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ABOUT COVER

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AIMS AND SCOPE

World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7th, 14th, 21st, and 28th each month. The *WJG* Editorial Board consists of 642 experts in gastroenterology and hepatology from 59 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

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ORIGINAL ARTICLE

Observational Study

HLA-DQ: Celiac disease *vs* inflammatory bowel disease

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Abstract

AIM

To determine the genetic predisposition to celiac

disease (CeD) in inflammatory bowel disease (IBD) patients by quantifying the frequency of CeD-related human leucocyte antigen (HLA) (HLA-CeD: HLA-DQ2 and -DQ8) in IBD patients globally, by type of IBD and gender, and by calculating the protective/risk contribution of these haplotypes in the development of the IBD disease.

METHODS

We conducted a prospective study with IBD patients from our Unit. Clinical information was gathered and blood was tested for HLA-CeD. The control group was made up of unrelated Valencian organ donors.

RESULTS

1034 subjects were analyzed: 457 IBD [207 ulcerative coliti (UC) and 250 Crohn's disease (CD)] patients and 577 healthy controls. 39% of the controls and 34% of the patients had HLA-CeD (P = 0.0852). HLA-DQ2 was less frequent in UC patients (P = 0.0287), and HLA-DQ8 in CD (P = 0.0217). In women with UC, the frequency of DQ2.5cis (DQB1*02:01-DQA1*05:01) was reduced $\geqslant$ 50% [P = 0.0344; preventive fraction (PF) = 13%]. PFs (7%-14%) were obtained with all HLA-CeD haplotypes. HLA DQB1*02:02-DQA1*02:01 (HLA-DQ2.2) was more frequent in CD patients with respect to controls (P = 0.001) and UC patients (etiological fraction = 15%).

CONCLUSION

HLA-CeD is not more frequent in IBD patients, with an even lower frequency of HLA-DQ2 and -DQ8 in UC and CD respectively. HLA-DQ2.5 confers protection from the development of UC, especially in women, and HLA-DQ8 does so for the appearance of CD. HLA-DQ2.2 is present in 34% of the CD patients and may constitute a genetic risk factor for CD development.

Key words: Genetic predisposition; Celiac disease; Inflammatory bowel disease; Crohn's disease; Human leucocyte antigen; Ulcerative colitis

Core tip: The higher risk for celiac disease (CeD) in inflammatory bowel disease (IBD) is controversial. Since the involvement of human leucocyte antigen (HLA)-DQ2 and -DQ8 antigens (HLA-CeD) in the susceptibility to CeD is clearly established and it has been accepted as a useful test to exclude CeD, we determined the frequency of HLA-CeD in IBD patients. We observed that HLA-CeD is not more frequent in IBD patients, with an even lower frequency of HLA-DQ2 and -DQ8 in ulcerative colitis and Crohn's disease respectively. On the other hand, HLA-DQ2.2 was present in 34% of the Crohn's disease patients and may constitute a genetic risk factor.

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INTRODUCTION

Celiac disease (CeD) and inflammatory bowel disease (IBD) are chronic intestinal disorders with progressively increasing incidences and prevalences[1-11]. Both diseases are thought to be secondary to the interaction of certain environmental factors which either directly cause or enable others to trigger the disease (gluten -cause of CeD-, infections, dysbiosis, *etc.*), in genetically predisposed patients, by producing an altered immunological response.

CeD is a life-long inflammatory condition of the small intestine represented by a gluten-sensitive enteropathy in genetically susceptible individuals[7]. CeD has defined diagnostic criteria[8], which include blood antibodies, genetic testing, upper endoscopy findings and, especially, histological small-bowel changes. The involvement of human leucocyte antigen (HLA) genes codifying HLA-DQ2 and -DQ8 antigens in the susceptibility to the disease is clearly established and HLA typing has been accepted as a useful test to exclude CeD, because only 0.5% of CeD patients lack both DQ2 and DQ8 antigens[9].

Genetic predisposition to CeD, associated to heterodimers HLA-DQ2, encoded by DQB1*02/DQA1*05 alleles [*cis*-encoded in DQB1*02:01-DQA1*05:01 haplotypes (HLA-DQ2.5*cis*) or *trans*-encoded in DQB1*02:02-DQA1*02:01 + DQB1*03:01-DQA1*05:05 genotypes (HLA-DQ2.2 + HLA-DQ7.5: HLA-DQ2.5*trans*)] and, to a lesser degree, HLA-DQ8, encoded by DQB1*03:02/DQA1*03 alleles, has been found to have a high negative predictive value[12,13]. The HLA-DQ2.2 heterodimer has binding properties that are similar to those of HLA-DQ2.5, but it is not considered to predispose for CeD unless it is expressed with the HLA-DQ2.5 or -DQ7.5 heterodimers[9,10].

CeD is more prevalent in women, with a ratio of 2:1 with respect to men, theoretically due to HLA inheritance[14].

IBD patients have historically been considered to be at higher risk for CeD[12], which could be supported by the fact that IBD and CeD are quite prevalent and due to a theoretically similar pathogenesis[11,13,15], with the interaction of genetic, immunological, and environmental factors (gut flora, gastroenteritis, *etc.*).

Several studies have tried to relate IBD and CeD with different results[1,16,17]. None of the studies analyzed the genetic predisposition, although Leeds *et al* suggested that a reduced frequency of HLA-DQ2 and -DQ8 in IBD would explain a similar or even reduced CeD expression in IBD.

Some studies have looked for a relationship between HLA class Ⅱ molecules and IBD. Most studies have

analyzed HLA alleles instead of complete haplotypes. They observed a tendency to lower frequency of HLA-DQ2 or -DQ8[17,18], and, mainly, -DR3 and -DR4 (because most studies are from the serologic HLA era), in IBD, as well as a higher frequency of HLA-DR7[17]. A study of DiGiacomo *et al*[19], which analyzed complete haplotypes in several immune-related diseases, found a reduced frequency of HLA-DQ2 and -DQ8 in IBD, although only 36 IBD patients were included.

The main objective of the study was to determine whether or not IBD patients are genetically predisposed to CeD; we conducted a study to analyze the frequency of CeD-related HLA (alleles encoding DQ2 and DQ8 dimers: HLA-CeD) in our IBD population [both in patients with ulcerative colitis (UC) as with Crohn's disease (CD)]. An analysis of HLA-CeD frequencies according to sex was also performed in our IBD population.

MATERIALS AND METHODS

Patients and controls

The study included 1034 subjects from the Community of Valencia, Spain: 457 adult patients with IBD and 577 organ donors HLA-typed at the Transfusion Center of the Valencian Community (TCVC). IBD patients cared from the out-patient-clinic and the IBD day-care unit of the University Clinic Hospital of Valencia, were prospectively and consecutively retrieved.

Clinical information was updated and gathered from the patients, the physical and online record and by means of our clinical database. Ethnicity, age, sex, diagnosis (CD or UC), disease location (Montreal Classification and anastomosis)[20], extraintestinal manifestations (arthralgia, ankylosing spondylitis, sacroiliitis, aphthous stomatitis, dermatologic, ocular and thrombotic events, and primary sclerosing cholangitis), disease complications (megacolon, hemorrhage, perforation and intraabdominal abscesses) and need of surgery were all recorded.

The blood was analyzed at the Histocompatibility Department of the TCVC (EFI Accreditation number: 09-ES-014.986) to determine the presence or absence of CeD risk HLA-haplotypes: haplotype HLA-DQA1*05:01-DQB1*02:01 (HLA-DQ2.5*cis*), the heterozygotic genotype HLA-DQA1*02:01-DQB1*02:02 + DQA1*05:05-DQB1*03:01 (HLA DQ2.2 + HLA-DQ7.5, HLA-DQ2.5*trans*), and haplotype HLA-DQA1*03-DQB1*03:02 (HLA-DQ8). HLA was considered to predispose for CeD (HLA-CeD) when one of these haplotypes was present.

Approval from the hospital's Ethics Committee was obtained (Ethics Committee record nº 238), as well as written informed consent from each participating subject.

HLA genotyping

HLA-DQA1 and -DQB1 low- and high-resolution genotyping was performed by polymerase chain reaction with sequence-specific primers (PCR-SSP) according to the method described by Olerup *et al*[21]. Genomic DNA was isolated from nucleated cells by Magtration® technology[22]. Each PCR reaction was performed on about 80 ng of extracted DNA, using 0.15 units of Taq DNA polymerase (AmpliTaq® DNA Polymerase, Applied Biosystems, The Netherlands), and Olerup commercial primers (Olerup SSP AB, Stockholm, Sweden), according to the manufacturer's instructions. PCR was carried out in a final volume of 10 μL in a GeneAmp PCR System 9700 (Applied Biosystems, The Netherlands). An initial denaturizing step at 94 ℃ for 2 min was followed by 10 two-temperature cycles (94 ℃ for 10 s and 65 ℃ for 60 s) and 20 three-temperature cycles (94 ℃ for 10 s, 61 ℃ for 50 s and 72 ℃ for 30 s). Detection of amplified alleles was carried out by agarose gel electrophoresis.

Statistical analysis

According to the published data, the prevalence of HLA-DQ2 and DQ8 in the Spanish general population is about 30%[8]. Therefore, considering a 95% confidence level (type I error of 0.05, and 0.8 statistical power), we needed a sample size of 323 patients to detect significant differences between groups.

Statistical analysis was done using the PASW 17.0 software (SPSS Inc, Chicago, IL, United States), Microsoft Office Excel 2003 and STATGRAPHICS Plus (version 5.1). We calculated the absolute and relative frequencies of the different variables. We considered significant a P value of less than 0.05. Statistical methods used were: χ^2 test, logistic regression to calculate the odds ratio (OR), and ANOVA tests. The attributable risk was measured using the phenotypic frequency, relative risk (RR), etiologic fraction -EF: risk that genes can confer for the development of a disease- (for RR > 1) and preventive fraction -PF: protection that genes confer- (for RR < 1).

The Holm-Bonferroni correction was used to determine if the relationship between an allele or a group of alleles with a disease (or phenotype expression) was true, when multiple determinations were made.

RESULTS

The study included 1034 caucasian subjects from the Community of Valencia, Spain. 457 adult patients with IBD (202 females and 255 males) were retrieved from January 2007 to March 2011. All patients had been diagnosed with IBD according to accepted clinical, endoscopic, radiological, and histological findings[23,24]. 250 patients had CD and 207 UC. The phenotypical characteristics of the IBD patients are listed in Table 1. The control group was made up of 577 (220 females and 357 males) unrelated organ donors HLA-typed at the Transfusion Center of the Valencian Community

Table 1 Phenotypical characteristics of inflammatory bowel disease patients *n* (%)

	All IBD patients	Crohn's disease patients	UC patients
Number of patients	457 (100)	250 (55)	207 (45)
Gender (female)	202 (44)	122 (49)	80 (39)
Disease location		L1: 60 (24.0), L2: 30 (12.0), L3: 128 (51.2), L1 + L4: 11 (4.4), L2 + L4: 1 (0.4), L3 + L4: 20 (8.0), perianal: 93 (37.2)	Proctitis: 19 (9.2), left colitis: 60 (29.0), extensive colitis: 128 (61.8)
Disease behavior		B1: 88 (35.2), B2: 102 (40.8), B3: 60 (24.0)	
Complications	54 (12)	46 (19.7)	8 (4.1)
Extraintestinal manifestations	163 (35.7)	100 (41.8)	63 (31.7)
Surgery[1]	166 (37.5)	146 (59.3)	20 (10.2)

[1]IBD related surgery: Intestinal or perianal; L1: Distal ileum; L2: Colonic; L3: Ileocolonic; L4: Upper disease; B1: Inflammatory (nonstricturing/nonpenetrating); B2: Stenotic/stricturing and B3: Penetrating/fistulizing.

Table 2 HLA-CeD, -DQ2.5 and -DQ8 for all inflammatory bowel disease patients, ulcerative colitis patients, and Crohn's disease patients, compared with controls

HLA	Controls (*n* = 577)	IBD (*n* = 457)	Crohn's disease (*n* = 250)	Ulcerative colitis (*n* = 207)
HLA-CeD	227, 39.34% (95%CI: 35.36%-43.33%)	156, 34.14% (95%CI: 29.78%-38.48%), *P* = 0.0852	90, 36% (95%CI: 30.05%-41.95%), *P* = 0.364	66, 31.88% (95%CI: 25.54%-38.23%), *P* = 0.0571, PF = 11%
HLA-DQ2.5	137, 23.74% (95%CI: 20.27%-27.22%)	99, 21.66% (95%CI: 17.89%-25.44%), *P* = 0.381	65, 26.0% (95%CI: 20.6%-31.4%), *P* = 0.4879	34, 16.43% (95%CI: 11.38%-21.47%), *P* = 0.0287, PF = 8%
HLA-DQ8	101, 17.50% (95%CI: 14.40%-20.60%)	60, 13.13% (95%CI: 10.03%-16.23%), *P* = 0.054, PF = 5%	28, 11.20% (95%CI: 7.29%-15.11%), *P* = 0.0217, PF = 7%	32, 15.46% (95%CI: 10.53%-20.38%), *P* = 0.501
HLA-DQ2.2	131, 22.70% (95%CI: 19.29%-26.12%)	134, 29.32% (95%CI: 25.15%-33.50%), *P* = 0.022, EF = 9%	85, 34% (95%CI: 28.13%-39.88%), *P* = 0.001, EF = 15%	49, 23.67% (95%CI: 17.88%-29.46%), *P* = 0.856

HLA: Human leucocyte antigen; PF: Preventive fraction.

(TCVC).

HLA-CeD was found in 37.0% (383 subjects) of the study population**.** HLA-CeD was more frequent in the control group: 39.34% *vs* 34.14% in IBD patients, but this difference did not reach statistical significance (Table 2).

HLA-CeD was found in 31.88% of the UC patients and 36% of the CD subjects (Table 2). We compared the frequencies of HLA-CeD in controls *vs* CD and UC and observed a tendency to a lower frequency of HLA-CeD in UC patients *vs* controls (*P* = 0.0571), with a preventive fraction (PF) of 11% (HLA-CeD could confer 11% protection from developing UC) and no differences between CD patients and controls.

Women with IBD had a lower frequency of HLA-CeD than the control women (34% *vs* 43%, *P* = 0.0565; OR = 0.68 and PF = 14%) According to the type of IBD we observed that UC female patients had HLA-CeD less frequently than controls, although it did not reach significance (*P* = 0.0613).

These tendencies became significant when exploring the frequencies of the different HLA-CeD haplotypes, by gender and type of IBD. HLA-DQ2 was less frequent in UC patients and HLA-DQ8 in CD patients. The frequency of HLA-DQ2.5 in UC patients (16.43%) was significantly lower than the one of the control group (23.74%), with a PF of 8% (Table 2). This was observed when calculating frequencies of HLA-DQ2.5*cis* only, *trans* alone and global frequencies (both *cis* and *trans*). In considering both sexes together, the presence of DQ2.5cis was significantly lower in UC, with a frequency of DQ2.5cis of 20.28% in controls compared to 13.53% in patients with UC (*P* = 0.0319; PF = 7%). When taking into account only UC women *vs* control women (16.25% of HLA-DQ2.5 *vs* 27.44%), the probability obtained with a logistic regression model of developing UC in women with HLA-DQ2.5 was reduced almost 50% (*P* = 0.0466), with a PF of 13%. In women with UC, the frequency of DQ2.5cis was reduced more than 50%, given that it was multiplied by 0.459 (*P* = 0.0344).

HLA-DQ8 also showed a tendency to be less frequent in IBD patients (13.13%) than controls (17.50%), mainly due to the significantly reduced frequency of -DQ8 in CD patients (11.20%) (Table 2). No differences between genders were seen.

HLA-DQ2.2 was significantly more frequent in CD patients (34%) than in controls (22.7%) or than in UC patients (23.67%), (Table 2). Of the patients with CD, 31% of the males and 37% of the females have HLA-DQ2.2, while only 26% and 24% of males with UC and controls, respectively, and 20% and 21% of females with UC and controls, respectively, have it. No statistically significant differences between sexes were seen.

DISCUSSION

Some authors consider CD[25] or UC[26] patients at high risk of presenting CeD[27-32] and others don't[26,32,33]. However, none determine the frequency of HLA-CeD in their patients, although Leeds points out that

HLA-CeD could be less frequent in IBD patients than in the general population[33]. A more recent article determines HLA-CeD frequency in functional and organic gastrointestinal diseases. They observe that HLA-CeD is not more frequent in the IBD group than in the controls, but the sample size of IBD patients (36 IBD patients) is very small[19].

Genome studies have observed that CeD and IBD share some non-*HLA* gene[33-36]. Analyzing the published studies of HLA-alleles related to IBD[18], we could deduce that the HLA-CeD alleles are less frequent in IBD (DR4, usually linked to DQ8, in UC, and DR3, normally linked to DQ2, in CD), but there are no published prevalences of them. This brings us to the possible conclusion that, in IBD and CeD, there is an overlap of non-HLA genes but maybe not of HLA-CeD genes, and it poses the question of if this could explain why CeD is not more frequent in IBD.

We performed this study to determine if the IBD population is an "at-risk" group for CeD by determining the genetic predisposition for this disease in IBD patients. We aimed to quantify the frequency of celiac disease-related HLA (HLA-DQ2 and HLA-DQ8) in the IBD population, compare it to that of the general population, and observe if it was related to a specific IBD phenotype or gender.

With the benefit (to draw conclusions, genetic studies need homogeneous populations) and the limitation of such a homogeneous study group, the results must be interpreted taking into account the 100% Caucasian race of both cases and controls.

In our study no statistical differences in HLA-CeD frequency were detected between the IBD group and the control group. DiGiacomo *et al*[19] analyze HLA-DQ2 and -DQ8 in several digestive diseases, including IBD. Their results are similar to ours, but they cannot be extrapolated because only 36 IBD patients are analyzed[19]. They obtain a prevalence of HLA-CeD in IBD patients of 38.9%, with no differences when compared to a previously published HLA-CeD frequency in the general Italian population (39%).

In addition to DiGiacomo's article, we have found no studies that analyze the complete heterodimers DQα + DQβ related to CeD, *i.e.*, not only alleles, nor their actual frequency in IBD patients. Most of the studies do not take into account gender, which is important in CeD because of the 2:1 preponderance of females. We observed that women with IBD tend to show differences with women in the control group, with a preventive fraction of 14%.

Although both CeD and IBD have chronic intestinal inflammation, with increased intestinal permeability and an altered immune response, the different genetic basis is probably responsible for the different interaction with the environment. This is better understood when exploring the individual HLA-DQ2.5 and -DQ8 haplotypes, which might even confer protection from the future development of IBD, as our results show.

Taking into account the type of IBD, we can see that HLA-CeD tends to be less frequent in UC patients (32%) than in CD (36%) and controls (39%), confering 11% protection from developing UC. These differences are even more notable when analyzing only women: UC 31%, CD 36% and 43% controls. The lower percentages of HLA-CeD in women with IBD are mainly justified by the lower prevalence of the heterodimer HLA-DQ2.5cis, which confers a preventive fraction of 9%.

To delve more deeply into the tendency of HLA-CeD being a protection factor against IBD, the interaction of the variables sex, type of IBD and frequency of HLA-CeD was analyzed for statistical significance. We observed that the frequency of DQ2.5cis was reduced more than 50%, in women with UC. The reduction in the risk of HLA-DQ2.5cis in UC was not only observed in women (PF: 13%); in considering both sexes together, the presence of DQ2.5cis was significantly lower in UC (PF = 7%). Similar results were obtained when analyzing both *cis* and *trans* HLA-DQ2.5 together: HLA-DQ2.5 was significantly reduced in the UC group, and even more remarkably in UC women. This demonstrated that being a woman with HLA-DQ2.5 bears 13% protection from developing UC.

According to our results, HLA-DQ8 is also less frequent in IBD patients than those in the control group. HLA-DQ8 was significantly reduced in CD patients (PF = 7%).

Summarizing, the frequency of HLA-CeD in IBD patients is similar to the general population; however, there is a significant decrease in the number of UC patients with HLA-DQ2.5 and of Crohn's disease patients with HLA-DQ8. The preventive fractions that oscillate between 5% and 14% suggest that CeD haplotypes protect from developing IBD. More specifically, HLA-DQ2.5 guards against the appearance of UC and HLA-DQ8 against the initiation of CD. The low preventive fractions are explained by the fact that CD and UC are multifactor illnesses that include many phenotypes, in which, save exceptions such as families with specific altered genes like IL-10, various factors interact to produce the disease.

Since HLA-DQ2.5 is the most closely related to CeD, and the most frequent in CeD, our results may suggest that the risk of celiac disease is lower in patients with IBD and, therefore, its expression as well. Extensive studies with duodenal biopsies from Spanish patients should be carried out to see if, as in the Italian study by Casella *et al*[37], the prevalence of CeD in IBD is lower than in the general population.

The role of the HLA-DQ 2.2 dimer (DQA1*02:01 + DQB1*02:02) is controversial in terms of its contribution to the predisposition to celiac disease. The majority of authors are detractors of the role of predisposition to CeD of HLA - DQ2.2[38]. One even suggests that it may act as a protective factor[39], but there is also an author who notes that it clearly predisposes to CeD[40]. In the

meta-analysis by Stokkers *et al*[18] a positive association of HLA-DRB1*07 was observed in CD patients, a gene that is normally closely bound to HLA-DQ2.2. The Italian study by Lombardi *et al*[41] in 2001 also observed that the haplotype DRB1*07-DQB1*02:02 was the most frequent in their population. The frequency of HLA-DR7 in the European CD population is high[42-44], ranging between 5% and 29%, unlike the Japanese, where it is only found in 1%[44].

Our study observed that the frequency of HLA-DQ2.2 was greatly increased in patients with CD; more than a third of the patients carry this haplotype. The relative risk of CD in patients with HLA-DQ2.2 is 1.75 (EF = 15%). Thus, the contribution of HLA-DQ2.2 as a risk factor of CD development is 15%.

As in other European studies, such as the Spanish study by Fernandez *et al*[45], where the HLA-DRB1*07 is found in a high proportion of CD patients with ileal involvement, in our population with IBD there is a high frequency of HLA-DQ2.2 among patients with CD with ileal involvement (35.5% of patients with ileal Crohn have HLA-DQ2.2). In a large-scale, international genetics study, published in 2016, Cleynen *et al*[46] observed a strong relationship between HLA-DRB1*07 and Crohn's disease.

This suggests that HLA-DQ 2.2 may be a supplementary tool to diagnose undetermined IBD. Future studies have to be performed to evaluate if using HLA-DQ2.2 can help reach a diagnosis or if it can be of use for IBD family-members' follow-up.

Is the IBD population an "at-risk" group for celiac disease? According to our results, genetically no. They have the same frequency of CeD-related HLA haplotypes globally and even a lower frequency of them when specifically looking at UC or CD, and gender.

In conclusion, our results, not only quantify the frequency of celiac disease related HLA haplotypes in the IBD population, but also show that they are not more frequent in the IBD population, and even more, that HLA-DQ2 is less frequent in UC patients, especially women, and HLA-DQ8 in CD patients, and that these haplotypes confer low grade protection from the development of future IBD. Our results also confirm a high frequency of HLA-DQ2.2 in our CD patients, and point out that HLA-DQ2.2 may actually act as a genetic risk factor for a future diagnosis of CD.

ARTICLE HIGHLIGHTS

Research background

Celiac disease (CeD) and inflammatory bowel disease (IBD) are chronic intestinal disorders with progressively increasing incidences and prevalences. Both diseases are thought to be secondary to the interaction of certain environmental factors which either directly cause or enable others to trigger the disease (gluten -cause of CeD-, infections, dysbiosis, *etc.*), in genetically predisposed patients, by producing an altered immunological response. CeD has defined diagnostic criteria, which include blood antibodies, genetic testing, upper endoscopy findings and, especially, histological small-bowel changes. The involvement of human leucocyte antigen (HLA) genes codifying HLA-DQ2 and -DQ8 antigens in the susceptibility to the disease is clearly established and HLA typing has been accepted as a useful test to exclude CeD, because only 0.5 % of CeD patients lack both DQ2 and DQ8 antigens. IBD patients have historically been considered to be at higher risk for CeD, which could be supported by the fact that IBD and CeD are quite prevalent and due to a theoretically similar pathogenesis, with the interaction of genetic, immunological, and environmental factors (gut flora, gastroenteritis, *etc.*). Two more recent studies have analyzed CeD-related antibodies and biopsies and observed that CeD is just as frequent or even less in the IBD population, but CeD is still included as a more prevalent disease in IBD in some texts. None of them have analyzed the frequency of HLA-DQ2 and 8 (HLA-CeD) in IBD patients. Only one study has done so but it only included 36 patients.

Research motivation

We wanted to know if IBD patients are genetically predisposed to CeD. Since negative HLA-CeD has a very high predictive negative value, not having it discards having CeD in most cases. We wanted to determine the frequency of HLA-CeD in IBD, which has never been calculated, and whether having the haplotypes is related to having ulcerative colitis (UC) or Crohn's disease (CD).

Research objectives

To determine whether or not IBD patients are genetically predisposed to CeD, we conducted a study to determine the frequency of CeD-related HLA (alleles encoding DQ2 and DQ8 dimers: HLA-CeD) in our IBD population (both in patients with UC as with CD). An analysis of HLA-CeD frequencies according to sex was also performed in our IBD population.

Research methods

We conducted a prospective study with IBD patients from our Unit. Clinical information was gathered and blood was tested for HLA-CeD. The control group was made up of unrelated Valencian organ donors.

Research results

A total of 1034 patients were analyzed: 457 IBD (207 UC, and 250 CD) patients and 577 healthy controls. 39% of the controls and 34% of the patients had HLA-CeD (P = 0.0852). HLA-DQ2 was less frequent in UC patients (P = 0.0287), and HLA-DQ8 in CD (P = 0.0217). In women with UC, the frequency of DQ2.5cis (DQB1*02:01-DQA1*05:01) was reduced $\geqslant$ 50% [P = 0.0344; preventive fraction (PF) = 13%]. PFs (7%-14%) were obtained with all HLA-CeD haplotypes. HLA DQB1*02:02-DQA1*02:01 (HLA-DQ2.2) was more frequent in CD patients with respect to controls (P = 0.001) and UC patients (etiological fraction = 15%).

Research conclusions

HLA-CeD is not more frequent in IBD patients, with an even lower frequency of HLA-DQ2 and -DQ8 in UC and CD respectively. HLA-DQ2.5 confers protection from the development of UC, especially in women, and HLA-DQ8 does so for the appearance of CD. HLA-DQ2.2 is present in 34% of the CeD patients and may constitute a genetic risk factor for CeD development. This helps answer the ongoing question of whether or not IBD patients have a higher risk of CeD. According to our study, IBD patients have the same genetic predisposition of CeD than the general population, showing an even lower frequency when subanalyzing by haplotypes and type of IBD. To our knowledge, it is the first time a frequency of the HLA-CeD haplotypes is given in a large enough IBD population. We also found a high frequency of HLA-DQ2.2 in Crohn's disease, pointing to it as a risk factor.

Research perspectives

This study supports the change in trend of the relationship between CeD and IBD, confirming it is not more frequent. We found HLA-DQ2 was less frequent in UC and HLA-DQ8 in CD, but we did not find any relationship with the presence or absence of CeD haplotypes and certain IBD phenotypes. We might need larger studies to find if these alleles can be related to phenotypes. Future studies will help confirm HLA-DQ 2.2 as a risk factor for Crohn's. This could help decision taking in unclear cases (example with indeterminate colitis). Studies are also needed to see if to correlates with disease severity.

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