enzymes are described in the literature, it is believed that these peptides interact with the intestinal epithelial cells and produce an inflammatory response before presenting themselves in the lamina propria, promoting gene alterations in this cell by mechanisms not yet fully elucidated [24].

In an *in vitro* cellular CD model by using $CaCo_2$ cells, intact gliadin and its immunogenic peptides from the 33-mer fragment (nondeaminated—P56-88, P57-68, P69-82, P31-43, and deaminated P57-68 E65 and P69-82 E72) were used for understanding this interaction mechanism in the first 24 and 48 h. Results showed that following interaction with $CaCo_2$ cells, these peptides modulated receptor gene transcripts such as TLR-4, cell permeability altering protein genes such as zonulin and occludin, as well as inflammatory cytokines (IL-1, IL-6, IL-8, and IL-15) very important for CD pathogenesis, besides increasing the production mediators of oxidative stress such as nitric oxide. Afterward, IL-6 and TNF-α levels revealed the secretion of these cytokines in culture supernatant, confirming the inflammatory process initiated in the first 24 and 48 h after interaction with these human epithelial cells when culture (unpublished data) [32]. Earlier data had previously confirmed that the peptide p31-43 activates the innate immune response through the activation of proinflammatory cytokines, while the p57-68 peptide has been identified as immunodominant and capable of activating the adaptive immune response through recognition by T cells-CD4 [33].

When gliadin peptides reach the lamina propria, they are modified by the action of the tissue transglutaminase 2 (tTG2) enzyme, which in the presence of calcium, converts glutamine residues to glutamic acid, the negative charge of glutamic acid increases the affinity of tTG2 for gliadin and the gliadin-tTG2 complex also increases the affinity of the gliadin-tTG2 complex and the gliadin peptides with the MHC class II molecules HLA-DQ2/DQ8 [15, 34–36].

These gliadin peptides are recognized and processed by the HLA-DQ2/DQ8 MHC class II antigen presenting cells (APCs) and are presented to CD4 T cells, which become active and begin to produce IFN-γ and IL-15. T-CD4 lymphocytes, activated by APCs on the lamina propria, differentiate into intraepithelial lymphocytes (IELTs) and infiltrate epithelial cells in response to IL-15 stimuli produced by enterocytes. Also, in response to IL-15, IELTs display cell membrane receptors for natural killers (NK), which promotes the cascade recruitment of new NK cells, which promote destruction of the epithelial barrier, cryptic hyperplasia, and atrophy of the intestinal villi [25, 37, 38].

APCs migrate to the mesenteric lymph node and display the gliadin peptides complexed with tTG2 to immature CD4 T cells. In mesenteric nodules, T-CD4 cells differentiate into effector T-CD4 cells (T-CD4^{+}), which increases the proliferation of reactive B cells to the gliadin-tTG2 complex. Reactive B cells differentiate into plasma cells and produce IgA and IgG antibodies, not only against glutamine residues modified to glutamic acid, but also against tTG2, which may still be complexed with these peptides [39, 40].

The continuous recognition by APCs of the gliadin-tTG2 complex as an immunogenic stimulus accentuates the immunological and proinflammatory response, triggering the autoimmune response found on CD [8]. However, in healthy individuals, the recognition of these peptides when presented by MHC of class II originated of HLA DQ2/DQ8 [41] also occurs.

The entire inflammatory process induced by gliadin and its peptides on CD is a result from the synergism between the innate and adaptive immune response that occurs in two distinct sites in the small intestine, that is, in the epithelium and in the intestinal lamina propria [31, 42].

Studies suggest that CD is primarily mediated by adaptive immunity, where CD4 T cells recognize gliadin peptides through MHC II molecules, which are encoded by the HLA (*Human Leukocyte Antigen*) DQ2 and DQ8 genes present in celiac patients, which confirms the strong genetic basis [15, 31, 42].

For all these reasons, CD is an excellent model for studying the genetic factors that contribute to the development of immune-mediated disorders. Among these reasons, we can highlight the fact that it has a well-known environmental triggering factor—gluten, an autoimmune disease with a well-described genetic predisposition associated to the MHC HLA DQ2/DQ8 alleles, the involvement existence of other non-MHC genes, and the high incidence of other immunological diseases reported in both celiac and familial patients, in which the innate and adaptive response plays a key role [43]. CD is also considered a multifactorial disease caused by the interaction of different genetic factors that act in consonance with nongenetic effects, since nonceliac individuals also have such alleles, suggesting that additional complementary mechanisms are necessary for the disease development [39].

Similar to other autoimmune diseases, CD is a polygenic disorder and the MHC gene is the most important genetic factor. Most celiac patients carry a specific genetic variance of HLA-DQ2 (DQA1 * 05: 01, DQB1 * 02: 01, known as DQ2.5), and those who are not HLA-DQ2.5 almost always carry the HLA variance -DQ8 (DQA1 * 03, DQB1 * 03: 02) or another variant of HLA-DQ2 (DQA1 * 02: 01, DQB1 * 02: 02), known as DQ2.2 [9]. Since all celiac patients carry specific HLA variations, this factor may be considered necessary for CD diagnosis, but alone it is not sufficient for CD development [25].

Recently, studies based on Genome Wide Association Studies (GWAS) has been allowing the identification of single-nucleotide polymorphisms (SNPs) in each gene in the human genome associated to a cell metabolic pathway or a specific phenotype such as CD. In general, GWAS tests hundreds of thousands of SNPs throughout the patient genome and matched the control ethnic group [44]. These SNPs often

affecting the recognition of transcription factors, resulting in differences in the expression of regulatory genes shared with other autoimmune diseases. After GWAS studies, it was possible to verify by immunochip analysis that several non-MHC genes have been related as CD susceptibility factors. Until then, 39 loci with 57 independent association signals were described, contributing 14% of the genetic variance for CD [45].

Many of these genetic variances are shared with other autoimmune diseases such as type 1 diabetes mellitus and rheumatoid arthritis [46]. After GWAS studies, once evidenced correlations with metabolic pathways and shared inflammatory response between CD and other autoimmune diseases, new strategies that make use of different cellular models can be applied to CD [47].

1.3 Laboratory diagnosis and HLA determination relevance

Clinical CD manifestations are very heterogeneous and often subtle, which may confuse the clinician and delaying the definitive diagnosis. According to the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), CD diagnosis depends on clinical manifestations, significant level of the presence of specific antibodies (positive serology), presence of predisposing HLA-DQ2 and/or HLA-DQ8 genes, and presence of histopathological abnormalities from the intestinal mucosa evidenced by the biopsy [8].

ESPGHAN advises that CD diagnosis should be considered in children and adolescents who present gastrointestinal (diarrhea, abdominal pain, nausea, vomiting, etc.) and extraintestinal manifestations (anemia, dermatitis herpetiformis, chronic fatigue, etc.). It is also recommended that CD diagnosis be evaluated in asymptomatic children and adolescents (but belong to a risk group for CD development). Risk CD groups are composed of individuals with type 1 diabetes, Down's syndrome, Turner's syndrome, Williams's syndrome, autoimmune thyroid disease, autoimmune liver disease, selective IgA deficiency, and first-degree relatives of celiac [8]. American Gastroenterology Association recommends that CD diagnosis be considered in any individual with a clinical condition indicative of CD or belonging to at-risk groups [48].

The production of anti-endomysium (EMA), anti-gliadin, antitransglutaminase (anti-tTG) and gliadin-tTG complexes is part of the CD pathogenesis process. Serological tests used in the laboratory CD diagnosis are intended to detect levels of these antibodies in the serum (CD-suspected individuals). The available CD diagnostic tests include anti-gliadin IgA and IgG antibodies, anti-EMA IgA and IgG, IgA and IgG anti-tTG [48, 49].

Anti-gliadin antibodies are not currently considered sufficiently sensitive or specific to be used in the CD diagnosis [20] and have been replaced by anti-gliadin deaminated (anti-DGP) antibodies of both IgA and IgG because they have greater sensitivity and specificity. Anti-DGP IgG test is used in IgA deficiency cases where anti-DGP IgG antibodies are detected [49]. Both IgA and IgG anti-DGP assays are commonly used as additional tests in patients who are negative for other serological tests but presenting characteristic clinical CD symptoms, especially in patients younger than 2 years old [8, 49].

Anti-tTG antibodies are commonly detected by ELISA method usually by human recombinant tTG as antigen [8]. Anti-tTG IgA serological test is considered the most sensitive method for diagnosing CD, with sensitivity close to 97% [20]. This test has high specificity, close to 99% [48]. Although anti-tTG IgA assay has high sensitivity and specificity, it is possible to find false-positive results in patients with liver disease, congestive heart failure, arthritis, and inflammatory bowel disease [48]. Anti-tTG IgA test is generally used as the first test in the initial

approach for diagnosing CD because it is a quantitative test that can be automated and does not depend on the observer interpretation such as the anti-endomysium test [8, 49].

Although the main methodology used for dosing tTG and gliadin is performed by ELISA, in the last two decades, new methodology is available; it is worth mentioning the indirect chemiluminescence immunoassay (CLIA) [50, 51] and the fluorescent enzyme immunoassay (FEIA or EliA) [52].

IgA-EMA antibodies are detected by indirect immunofluorescence, which requires microscopic evaluation. This method is of subjective evaluation, being subject to variations depending on different observer interpretations. However, when well interpreted by the experienced observer, the specificity of the IgA-EMA serological test is close to 100% [48], being considered a reference test for detecting specific CD antibodies [8].

For the anti-endomysium (EMA), although new methods have not been developed, it is now possible to carry out the technical procedure in a fully automated way, and reading by integrated software. Even with this great advance and agility in sample processing time, and in the technical standardization of the employed method, the existence of characteristic fluorescence patterns still requires that the analyzes be interpreted according to the knowledge and subjective observation of the microscopist or the observed, which causing high intra- and interlaboratory variability, which in laboratory practice is considered the major problem for diagnosing autoimmune diseases in general.

Also, the use of molecular methodologies in the laboratory diagnosis currently allows the detection of HLA genotypes associated to CD, in a highly specific way, mainly using the RT-PCR methodology.

1.4 HLA and the importance of risk genotypes in laboratory genotyping

CD is an example of a multifactorial disorder in which the genetic test is of great clinical relevance, since the disease rarely develops in the absence of HLA-specific genes (HLA-DQ2 and HLA-DQ8) [15, 53]. The HLA-DQ2 and HLA-DQ8 genes are required for developing CD but are not sufficient [54]. If an individual carries these genetic markers, it does not necessarily mean that the subject will develop CD, but having a risk for developing the disease. Therefore, the absence of the HLA-DQ2 and HLA-DQ8 genes has a high negative predictive value for the diagnosis of CD, ie, the chance of an individual who does not have these genes develop CD is extremely low, whereas the presence of these genes markers has a relevant positive predictive value [55].

HLA typing can be used to rule out the diagnostic hypothesis of CD in patients with doubtful diagnosis, excluding the disease possibility in individuals who do not have these genes. Chang and Green [53] suggested that HLA typing be performed prior to serological testing to reducing the number of false-positive results and thereby decreasing the number of biopsies required. However, ESPGHAN recommends that the HLA test be performed prior to the serological tests only in the case of asymptomatic patients belonging to risk groups (first-degree relatives of celiac, type 1 diabetic patients, and Down syndrome, for example) [8].

In CD, the heterodimers are called human leukocyte antigen (HLA) and belong to HLA-DQ loci present on chromosome 6. Genotypes that are strongly associated to the onset of the immune response triggered by gluten are HLADQ2.5, HLA-DQ2.2, and HLA-DQ8 [56–58]. It is known that genotypes HLA-DQ2.5 (DQA1 * 05: 01, DQB1 * 02: 01), HLADQ2.2 (DQA1 * 02: 01, DQB1 * 02: 02), and HLA-DQB1 * 03: 02) are necessary but not sufficient for developing CD, since more than 30% of the general population in the world have these genotypes and only 3–5% will develop CD [9, 59–61].

Virtually, all CD patients carry the alleles encoding the HLA-DQ2 and/or DQ8 molecules or at least one DQ2 heterodimer chain, usually the DQB1 * 02 allele-encoded strand. The CD occurrence in the absence of these risk factors in DQ is extremely rare, but the presence of these molecules also fails to predict with precision when and if the CD will develop, since they are present in 25–50% of the general population, although the vast majority of these individuals never develop the disease throughout life [58].

Even with this knowledge, performing HLA-DQ typing for determining future CD risk has been widely discussed, although its practical use is mostly associated to risk groups where genetic testing of individuals could eliminate the need for future antibody tests in more than 60% of the population considered to be at low CD risk (DQ2 or DQ8 negative). On the other hand, the identification of high-risk individuals would allow a safer prospective screening, allowing an early therapeutic intervention [5], and a more precise monitoring, since the risk of developing the disease is more likely in these individuals. In the scientific literature, the first study that calls attention to the determination of CD risk development associated to the presence of HLA-DQ genotypes was performed by Megiorne et al. [62] in the Italian population, the best characterized thesis in the world. Results showed that considering the prevalence of 1: 100 established in this population, which corresponds to 1% that is the prevalence in populations of Caucasian origin in the world population, the risks for developing CD were higher when associated to the presence of genotypes DQ2.5/DQ2.5 and DQ2.5/DQ2.2, in addition to DQ2.5/DQ8, where the risk found was 1: 7, 1:10, and 1:24 (**Figure 1**).

After this publication, rare study has appeared, is the case of Almeida et al. [2] and Murad et al. [64], that given the existence of the estimated prevalence of these populations in other studies in the same region, were able to calculate the CD risk development in the populations of Brazil and Syria, respectively.

Results found by Almeida et al. [2] showed that the risks associated to DQ2.5/DQ2.5, DQ2.5/DQ2.2 and DQ2.5/DQ8 genotypes in the Brazilian population were 1:7, 1:10, and 1:19, respectively, such as described by Megiorni et al. [62].

Murad et al. [64] found in the Syrian population, a slightly different risk for DQ2.5/DQ2.5, DQ2.5/DQ2.2, and DQ2.5/DQ8 genotypes and the associated risks were, respectively, 1:12.5, 1:20, and 1:10, emphasizing that in this population of origin other than Caucasians, the risk associated to these genotypes are somewhat different in terms of prevalence, but they continue to confer the greatest risks for developing CD (**Figures 2** and **3**).

Disease risk

	Patients%	Controls%	Risk
DQ2 and DQ8	2.5	0.2	1:7
DQ2, *B1*02/*02*	23.1	2.4	1:10
DQ8, *B1*02* pos.	3.0	0.7	1:24
β2, *B1*02/*02*	1.4	0.4	1:26
DQ2, *B1*02/X*	55.1	19.2	1:35
DQ8, *B1*02* neg.	7.3	6.5	1:89
β2, *B1*02/X*	4.6	9.7	1:210
α5	2.1	37.9	1:1842
Other	0.9	23.0	1:2518

Figure 1.
Risk calculated by Megiorni et al. [62] in the Italian population. Adapted from Megiorni et al. [62].

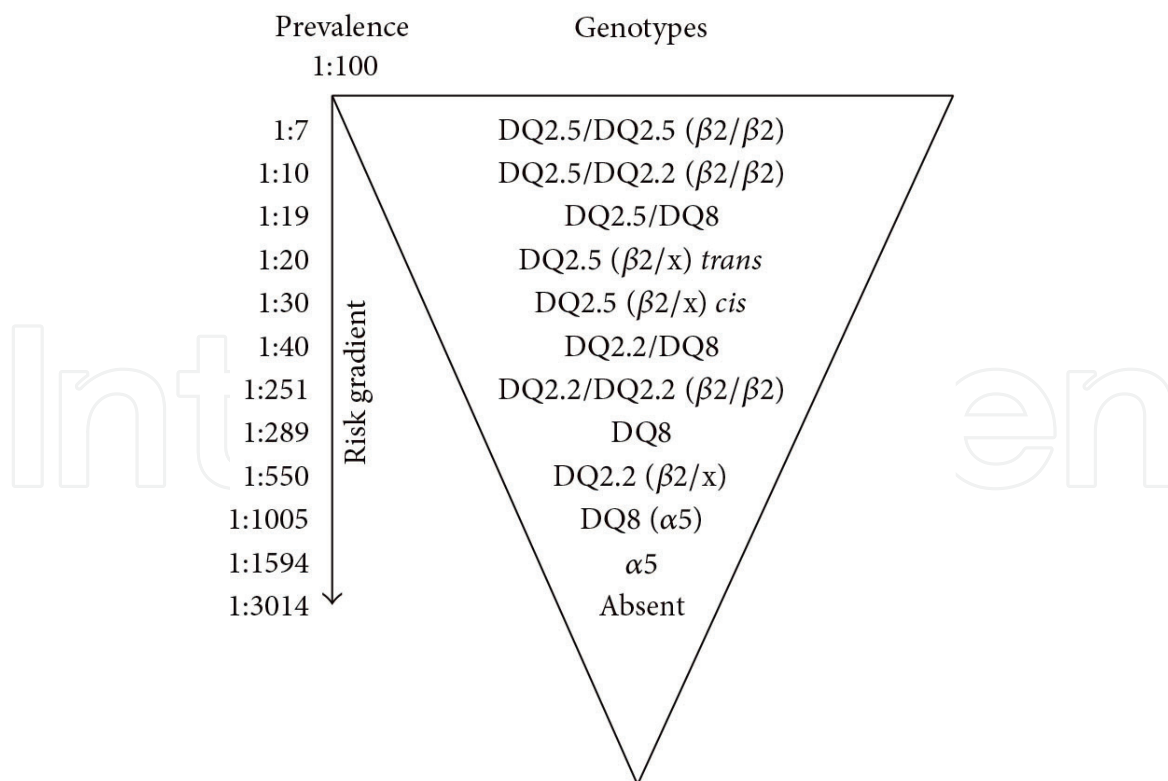

Figure 2.
Calculated Risk (Brazilian population)—Almeida et al. [2].

HLA Genotype	Patient (*n* = 49)		Control (*n* = 58)		Odds ratio	95% CL	Relative risk	*P*-value
	n	Fr (%)	*n*	Fr (%)				
DQ2.5/DQ8	5	10.2	1	1.7	6.48	0.73–57.46	1/10	0.09
DQ2.5/DQ2.5	24	49	6	10.3	8.32	3.02–22.93	1/12.5	< 0.01
DQ2.5/DQ2.2	5	10.2	2	3.4	3.18	0.59–17.19	1/20	0.18
DQ8/DQX	4	8.2	2	3.4	2.49	0.44–14.21	1/25	0.31
DQ2.5/DQ7	8	16.3	4	6.9	2.63	0.74–9.35	1/25	0.13
DQ2.2/DQ8	1	2	1	1.7	1.19	0.07–19.92	1/50	0.90
DQ2.2/DQ2.2	2	4.1	3	5.2	0.78	0.13–4.87	1/100	0.79
DQ2.x	0	0	4	6.9	0.12	0.01–2.33	0	0.16
DQX/DQX	0	0	35	60.3	0.01	0.00–0.11	0	< 0.01

Figure 3.
Calculated Risk—Murad et al. [64].

Because it is not possible to calculate the risk for the various world populations, there are many where the absence of disease prevalence data does not allow this calculation to be carried out, an estimate for populations of Caucasian origin seems to produce very close results suggesting that calculations are accurate in these populations. Considering the relevance of risk demonstrated by the most prevalent and important genotypes for the development of CD, DQ2.5/DQ2.5, DQ2.5/DQ2.2, and DQ2.5/DQ8, it can be recommend that population studies, especially those for clinical diagnosis, which until now considering the risk for development CD associated only to the presence of the DQ2.5/DQ2.5 and DQ2.5/DQ8 genotypes, which consider the inclusion of the DQ2.5/DQ2.2 genotype in their research, because this genotype does indeed pose a high risk for CD development and should not be neglected.

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