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HLA associations in sarcoidosis: a study of two ethnic groups

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ABSTRACT We report results of HLA-A, B, C, and DR typing in groups of white Caucasians of English descent and black West Indians of African descent with sarcoidosis. In the English patients we found a significantly increased frequency of Cw7, which was not found in the West Indian patients. Our results also suggest that DR3 and, in particular, inheritance of the B8/Cw7/DR3 haplotype is associated with good prognosis in English patients with sarcoidosis. There was no association between any HLA antigen and prognosis in the West Indian patients in this study.

The sarcoid granuloma results from an immune response in which abnormal macrophage and T lymphocyte function may play a part. Immune dysfunction in sarcoidosis manifests itself as both cutaneous anergy and peripheral blood hyporesponsiveness, as well as exaggerated humoral responses.[1 2] The association of particular HLA antigens with disease has suggested an important role for HLA linked immune response genes and disease susceptibility,[3] and has been shown to have various implications for disease classification, diagnosis, and prognosis.[4]

Previous workers have suggested an association between HLA-B8 and spontaneous resolution of sarcoidosis[5] and between HLA-B8 and acute features of sarcoidosis.[6] No data are currently available on the prevalence of DR antigens in sarcoidosis, or on the association of any HLA antigens with sarcoidosis in black West Indians of African descent. There is considerable interest in HLA-DR antigens since they are thought to be important in effective cooperation between immunocompetent cells.[7] It is therefore relevant to assess their frequency in patients with sarcoidosis.

Methods

HLA typing for the A, B, C, and DR loci was performed at the Royal Marsden Hospital on 62 patients with saroidosis attending clinics at St Thomas's Hospital and the Royal Northern Hospital from August 1981 to May 1982. All lived in the Greater London area. Fifty seven patients had biopsy evidence supporting the diagnosis of sarcoidosis. Of the remaining five, one had lupus pernio and bone cysts and four had had bilateral hilar lymphadenopathy in addition to other systemic sarcoid disease, having been followed in the clinics for several years.

Time since diagnosis was used as the most objective measure of duration of disease for a cross-sectional study of a clinic population, since any other index of disease activity would require exclusion of patients and the possible introduction of bias.

ENGLISH GROUP

Tissue typing was performed on 34 white Caucasian patients of English descent, of whom 19 were male. In each case both parents were English and any subjects with Irish, Scottish, or Welsh parentage were excluded. Ages ranged from 21 to 80 years with a mean of 38·4 years. The duration of disease from diagnosis ranged from 0 to 32 years with a mean of 6·1 years. Table 1 summarises the extent of systemic disease in the group. The English control group comprised 96 normal healthy volunteers who were laboratory workers in London and Newcastle upon Tyne and whose ages ranged from 20 to 40 years.

WEST INDIAN GROUP

Twenty eight black West Indians, of whom 15 were

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Table 1 *Clinical features in English and West Indian patients with sarcoidosis*

	No of patients	
	West Indian (n = 28)	*English (n = 34)*
Erythema nodosum	1	9
Uveitus or conjunctivitis, iritis	11	9
Arthralgia	5	10
Bilateral hilar lymphadenopathy	24	27
Pulmonary infiltrates	14	23
Lupus pernio	4	3
Other skin lesions	11	10
Bone cysts	3	2
Lymphadenopathy	9	7
Parotid or lacrimal gland lesions	8	2
Splenomegaly	8	0
Hepatomegaly	9	0
Hypercalcaemia	1	1
Neurological lesions	2	3
Positive tissue or Kveim test biopsy specimen	27	30

male, were tissue typed. Both parents of each patient were of African West Indian origin. The ages of the patients ranged from 22 to 64 years with a mean of 42·9. The duration of disease from diagnosis varied from 0 to 18 years with a mean of 6·0 years. Table 1 shows the extent of systemic disease in the group. The control group comprised 57 black subjects of African West Indian origin attending the genitourinary medicine clinic of St Thomas's Hospital.

HLA TYPING

Lymphocytes separated from peripheral blood were typed for HLA-A, B, and C locus antigens by the two stage cytotoxicity test.[8] Lymphocyte viability was assessed by the trypan blue exclusion method.[8] The two colour fluorescence method was used to type for HLA-DR antigens.[9]

The relative risk associated with each antigen was calculated as follows:

$$\text{Relative risk} = \frac{\text{Number of antigen positive patients} \times \text{number of antigen negative controls}}{\text{Number of antigen positive controls} \times \text{number of antigen negative patients}}$$

Tests were carried out for 31 antigens at the A, B, and C loci and nine at the DR locus.

STATISTICAL TESTS

A χ^2 test was performed for each antigen where the relative risk was over 2·0. Yates's correction was applied where necessary, and the probability values (p) were corrected for the number of antigens tested (pc) by multiplying them by the number of antigens tested.

Results

HLA ASSOCIATION WITH DISEASE SUSCEPTIBILITY

Table 2 shows the relative risk of sarcoidosis associated with each DR antigen in both ethnic groups. Antigens at the A, B, and C loci which were associated with relative risks greater than 2·0 for either group are also shown.

In the English group there was an increased relative risk for B8 and Cw7. The association of Cw7 with disease susceptibility was highly significant (pc $< 0{\cdot}001$) (table 3), and remained significant after application of Yates's correction (pc $< 0{\cdot}001$). The frequency of these antigens in the English control group agreed with the expected frequency of B8 (29·2%) and Cw7 (1·4%).[10]

In the West Indian patients with sarcoidosis there was an increased relative risk with B5, DR3, and DR7 (table 2) but only with DR7 did it approach significance (table 3). The frequency of these antigens in the West Indian control group agreed with their expected frequency in black Africans (1·4%, 30%, and 9% respectively).[10]

HLA ASSOCIATION WITH DURATION OF DISEASE FROM DIAGNOSIS

In the English patients a significant association between B8 and DR3 and duration of disease since diagnosis was observed (fig 1). For B8 positive individuals the median duration from diagnosis was two years (range 0–21) compared with a median of five years (range 1–32) for B8 negative individuals (difference not significant). The DR3 antigen, however, was significantly associated with short duration of disease from diagnosis. The median duration for DR3 positive individuals was 1 year (range 0–8) compared with 5·5 years (range 1–32) for DR3 negative individuals ($p = 0{\cdot}002$, Wilcoxon's rank sum test). The Cw7 antigen did not correlate with the duration of disease from the time of diagnosis when used on its own in the analyses. Eight of nine Cw7 positive English patients, however, were B8 positive and seven were positive for Cw7, B8, and DR3. Of these seven, five were newly diagnosed, five had erythema nodosum, five had bilateral hilar lymphadenopathy, and four had arthralgia.

For the West Indian patients there was no significant association between any HLA antigen and the duration of disease.

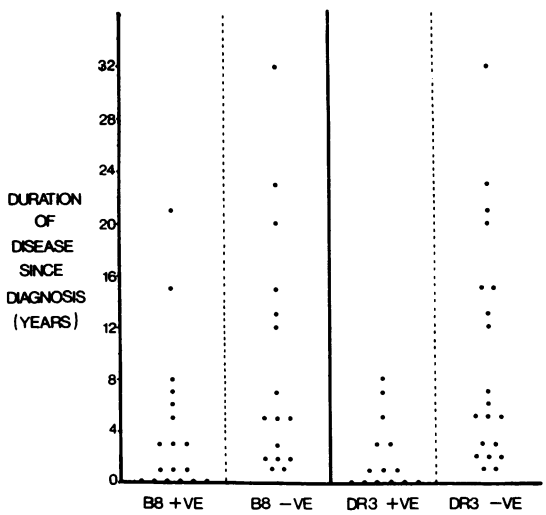
Table 2 *Frequency of and relative risks associated with DR antigens and with HLA antigens at the A, B, and C loci (if relative risk over 2·0) in English and West Indian patients with sarcoidosis*

Antigen	*English*			*West Indian*		
	No (%) of subjects with antigen			*No (%) of subjects with antigen*		
	Patients (n = 34)	*Controls (n = 96)*	*Relative risk*	*Patients (n = 28)*	*Controls (n = 57)*	*Relative risk*
DR 1	4 (11·8)	13 (13·5)	0·85	2 (7·1)	15 (26·3)	0·21
DR 2	5 (14·7)	30 (31·3)	0·47	8 (28·6)	23 (40·4)	0·59
DR 3	15 (44·1)	31 (32·3)	1·47	16 (57·1)	17 (29·8)	3·13
DR 4	10 (29·4)	35 (36·5)	0·73	5 (17·9)	6 (10·5)	1·85
Dr 5	6 (17·6)	21 (21·8)	0·76	8 (28·6)	23 (40·3)	0·59
DRw6	9 (26·5)	15 (15·6)	1·94	3 (10·7)	15 (26·3)	0·34
DR 7	7 (20·6)	21 (21·8)	0·93	9 (32·1)	5 (8·8)	4·93
DRw8	0	2 (2·0)	0·0	0	0	
DRw9	1 (2·9)	1 (1·0)	2·88	0	0	
B5	2 (5·9)	12 (12·5)	0·44	5 (17·9)	1 (1·8)	11·20
B8	18 (52·9)	32 (33·3)	2·25	2 (7·1)	7 (12·3)	0·54
Cw7	9 (26·5)	1 (1·0)	34·2	3 (10·7)	7 (12·3)	0·86

Table 3 *Statistical analysis of HLA antigens with relative risk of over 2·0 for association with sarcoidosis in English and West Indian patients.*

	English		*West Indian*		
	B8	*Cw7*	*DR3*	*DR7*	*B5*
χ^2	4·07	22·86	5·89	7·45	7·42
p	0·04	0·000017	0·015	0·0063	0·0065
pc	1·33*	0·00053	0·13*	0·0567	0·2*

*Not significant.
Pc—p value corrected for number of antigens tested.



B8 and DR3 association with duration of disease from diagnosis in the English group of patients with sarcoidosis.

Discussion

This is the first report of HLA-DR typing in a group of English and West Indian patients with sarcoidosis. Association of diseases with HLA antigens probably occurs because genes for disease susceptibilities are in linkage disequilibrium with certain HLA antigens. Our data support the idea that the same disease may be linked with different HLA antigens in different ethnic groups. Woodrow and coworkers also noted this in a study of HLA antigen linkage in rheumatoid arthritis in two different ethnic groups.[11] In addition, previous workers have reported an association between HLA-B7 and sarcoidosis in Scandinavian patients,[12] which we have not confirmed in English or West Indian patients with sarcoidosis.

It has been suggested by previous workers that HLA-B8 is associated with sarcoidosis.[13] In European Caucasians B8 is in linkage disequilibrium with Cw7 (p 0·001).[10] Our data support this (eight out of nine Cw7 positive individuals were B8 positive) and suggest that the gene for susceptibility to sarcoidosis is more closely linked with Cw7 than B8 in English patients. In African blacks B8 and Cw7 are not in linkage disequilibrium,[11] which would be consistent with our finding that there was no association of Cw7 and B8 in the West Indian sarcoid and control groups.

Smith and colleagues reported an association between HLA-B8 and spontaneous resolution of sarcoidosis,[5] and Neville and coworkers commented on the apparent association between B8 and features of acute sarcoidosis.[6] Our data on the English patients support an association between B8 and a shorter duration of disease since diagnosis, but they show a more significant association of this feature

with DR3, and also with inheritance of the B8/Cw7/DR3 haplotype. A high proportion of HLA-B8Cw7/DR3 positive individuals showed combinations of erythema nodosum, arthralgia, and bilateral hilar lymphadenopathy—all features of acute sarcoidosis, which tends to resolve more rapidly.[6] Our study represents a cross-sectional survey of acute and chronic sarcoidosis seen in hospital clinics, and our data may imply that B8/Cw7/DR3 individuals recover more quickly and are discharged early from outpatient follow up.

DR3 is known to be in linkage disequilibrium with B8 in European Caucasian subjects.[10] The antigens B8 and DR3 are frequently linked with diseases in which there is immunological dysfunction.[4] Lawley and coworkers reported that HLA-B8/DR3 positive individuals tended to have a reduction in the number of T lymphocytes with Fc receptors for IgG, which are associated with suppressor function.[14] Such people are thought to be more prone to development of autoimmune disease.[15] It has also been suggested that B8/DR3 positive individuals may be able to mount a more vigorous immune response[16]; our data would support this idea.

Our West Indian group may have comprised a larger proportion of patients with chronic sarcoidosis than our English group. This is supported by the observation that splenomegaly and hepatomegaly occurred in eight and nine patients respectively in our West Indian group but in none of the patients in the English group (table 1). Erythema nodosum was present in only one West Indian but in nine English patients. This may explain why we found no association between an HLA antigen and duration of disease from diagnosis in the West Indian group.

In conclusion, we have shown a significant association between sarcoidosis and Cw7 in English patients with sarcoidosis, which is not observed in West Indian patients with sarcoidosis. In addition, possession of the DR3 antigen, and in particular the B8/Cw7/DR3 haplotype, may be associated with a good prognosis in English patients with sarcoidosis.

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