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HLA DQ Gene Dosage and Risk and Severity of Celiac Disease

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Abstract

Background & Aims—Celiac disease (CD) is a chronic inflammatory disorder of the small intestine that is strongly associated with certain HLA molecules encoded by DQA and DQB genes. The aim of this study is to examine the role of DQA and DQB alleles in determining the risk for and the age of onset and severity of CD in an American population.

Methods—High-resolution class 2 HLA genotyping was performed in a population-based sample (n=84) of Southeastern Minnesota residents with CD and a comparable control group (n=102) to determine the contribution of DQA and DQB alleles to disease risk. Logistic regression modeling was used to examine the relative and absolute risk of CD.

Results—Ninety-seven percent of CD patients carried both of the HLA alleles, DQA1*05 and DQB1* 02. Those who carried a second allele of DQB1*02 were 5 times more likely to have CD as those with just one (95% CI:1.4-18.1). The carriage of 2 copies of DQB1*02 did not predict either an earlier age of onset or severity of disease.

Conclusions—Both HLA alleles DQA1*05 and DQB1* 02 are associated with a greatly increased risk of CD, though the latter has the greater effect. Carrying 2 copies of DQB1*02 was associated with an even greater risk for disease but did not predict an earlier age of onset and diagnosis or disease severity. Assessing the copy number of the DQB1*02 allele may allow for the stratification of disease risk.

Keywords

sprue; genetics; HLA; population study

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INTRODUCTION

Celiac disease (CD) is a chronic inflammatory disorder affecting the proximal small intestine that, in susceptible people, results from the ingestion of gluten and related proteins found in cereal grains such as wheat, barley and rye.[1,2, 3] CD is characterized by small intestinal mucosal inflammation resulting from a genetically-based intolerance to ingested gluten.[4-6] Thus, CD is strongly associated with the extended HLA-haplotypes, B8, DR3, DQ2 but most specifically the alleles DQA1*05 and DQB1* 02 that, together, encode the serotypes DQ2.[7, 8] Siblings who share the DR3-DQ2 haplotypes have a substantially greater likelihood of concordance with CD than the general estimated risk for siblings.[9] A small percent of CD patients are DQ2 negative. These are usually DR4 positive and carry the alleles, DQA1*03 and DQB1*0302, that encode the class 2 antigen, DQ8.[10]

While it has been estimated that these class 2 HLA genotypes (DQA1*05:DQB1*02 and DQA1*03:DQB1*302) contribute only 40% of the genetic risk in families, it appears that these HLA alleles are virtually required for CD to occur in individuals originating in Caucasian populations. [11, 12] Recently, it has become apparent that the incidence and prevalence of CD in the United States are no different from that found in European countries. [13, 14] However, it is not clear what degree of risk is conferred by HLA class 2 genes in the ethnically more heterogeneous population of the United States, as compared to the historical ethnic and presumably genetic homogeneity of most European countries in which this issue has been studied. [11, 12] In particular, HLA genotyping has been used as a “rule out” test for CD in certain at-risk populations, such as patients with Down’s syndrome and family members of those affected with CD, but the recent introduction of commercially available HLA genotyping specifically directed at assessing CD risk allows us to address whether associations based on ethnically more homogenous European populations apply to the ethnically mixed patients of this country. [15] One recent study suggested that DQ8 may be more common in CD patients from the East Coast United States than in a French cohort. [16]

While it appears that carriage of these HLA alleles is permissive for CD, studies based on DR typing suggested that a double dose of DR3 (often associated with DQ2) may be associated with a higher risk. [17 18] The data using direct DQ genotyping are limited to studies in European and North African countries.[19-22] There is also some evidence of a dosage effect of these genes: Studies in predominantly pediatric Norwegian and Sardinian populations suggested that those who are homozygous for DQB1*02 in the presence of DQA1*05 have a higher risk of developing CD and do so with greater severity.[23,24,21] A second study from Spain suggested that a double dose of DQB1* 02 was associated with earlier age of onset and shorter delay to diagnosis. [25] However, this is not a universal finding. [22] There is also substantial heterogeneity in the HLA risk associations between northern and southern European populations. [26] It is not known what role gene dosage of DQB1*02 alleles plays in the ethnically diverse United States population in which CD seems to present predominantly in adulthood.[14]

The aims of this study were to quantify the effect of DQA1*05 and DQB1* 02 alleles on the risk for, the severity, and age of onset of CD in an ethnically mixed but geographically circumscribed, predominantly adult North American population.

METHODS

Study Setting

This was a genetic epidemiology study performed in a geographically restricted area for which the incidence and prevalence of CD has already been determined.[14] Olmsted County is a medically well-defined population in the upper Midwest. Until recently the population was almost entirely composed of Caucasians of European extraction. The ethnic mix of the

population of Southeastern Minnesota is largely the same as that in Olmsted County. The Mayo Clinic is a large tertiary referral center that also provides secondary referral for patients with gastrointestinal problems and also has provided care for most community-based cases of CD in the geographic region of Southeastern Minnesota.

Study Subjects

Subjects with CD were recruited from those identified by the Rochester Epidemiology Project with a potential diagnosis of CD made between January 1, 1950 and December 31, 2001. [27] The cases include at least 90% of known celiacs resident in Olmsted County, Minnesota on December 31, 2001. Additionally, the membership rolls of the local CD support group and the records of the Mayo Clinic Department of Pathology and Laboratory Medicine were scrutinized. Additional patients were recruited from the attendees at the CD clinic and the pediatric gastroenterology clinics of the Mayo Clinic. All subjects were residents in Olmsted County (n=47) or the contiguous counties of Southeastern, Minnesota (n=37).

The complete inpatient and outpatient medical records of each candidate case were reviewed, as were the biopsy slides of the small intestinal samples taken at the time of the original diagnosis. The following information was obtained by abstraction of the contemporary records or by application of a validated gastrointestinal questionnaire. : 1) clinical features, at or preceding diagnosis such as diarrhea, weight loss, body mass index, steatorrhea, iron deficiency anemia, neuromuscular symptoms, bone disease, and dermatitis herpetiformis; 2) clinical and/or histological improvement after gluten-free diet; and 3) anti-endomysial, anti-gliadin and anti-reticulin antibody status, if performed. Intestinal biopsies were reviewed for all subjects prior to inclusion, thereby reducing the dependency on external reports of biopsy results and the attendant risk of an incorrect diagnosis. Histology was categorized into those with partial villous atrophy or total villous atrophy. The grading was based on the greatest degree of morphological change apparent in well-oriented samples.

To be defined as CD, each case was required to have: 1) proximal small intestinal biopsies compatible with CD and 2) clinical and/or histological improvement with a gluten-free diet fulfilling the accepted criteria for CD.[28] If more than one member of a family was affected with CD, only the first clinically apparent member of the family was used.

Age at onset was the age at which the patient first complained of symptoms subsequently explained by CD. Age at diagnosis was established as the date of the interpretation of the initial pretreatment intestinal biopsy. A clinically ‘severe’ onset was defined as a presentation that included at least a 10-pound weight loss accompanied by diarrhea and/or steatorrhea.

The controls consisted of 102 healthy adult blood donors recruited from Olmsted County. All denied and had no history of GI or other chronic disease. Subjects and controls were unrelated. The ethnic background is known based on self-assessment report of the country or region of origin of grandparents or more distant forebears if not Native American in origin. Their ethnic backgrounds were similar to those of our patient population, including varying mixtures of German, French, English, Norwegian, Irish, Polish, Bohemian, Dutch, Swiss, Danish, Scottish and Swedish). Fifty-nine subjects were women (58%), and their mean age was 40±1 years (range, 26-68 years). Each had indicated the absence of major illness on a standard blood-donation questionnaire.

The study was approved by the institutional review boards of both the Mayo Clinic and the Olmsted Medical Center.

HLA Class 2 Testing

Complete HLA typing for DR and DQ alleles was performed using DNA extracted from peripheral blood. Typing methodology was polymerase chain reaction with sequence-specific primers (PCR-SSP), low resolution (One Lambda, Canoga Park, CA) and high resolution (Genovision, West Chester, PA).[29]

Statistical Analysis

Logistic regression was used to assess the association between CD status (y/n) and HLA types after adjusting for gender. One model included predictors indicating presence of DQA1*05 (y/n) and DQB1*02 (y/n). A second model used predictors indicating both DQA1*05 (y/n) and DQB1*02 alleles present (y/n) and one present (y/n). A third model included variables indicating the number of DQB1*02 alleles (one allele [y/n] and two alleles [y/n]). Odds ratios and predicted probabilities for having CD (and 95% CI's) were computed from the logistic regression model coefficients. The estimated odds ratios from these models comparing HLA subtypes can be used as estimates of relative risk, considering that the risk of CD is small. Pearson's chi-square test (or Fisher's exact test as appropriate) was used to measure the association between DQB1*02 gene dosage and clinical CD severity (severe vs. not severe) and endomysial antibody titer. To test whether DQA1*05 or DQB1*02 was a better predictor of CD, we compared their sensitivities and specificities using McNemar's test (or an exact binomial test as appropriate). Exact binomial 95% CI's were computed for the sensitivities. Finally, linear regression was used to assess the association between diagnosis age and age of onset of clinical symptoms/ signs of CD, and the number of copies of DQB1*02. All hypothesis tests were done at the α=0.05 level.

We estimated the number of non-celiac Caucasian men and women residing in Olmsted County based on the 2000 census and our previous ascertainment of those with CD residing in the community on December 1st 2001. [14] We had previously identified known frequencies of HLA type combinations (DQA*05 [y/n] and DQB*02 [y/n]) in this community among healthy normal blood donors. [30,31] We approximated the number of Olmsted county residents with each HLA type combination using the published rates among the general population and the observed rates in our study for the CD cases. From these totals, we estimated the rate of diagnosed CD per 100,000 in the county. Exact 95% binomial confidence intervals (CI) were calculated for the prevalence rates. We used a similar method to estimate the prevalence of CD (per 100,000) based on the number of DQB1*02 alleles a person carries. Again, we used the total number of Caucasian people residing in Olmsted County in 2000, distinguished by gender and celiac diagnosis. We also used the observed DQB1*02 frequencies from the blood donor controls in our study and pooled them with controls from another study, which investigated the immunization reaction of school children within Olmsted County. [32] Since blood donation rates are high in Olmsted County, we presumed that the HLA demographics of the blood donors reflected those in the local general population. Exact 95% binomial CI's were again computed for the resulting CD rates.

RESULTS

Demographics of the study population

Demographics of CD cases and controls were generally similar except that the celiac patients had a preponderance of females compared to controls (73.8 vs. 58.8%) and were largely adults at diagnosis (median age, 49 years, range 0-84). This CD cohort included 3 subjects with Type 1 diabetes mellitus, 6 with dermatitis herpetiformis and 5 subjects with malignancies, none of which affected the GI tract. A single individual had Down's syndrome. No patients had refractory sprue or developed lymphoma during their period of followup. Essentially all

subjects cases and controls alike, attested to an ethnically mixed European background with ancestors originating in two or more European countries.

Distribution of HLA Class 2 Genotypes

The distribution of HLA DQA:DQB genotypes in CD cases and controls is shown in Table 1. Seventy-nine of 84 patients with CD had at least one copy each of DQA1*05 and DQB1*02. Ten of these 79 had DQA1*05:DQB1*02 and DQA1*0301:DQB1*0302 as compared to just one of 102 controls with this combination. Just 3 of 84 had DQ1*0302 without DQA1*05:DQB1*02 , though 2 of these had DQA1*0201:DQB1*02. One subject had 2 copies each of DQA1*0201 with 2 copies of DQB1*02, and a single subject had neither DQA1*05: DQB1*02 nor DQA1*0301:DQB1*0302 despite carefully validated CD (Table 1).

In all, 34 subjects with CD had 2 copies of DQB1*02 as compared to only 4 controls. Most celiacs who have 2 copies of DQB1*02 do not have 2 copies of DQA1*05 as the accompanying allele. High resolution typing of the DQB alleles indicated that the second DQB1 allele was as often DQB1*0202 as DQB1*0201. (Table 2). However for the purpose of analysis, we have considered the dose of DQB1* 02 without distinguishing which allele of DQB1*02 was present.

Risk associated with DQB1*02 and DQA1*05

We examined the association between CD and HLA types using three different models, each adjusted for gender: In Model 1, the presence of DQA1*05 (vs. not) and DQB1*02 (vs. not) were significantly and independently associated with an increased odds of having CD ($p<0.01$, Table 3). In model 2, the presence of both HLA alleles (vs. none) was associated with a higher rate of CD ($p< 0.0001$), but having only one (of the two) was not significant ($p= 0.43$). Further, having both DQA1*05 and DQB1*02 versus having only one or the other was associated with increased risk of CD ($p<0.0003$) (Table 3) Model 3, after adjusting for DQA05, the number of copies of DQB02 is associated with CD risk; two copies of DQB02 is associated with a higher odds of having CD, than one copy ($p=0.021$). (Table 4). Models including interactions between alleles were considered, but the small sample sizes for some allele combinations led to unstable estimates and thus are not presented.

Sensitivity of DQ genes as a diagnostic test for celiac disease

In this cohort of 84 CD patients, the diagnostic sensitivities of DQA1*05 and DQB1*02 were 94% (95% CI, 87%, 98%) and 98% (95% CI 92%, >99%) respectively (p= NS, McNemar's test). The sensitivity for the possession of both DQA1*05 and DQB1*02 was 94 % (95% CI, 87%, 98%) for this population.

Effect of gene dosage on age of onset, diagnosis age and severity of celiac disease

The age at diagnosis and age of onset of symptoms attributable to CD were not associated with the number of copies of DQB1*02 ($p= 0.589$). Twenty-two of 84_patients with CD were classified as having severe disease. Severity was not found to be associated with DQA1*05 (y/n), DQB1*02 (y/n), or number of copies of DQB1*02, ($p=0.605$, 0.462 and 0.625, respectively).

Effect of DQB1*02 gene dosage on serological levels or histopathological severity

Forty of 84 celiac patients had endomysial antibody testing performed in our laboratory before being placed on a gluten free diet. All of them were diagnosed in the last 4 years. There was no association between the titer of EMA positivity and DQB1*02 gene dosage affect ($P= 0.37$). There was also no association between the gene dosage and the degree of villous change on biopsy (partial versus total) ($P=1.00$).

HLA predicted risk of celiac disease

Using our knowledge of the known expression of HLA types in the local population and the known prevalence of CD[32], we estimated the expected rates of CD in people with HLA types for each gender.[32] The carriage of both DQA1*05 and DQB1*02 was associated with a higher rate of CD than either alone, which was greater than some not carrying either (Table 5). The number of copies of DQB1*02 also predicted a dose-dependent increase in CD risk, with a substantial female predominance when only one copy is present (Table 6).

DISCUSSION

This study both confirms and extends evidence for a strong genetic predisposition for CD associated with the class 2 HLA alleles, DQA1*05:DQB1*02 encoding the serological equivalent DQ2 in the ethnically diverse United States population. The potential clinical application of HLA typing in someone suspected to have CD, or be predisposed to it, is the negative predictive value of the absence of the heterodimers encoding these at-risk HLA types. In our study and in most others reported, the negative predictive value is at least 98%.[22, 33] However as good that statistic is, it is only one part of the equation. While the sensitivity for CD is almost 100%, there is still only a low absolute probability that someone with DQA1*05:DQB1*02, or even less so someone with DQA1*03:DQB1*302, could develop the disease.

HLA typing has not been used as a routine test in clinical practice primarily due to the low specificity for CD and the high cost of the test. As this type of test becomes more readily available, it is necessary to critically assess how useful it will be in discriminating between those at risk for CD and those in whom the condition is very unlikely indeed. If one were to HLA genotype the general population, it would be possible to identify about 70% of the population who, by the absence of DQA1*05:DQB1*02 gene combination, would be extremely unlikely to get CD. However this strategy is hampered by two factors: First is the possibility that an alternate CD-associated HLA genotype DQA1*0301:DQB1*0302 (encoding the serological equivalent DQ8) may on occasion or in certain populations enable CD in the absence of the HLA alleles, DQA1*05:DQB1*02 (encoding DQ2). [16] Including DQA1*03:DQB1*0302 (encoding the serological equivalent DQ8) as an alternative at-risk HLA type decreases the discriminative power of this strategy, leaving only 61% of the general population who can be reassured. Secondly, the patient may, by having another DQ2-associated disease like type 1 diabetes or having a relative with CD, have a higher carriage of DQ8 or DQ2 encoding alleles further reducing the specificity in that setting. [34]

The negative impact of telling someone that they carry a genetic risk for CD may affect them well beyond the level justified by their relatively low absolute risk of getting the disease. Doctors must go to great lengths to reassure patients that, while they carry the genes, they are still very unlikely to have or even to develop the disease. It is similarly not clear if patients carrying the at-risk HLA types need to be followed for the development of CD if initial serological testing is negative. However, if the patient is an at-risk family member and a child at the time of first serological screening, CD may occur later in those who carry the HLA type associated with CD.[35] However, the lifetime risk for celiac disease development is extremely low in those fortunate few family members without the susceptibility alleles. This may be less of an issue for those patients who have been investigated for GI symptoms. Patients who adopted a gluten free diet before any tests for CD were done, and who now want to know if they have the condition, pose a particularly difficult problem diagnostically. Those who lack the HLA risk types can be reassured that they are very unlikely to have or to get CD; however, those who do carry DQA1*05:DQB1*02 or possibly DQA1*0301:DQB1*0302 would need a gluten challenge of sufficient duration and intensity to positively identify CD. Clinical experience suggests that many are unwilling to do so.

One of the strengths of this study is the use of geographically restricted case and control groups, thereby providing sound genetic epidemiology data upon which to calculate the risk of having a diagnosis of CD attributable to specific HLA DQ types. Most (56%) subjects were residents of Olmsted County and the rest were from the contiguous counties of Southeastern Minnesota who do not differ in terms of age distribution, clinical presentation or ethnic origin from Caucasian Olmsted county residents. Also, by only using a single index case from members of the few multiplex families we avoid overestimating HLA risk.

One of the potential weaknesses of this study is that it is based on clinically diagnosed CD only, and these results might not apply to the possibly many undiagnosed individuals with the condition. Our study does include a substantial number of recently detected individuals, many of whom did not have the classical malabsorptive presentation. Our estimates for risk of clinically detected disease similarly ignore the asymptomatic subject. However, it has not been convincingly demonstrated that asymptomatic celiacs are genetically different from those clinically detected. Moreover, Hoffenberg et al. have demonstrated that those members of a birth cohort who carry 2 copies DR3, as a surrogate for DQB1.02, have a high relative risk of developing persistent tissue transglutaminase antibodies as a surrogate marker for CD. This risk is especially high if the child is exposed to gluten before 3 months or after 7 months of age [36]. These children were, by and large, asymptomatic. [37] It seems logical that they would grow up to populate the entire spectrum of CD, with many or most remaining undetected well into adulthood as we have observed in our population [14]. Apparent homozygosity for DQ2, or at least the carriage of 2 copies of the DQB02 alleles, may result in a greater risk of CD by generating a wider range of and increased degree of T lymphocyte responsiveness compared to that seen in heterozygous individuals.[38,39] Another potential bias could be the use of blood donors as controls who are healthy by definition. However the prevalence of DQB and DQA alleles seems similar between these controls and another study of schoolchildren in our community. [32].

Although the primary use of HLA testing is as a way of ruling out CD, it may be possible to quantify the genetic risk of CD based on complete class 2 HLA typing. We can do better than just determine the at-risk versus not at-risk status based on presence or absence of the disease susceptibility alleles. There may be some utility in estimating the number of copies of DQB alleles, as this would go beyond the mere identification of yes/no risk and allow for a more precise genetic risk assessment. Those with 2 copies of DQB1*02 would be much more likely to get CD than those with a single copy, who in turn are much more likely to get it than someone without a copy. For example, in a specific population, the possession of a haplotype such as DQA1*03:DQB1*0302 (DQ8 serotype equivalent) may confer a low risk of CD, whereas the carriage of 2 copies of DQA1*05:DQB1*02 may confer a much greater risk of disease. This risk association may be influenced by the population in question; for example, among those with eastern European Jewish ancestry, a population not frequent in Southern Minnesota., the carriage of DQ8 may be a common type [16]

Being able to provide a finite risk assessment based on genetic testing helps put in perspective the low absolute risk of CD, thereby dispelling the natural tendency to overestimate the risk of disease that is inherent, but unintended, when interpreting a simple present/absent susceptibility risk currently provided. In order to provide a gene dosage estimation, it will be necessary to undertake sufficiently detailed class 2 typing to accurately calculate the copy number of the DQB1*02 alleles in addition to the carriage of DQA alleles. The current trend for undertaking CD testing that uses customized primer sets that can only tell if a specific allele is present or not does not allow for calculation of the copy number of the at-risk alleles. Providing the precise copy number of alleles may allow the clinician to stratify genetic risk.

Would this stratification be important? It may be, especially when, in a population such as ours, up 40% has one or both alleles encoding either DQ2 or DQ8. More work is necessary to determine how to combine HLA data with the clinical scenario and serological data to estimate the likelihood of disease in specific patient groups. It is important that clinicians be aware of the limitations of HLA typing in this regard. The absence of the gene pairs that encode the HLA antigen thought to be virtually required for celiac disease has likely a high negative predictive value in most populations. However the possession of these genes is common in the general population and even more frequent in family members or those with type 1 diabetes mellitus such that their positive predictive value is very low indeed. Unfortunately, commercial interest in celiac disease detection has brought this type of genetic testing directly to patients who may be even more challenged by these issues than physicians.

Our study did not find an association between disease onset or age at diagnosis and gene dosage as had been reported in European studies, [21, 25] though the data were not uniform on this point. [22, 23] However, ours is a predominantly an adult group, whereas most of the European patients were diagnosed in childhood. As our study was geographically based and we included cases of all ages, the differences in age of onset may be the results of environmental factors such as the quantity of gluten in the infant diet or some other environmental exposure or trigger. It may also be possible that, in the more ethnically mixed Caucasian population of this country, some propensity to early onset of disease is lacking or diluted by mixing of ethnic backgrounds. The majority of the cases were female which reflects the greater rate of CD diagnosis in women. There may be an interaction between female gender and HLA type, however our study had inadequate power to address this issue. Other explanations for the commonly seen predominance of females in diagnosed celiac disease include greater attendance for routine medical care by women, or reticence of men to complain about subtle GI symptoms. We did not see any difference in the severity between genders (data not shown).

The role of *DQB1*02* copy number in predicting the age of onset of symptomatic disease may have implications when interpreting data from family studies that primarily use children as probands. It is possible that this early onset disease is more commonly associated with 2 copies of *DQB1*02* alleles and may differ from studies where the proband is an adult. However, the carriage of 2 copies of DQB1*02 in our subjects was similar to that reported in the European studies but lower than that reported in United States families with 2 or more affected siblings. [40] It is possible that symptoms present at an earlier age were not reported or recorded. This limitation may have affected the or the determination age of onset of symptoms resulting from celiac disease. However the age at which symptoms were such as to be reported and recorded in the medical records may itself be a measure of severity of the disease. One recent study suggested that homozygosity for DQ2 may be associated with refractory celiac disease with clonal t cells or enteropathy-associated lymphoma in a large Dutch cohort. Whether this applies to other ethnic groups or the US population is unknown. [41]

In summary, in this community-based cohort of patients with CD, the same disease-permitting HLA genotypes are identified as earlier European studies. There is a definite gene dosage affect of carriage of DQB 02* alleles, and genotype-specific quantifiable risks are presented for the population. The lack of a gene dosage effect on age of onset or on severity of clinical presentation suggests that HLA confers risk of disease but that other factors determine severity. The rare occurrence of CD in the absence of these DQ alleles suggests that the lack of possession of these alleles effectively renders CD very unlikely though not impossible as illustrated by the one patient in our cohort who lacked those gene pairs. [26]

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Abbreviations

CD
: celiac disease

DH
: dermatitis herpetiformis

HLA
: human leucocyte antigen

EMA
: endomysial antibody

Table 1

HLA Distributions in the Celiac Disease (CD) Cases and Controls

Serotype	Alleles Categories	CD	Control
DQ2	DQA1*05- DQB1*02	79	21
DQ8/DQ2-	DQA1*0301-DQB1*0302	3	22
Alt DQ2/DQx	DQA1*0201-DQB1*02	1	9
DQ2-/DQ8-	DQA1*xxxx-DQB1*0301	1	50
TOTALS		84	102

Table 2

Distributions of DQB1*02 Alleles in Celiac Disease (CD) Patients and Controls

Genotype	CD	Controls
DQB1*0201/0201	17	1
DQB1*0201/0202	17	2
DQB1*0202/0202	0	1
DQB1*0201/----	43	16
DQB1*0302/---	2	1
DQB1*0202/----	1	9
DQB1*0202/DQA05	2	2
Other	1	52
TOTALS	84	102

Table 3

Odds Ratio (OR) of Celiac Disease Given Presence of DQA1*05 & DQA1*02

The table displays odds ratios (95% CI's; adjusted for gender) and p-values for the association between celiac disease and HLA types from three different models: 1) *DQA1*05* (y/n) and *DQA1*02* (y/n), 2) combined presence of *DQA1*05* and *DQB1*02* (none vs. either one vs. both), and 3) DQA1*05 and number of copies of *DQB1*02* (0, 1, or 2).

DQA1*05/DQB1*02 (presence)	OR (95% CI)
One (or the other) vs. None	3.1 (0.2, 53.3)
Both vs. None	157.5 (19.6, 1263.7)
Both vs. One (or the other)	50.2 (6.2, 409.2)

Table 4

Odds Ratio (OR) for Celiac Disease Given Number of DQβ02 Alleles

#DQβ02 Copies	OR (95% CI)
1 vs. 0	93.9 (11.8, 745.3)
2 vs. 0	465.7 (45.1, 4813.7)
2 vs. 1	5.0 (1.4, 18.1)

Table 5

Estimated Incidence of Diagnosed Celiac Disease per 100,000 Given Presence of DQα05 & DQβ02

DQα05/DQβ02 (presence)	Males rate (95% CI)	Females rate (95% CI)	Total rate (95% CI)
-/-	0.0 (0.0, 10.4)	2.7 (0.1, 15.0)	1.4 (0.0, 7.7)
+/- or -/+	0.0 (0.0, 30.3)	7.8 (0.2, 43.6)	4.0 (0.1, 22.3)
+/+	138.7 (66.5, 254.9)	473.6 (331.9, 655.1)	310.6 (227.4, 414.0)

Table 6

Estimated Incidence of Diagnosed Celiac Disease per 100,000 Given Number of DQβ02 Alleles

#DQβ02 Copies	Males rate (95% CI)	Females rate (95% CI)	Total rate (95% CI)
0	0.0 (0.0, 11.3)	2.5 (0.1, 14.1)	1.4 (0.0, 7.7)
1	29.8 (9.7, 69.4)	173.0 (110.9, 257.3)	94.5 (63.3, 135.7)
2	94.6 (30.7, 220.6)	310.0 (165.1, 529.5)	189.9 (112.6, 300.0)