HLA antigens in psoriasis and psoriatic arthritis

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SUMMARY HLA phenotypes were determined in 50 patients with psoriasis alone and in 50 patients with psoriasis and psoriatic arthritis. Positive associations were found in both groups with B13, B17, B37, Cw6, and DR7, and in addition with C4A6. Higher relative risks were found in respect to the patients with psoriasis alone compared with those with arthritis, and this suggests the involvement of additional genetic factors predisposing to peripheral arthritis. In patients with psoriasis only, the presence of Cw6 was associated with a significantly earlier age of onset.

Analysis of the pattern of familial aggregation of psoriasis suggested the likelihood that several genetic loci might be involved in producing increased susceptibility.^{1,2} That HLA linked loci are involved was shown by the demonstration of positive associations between psoriasis and several HLA antigens, and in particular with B17, B13, Cw6, and DR7.³⁻⁹ Evidence for familial aggregation of psoriatic arthritis¹⁰ and for the association of the presence of arthritis with HLA-B27¹¹ and possibly other HLA antigens¹² suggested that additional genetic factors might predispose to the development of joint disease.

The present study was aimed at examining further the relationship between the HLA-A, B, C, and DR polymorphisms in groups of patients with psoriasis only or with psoriasis and peripheral psoriatic arthritis, together with a study of the C4 polymorphism (the C4A and C4B loci being closed linked to the HLA-B and DR loci). Evidence has previously been put forward for heterogeneity in relation to age of onset of psoriasis,^{4,11} and this was looked at again in the light of the more recently discovered associations.

Patients and methods

Fifty successive patients with psoriasis vulgaris but without evidence of peripheral psoriatic arthritis were ascertained in a dermatological outpatient department. A further 50 patients with psoriasis and with a chronic peripheral arthritis judged to be of a clinical pattern known to be associated with psoriasis (groups 1, 2, 3, and 4 in a previous study of psoriatic arthritis¹¹) were ascertained in a rheumatological unit.

Control subjects were laboratory and nursing staff

and medical students residing in the same geographical area as the patients. HLA-A, B, and C typing was carried out by a two stage lymphocytotoxicity microassay¹³ and HLA-DR typing was performed using an adaptation of the two colour fluorescence method.¹⁴ C4 phenotyping was carried out by electrophoresis and immunofixation.¹⁵ Statistical analysis was carried out using Woolf's method¹⁶ with modification by Haldane¹⁷ and, in the case of the comparison of age of onset distributions, by the Wilcoxon rank sum test.

Results

The data obtained from testing patients and controls for HLA-A and B locus antigens are shown in table 1a and for HLA-C and DR antigens in table 1b.

With regard to C4A and C4B phenotyping, the notable finding was that 12 out of 105 controls (11.4%) typed as C4A6 compared with 19 out of 50 psoriatic (38%) and 11 out of 50 (22%) psoriatic arthritic patients. The excess of C4A6 in psoriatic patients was associated with a probability of $p=0.0003$.

Table 2 gives the relative risks for both groups of patients for various phenotypes which showed positive associations.

The results support the previously shown positive associations of psoriasis with HLA-B13, B17, B37, Cw6, and DR7. The previously reported association of psoriatic arthritis with B27 was confirmed. C4A6 was found to be significantly associated with psoriasis with a relative risk of 4.63, the risk being somewhat lower in the case of psoriatic arthritis. The various positive associations with antigens determined at the different loci point to certain haplotypes being associated with increased liability to disease, C4A6 being involved in these haplotypes. The association of C4A6 in haplotypes

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TABLE 1a Frequencies of HLA-A and B phenotypes in the two groups of patients and in controls.

	Controls (550)		Psoriasis (50)		RR	p	Psoriatic arthritis (50)			
	No	%	No	%			No	%	RR	p
A1	193	35.1	27	54	2.2	0.01	22	44	1.46	0.27
A2	245	44.6	29	58	1.7	0.09	35	70	2.85	0.009
A3	154	28.0	10	20	0.67	0.25	6	12	0.37	0.02
A9	101	19.4	5	10	0.53	0.20	5	10	0.53	0.20
A10	51	9.3	4	8	0.94	0.97	5	10	1.17	1.0
A11	74	13.5	3	6	0.47	0.20	4	8	0.62	0.38
A28	30	5.9	1	2	0.47	0.41	2	4	0.81	0.81
A29	36	7.2	4	8	1.2	1.0	4	8	1.24	1.0
A30	1	1.4	0	0	0.46	1.0	0	0	0.47	1.0
A32	33	6.6	1	2	0.42	0.33	0	0	1.34	0.12
B5	49	8.9	3	6	0.75	0.66	2	4	0.52	0.35
B7	161	29.3	7	14	0.42	0.03	8	16	0.48	0.07
B8	156	28.4	6	12	0.37	0.02	13	26	0.91	0.85
B12	166	30.2	10	20	0.60	0.18	4	8	0.22	0.002
B13	26	4.7	7	14	3.41	0.015	9	18	4.53	4.3×10^{-4}
B14	40	7.3	3	6	0.92	0.96	4	8	1.22	1.0
B15	64	11.6	8	16	1.5	0.50	3	6	0.56	0.33
B16	8	4.3	2	4	1.1	1.0	1	2	0.64	0.74
B17	48	8.7	21	42	7.6	8.6×10^{-12}	16	32	5.0	1.1×10^{-6}
B18	30	5.5	3	6	1.3	1.0	3	6	1.26	1.0
B21	5	4.8	6	12	2.7	0.19	0	0	0.18	0.28
B22	30	5.5	2	4	0.88	0.91	0	0	0.17	0.18
B27	50	9.1	4	8	0.96	1.0	13	26	3.57	4.8×10^{-4}
B35	65	11.8	2	4	0.38	0.15	7	14	1.28	0.82
B37	7	2.9	7	14	5.4	0.003	3	6	2.30	0.50
B40	64	11.6	2	4	0.39	0.16	4	8	0.73	0.59

TABLE 1b Frequencies of HLA-C and DR phenotypes in the two groups of patients and in controls.

	Controls (115)		Psoriasis (50)		RR	p	Psoriatic arthritis (50)			
	No	%	No	%			No	%	RR	p
Cw1	13	11.3	3	6	0.56	0.44	9	18	1.74	0.36
Cw2	3	2.6	3	6	2.37	0.54	6	12	4.70	0.04
Cw3	30	26.1	12	24	0.91	0.93	7	14	0.48	0.13
Cw4	19	16.5	2	4	0.26	0.05	6	12	0.72	0.61
Cw5	19	16.5	6	12	0.72	0.61	7	14	0.85	0.86
Cw6	27	23.5	36	72	8.10	1×10^{-8}	25	50	3.22	0.0014
Cw7	48	41.7	17	34	0.73	0.45	15	30	0.61	0.21
Controls (168)										
DR1	32	19.1	8	16	0.84	0.78	11	22	1.22	0.80
DR2	48	28.6	14	28	0.99	1.0	7	14	0.43	0.06
DR3	44	26.2	6	12	0.41	0.06	16	32	1.34	0.53
DR4	59	35.1	16	32	0.88	0.81	16	32	0.88	0.81
DR5	21	12.5	5	10	0.83	0.82	5	10	0.83	0.82
DR6	26	15.5	8	16	1.08	1.0	18	36	3.06	0.003
DR7	49	29.2	31	62	3.90	4.9×10^{-5}	17	34	1.26	0.63

TABLE 2 Relative risk^{16 17} for various HLA phenotypes in patients with psoriasis alone and with psoriatic arthritis.

	Psoriasis	Psoriatic arthritis
B13	3.4	4.5
B17	7.6	5.0
B37	5.4	2.3
Cw6	8.1	3.2
DR7	3.9	1.3
C4A6	4.6	3.2
B27	0.96	3.6

involving B17 and DR7 was suggested in the case of the normal population by Awdeh *et al*¹⁸ and is strongly supported by the present study. Ten out of 12 C4A6 positive controls were also Cw6 positive, compared to nine out of 93 C4A6 negative subjects. Eight of the 10 were B17 positive and seven also DR7 positive. It appears likely, therefore, that B17, Cw6, DR7, and C4A6 are in linkage disequilibrium. Of the 19 C4A6 patients with psoriasis only, all were Cw6 positive and, of these, 18 were also B17 positive and one B13 positive, and 16 were DR7

positive. In the case of patients with psoriatic arthritis, 11 were C4A6 positive, of whom nine were Cw6 positive, all were B17 positive, and eight were DR7 positive.

It is to be noted from table 2 that for each phenotype showing a positive association with psoriasis, with the exception of B13, the relative risk was lower in the case of psoriatic arthritis. Taking the risks for Cw6 as an example, the difference between 8.2 and 3.2 was significant ($p=0.04$).

AGE OF ONSET

Table 3 shows the statistics relating to the age at onset of psoriasis for the various subgroups. It is seen that when all the patients are considered together, Cw6 positive subjects tend to have an earlier age of onset than those negative for this antigen ($p=0.015$). Analysis of the two patient groups separately shows that the difference is only apparent in the group with psoriasis alone ($p=0.013$). There is a tendency for the age of onset of psoriasis to be somewhat earlier in the psoriasis only group, irrespective of Cw6, but the difference is not significant.

Discussion

It appears likely that haplotypes involving three B locus antigens (B13, B17, and B37), Cw6, DR7, and C4A6 are the ones that particularly carry genes involved in susceptibility to psoriasis. Linkage disequilibria between these phenotypes have been established from normal population data.^{18 19}

An unsolved problem is to determine from the association data which of the loci showing positive associations is either directly involved in providing disease susceptibility genes or is the most closely linked to the susceptibility gene locus. Thus, it is possible that Cw6 itself is the product of the disease susceptibility gene or it may be in strong linkage

disequilibrium with that gene. Theoretical considerations suggest that the phenotype showing the strongest association is at the locus closest to the disease susceptibility gene locus. The problem arises as to how best to measure the strength of association and what genetic interpretation to give to it.

Bengtsson and Thomson²⁰ have discussed this problem and suggested that a measure of 'attributable risk', signified as δ , was superior in the present context than the relative risk as measured by the cross product ratio. They suggested that δ can be used as an estimate of the normalised linkage disequilibrium between the HLA phenotype and the disease susceptibility gene and that comparison of the values obtained for various HLA phenotypes could allow one to decide which has the strongest association from the genetic point of view.

Table 4 gives the δ values calculated from the data in the present study. In general they follow a similar pattern to that seen when the odds ratios are tabulated (table 2), that is, the highest values for both δ and the odds ratio are those for Cw6. A combined analysis of the data from five recently published studies in addition to the present one shows a higher relative risk for B13, B17, Cw6, and DR7 in patients with psoriasis alone than in those with arthritis in addition.²¹

The reason for these differences probably lies in the likelihood that the genetic factors predisposing to the psoriasis is the same for both groups but that important additional genetic factors are operating in the cases of those with arthritis. Therefore, the role of psoriasis inducing genes relative to the total genetic predisposition is relatively smaller in the arthritis patients, leading to lower relative risk and lower values for δ . The fact that HLA-B27 is associated with an approximately fourfold increase in relative risk for psoriatic arthritis will of itself lead to some reduction in the relative risk for other B locus antigens, but it is very unlikely that this accounts for the finding. Evidence has been put forward for the splits of HLA-Bw16 (B38 and B39) being involved in increased susceptibility for psoria-

TABLE 3 Comparison of age of onset of psoriasis between various subgroups.

		Age of onset (y)		
		Mean	Median	p^*
All patients	Cw6 positive	32.2	25.0	0.0153
	Cw6 negative	23.7	18.0	
Psoriasis alone	Cw6 positive	34.4	25.5	0.013
	Cw6 negative	21.3	16.0	
Psoriatic arthritis	Cw6 positive	30.7	25.0	0.49
	Cw6 negative	27.1	25.0	
Psoriasis alone		25.1	17.5	0.16
Psoriatic arthritis		28.9	25.0	

*Wilcoxon rank sum test.

TABLE 4 Values for δ^* for various HLA antigens in the two disease groups.

	Psoriasis	Psoriatic arthritis
B13	0.1	0.035
B17	0.365	0.255
B37	0.156	0.021
Cw6	0.634	0.346
DR7	0.463	0.068
C4A6	0.3	0.119
B27	-0.01	0.186

* $\delta = \frac{d-p}{1-p}$ where d is the frequency of the antigen in the disease group and p the frequency in the general population.

tic arthritis,^{12 22-25} but the present study and presumably the study of Armstrong *et al*²⁶ provide no evidence to support this suggestion and there is considerable heterogeneity between the different series. There remain additional genetic factors to be discovered which predispose to psoriatic arthritis and these may be HLA linked or unlinked.

AGE OF ONSET

Previous studies showed good evidence that patients with psoriasis who were B13 and particularly B17 positive were more likely to have a clinical onset in the first two decades than those negative for these antigens.^{4 5} There is support for this in the present study in which, when one includes all the patients, the median age of onset of psoriasis is lower for the Cw6 positive subjects than for those negative for this antigen. This difference, however, only applied to the group with psoriasis alone. The age of onset distribution in the case of patients with psoriatic arthritis was no different in Cw6 positive from that in Cw6 negative patients. It is possible to speculate that other genetic factors, possibly non-HLA linked, predispose to both psoriasis and psoriatic arthritis, and the role of Cw6 (or of a gene in linkage disequilibrium with Cw6) in determining a relatively early age of onset of psoriasis is relatively speaking reduced.

It is very likely that psoriasis is genetically heterogeneous and that various environmental triggers interact with the different genotypes involved. Thus an earlier onset may be the result of factors, such as infection, having the liability to precipitate the onset of psoriasis in the earlier decades in the presence of particular HLA linked genes.

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