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World J Gastroenterol 2006 December 28; 12(48): 7762-7767
World Journal of Gastroenterology ISSN 1007-9327

GASTRIC CANCER

Role of the HLA-DQ locus in the development of chronic gastritis and gastric carcinoma in Mexican patients

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Supported in part by Consejo Nacional de Ciencia y Tecnología grant, México, No. 153237
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Received: 2006-09-22 Accepted: 2006-11-20

Abstract

AIM: To determine the HLA-DQ locus in Mexican patients with Chronic gastritis and gastric adenocarcinoma.

METHODS: Oligotyping for HLA-DQ locus was performed in 45 Mexican patients with chronic gastritis and 13 Mexican patients with diffuse-type gastric adenocarcinoma, and was then compared with 99 clinically healthy unrelated individuals. *H pylori* infection and CagA status were assessed in patients by enzyme-linked immunosorbent assay (ELISA) method.

RESULTS: We found a significant increased frequency of HLA-DQB1*0401 allele in *H pylori*-positive patients with chronic gastritis when compared with healthy subjects [19 *vs* 0%, $P = 1 \times 10^{-7}$, odds ratio (OR) = 4.96; 95% confidence interval (95% CI), 3.87-6.35]. We also found a significant increased frequency of HLA-DQB1*0501 in patients with diffuse-type gastric carcinoma in comparison with healthy individuals ($P = 1 \times 10^{-6}$, OR = 13.07; 95% CI, 2.82-85.14).

CONCLUSION: HLA-DQ locus may play a different role in the development of *H pylori*-related chronic gastritis and diffuse-type gastric adenocarcinoma in the Mexican Mestizo population.

Key words: HLA-DQ; HLA-DQ5; HLA-DQB1*0501; *H pylori*; Chronic gastritis; Gastric cancer; Diffuse-type adenocarcinoma

Herrera-Goepfert R, Yamamoto-Furusho JK, Oñate-Ocaña LF, Camorlinga-Ponce M, Muñoz L, Ruiz-Morales JA, Vargas-Alarcón G, Granados J. Role of the HLA-DQ locus in the development of chronic gastritis and gastric carcinoma in Mexican patients. *World J Gastroenterol* 2006; 12(48): 7762-7767

http://www.wjgnet.com/1007-9327/12/7762.asp

INTRODUCTION

H pylori infection is, in addition to being the main etiologic agent for chronic gastritis, a major cause of peptic ulcer and gastric cancer[1]. In developing countries, prevalence of *H pylori* infection is > 80% among middle-aged adults, whereas in developed countries prevalence ranges from 20%-50%. Approximately 10%-15% of infected individuals will develop peptic disease and 3% a gastric neoplasm[2]. Therefore, *H pylori* infection is a necessary but not a sufficient cause of severe forms of gastric disease. In 1994 the International Agency for Research in Cancer (IARC), a branch of the World Health Organization (WHO), declared *H pylori* to be a Group 1 carcinogen, a definitive cause of cancer in humans[3]. Host genetic constitution is also thought to play a role in gastric carcinogenesis[4]. Among genetic factors, individual differences in inflammatory responses may protect or predispose to malignant transformation of the gastric mucosa. Human leukocyte antigens (HLA) class Ⅱ genes of the Major histocompatibility complex (MHC) are a group of highly polymorphic genes located in the short arm of chromosome 6 and are particularly important in controlling specific immune recognition[5]. HLA class Ⅱ antigens are capable of binding tumor peptides, and T-cell recognition of a combination of HLA class Ⅱ and bound tumor antigen may result in either induction of an effective anti-tumor immune re-

sponse or suppression of such immune response[6,7]. Moreover, adherence of *H pylori* to HLA class Ⅱ molecules expressed in gastric epithelial cells has been demonstrated[8].

Previous investigations have linked specific HLA-DQ alleles to gastric diseases, among others; Azuma *et al*[9] found increased susceptibility for *H pylori* infection in patients carrying the HLA-DQA1*0301 allele, whereas those displaying the HLA-DQA1*0102 allele were resistant to the infection; in other words, in Japan the HLA-DQA1*0102 allele has a lower frequency in *H pylori*-positive patients with atrophic gastritis compared with those with superficial gastritis and normal controls[10]. Conversely, the HLA-DQB1*0401 allele was found to be associated with atrophic gastritis in *H pylori*-infected patients[11]. On the other hand, the HLA-DQB1*0301 allele has been found more commonly in Caucasian patients with gastric adenocarcinoma[12]. The aim of this study was to investigate the relationship between HLA-DQ locus and presence of chronic gastritis and gastric adenocarcinoma in a Mexican population.

MATERIALS AND METHODS

Subjects

Forty five patients with chronic gastritis and 13 patients with diffuse-type gastric adenocarcinoma, all of them histologically confirmed, were studied. All patients were attended at the outpatient clinic of the Instituto Nacional de Cancerología (INCan) in Mexico City, because of gastric symptoms. A HLA-DQ database obtained from ninetynine healthy Mexican Mestizo asymptomatic subjects, without clinical evidence of chronic gastritis, peptic ulcer disease, gastric cancer, and personal or familiar history of autoimmune diseases was used for comparative purposes. Mexican Mestizo individuals included in the present study have a proportion of 56% Native American Indian genes, 40% White genes, and 4% Black genes[13]. Informed consent was obtained from all individuals considered in the present study.

Diagnosis of H pylori infection

H pylori status was assessed in patients by serologic analysis. Briefly, immunoglobulin G (IgG) antibodies against *H pylori* were tested in sera from 58 cases employing an enzyme-linked immunoabsorbent assay (ELISA) that was previously validated in Mexican population[14]. A pool of whole antigen preparation was obtained from sonicated preparations of three *H pylori* strains. Serum samples were diluted 1:1000, and 100-μL aliquots were plated. Next, a 1:1000 dilution of antihuman IgG monoclonal antibodies conjugated to alkaline phosphatase (Southern Biotech, Birmingham, AL, USA) was applied. A 1-mg/mL solution of p-nitrophenylphosphate was used as substrate and absorbance was read at 405 nm. All samples were analyzed by duplicate, the final value being the average of the two measurements.

ELISA for IgG anti-CagA

IgG antibodies for cytotoxin-associated gene A (CagA) protein were tested in patient sera utilizing an ELISA assay previously validated by our group[14]. A total of 0.1 μg/well of recombinant CagA antigen (Acambis, Cambridge, MA, USA) was used and serum at a 1:200 dilution was added. Next, a 1:1000 dilution of antihuman IgG monoclonal antibodies conjugated to alkaline phosphatase (Southern Biotech) was applied. A 1-mg/mL solution of p-nitrophenylphosphate was used as substrate and absorbance was read at 405 nm.

HLA-DQ typing

Genomic DNA was obtained from peripheral blood leukocytes and extracted by standard techniques[15,16].

Amplification of genomic DNA

HLA-DQA1 and -DQB1 typing were performed by a polymerase chain reaction (PCR) procedure using Taq DNA polymerase (Promega, Madison, WI, USA) and hybridization with PCR sequence-specific oligonucleotide probes (PCR-SSOP). Primers used for HLA-DQ amplification included DQAAMP-A, -B, DQBAMP-A, and -B. These were synthesized in a DNA-SM automated synthesizer (Beckman, Palo Alto, CA, USA). These typing techniques were approved by the 12th International Histocompatibility Workshop.

Dot blot hybridization

Five percent of the amplified DNA was denatured in 0.4 mol/L NaOH for 10 min, neutralized in 1 mol/L of ammonium acetate, and transferred to a Hybond-N membrane (Amersham, Bucks, UK). The filters were prehybridized at 42℃ for 30 min in a solution containing 6X SSPE (30X SSPE: 4.5 mol/L NaCl, 0.3 mol/L NaH_2PO4, 30 mmol/L EDTA, pH = 7.4), 5X Denhard solution (2% bovine serum albumin, 2% polyvinylpyrrolidone 40, 2% Ficoll 400), 0.1% Lauryl-sarcosine, and 0.02% SDS. Then, the oligonucleotide probes labeled with Digoxygenin dideoxy-Uridine-Triphosphate (Dig-11-ddUTP) were added and hybridized at 42ºC for 3 h. The filters were washed twice in 2X SSPE, 0.1% SDS at room temperature for 10 min, once in TMAC solution [50 mmol/L Tris-HCl (pH = 8.0), 3 mol/L tetramethylammonium chloride, 2 mmol/L EDTA, 0.1% SDS] at room temperature for 10 min, and twice at 60℃ for 10 min. Dots were revealed using the Dig Nucleic Acid Detection Kit (Boehringer Mannheim Biochemical, Mannheim, Germany).

Oligonucleotide probes

Information on the sequences and specificities of the DQA1 and -B1 oligonucleotides was gathered from the 12th International Histocompatibility Workshop. Oligonucleotide synthesis performed using the cyanoethyl phosphoramidite technique in a Beckman DNA-SM automated DNA synthesizer following the manufacturer's protocol.

Statistical analysis

Gene frequencies were compared using a 2 × 2 contingency table and χ^2 test. Odd ratios (OR) and 95% confidence intervals (95% CI) have been calculated for the disease in carriers of specific alleles; OR were not adjusted by gender or age. Comparisons of allele frequencies between sub-groups were carried out using the EPIINFO statistical package (Version 5.0, USD Incorporated 1990, Stone Mountain, GA, USA). All *P* values quoted were corrected

Table 1 HLA-DQB1 allele frequencies in Mexican patients with chronic gastritis according to *H pylori* status

DQB1*	*H pylori* + *n* = 48		*H pylori* - *n* = 32		Healthy *n* = 198	
	n	af	*n*	af	*n*	af
*0401	11	0.229[a,b]	2	0.062	0	0
*0301	10	0.208	5	0.156	34	0.171
*0302	7	0.145	11	0.343	48	0.242
*0501	5	0.104	1	0.031	12	0.060
*0201	3	0.062	4	0.125	33	0.166
*0304	2	0.034	0	0	1	0.005
*0602	1	0.017	1	0.031	15	0.075
*0601	1	0.017	3	0.093	0	0
*0603	1	0.017	0	0	4	0.020
*0604	1	0.017	0	0	3	0.015
*0303	1	0.017	1	0.031	0	0

af: Allele frequencies; [a]$P = 0.04$, *vs H pylori* -, OR = 4.46; 95% CI: 1.12-31.7; [b]$P = 1 \times 10^{-7}$, *vs* healthy individuals, OR = 6.5, 95% CI: 4.73-8.54.

Table 2 HLA-DQA1 allele frequencies in Mexican patients with *H pylori*-associated chronic gastritis according to CagA status

DQA1*	CagA + *n* = 28		CagA - *n* = 20		Healthy *n* = 198	
	n	af	*n*	af	*n*	af
*0501	15	0.535[a,b]	2	0.100	45	0.227
*0401	5	0.178	6	0.300	33	0.166
*0301	4	0.142	6	0.300	51	0.257
*0101	1	0.035	3	0.150	20	0.101
*0201	1	0.035	1	0.050	22	0.111
*0303	1	0.035	0	0	0	0
*0102	1	0.035	1	0.050	17	0.085
*0103	0	0	0	0	5	0.040
*0104	0	0	2	0.100[c]	0	0
*0105	0	0	1	0.050	0	0
*0503	0	0	1	0.038	0	0
*0601	0	0	1	0.038	0	0
*0302	0	0	1	0.038	0	0

af: Allele frequencies; [a]$P = 0.002$, *vs* CagA-, OR = 10.38, 95% CI: 1.76-79.51; [b]$P = 0.0005$, *vs* healthy individuals, OR = 3.92, 95% CI: 1.62-9.55; [c]$P = 0.008$, *vs* CagA+ and healthy individuals, OR = 12; 95% CI: 7.71-18.68.

by Bonferroni test for multiple comparisons taking into account the number of alleles studied. Statistical significance was considered as $P < 0.05$.

RESULTS

Subjects

Among patients with chronic gastritis, there were 35 female and ten male patients with a mean age of 56.3 years (range, 22-87 years). Thirteen patients with diffuse-type adenocarcinoma were also studied; there were eight women and five men with a mean age of 65.5 years (range, 41-90 years). Among patients suffering from chronic gastritis, 24 individuals were serologically positive for *H pylori* (17 females and seven males), while 14 patients were serologically positive for CagA (12 females and two males, respectively); five patients (four woman and one man) were eliminated because they were CagA-seropositive but *H pylori*-seronegative yielding thus a false-positive reaction, as previously stated[17]. Mean age of patients harboring *H pylori* infection was 58.9 years and for CagA-positive individuals, 56.7 years; mean age of *H pylori*-negative individuals was 53.2 years. Conversely, in the group of gastric carcinoma cases there were four patients with serologic evidence of *H pylori* infection (three women and one man), whereas solely one female patient was *H pylori* CagA-positive. Mean age of *H pylori*-positive patients was 74 years, whereas for *H pylori*-negative patients this was 61.7 years. CagA was positive only in one woman 57 years of age. Group of clinically healthy subjects no serologically-tested consisted of 47 women and 52 men, with a mean age of 33 years.

HLA genotyping in patients with chronic gastritis

HLA-DQA1 allele frequencies were distributed similarly between *H pylori*-positive and -negative patients with a diagnosis of chronic gastritis (data not shown).

In addition, regarding HLA-DQB1 locus a significant increased frequency of HLA-DQB1*0401 was observed in the *H pylori*-positive group compared with the *H pylori*-negative group and clinically healthy individuals (Table 1). A significantly increased frequency of the HLA-DQA1*0501 allele was found in the group of chronic gastritis and CagA-positive patients compared with CagA-negative patients and clinically healthy individuals. Moreover, DQA1*0104 allele frequency was increased in patients with chronic CagA-negative gastritis compared with patients with CagA-positive chronic gastritis and clinically healthy individuals (Table 2).

Table 3 shows an increased frequency of the HLA-DQB1*0501 and DQB1*0401 alleles in the group of patients with CagA-negative chronic gastritis compared with patients with CagA-positive chronic gastritis and clinically healthy subjects.

Haplotype analysis revealed significant increased frequency of HLA DQA1*0401-DQB1*0401 in *H pylori*-positive patients compared with clinically healthy subjects (Table 4).

HLA genotyping in patients with gastric diffuse-type adenocarcinoma

No significant differences were observed in the allele frequency of DQA1 locus between patients with diffuse-type gastric adenocarcinoma and clinically healthy individuals (data not shown). On the other hand, the HLA-DQB1 locus showed an increased frequency of the HLA DQB1*0501 allele in patients with gastric adenocarcinoma compared with clinically healthy individuals ($P = 1 \times 10^{-6}$, OR = 13.07; 95% CI, 2.82-85.14) but not when *H pylori*-positive and *H pylori*-negative subjects were compared ($P = 0.38$) (Table 5). In addition, HLA-DQB1*0501 allele frequency in *H pylori*-negative patients was also significant when compared with healthy subjects. No significant differences were found in the analysis between patients with gastric adenocarcinoma according to CagA status and clinically healthy individuals (data not shown). In addition, haplotype analysis did not show significant differences between HLA-DQA1-DQB1 haplotypes in patients with gastric diffuse-type adenocarcinoma and clinically healthy individuals (data not shown).

Table 3 HLA-DQB1 allele frequencies in Mexican patients with *H pylori*-associated chronic gastritis according to CagA status

DQB1*	CagA + *n* = 28		CagA - *n* = 20		Healthy *n* = 198	
	n	af	*n*	af	*n*	af
*0301	7	0.250	3	0.150	34	0.171
*0302	3	0.107	5	0.250	48	0.242
*0401	3	0.107	8	0.400[a,b]	0	0
*0201	2	0.071	1	0.050	33	0.166
*0304	2	0.071	0	0	0	0
*0501	0	0	5	0.250[c,d]	12	0.060
*0602	1	0.035	0	0	15	0.075
*0601	1	0.035	0	0	0	0
*0603	0	0	1	0.050	4	0.020
*0604	1	0.035	0	0	3	0.015
*0303	0	0	1	0.038	0	0

af: Allele frequencies; [a]$P = 1 \times 10^{-7}$, *vs* healthy individuals, OR = 17.5, 95% CI: 10.1–30.31; [b]$P = 0.01$, *vs* CagA + , OR= 5.67, 95% CI: 1.22-28.07; [c]$P = 0.03$, *vs* CagA +, OR = 9.0, 95% CI: 1.86-223.8; [d]$P = 0.01$, *vs* healthy individuals, OR = 5.17, 95% CI: 1.37-18.83.

Table 4 Haplotype allele frequencies in patients with chronic gastritis according to *H pylori* status

DQA1-DQB1*	*H pylori* + *n* = 48		*H pylori*- *n* = 32		Healthy *n* = 198	
	n	af	*n*	af	*n*	af
0401–0401	10	0.172[a,b]	1	0.031	0	0
0501–0301	10	0.172	3	0.093	27	0.136
0301–0302	11	0.189	10	0.312	48	0.242
0501–0201	8	0.137	2	0.062	10	0.050
0101–0501	5	0.086	0	0	10	0.050
0201–0201	3	0.051	0	0	22	0.111
0301–0401	2	0.034	1	0.031	0	0
0302-0302	1	0.017	0	0	0	0

af: Allele frequencies; [a]$P = 1 \times 10^{-7}$, *vs* healthy individuals, OR = 6.08, 95% CI: 4.56–8.10; [b]$P = 0.03$, *vs H pylori* -, OR = 7.15, 95% CI: 1.2-158.8.

Table 5 HLA-DQB1 allele frequencies in Mexican patients with gastric cancer according to *H pylori* status

DQB1*	*H pylori* + *n* = 8		*H pylori* - *n* = 18		Healthy *n* = 198	
	n	af	*n*	af	*n*	af
*0501	4	0.500[a]	5	0.277[b]	12	0.060
*0201	2	0.250	0	0	33	0.166
*0401	1	0.040	1	0.100	0	0
*0602	1	0.125	0	0	15	0.075
*0604	0	0	1	0.055	3	0.015
*0301	0	0.125	7	0.388	34	0.171
*0302	0	0.125	4	0.222	48	0.242

af: Allele frequencies; [a]$P = 0.001$, *vs* healthy individuals, OR = 15.5, 95% CI: 2.80-87.68; [b]$P = 0.007$, *vs* healthy individuals, OR = 5.96, 95% CI: 1.55-22.55.

DISCUSSION

Several previous studies have reported an association between HLA class II molecules and gastric diseases. In this study, we found significant increased frequencies of HLA-DQA1*0501 in patients with *H pylori* CagA-positive serology when compared with *H pylori* CagA-negative individuals as well as clinically healthy subjects, and HLA-DQA1*0104 in *H pylori* CagA-negative patients when compared with *H pylori* CagA-positive patients and clinically healthy individuals. Among patients harboring *H pylori*-associated gastritis, those who were CagA-negative showed a significant increased frequency of HLA-DQB1*0401 and HLA-DQB1*0501 alleles compared with CagA-positive patients and clinically healthy Mexican Mestizo individuals. HLA-DQA1*0401-HLA-DQB1*0401 haplotype showed to be a combination with higher susceptibility for *H pylori*-related gastritis. The finding of a high frequency of the HLA-DQB1*0601 allele in patients with chronic *H pylori*-negative gastritis emphasizes the participation of pathogenic mechanisms other than *H pylori* infection. This association has not been reported previously, and it is important to note that a larger sample size should be studied to maintain such an association.

Regarding patients harboring *H pylori*-associated gastritis, Sakai *et al*[11] also found an association between HLA-DQB1*0401 allele and presence of atrophic gastritis.

On the other hand, the HLA-DQA1*0501 allele was associated in patients with chronic *H pylori*-positive, CagA-positive gastritis. HLA-DQ5 has been also reported in association with atrophy and intestinal metaplasia of the gastric mucosa[18]. Other associations between HLA-DQA locus and gastric diseases have been described: Azuma *et al* found a protective effect of the HLA-DQA1*0102 allele against *H pylori* infection and intestinal-type adenocarcinoma[10], as well as a high susceptibility for *H pylori* gastritis and duodenal ulcer in patients carrying the HLA-DQA1*0301 allele[19].

Separately, Magnuson *et al*[20] found that HLA-DQA1*0102 was inversely associated with *H pylori*-seropositivity with no correspondence with a reduced risk for gastric cancer; this more notorious with diffuse-type carcinoma.

Moreover, Watanabe *et al*[21] have recently shown an increased allele frequency of HLA-DQB1*0401 in patients suffering from intestinal-type adenocarcinoma compared with individuals with *H pylori*-infected non-ulcer dyspepsia. In a Mexican study, Garza-González *et al*[22] concluded that HLA-DQA1*0503 allele could confer resistance to development of carcinoma and high-grade dysplasia of the stomach. Nevertheless, in our study we confirmed no protective effect of HLA-DQ alleles. We also found an association between HLA-DQB1*0501 and diffuse-type gastric adenocarcinoma as compared with clinically healthy individuals.

Interestingly, HLA-DQB1*0501 allele frequency was statistically significant only in patients with gastric carcinoma despite the fact that the majority of patients with gastric carcinoma were *H pylori*-negative and those who were infected, CagA-negative. This association was strong, considering the small number of cases under study; however, it is necessary to increase the sample size in order to confirm such an association. HLA class Ⅱ molecules are closely associated with gastric diseases, particularly the HLA-DQ locus.

Risk for gastric diseases among ethnic groups with different HLA class Ⅱ allele expression reflects several polymorphisms of this and other loci, as genes related

to mucosa protection (i.e. mucins, and trefoil peptides), inflammatory responses (i.e. interleukin-1β; interleukin-1 receptor antagonist, and tumor necrosis factor), and metabolic detoxifying enzymes (phase I enzymes like cytochrome P450 superfamily, and phase II enzymes like glutathione S- and N-acetyl transferases)[4]. The subtle mechanism by which such polymorphisms may drive the immune response and host susceptibility related with a particular stimuli is unclear; nevertheless, in this case, the participation of a unknown and as yet uncharacterized neighboring HLA class Ⅱ antigen could not be ruled out.

Oncogenes and tumor suppressor genes may also participate in several ways; for example, a 13Gly→Asp mutation of the K-ras oncogene has been related with improved prognosis in patients suffering from colorectal carcinoma; this is due to better recognition of partially overlapping epitopes with the 13Asp peptide and presented with HLA-DQ7 molecules by CD4+ T-lymphocyte clones[23].

In Caucasians, HLA-DQB1*0301 has been linked with gastric carcinoma[12], even in the absence of *H pylori* infection; however, this allele is also significantly frequent in patients with carcinoma of the cervix uteri[24] and melanoma[25]. It is noteworthy that the HLA-DQB1*0301 allele is common in healthy Mexican population (G Vargas-Alarcón, personal communication).

Moreover, Wu *et al*[26] reported lower seropositivity of *H pylori* and a higher ratio of diffuse/intestinal-type carcinoma in Taiwanese patients carrying the HLA-DQB1*0301 allele, whereas the HLA-DQB1*0602 allele was associated with susceptibility to proximal gastric cancer. The role of the HLA-DQB1 locus in gastric cancer development was also confirmed by Quintero *et al*[27], who found a significant association between the HLA-DQB1*0602 allele and CagA-positive status with distal gastric cancer in Spanish population. In a Chinese population, Li *et al*[28] found an increased risk for gastric cancer in patients carrying both the CW*03 and DRB1*01 alleles, particularly among those infected with *H pylori*.

Current evidence indicates that the majority of individuals harboring *H pylori* infection remain asymptomatic during their lifetime, with no clinical consequence from their infection. In a community-based seroepidemiologic study in Mexico[29], seropositivity for *H pylori* infection was 66%, and > 80% of adults were infected by age 25 years; seroprevalence remained nearly unchanged after the third decade of life, with an increment in seropositivity of < 0.5% per year in persons between 30 and 69 years. Taken together, these data suggest that risk for gastric diseases depends on factors other than *H pylori* infection and age.

According to histo-epidemiologic classification, gastric adenocarcinoma is divided into intestinal- and diffuse-type adenocarcinomas[30]. In intestinal-type adenocarcinoma, a multi-step process that includes gastritis, atrophy, and intestinal metaplasia of the gastric mucosa has been claimed as the initial event preceding the appearance of gastric carcinoma[31]. Intestinal-type adenocarcinoma, which is more frequent in the distal portion of the stomach, is related to a greater degree with *H pylori* CagA-positive infection[32]. In this case, the mechanism of neoplastic transformation could be mediated by translocation of CagA protein into the gastric cells through a type Ⅳ secretion system[33]. Diffuse-type adenocarcinoma has been also associated with *H pylori* infection, although there are controversial reports on this issue; prevalence of *H pylori* infection in gastric cancer series has been reported from 29% to 100%[3]; allele comparisons between diffuse- and intestinal-type adenocarcinoma are further warranted. Thus, we hypothesize that HLA-DQB1*0501 is associated with genetic susceptibility for developing diffuse-type gastric adenocarcinoma in Mexican Mestizo population regardless of *H pylori* status.

Interestingly, HLA-DQB1*0501 confers protection from malaria anemia and malaria reinfections in Gabonese children[34]. This association appears to be dependent on the cytokine profile, predominantly interferon-γ (INF-γ) production by T-cells and supports the notion that HLA can direct the immune response toward Th1 or Th2 phenotype[35].

In conclusion, our results, together with the body of evidence published in the literature, support that genetic constitution through HLA-DQ locus determines the mechanism of disease as well as clinical and pathologic outcomes, triggered by the interaction between environmental factors and the gastric milieu. In other words, immunogenetic background among different ethnicities is manifested as resistance or susceptibility to the development of chronic gastritis and gastric adenocarcinoma.

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COMMENTS

Background
Gastric cancer is multifactorial in origin; HLA genes confer susceptibility and resistance to diseases.

Research frontiers
HLA-DQ alleles are linked to gastric diseases; HLA-DQ locus drives different mechanisms of gastric disease.

Innovations and breakthroughs
HLA-DQB1*0501 is associated with diffuse type gastric carcinoma; HLA-DQB1*0601 is associated non-*Helicobacter pylori* gastritis.

Applications
Genotyping of HLA-DQ alleles is useful for determining individual susceptibility and/or resistance to gastric diseases; Knowing individual HLA constitution is useful for prevention, early detection and opportune therapeutics of gastric diseases, particularly, gastric cancer.

Terminology
Human leukocyte antigens (HLA) class II genes of the Major histocompatibility complex (MHC) are a group of highly polymorphic genes located in the short arm of chromosome 6, and are particularly important in controlling specific immune recognition; HLA class II antigens are capable of binding tumor peptides, and T-cell recognition of a combination of HLA class II and bound tumor antigen may result in either induction of an effective anti-tumor immune response or suppression of such immune response.

Peer review
The authors reported HLA-DQ locus may play a different role in the development of Helicobacter pylori-related chronic gastritis and diffuse-type gastric adenocarcinoma in the Mexican Mestizo population. Their results together with the body of evidence published in the literature support that genetic constitution through HLA-DQ locus determines the mechanism of disease as well as clinical and pathologic outcomes, triggered by the interaction between environmental factors and the gastric milieu. This is an interesting and important study.

S- Editor Liu Y **L- Editor** Alpini GD **E- Editor** Bi L