

HLA class I and class II antigens in Turkish patients with chronic ordinary urticaria

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Summary

Background. Chronic urticaria is a common disease with an unclear pathogenesis, which may be resistant to therapy. Recent studies have focused primarily on a possible autoimmune basis.

Aim. To investigate HLA class I and II antigens in a Turkish population with chronic ordinary urticaria (COU; not physical, vasculitic or contact), and identify susceptible HLA antigens.

Methods. HLA antigens were investigated in 55 patients diagnosed with COU, using a two-stage microdroplet lymphocytotoxicity test, with 104 healthy and genetically unrelated individuals evaluated as the control group.

Results. HLA Bw4 and HLA DQ1 antigens were significantly higher in the study group (odds ratio (OR) = 2.93, 95% CI 1.47–5.85, $P = 0.003$ and OR = 7.81, 95% CI 1.96–28.50, $P = 0.001$, respectively) whereas HLA-A24 antigen was higher in controls (OR = 0.36, 95% CI 0.15–0.86, $P = 0.03$).

Conclusion. We propose that HLA-Bw4 and DQ1 antigens may be responsible for susceptibility to COU while HLA-A24 may have a protective role in the Turkish population.

Introduction

Chronic urticaria is characterized by widespread, transient and itchy cutaneous swellings affecting patients for 6 weeks or longer, with individual lesions lasting less than 24 h.¹ The term chronic 'ordinary' urticaria (COU) has been proposed to classify chronic urticaria by clinical presentation rather than aetiology, as up to 40–50% of patients previously diagnosed as 'idiopathic urticaria' have an autoimmune basis for their disorder.² The term 'COU' can be used when predominantly physical, vasculitic and contact urticarias have been excluded.² The exact incidence and prevalence of COU are not known, although it occurs in at least 0.1% and possibly up to 3%

of the population.³ Severe COU is a disabling condition and may be distressing. It may be difficult to treat, with little response to conventional antihistamine therapy.^{1–3}

The pathogenic mechanisms of the disease are not well-understood, but the primary effector cell is the mast cell. Recent investigations have shown that about one-third of patients with the ordinary presentation of CU have IgG (histamine-releasing) autoantibodies against the high-affinity IgE receptor, FcεRI or IgE.^{4–6} The major histocompatibility complex (MHC) class I and II molecules act as a marker for initiation and maintenance of immune responses and self recognition during T-cell ontogeny, and are associated with the pathogenesis of many autoimmune diseases.⁷ In accordance with the proposed autoimmune basis of this subset of patients with chronic urticaria, a link between chronic idiopathic urticaria and human leukocyte antigen (HLA) class II (especially certain HLA-DR and HLA-DQ alleles that are characteristically known to show increased frequency in autoimmune diseases) has been reported previously.^{8–10} Immunotherapy using plasmapheresis, intravenous

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immunoglobulins and ciclosporin may be valuable in severely affected patients with treatment-resistant disease.^{1,2} The response to immunomodulation and the recent findings of an association with HLA class II antigens lend further support for an autoimmune basis to COU in some patients.

We aimed to investigate the relationship between HLA class I and II antigens with the immune pathogenesis of COU in Turkish patients.

Materials and methods

Patients and controls

This study included 55 patients (16 M/39 F; mean $\pm$ SD age 37.09 $\pm$ 8.68 years, range 22–65) with COU and 104 healthy individuals (35M/69F; age 39.12 $\pm$ 7.34 years) matched for age, sex and ethnic composition with no personal or family history of chronic urticaria. The diagnosis of COU was based on typical clinical features and results of normal or negative routine investigations including complement, circulating immune complexes, autoantibodies (antinuclear antibody, antigastric parietal cells, antismooth muscle, antithyroglobulin) anti-*Helicobacter pylori* antibodies, thyroid function, family history of atopy or personal atopic symptoms). None of the patients had features of vasculitic urticaria such as abdominal or joint pain, persistence of lesions for more than 24 h, increased erythrocyte sedimentation rate or decreased serum complement levels. Patients with clinical suspicion of urticarial vasculitis were excluded by histopathological examination of lesional skin biopsies. Other underlying aetiologies were also excluded (systemic lupus erythematosus and related disorders, Cushing's disease, active inflammatory bowel disease, food intolerance, specific allergies). Histamine-releasing autoantibodies were not investigated by functional or immunochemical tests in patients or controls.

HLA antigen typing

HLA-A, -B and -C typing were performed on peripheral blood samples, according to the standard microdroplet lymphocytotoxicity technique¹¹ modified to use 0.5 μ L of serum. HLA antigens assessed are shown in Table 1. The 180 commercial antisera (Biotest; Behring, Marburg, Germany) were used to determine these specificities. For the class II antigens (DR and DQ), lymphocytotoxicity technique and immunofluorescence using immunobeads to isolate B cells were used. Rabbit complement lysis and eosin-dye staining methods were used. Results were evaluated using an inverted phase-contrast microscope.

Table 1 HLA antigens assessed.

Locus	Antigens
A	1–3, 9–11, 19, 23–26, 28, 29–34, 36, 43, 66, 68, 69, 74
B	5, 7, 8, 12–18, 21, 22, 27, 35, 37–42, 44–77, Bw4, Bw6
C	w1, w2, w3, w4, w5, w6, w7, w8, w9, w10, w12, w14, w16, w17
DR	1–18
DQ	1–9

Phenotype frequencies were calculated by direct counting.

Statistical analysis

The frequency of antigens from patients and controls were compared using χ^2 analysis with Yates' correction and Fisher's exact probability test of 2×2 tables. The strength of association was estimated by calculating the odds ratio (OR) and 95% confidence interval, which were generated by simple binary logistic regression analysis. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS computer software package (version 11.5 for Windows; SPSS Inc., Chicago, IL, USA).

Results

HLA class I and II antigen frequencies are given Table 2. Of the HLA-B antigens, Bw4 was significantly higher in the study group ($P = 0.003$, OR = 2.93; 95% CI 1.47–5.85). Frequencies of HLA-C antigens did not differ significantly between the study and control groups. Conversely, HLA-A24 was significantly higher in the control than in the study group ($P = 0.03$, OR = 0.37, 95% CI 0.15–0.86). Of the HLA class II antigens, HLA DQ1 was significantly higher in the study group ($P = 0.001$, OR = 7.48, 95% CI 1.96–28.50) than in the control group (Table 1). Further assessment on coexistence of positively and negatively correlated HLA antigens revealed a significant negative correlation of HLA Bw4+ A24– and HLA DQ1+ A24– and a positive correlation of HLA Bw4+ DQ1 + antigens in the study and the control groups ($P = 0.0003$, $P = 0.008$ and $P = 0.03$, respectively). No statistically significant difference was noted in antigen frequencies between men and women.

Discussion

HLA molecules are polymorphic membrane glycoproteins that can be expressed on the surface of all nucleated cells (HLA class I molecules) and cells mainly involved in the immune response (HLA class II

Table 2 Frequencies of HLA class I and HLA class II antigens in COU patients.

HLA	Study group (n = 55); n (%)	Control group (n = 104); n (%)	P	OR	95% CI
A1	13 (23.6)	18 (17.3)	NS		
A2	20 (36.3)	46 (44.2)	NS		
A3	12 (21.8)	24 (23)	NS		
A9	2 (3.63)	1 (0.9)	NS		
A11	6 (10.9)	17 (16.3)	NS		
A23	3 (5.4)	5 (4.8)	NS		
A24	8 (14.5)	33 (31.7)	0.03	0.37	0.15–0.86
A25	2 (3.6)	1 (0.9)	NS		
A26	2 (3.6)	10 (9.6)	NS		
A28	3 (5.4)	0 (0.0)	NS		
A29	2 (3.6)	5 (4.8)	NS		
A30	5 (9.1)	7 (6.7)	NS		
A31	2 (3.6)	2 (1.9)	NS		
A32	3 (5.4)	3 (2.8)	NS		
A33	3 (5.4)	5 (4.8)	NS		
B5	2 (3.6)	0 (0.0)	NS		
B7	5 (9.1)	12 (11.5)	NS		
B8	3 (5.4)	10 (9.6)	NS		
B13	6 (10.9)	11 (10.5)	NS		
B14	3 (5.4)	4 (3.8)	NS		
B18	4 (7.2)	14 (13.4)	NS		
B27	3 (5.4)	6 (5.7)	NS		
B35	12 (21.8)	19 (18.2)	NS		
B37	3 (5.4)	1 (0.9)	NS		
B38	4 (7.2)	6 (5.7)	NS		
B39	1 (1.8)	4 (3.8)	NS		
B40	1 (1.8)	5 (4.8)	NS		
B41	2 (3.6)	6 (5.7)	NS		
B44	7 (12.7)	17 (16.3)	NS		
B49	2 (3.6)	5 (4.7)	NS		
B50	2 (3.6)	6 (5.7)	NS		
B51	7 (12.7)	14 (13.4)	NS		
B52	6 (10.9)	5 (4.8)	NS		
B53	3 (5.4)	1 (0.9)	NS		
B55	2 (3.6)	10 (9.6)	NS		
B57	5 (9.1)	4 (3.8)	NS		
B58	0 (0.0)	3 (2.8)	NS		
B60	2 (3.6)	1 (0.9)	NS		
B61	1 (1.8)	2 (1.9)	NS		
B65	1 (1.8)	1 (0.9)	NS		
B70	1 (1.8)	1 (0.9)	NS		
Bw4	38 (69.1)	45 (43.2)	0.003	2.93	1.47–5.85
Bw6	41 (74.5)	75 (72.1)	NS		
Cw1	3 (5.4)	4 (3.8)	NS		
Cw2	3 (5.4)	7 (6.7)	NS		
Cw3	10 (18.2)	16 (15.3)	NS		
Cw4	19 (34.5)	36 (34.6)	NS		
Cw5	2 (3.6)	9 (8.6)	NS		
Cw6	11 (20)	18 (17.3)	NS		
Cw7	12 (21.8)	30 (28.8)	NS		
Cw8	2 (3.6)	6 (5.7)	NS		
Cw12	0 (0.0)	3 (2.8)	NS		
Cw14	0 (0.0)	1 (0.9)	NS		
Cw16	0 (0.0)	1 (0.9)	NS		
Cw17	1 (1.8)	3 (2.8)	NS		
DR1	10 (18.1)	17 (16.3)	NS		

Table 2 Continued.

HLA	Study group (n= 55); n (%)	Control group (n=104); n (%)	P	OR	95% CI
DR4	14 (25.4)	24 (23)	NS		
DR7	11 (20)	20 (19)	NS		
DR8	2 (3.6)	10 (9.6)	NS		
DR11	15 (27.2)	38 (36.5)	NS		
DR12	4 (7.2)	4 (3.8)	NS		
DR13	8 (14.5)	15 (14.4)	NS		
DR14	3 (5.4)	7 (6.7)	NS		
DR15	12 (21.8)	23 (22.1)	NS		
DR16	5 (9.1)	11 (10.5)	NS		
DR17	9 (16.3)	13 (1.2)	NS		
DQ1	10 (18.1)	3 (2.8)	0.001	7.81	1.96–28.50
DQ2	18 (32.7)	25 (24)	NS		
DQ3	3 (5.4)	5 (4.7)	NS		
DQ4	1 (1.8)	5 (4.7)	NS		
DQ5	11 (20)	30 (28)	NS		
DQ6	12 (21.8)	25 (24)	NS		
DQ7	25 (45.4)	38 (36.5)	NS		
DQ8	4 (7.2)	6 (5.7)	NS		
DQ9	3 (5.4)	2 (1.9)	NS		

OR, odds ratio; CI, confidence interval; NS, not significant.

molecules). The HLA molecules serve as marker for self during the thymic maturation of T cells, which always recognize foreign antigenic peptides in the context of self HLA molecules. More autoimmune diseases have been shown to be associated with alleles of the HLA region than with any other genetic region. Extensive differences are found in the distribution of HLA antigens among various populations. Several different class I and II genes have been directly implicated in the pathogenesis of human and experimental autoimmunity.⁷

Many questions still remain to be answered in CU such as the triggering of the autoimmune process, temporary spontaneous remissions and the genetic heterogeneity of patients.^{1,2} Many studies have investigated the aetiology of CU. Recent studies have focused primarily on an autoimmune basis and genetic mechanism.^{4–6,8–10}

In a MedLine search (1966 to April 2005) concerning the genetic mechanism of urticaria, various class I and II HLA antigens have been reported to be associated with chronic urticaria^{8–10} or urticarial-related diseases such as hereditary angio-oedema, mastocytosis, dermatographism, familial exercise-induced anaphylaxis and drug-induced urticaria or angio-oedema^{12–24} (Table 3). Only four studies have been performed concerning the association between chronic urticaria (or CIU) and HLA (Table 3). In 1978, Van Neste *et al.*¹⁵ investigated HLA class I antigens in 27 patients with CIU in Belgium, but could not show any significant differences between patient and control groups. More recently, Ossi *et al.*⁹

Table 3 HLA class I and II genotypes in urticaria-related disorders.

Author	Country	n (Diagnosis)	Method	HLA class	Findings
Tanimoto <i>et al.</i> ¹²	Japan	9 (Hereditary angio-oedema)*	LCT	I	No correlation
Ohela <i>et al.</i> ¹³	Finland	11 (Hereditary angio-oedema)*	LCT	I	No correlation
Blumental <i>et al.</i> ¹⁴	USA	81 (Hereditary angio-oedema)	LCT	I	No correlation
Van Neste & Bouillenne ¹⁵	Belgium	27 (Chronic idiopathic urticaria)	LCT	I	No correlation
Seignalet <i>et al.</i> ¹⁶	France	11 (Hereditary angio-oedema)*	LCT	I	Increased HLA A29, B12, Cw5
Eggert <i>et al.</i> ¹⁷	Denmark	19 (Hereditary angio-oedema)	LCT	I	No correlation
Olafsson <i>et al.</i> ¹⁸	Iceland	50 (Mastocytosis)	LCT	I	Increased HLA B12
Longley & Panush ¹⁹	USA	5 (Familial exercise-induced anaphylaxis)*	LCT	I, II	Increased HLA A3, B8, DR3
Pasero <i>et al.</i> ²⁰	Italy	4 (Urticaria/arthritis syndrome)*	LCT	I	Increased HLAB51
Salazar-Villa <i>et al.</i> ²¹	Mexico	25 (Dermographism)	LCT	I	Increased HLA A1, A2, B5, B16
Kowalski ²²	Poland	26 (Pyrazolone induced urticaria, angio-oedema)	LCT	II	Increased HLA DQ7
Quiralte <i>et al.</i> ²³	Spain	21 (NSAID-induced anaphylactoid reaction)	PCR-SSP	II	Increased HLA DR11
O'Donnell <i>et al.</i> ⁸	UK	100 (Chronic idiopathic urticaria)	PCR-SSP	II	Increased HLA DR4, DQ8; decreased HLA DR15, DQ6
Ossi <i>et al.</i> ⁹	Italy	13 (Chronic idiopathic urticaria)	LCT	I	Increased HLA B44/B35
Oztas <i>et al.</i> ¹⁰	Turkey	42 (Chronic urticaria)	PCR-SSP	II	No correlation
Kim <i>et al.</i> ²⁴	Korea	94 (Aspirin-induced urticaria)	PCR-SSP	II	Increased HLA DR4
Our study	Turkey	55 (Chronic ordinary urticaria)	LCT	I, II	Increased HLA DR18, DQ6, DR2
					Increased HLA Bw4, DQ1

*Case reports and series. LCT, lymphocytotoxicity assay; PCR-SSP, polymerase chain reaction sequence-specific primers.

found an increased frequency of HLA B44 and B35 usually related to autoimmune disease (61% vs. 15.5% of controls), but could not show any significant association among class II antigens in this small study group of an Italian population with CIU. O'Donnell *et al.*⁸ performed an HLA class II study using PCR in 1999 in a British population. They found a strikingly increased frequency of HLA-DR4 and its associated allele DQ8 (with a particularly strong correlation for patients with a positive autologous serum test) and a decreased frequency of HLA DR5 and DQ6. The PCR-based study of Oztas *et al.*¹⁰ also revealed that HLA DR4 is a common DR locus antigen in Turkish patients with CU (42.9% vs. 22.6% of controls). Thus, in both studies, the status of HLA class II antigens, especially DR4, was stronger in CIU.^{8,10} According to O'Donnell *et al.*⁸ and Oztas *et al.*,¹⁰ strong positive DR4 allele association suggests a 'genetic component' in the pathogenesis of CU or CIU, but the importance of HLA associations in the mechanisms of autoimmunity is not completely understood. Several hypotheses (linked gene, molecular mimicry, immunogenic peptide, promiscuous peptide, altered self, defective immunity, thymic selection and cytokine modulation) for the basis of HLA associations with disease have been put forward.⁷ Different hypotheses apply to different diseases and they are not mutually exclusive, with combinations being applied to some diseases.

HLA class II molecules play a crucial role in antigen presentation to CD4+ cells, and more generally, in

regulating the immune response.⁷ A positive association between HLA antigens and chronic urticaria may reflect more efficient presentation of a particular antigen to T-helper cells, thus promoting the process of T-cell switching to Th2 lymphocytes and IgE response.²² Indeed, the expression of MHC class II molecules has been also reported by Haas *et al.*²⁵ to increase on the surfaces of infiltrating cells and on the endothelial cells of superficial capillaries and postcapillary venules and the eccrine ductal cells in the skin tissue of various types of urticaria, including chronic recurrent urticaria (CRU). These MHC class II-positive cells may have various functions in the skin tissue of patients with CRU; besides the potential ability of all MHC class II-positive cells to present antigens, they may promote the escape of specific inflammatory cells from the vascular tree, or they may result from a process of systemic activation, e.g. via circulation antigens, inflammatory mediators or cytokines such as interferon- α .²⁵

These data indicate that expression of MHC class II molecules is involved in persistent wealing reactions/chronic urticaria. This underlines the concept that the pathological events in urticarial lesions involve a far more complex cascade of inflammatory and immunological reactions than would be possible by histamine-dependent processes alone.²⁵

We could not find any significant association between HLA DR group genotyping in our study group. HLA Bw4 and DQ1 antigen positivities were found to be

significantly high in our study group (69.1% vs. 43.2% of controls, $P = 0.003$, 16.3% vs. 2.8% of controls, $P = 0.003$, respectively), whereas HLA A24 antigen positivity was high in controls (31.7% vs. 14.5% of study group, $P = 0.03$). Assessment on coexistence of positively and negatively correlated HLA antigens (HLA Bw4+ A24– and HLA DQ1+ A24–) revealed a significant negative correlation of these antigens and a significant positive correlation for HLA Bw4+ DQ1+ antigens between the study and control groups.

We could not find any previous reports consistent with the HLA associations of our study group, presumably in part due to the different assays used in the previous two reports, rather than the lymphocytotoxicity test used in our study.^{8–10} Our results differed also from the data presented in the previous report concerning the HLA DR locus in other Turkish patients with CU in inner Anatolia.¹⁰ Different ethnic populations may have different antigen frequencies in HLA–CU association. We think that the possible reason for this may be due to the fact that our region (southern Marmara) is a common destination for Turkish immigrants from Balcanian, unlike other regions of our country, including inner Anatolia. This study supports that notion that the influence of alternative genetic and environmental factors may also play a role in the development of CU.

In conclusion, we propose that HLA DQ1 and Bw4 antigens (positively correlated antigen, possible susceptibility antigen) may play a major role in the occurrence of COU, while HLA A24 antigen (negative correlated antigen, possible protective antigen) may protect against COU among Turkish people, particularly Turkish immigrants from Balcanian. Similar studies on larger COU series are needed to clarify the role of HLA variations in these patients. To confirm the direct involvement of these antigens in COU, both phenotypic and genotypic analysis including family studies should be also carried out for all classes of HLA.

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