ORIGINAL ARTICLE

Is celiac disease better identified through HLA-DQ8 than through HLA-DQ2 in Mexican subjects?∗

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Received 24 May 2017; accepted 25 January 2018
Available online 23 June 2018

KEYWORDS
Celiac disease;
HLA-DQ2;
HLA-DQ8

Abstract
Introduction and aims: A strong genetic association between celiac disease (CD) and the human leukocyte antigen (HLA) has been widely demonstrated. In Europe, the HLA-DQ2 allele is predominant. However, studies in Latin America indicate that HLA-DQ8 could be more frequent. In Mexico, the frequency of those alleles has not been reported in subjects with CD. Therefore, the aim of the present study was to evaluate the distribution of HLA-DQ2 and HLA-DQ8 in Mexican individuals with CD.

Material and methods: An exploratory study was conducted on a cohort of 49 subjects with chronic diarrhea. Autoantibodies for CD, duodenal atrophy, and HLA haplotypes were determined.

Results: Thirty individuals had CD (23 women, mean age 54.2 ± 15.5 years), 24 (80%) of whom expressed HLA-DQ8, 15 (50%) expressed HLA-DQ2, and 11 (37%) presented with both alleles. However, neither the HLA-DQ2 nor the HLA-DQ8 allele was found in 5 (10%) individuals. In subjects with chronic diarrhea that did not have CD, 12 (63%) presented with HLA-DQ2, and 7 (37%) with HLA-DQ8. Individuals with CD expressed the combinations of the HLA-DQ8/DQ2 alleles (37 vs. 5%) and the HLA-DR4/DQ8 alleles (60 vs. 26%) more frequently than the subjects without CD.

Please cite this article as: Cerda-Contreras E, Ramírez-Cervantes KL, Granados J, Mena L, Núñez-Álvarez C, Uscanga L. ¿Es posible una mejor identificación de la enfermedad celiaca en sujetos mexicanos por medio de HLA-DQ8 que de HLA-DQ2? Revista de Gastroenterología de México. 2018;83:410–413.

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Introduction and aims

Celiac disease (CD) is one of the most common food-related intestinal disorders. This condition is characterized by an abnormal immune response to the ingestion of gluten and related proteins in genetically susceptible individuals that have a polygenic disorder, with the participation of both human leukocyte antigen (HLA) genes and non-HLA genes.\(^1\) HLA-DQ2 and HLA-DQ8 are the most frequent, and the DQA1*05/DQB1*02 heterodimer is observed in 90-95% of the cases.\(^2\)

In most European subjects with CD, HLA-DQ2 is more prevalent,\(^3,4\) but that same assumption remains controversial for Latin American populations. For instance, in a study conducted on pediatric and adult Amerindian subjects with CD, there was a higher frequency of HLA-DQ8.\(^5,6\) In addition, the authors of a population-based study carried out in different regions of Mexico found a distribution of 16% for HLA-DQ2 and 24% for HLA-DQ8,\(^7\) suggesting that the Mexican population could share some of the characteristics found in other Latin American countries.

The diagnostic criteria for CD include the combination of positive serologic auto-antibodies, such as anti-endomysium (EmA IgA), anti-transglutaminase (anti-tTG IgA/IgG), and anti-deamidated gliadin peptide (AGA-DGP IgA/IgG), together with the histologic demonstration of villous atrophy of the second part of the duodenum.\(^8,9\) However, in certain clinical situations, it is recommended to investigate the presence of HLA-DQ2/DQ8 to rule out the disease.\(^9\)

In Mexico, the frequency of CD is similar to that described worldwide,\(^11\) but the distribution of HLA-DQ8/DQ2 in subjects with CD has not been reported. Therefore, the aim of the present study was to determine the distribution of the HLA-DQ2 and HLA-DQ8 alleles in Mexican subjects with CD.

Materials and methods

An exploratory study was conducted on 49 consecutive Mexican patients (38 women) with a mean age of 53 ± 14.5 years with chronic diarrhea (watery or loose stools for more than four weeks) and symptoms consistent with CD that were seen at the outpatient unit of a tertiary care referral center in Mexico City.

The study subjects underwent blood chemistry screening tests, serum levels of anti-tTG IgA/IgG and EmA IgA (INova...
Diagnostics, Inc., San Diego, CA, USA), stool analysis for parasites, and stool cultures. The individuals were also studied under the institutional protocol for chronic diarrhea, in which malabsorption is a serum beta-carotene level lower than 60 μg/dl in females, and 50 μg/dl in males, values consistently related to significant steatorrhea (stool fat 10 g/d). In individuals with steatorrhea, a D-xylose absorption test in urine was performed (normal > 5 g/vol).  

All the individuals had upper gastrointestinal endoscopies and duodenal aspirates, and at least four fragments of the second part of the duodenum were taken for analysis. Histologic findings were classified according to the Marsh-Oberhuber criteria, and CD was diagnosed through compatible intestinal biopsy histology (Marsh II-IV), and positive antibody tests (tTg-IgA/IgG/EmA IgA). Small intestinal bacterial overgrowth (SIBO) was defined when bacterial populations in the small intestine exceeded 10^9-10^10 organisms/ml.

Class II antigens (HLA-DRB1, HLA-DQB1) were typed by the PCR-SSP procedure (Pel-Freez HLAA/B/DR/DQ SSP Unity, Brown Deer, Wisconsin, USA), and the HLA-DQ8 allele was determined as a generic category (broad antigen).

A Mexican mestizo was defined as a person born in Mexico, whose last two ascending generations were also born in Mexico. Demographic data were collected, and the patients were classified into two groups: group A, patients with celiac disease and group B, patients with chronic diarrhea from other causes. The physicians that classified the patients were blinded to the results of the HLA analysis.

All participants signed written statements of informed consent and the study was approved by the Institutional Review Board for Biomedical Studies on Humans Beings (ref. 1719).

Statistical analysis

The distribution of the HLA-DQ2 and HLA-DQ8 alleles was reported. The frequencies were compared between patients with CD and those with chronic diarrhea from other causes, but no statistical comparisons were performed between the 2 groups.

Results

The demographic characteristics are shown in Table 1. The diagnosis of CD was established in 30 subjects (23 women) with a mean age of 54.2 ± 15.5 years. In the rest of the individuals, SIBO was the most common diagnosis (15 women), mean age 50.7 ± 12.5 years.

The expression of HLA-DQ2 was similar between the 2 study groups (50% vs. 63%), but HLA-DQ8 was more frequent in patients with CD (80% vs. 37%). The frequency of HLA-DQ8 persisted after including the prevalence of HLA-DR4/DQ8 haplotype, and the combination of both HLA-DQ2 and HLA-DQ8 was more frequent in subjects with CD (37% vs. 5%).

Table 1  Characteristics of the study subjects.

| Age, years (mean ± SD) | 53 ± 14.5 |
| Female sex | 38 (78%) |
| BMI (mean ± SD) | 21 ± 4.6 |

Diagnosis

| CD | 30 (61%) |
| SIBO | 10 (20%) |
| Autoimmune enteropathy | 2 (4%) |
| Lymphocytic colitis | 2 (4%) |
| Pancreatic insufficiency | 2 (4%) |
| Intestinal tuberculosis | 1 (2%) |
| IBS-D | 1 (2%) |
| Without diagnosis | 5 (10%) |

CD: Celiac disease; IBS-D: Irritable bowel syndrome-diarrhea; SIBO: Small intestinal bacterial overgrowth.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.
Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Financial disclosure

No financial support was received in relation to this study/article.

Conflict of interest

The authors declare that there is no conflict of interest.

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