

Analysis of HLA Antigens in Croatian Patients with Psoriasis

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In common with most autoimmune diseases, psoriasis is associated with some HLA antigens. We studied the distribution of HLA antigens in Croatian patients with psoriasis: 108 patients were divided into groups according to family history and age of disease onset. HLA antigens were analyzed serologically and HLA-C alleles were analyzed using polymerase chain reaction. We found significant increases in HLA-A2, -B17, -B37 and -B13 antigens and highly significant increases in HLA-Cw*0602 and DR7 antigens in psoriatic patients compared with controls. Patients with type I psoriasis (early onset, positive family history) showed highly significant associations with Cw*0602 [$p < 0.00001$; relative risk (RR)= 14.45] and DR7 ($p < 0.00001$; RR= 15.09) antigens. Patients with type II psoriasis (late onset, no family history) had a significant association with Cw*03 antigen ($p = 0.008$; RR= 0.17). In conclusion, HLA-B13, -B17, Cw*0602 and -DR7 antigens are associated with a significant risk of psoriasis in the Croatian population and the Cw*0602 allele has the strongest association, especially for type I psoriasis. **Key words:** psoriasis; HLA antigens; polymerase chain reaction.

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INTRODUCTION

Psoriasis is a T cell-mediated disease associated with some HLA antigens, as is common for most autoimmune diseases (1). The relative risk of developing disease is increased in individuals carrying the HLA-Cw6, -B13, -B17 and -DR7 antigens (2). To our knowledge, psoriasis is the only disease linked to HLA-C genes. Recently, the presence of an alanine residue instead of threonine at position 73 on the $\alpha 1$ domain within the epitope-binding cleft of the HLA-C molecule was observed in psoriatic patients. This substitution is associated with a 5–7-fold increased risk of developing psoriasis (3).

Two types of psoriasis have been defined. Type I is inherited, has an early onset and shows a strong association with HLA-B13, -B17, -Cw6 and DR7 antigens. Type II occurs sporadically, has a late onset and shows only a weak correlation with HLA-Cw2 and -B27 antigens (4). HLA studies in different populations showed that the presence of some HLA antigens, especially Cw6, is associated with a clinically significant risk of developing psoriasis (5, 6). Therefore, we studied the distribution of HLA-A, -B, -C and DR antigens in Croatian patients with psoriasis by means of serology and hybridization with specific primers.

MATERIALS AND METHODS

Unrelated patients ($n = 108$) with chronic stable psoriasis from the Department of Dermatology, University Hospital Rijeka, were divided into groups according to family history and age of disease onset. Patients with a positive family history and disease onset at < 30 years were assigned as type I while patients with a negative family history and onset of disease at > 40 years were referred to as type II. Healthy unrelated individuals ($n = 139$) served as controls.

Typing of HLA class I and II antigens was performed by a standard microlympho-cytotoxicity test. HLA-C alleles were analyzed using amplification refractory mutation system-polymerase chain reaction (ARMS-PCR) in a Perkin-Elmer thermal cycler (7). A salting-out method was used to prepare genomic DNA from peripheral blood lymphocytes. The C locus was determined by 23 primer mixes (Dynal[®]). Ethidium bromide was used to visualize PCR products on 2.0% agarose gel.

Statistical evaluations were done using χ^2 test and Fisher's exact test. p -values were corrected using Yates' correction and also for the number of HLA antigens under investigation (p_{corr}). Relative risks (RRs) were calculated according to Woolf (8).

RESULTS

The frequencies and RRs of significantly elevated HLA-A, -B, -C and -DR antigens in 108 patients with psoriasis vulgaris compared with controls are shown in Table I. We found significant increases in HLA-A2 ($p = 0.017$; RR= 1.92), -B17 ($p = 0.036$; RR= 2.28), -B37 ($p = 0.02$; RR= 6.23) and -B13 ($p = 0.0036$; RR= 3.49) antigens, but only before correction of the p -values. We also observed highly significant increases in HLA-Cw*0602 ($p < 0.00001$; RR= 21.01) and DR7 ($p < 0.00001$; RR= 3.83) antigens, even after correction of the p -values. The RR of developing psoriasis was greatest for Cw*0602 allele carriers (RR= 21.01).

Based on the anamnestic data, 44 patients were assigned to the type I psoriasis group and 21 patients to the type II psoriasis group. The frequencies and RRs of HLA-A, -B, -C and -DR antigens in these groups of patients are shown in Table II. Highly significant increases in Cw*0602 ($p < 0.00001$; RR= 14.45) and DR7 ($p = 0.00004$; RR= 15.09) antigens were found in patients with type I psoriasis in comparison with those with type II, even after correction of the p -values. We

Table I. Frequencies of HLA antigens in patients with psoriasis

HLA antigen	Patients $n = 108$ (%)	Controls $n = 139$ (%)	p	p_{corr}	RR
A2	64 (59.26)	60 (43.16)	0.017	0.36	1.92
B13	21 (19.44)	9 (6.47)	0.004	0.10	3.49
B17	22 (20.37)	14 (10.07)	0.04	1.04	2.28
B37	9 (8.33)	2 (1.44)	0.022	0.57	6.23
Cw*0602	64 (59.26)	9 (6.47)	0.00001	0.0002	21.01
DR7	48 (44.44)	24 (17.27)	0.00001	0.0002	3.83

Table II. Frequencies of HLA antigens in type I and type II psoriasis

HLA antigen	Type I n= 44 (%)	Type II n= 21 (%)	p	p _{corr}	RR
B13	12 (27.27)	1 (4.76)	0.025	0.53	9.38
B17	15 (34.09)	2 (9.52)	0.025	0.65	4.91
Cw*03	5 (11.36)	9 (42.86)	0.008	0.21	0.17
Cw*0602	34 (77.27)	4 (19.05)	0.00001	0.0002	14.45
DR7	27 (61.36)	2 (9.52)	0.00004	0.0008	15.09

also found significant increases in HLA-B13 ($p=0.025$; $RR=9.38$) and -B17 ($p=0.025$; $RR=4.91$) antigens in type I psoriasis, but only before correction of the p -values. The Cw*03 allele was significantly elevated in patients with type II psoriasis before correction of the p -values ($p=0.008$; $RR=0.17$).

DISCUSSION

Although the pathogenesis of psoriasis is still unclear there is increasing evidence to suggest that psoriasis is a T cell-mediated autoimmune disease (9). Therefore, data on the expression of HLA molecules may be important in elucidating the pathomechanism of this disease.

Our results showed highly significant increases in Cw*0602 and DR7 antigens in patients with psoriasis compared with controls. It seems that only the Cw*0602 allele is associated with a highly significant risk of developing psoriasis. The importance of Cw6 in psoriasis was also confirmed by other studies (10, 11). It is emphasized that the presence of Cw6 is sufficient to indicate a clinically significant risk of psoriasis (5). In our study, antigens HLA-A2, -B17, -B37, -B13 and Cw*02 were significantly increased in patients with psoriasis only before correction of the p -values.

When we compared type I and type II psoriasis, Cw*06 and DR7 antigens were very significantly elevated in patients with type I psoriasis. An increased frequency of DR7 antigen in psoriatic patients was noted previously (12). Schmitt-Egenolf et al. (13) found a correlation between the HLA-DR7 antigen and type I, but not type II, psoriasis. They also observed that the B57 and Cw6 antigens conferred a significantly elevated relative risk of developing type I psoriasis.

In our patients, type II psoriasis showed a significant association with the Cw*03 allele, but only before correction of the p -values. Schmitt-Egenolf et al. (13) did not find any significant association between HLA antigens and type II psoriasis. Previous reports (4) have indicated a weak correlation between type II psoriasis and the Cw2 antigen; however, we failed to confirm this.

In conclusion, type I psoriasis is strongly associated with

the Cw*06 allele and type II with the Cw*03 allele in Croatian patients. The inheritance of psoriasis is polygenic and the Cw6 and DR7 antigens seem to be important in the development of psoriasis. However, it is important to stress that the HLA region on chromosome 6 is only one of the psoriasis susceptibility loci determined so far and the increased frequency of certain HLA antigens is probably due to linkage disequilibrium to the true susceptibility gene.

REFERENCES

1. Nepom GT, Ehrlich H. MHC class-II molecules and autoimmunity. *Annu Rev Immunol* 1991; 9: 493–525.
2. Brenner W, Gschnait F, Mayr RW. HLA B13, B17, B37 and Cw6 in psoriasis vulgaris: association with the age of onset. *Arch Dermatol Res* 1978; 262: 737–739.
3. Asahina A, Akazaki S, Nakagawa H, Kuwata S, Tokunaga K, Ishibashi Y, et al. Specific nucleotide sequence of HLA-C is strongly associated with psoriasis vulgaris. *J Invest Dermatol* 1991; 97: 254–258.
4. Henseler T, Christophers E. Psoriasis of early and late onset: characterization of two types of psoriasis vulgaris. *J Am Acad Dermatol* 1985; 13: 450–456.
5. Ikäheimo I, Tiilikainen A, Karvonen J, Silvennoinen-Kassinen S. HLA risk haplotype Cw6, DR7, DQA1*0201 and HLA-Cw6 with reference to the clinical picture of psoriasis vulgaris. *Arch Dermatol Res* 1996; 288: 363–365.
6. Enerback C, Martinsson T, Inerot A, Wahlstrom J, Enlund F, Yhr M, et al. Evidence that HLA-Cw6 determines early onset of psoriasis, obtained using sequence-specific primers (PCR-SSP). *Acta Derm Venereol* 1997; 77: 273–276.
7. Newton CR, Graham A, Heptinstall LE, Powell SJ, Summers C, Kalsheker N, et al. Analysis of any point mutation in DNA. The amplification refractory mutation system (ARMS). *Nucleic Acid Res* 1989; 17: 2503–2516.
8. Woolf B. On estimating the relationship between blood group and disease. *Ann Hum Genet* 1955; 19: 251–253.
9. Valdimarsson H, Baker BS, Jonsdottir I, Powles A, Fry L. Psoriasis: a T-cell mediated autoimmune disease induced by streptococcal superantigens? *Immunol Today* 1995; 16: 145–149.
10. Ikäheimo I, Silvennoinen-Kassinen S, Karvonen J, Tiilikainen A. Alanine at position 73 of HLA-C is associated with psoriasis vulgaris in Finland. *Br J Dermatol* 1994; 131: 257–259.
11. Enerback C, Martinsson T, Inerot A, Wahlstrom J, Enlund F, Yhr M, et al. Significantly earlier age at onset for the HLA-Cw6-positive than for the Cw6-negative psoriatic sibling. *J Invest Dermatol* 1997; 109: 695–696.
12. Tiwari JL, Lowe NJ, Abramovits W, Hawkins BR, Park MS. Association of psoriasis with HLA-DR7. *Br J Dermatol* 1982; 106: 227–230.
13. Schmitt-Egenolf M, Eiermann TH, Boehncke WH, Ständer M, Sterry W. Familial juvenile onset psoriasis is associated with the human leukocyte antigen (HLA) class I side of the extended haplotype Cw6-B57-DRB1*0701-DQA1*0201-DQB1*0303: A population and family based study. *J Invest Dermatol* 1996; 106: 711–714.