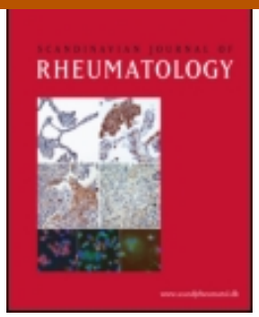

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LETTERS

HLA class II allele polymorphism in Hungarian patients with primary Sjögren's syndrome

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Previous data suggest that human leucocyte antigen (HLA) class II allele polymorphisms are involved in the development of primary Sjögren's syndrome (pSS). HLA DR3, DR2, and DR5 (DRB1*03, *15/16, *11/12) have been found with elevated frequency in pSS and the DR3 positivity correlates with the anti-Ro(SSA) and anti-La(SSB) autoantibody positivities and extraglandular manifestations (1, 2). In Greek pSS patients, the incidence of the DR5 allele was significantly increased, whereas no differences in HLA were found between anti-Ro(SSA)-positive and -negative SS patients (3). Finnish pSS patients with the HLA-DRB1*0301-DQA1*0501-DQB1*0201 haplotypes were observed to have significantly higher anti-SSA/Ro and anti-SSB/La antibody levels than did the patients without this haplotype (4). This autoantibody response likewise associated positively with DRB1*03-DQB1*02 and DRB1*03/DRB1*15-DQB1*02/DQB1*0602 heterozygosity in a German population (5). In French patients (6), the HLA alleles predisposed to autoantibody secretion without being associated with a clinical outcome (DRB1*15 favoured anti-SSA, and DRB1*03 both anti-SSA and anti-SSB production). In Norwegian pSS patients, similar HLA allele findings (DRB1*0301 and DRB3*0101 alleles) were reported, and these alleles were more closely associated with the presence of anti-Ro autoantibodies than with pSS itself (7).

Our aim was to determine the HLA class II allele polymorphisms, and to analyse the pheno- and genotype correlations in 48 Hungarian pSS patients, who all fulfilled the classification criteria for pSS syndrome (8). Forty-seven females and one male, with a mean age at the time of the examination of 55 years (range 33–83), and 50 healthy blood donors matched for age and sex as controls were studied. HLA-DRB1 was genotyped with the Dynal RELI SSO HLA-DRB kit, DRB1*15/16 was subtyped with the method of Ota et al (9), DQA1 by the method of Ota et al (10), and DQB1 with the INNO-LiPA DQB kit (Norway). A χ^2-test with Yates' and Bonferroni's corrections was performed, and odds ratios (ORs) were also calculated.

In the pSS patients, DRB1*03-DQA1*05011-DQB1*0201 proved to be the haplotype of susceptibility, even when Bonferroni's correction was used ($p \leqslant 0.01$, Table 1). The DRB1*1601 (OR 3.5) and DQA1*0102 (OR 2.5) alleles also occurred more frequently ($p \leqslant 0.05$), compared with the controls. By contrast, the DRB1*01-DQA1*0101-DQB1*0501, DRB1*04-DQA1*0301-DQB1*0302 and DRB1*11/12-DQA1*05012-DQB1*0301 haplotypes were less common in the pSS patients ($p < 0.05$ and $p < 0.02$, respectively, Table 1). However, after the use of Bonferroni's correction, the difference did not remain significant.

We analysed the HLA class II alleles in the SS subgroups separated according to the anti-SSA/anti-SSB seropositivity and to seronegativity. In the 20 anti-SSB-positive pSS patients, the DRB1*03 allele frequency was significantly higher than in the 28 anti-SSB negative cases (17/40 vs. 12/56, $p < 0.05$), but there was no similar difference between the patients with anti-SSA positivity or anti-SSA negativity (22/66 vs. 6/30, ns). By contrast, the DRB1*15/16 (DR2) alleles were detected significantly more frequently in the anti-SSB-negative than in the anti-SSB-positive patients (18/56 vs. 3/40, $p < 0.05$), and in the anti-SSA plus anti-SSB-negative patients compared with the anti-SSA plus anti-SSB-positive patients (8/24 vs. 4/34, $p = 0.02$).

The DRB1*03 allele was more common in nine pSS patients who exhibited purpura than in those without this vascular manifestation (9/18 vs. 21/78, ns). By contrast, the DRB1*15/16 alleles were less frequent in the patients with purpura (2/18 vs. 21/78, ns). Eleven pSS patients developed renal tubular acidosis, and DRB1*03 proved to be an allele of susceptibility (12/22 vs. 18/74, $p < 0.02$), and DRB1*11/12 one of resistance (0/22 vs. 11/74, $p < 0.05$) as compared with the patients without kidney involvement. Malignant lymphomas developed in five pSS patients (Hodgkin

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Table 1. HLA-DRB1*, -DQA1* and -DQB1* alleles in 48 Sjögren's syndrome patients and 50 controls.

HLA alleles	DRB1*					DQA1*					DQB1*				
	No. of alleles		Significance		OR	HLA alleles	No. of alleles		Significance		OR	HLA alleles	No. of alleles		Significance		OR
	Ps n/96	Cs n/100	p	pc			Ps n/96	Cs n/100	p	pc			Ps n/96	Cs n/100	p	pc	
*01	3	9	<0.05 ↓	ns	0.3	*0101	3	9	<0.05 ↓	ns	0.3	*0501	3	11	<0.02 ↓	ns	0.3
*1501/2	8	6	ns	ns	1.4	*0102	26	13	<0.05 ↑	ns	2.5	*0601/2	10	4	ns	ns	2.8
*1601	15	5	0.05 ↑	ns	3.5	*0103	6	8	ns	ns	0.8	*0502	11	7	ns	ns	1.7
*03	30	10	<0.001 ↑	<0.01 ↑	4.1	*05011	31	9	<0.001 ↑	<0.01 ↑	4.8	*0201	27	8	<0.001 ↑	0.01 ↑	4.5
*04	7	16	<0.05 ↓	ns	0.4	*0301	8	17	<0.05 ↓	ns	0.4	*0302	4	12	<0.05 ↓	ns	0.3
*11/12	11	25	<0.01 ↓	ns	0.4	*05012	14	30	<0.01 ↓	ns	0.4	*0301	18	33	<0.02 ↓	ns	0.5
*08	4	1	ns	ns	4.3	*0104	–	6	<0.01 ↓	ns	0.1	*0402	3	–	ns	ns	7.5
*10	–	2	<0.05 ↓	ns	0.2	*0401	4	–	ns	ns	9.8	*0202/3	5	5	ns	ns	1.0

Significance (p), corrected significance (pc), and odds ratio (OR) values; ns, nonsignificant; Ps, patients; Cs, controls.
The frequencies of the DRB1*13/14, *07, *09, DQA1*0201, DQB1*0503, *0202/3, *0603/4/5, and *0303 alleles did not differ significantly in the patients and the controls.

in one and non-Hodgkin in four); all of them carried the DRB1*03 allele (6/10 vs. 24/86 alleles, $p < 0.05$, Yates's correction; ns).

To summarize, in 48 Hungarian pSS patients, DRB1*0301-DQA1*05011-DQB1*0201 proved to be the haplotype of susceptibility. The DRB1*03 allele exhibited a positive correlation with anti-SSB autoantibody production, the presence of renal tubular acidosis, and the development of malignant lymphoma. The DRB1*15/16 (DR2) alleles were detected more frequently in the anti-SSB-negative patients than in the anti-SSB-positive patients, and in the anti-SSA plus anti-SSB-negative patients than in the anti-SSA plus anti-SSB-positive patients. Our results suggest a model of HLA-restricted presentation of Ro/La peptide determinants in pSS.

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