

Involvement of clinical characteristics and HLA-DQ2 genotypes in paediatric patients with coeliac disease suffering from allergies

The first description on the association of coeliac disease (CD) with allergic conditions dates in the 1970s, when was found the co-occurrence of asthma, eczema and rhinitis in adult patients with CD. Later, this likely connection was screened in both paediatric and adult populations, although with conflicting results.^{1,2} Hence, the relationship between CD and allergy is scarcely known.

Allergic diseases, similarly to autoimmune conditions, are developed on the basis of both genetic and environmental factors. Indeed, the genome-wide association studies (GWAS) have showed the existence of common genetic variants to both allergic and autoimmune diseases. Among these, genetic variants are the HLA class II genes, such as HLA-DQ and -DR. Recently, we have identified in patients with CD a negative association between the presence of the DQ2.5/DQ2.2 heterozygous genotype and allergy to airway allergens.³ This association has led us to undertake a study on the prevalence and associations of clinical features, as well as HLA-DQ genotypes between patients with CD and those with the co-occurrence of allergic diseases.

A cohort consisted of two hundred and seventy-nine paediatric patients with CD ($n = 279$) diagnosed between 2014 and 2019 in the Paediatric Gastroenterology and Nutrition Unit at the Málaga University Regional Hospital was investigated for the presence of allergic diseases. All enrolled patients were retrospectively evaluated and fulfilled the diagnostic criteria of the 2012 European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines.⁴ Allergic diseases were investigated upon the presence of a history of allergic symptoms and sensitisation to allergens documented by positive skin prick tests (SPTs) and/or positive specific IgE (sIgE) antibodies at the Allergy Unit. Upon revision of medical records, forty-one ($n = 41$) out of 279 patients with CD presented some form of allergic diseases: (a) rhinoconjunctivitis (58.53%), (b) atopic dermatitis (46.34%), (c) asthma (46.34%), (d) rhinitis (14.63%), (e) food allergy (14.63%), (f) drug hypersensitivity (4.87%) and (g) urticaria (2.43%). The case-control study was approved by the Ethics Committee of the Carlos Haya University Hospital. Informed consent was obtained from parents or legal guardians of all participants.

The control group formed by 238 patients diagnosed of CD and without history of allergy was compared with cases of patients with CD suffering from allergies ($n = 41$). Clinical features and HLA-DQ

genotypes were studied between the control group and cases. The following clinical characteristics were taken into account: age at diagnosis, gender, level of anti-tissue transglutaminase IgA (tTG-IgA) antibodies (>10 times the upper normal limit), villous atrophy (Marsh 3a-b and Marsh 3c), ferropenic anaemia, diarrhoea, failure to thrive, neurological manifestations (irritability and/or headaches), IgA immunoglobulin deficiency, autoimmune-associated diseases, classical CD, mono-symptomatic CD and subclinical CD. Among the clinical characteristics studied, no differences were found either on the prevalence or in the associations. Nevertheless, in the HLA-DQ genotyping study, the cases carrying the DQ2.5 heterozygous genotype presented a higher prevalence regarding controls ($P = .033$; Table 1). In addition, the presence of the heterozygous genotype for DQ2.5 (DQ2.5/DQX) represented a risk factor for developing allergic diseases in patients with CD (OR = 2.047, $P = .036$; Table 1). Conversely, cases with double dose of HLA-DQ2 (DQ2.5/DQ2.2) had a lower prevalence compared with controls ($P = .017$; Table 1). The association study of the HLA-DQ genotypes showed to the DQ2.5/DQ2.2 heterozygous genotype as a protection factor for developing allergies (OR = 0.320, $P = 0.022$; Table 1). The allergens found in patients with CD are summarised in Table S1.

It is well established in CD their association with other autoimmune conditions. However, currently the relationship with allergic diseases is barely known. We investigated whether the presence of allergic diseases represents a co-morbidity factor in patients with the co-occurrence of CD. However, taking into consideration the total number of clinical features analysed no differences were found. In contrast, the study of HLA-DQ genotypes showed significant genetic associations. Indeed, we have found an undescribed link between CD and the presence of allergic diseases in patients carrying the DQ2.5/DQX heterozygous genotype (OR = 2.047). The GWAS have highlighted the relationship between the HLA-DQ gene and allergic diseases.⁵ The HLA-DQ2 heterodimers represent the main genetic risk factor known in CD. Antigen-presenting cells (APCs) expressing DQ2.5 and/or DQ2.2 heterodimers preferably present deamidated gliadin peptides from gluten to specific CD4+ T cells in the intestinal lamina propria developing an immune response mediated by Th1-type cytokines. It is arguably that similarly, the DQ2.5 heterodimers in patients with CD could present in APCs peptides

TABLE 1 HLA-DQ genotypes in the control group and cases suffering from allergies

DQ genotypes	Control group (n = 238) n (%)	Patients with allergy (n = 41) n (%)	P value (χ^2)	OR (95% CI), P value	PR (95% CI), P value
DQ2.5/DQ2.5	29 (12.18%)	5 (12.19%)	ns	1.001 (0.364-2.756), ns	0.973 (0.399-2.375), ns
DQ2.5/DQX ^a	86 (36.13%)	22 (53.65%)	*P = .033	2.047 (1.049-3.993), *P = .036	1.444 (1.034-2.016), *P = .031
DQ2.5/DQ2.2	72 (30.25%)	5 (12.19%)	*P = .017	0.320 (0.121-0.966), *P = .022	0.477 (0.234-0.971), *P = .041
DQ2.2/DQ7.5	16 (6.72%)	3 (7.31%)	ns	1.095 (0.304-3.941), ns	1.058 (0.322-3.473), ns
DQ2.2/DQX ^b	6 (2.52%)	2 (4.87%)	ns	1.983 (0.386-10.180), ns	1.881 (0.393-9.008), ns
DQ2.5/DQ8	16 (6.72%)	4 (9.75%)	ns	1.500 (0.475-4.735), ns	1.411 (0.496-4.013), ns
DQ8/DQX ^a	6 (2.52%)	0	-	-	-
DQ8/DQ8	2 (0.84%)	0	-	-	-
DQ2.2/DQ8	5 (2.10%)	0	-	-	-

Abbreviations: CI, confidence interval; ns, not significant; OR, odds ratio; PR, prevalence ratio (Poisson regression model).

DQX^a ≠ DQ2.5, DQ2.2 and DQ8; DQ^b ≠ DQ2.5 and DQ8.

*P < .05.

derived from different types of allergens and thus triggering a Th2-type immune response. Conversely, heterozygous patients for DQ2.5 and DQ2.2 had a protection factor for developing allergic diseases (OR = 0.320). It is plausible to speculate that DQ2.2 heterodimers in heterozygous state with DQ2.5 could disturb the antigen presentation of allergenic peptides but nevertheless do not affect the presentation of deamidated gliadin peptides. In conclusion, there are common genetic variants not described until now, the DQ2.5 and DQ2.2 heterodimers that increase and reduce, respectively, the risk of developing allergies in patients with CD. Obviously, further investigations are necessary to clarify the relationships between Th1-type diseases such as CD and Th2-mediated allergic diseases.

CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors.

Carmen M. Cabrera¹ 
Lorenzo Sánchez-Godoy²
Víctor M. Navas-López³
José M. Urra^{4,5}

¹Immunology Section, Department of Haematology, Carlos Haya University Regional Hospital, Málaga, Spain

²Clinical Laboratory Service, Carlos Haya University Regional Hospital, Málaga, Spain

³Paediatric Gastroenterology and Nutrition Unit, Carlos Haya University Regional Hospital, Málaga, Spain

⁴Immunology Section, Ciudad Real University General Hospital, Ciudad Real, Spain

⁵Faculty of Medicine of Ciudad Real, University of Castilla-La Mancha, Málaga, Spain

Correspondence

Carmen M. Cabrera, Immunology Section, Carlos Haya University Regional Hospital. Avenida de Carlos Haya, s/n; CP: 29010, Málaga, Spain.
Email: carmenmcabrera@gmail.com

ORCID

Carmen M. Cabrera  <https://orcid.org/0000-0002-1604-269X>

REFERENCES

1. Kelly CP, O'Shea B, Kelly J, Feighery C, Weir DG. Atopy and childhood coeliac disease. *Lancet*. 1987;2:109.
2. Greco L, De Seta L, D'Adamo G, et al. Atopy and coeliac disease: bias or true relation? *Acta Paediatr Scand*. 1990;79:670-674.
3. Cabrera CM, Sánchez-Godoy L, Navas-López VM. Is the double gene dose of DQ2.5 or DQ2.5/DQ2.2 an involved factor in the clinical features of celiac disease? *Scand J Gastroenterol*. 2019;54:960-964.
4. Husby S, Koletzko S, Korponay-Szabó IR, et al. European Society for pediatric gastroenterology, hepatology-nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr*. 2012;54:136-160.
5. Waage J, Standl M, Curtin JA, et al. Genome-wide association and HLA fine-mapping studies identify risk loci and genetic pathways underlying allergic rhinitis. *Nat Genet*. 2018;50:1072-1080.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Table S1. Allergens found in the group of patients with CD (n = 41) according to the HLA-DQ genotypes

*Allergens (overall percentage)	DQ2.5/DQX^a (n = 22)	DQ2.5/DQ2.5 (n = 5)	DQ2.5/DQ2.2 (n = 5)	DQ2.2/DQ7.5 (n = 3)	DQ2.2/DQX^b (n = 2)	DQ2.5/DQ8 (n = 4)	n (%)
Mites (39.63%)							
<i>Dermatophagoides pteronyssinus</i>	14	4	2	2		3	25 (60.97%)
<i>Dermatophagoides farinae</i>	7	2	1	2		2	14 (34.14%)
<i>Lepidoglyphus destructor</i>	2	1	1			1	5 (12.19%)
Grass pollens (11.71%)							
<i>Lolium perenne</i>	3	2	1		1	1	8 (19.51%)
<i>Phleum pratense</i>	1		2			1	4 (9.75%)
<i>Cynodon Dactylon</i>			1				1 (2.43%)
Weed pollens (9.90%)							
<i>Parietaria judaica</i>	2	3			1	1	7 (17.07%)
<i>Artemisa vulgaris</i>	2			1	1		4 (9.75%)
Tree pollens (18.01%)							
<i>Olea europea</i>	8	3	2	1	1	2	17 (41.46%)
<i>Cupressus sempervirens</i>	1	1				1	3 (7.31%)
Animal proteins (12.6%)							

Cat dander	2	1	2		1	2	8 (19.51%)
Dog dander	3	1	1			1	6 (14.63%)
Molds (0.9%)							
<i>Alternaria alternata</i>						1	1 (2.43%)
Food allergens (5.4%)							
Milk	2 [‡]	1		1 [‡]			1 (2.43%)
Egg	4 [‡]			1 [‡]			0%
Tree nut	1			1			2 (4.87%)
Kiwi	1						1 (2.43%)
Lentils			1				1 (2.43%)
Banana						1	1 (2.43%)
Drugs (1.8%)							
Amoxicillin	1						1 (2.43%)
Dextromethorphan		1					1 (2.43%)

*Positive allergens with specific-IgE antibodies > 0.35 KU/L (ImmunoCAP, Phadia AB, Uppsala, Sweden) and/or positive skin prick-test; [‡]sensitization.

DQX^a ≠ DQ2.5, DQ2.2 and DQ8; DQ^b ≠ DQ2.5 and DQ8