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The relationship of HLA-B and DR phenotypes to Behcet's syndrome, recurrent oral ulceration and the class of immune complexes

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Summary. A series of eighty Caucasian patients was divided into four groups with the mucocutaneous, arthritic, neurological and ocular types of Behcet's syndrome (BS) and a fifth group of patients with recurrent oral ulcers. The immunogenetic basis of the four types of BS was extended from HLA-B locus to the DR locus. Whereas B5 and more precisely the Bw51 split is the most discriminating marker of the ocular type of BS, DR7 also shows a significant increase in the ocular and neurological types. Indeed, most if not all patients with the ocular type have B5 and/or DR7. B12 and/or DR2 is significantly increased at the less severe end of the spectrum, the mucocutaneous and arthritic types. Patients with recurrent oral ulcers also show an increase in B12 and/or DR2. However, B12 and/or DR7 shows an increase in the relative risk in all four types of BS. These results suggest that HLA-B12, B5, DR7 and DR2 might in some way be associated with tissue localization of disease. Alternatively, since patients with HLA-B12 show a significantly greater ratio of IgG:IgA circulating immune complexes than those with B5/DR7/DR2, tissue localization might be influenced by the immune complex isotype. A significant relationship was also found between the MT2 and MT3 B cell alloantigen system and BS, with particular reference to MT2 and the neurological type and MT3 and the ocular type of BS.

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INTRODUCTION

Behcet's syndrome (BS) is a multifocal disease which may affect the mouth, genitals, skin, joints, eyes and brain. The syndrome has been grouped into four types on the basis of tissue involvement (Lehner, Batchelor, Challacombe & Kennedy, 1979a) and HLA-A and B studies have shown that three of the four types of BS have an immunogenetic basis. The mucocutaneous type is significantly associated with HLA-B12 (Lehner *et al.*, 1979a), the arthritic type might be related to B27 and the ocular type is strongly associated with B5 (Ohno, Nakayama, Sugiura, Itakura, Aoki & Aizawa, 1975). Only the neurological type failed to show a significant association with any of the HLA-A or B loci. Recurrent oral ulcers (ROU) are common to all four types of BS and share with the mucocutaneous type a significant increase in the prevalence of B12 (Challacombe, Batchelor, Kennedy & Lehner, 1977, Lehner *et al.*, 1979a).

Antigens within the B locus show cross reactions and on the basis of a leucoagglutination test two subgroups have been defined; HLA-Bw4 and HLA-Bw6 (4a and 4b of Van Rood & Van Leeuwen

1963). It has been noted that the three HLA-B associated antigens of BS, HLA-B5, B27 and B12 are located on HLA-Bw4 (Lehner & Batchelor, 1979). However, many of the cross-reacting groups of antigens on lymphocytotoxicity testing cut across their subdivision into Bw4 and Bw6 associated antigens and display 'public' specificities (Joysey & Wolf, 1978). It has been suggested that the cross-reacting HLA-B5, B15, B18, Bw35 and possibly Bw21 might be more closely associated with the pathogenesis of BS than B5 (Schwartz, Luehrman & Rodey 1980). We have now extended the HLA typing to the C and D loci, in order to explore the possibility that there are further associations in BS with antigens particularly in the D locus which is thought to be closely related to the Ia genes. MT typing has also been carried out as there is a preliminary report suggesting that the prevalence of MT2 is increased in a Japanese population of patients with BS (Sasazuki, Nishimura, Mineshita, Miyashita & Inaba, 1982; Ohno, Ohguchi, Matsuda, Wakisaka & Aizawa, 1982). Of special importance is the relationship between the immune responses and HLA antigens and this was investigated by determining cold precipitable immune complexes in patients with BS and ROU (Lehner, Losito & Williams, 1979b) and analysing these according to the HLA type of these patients.

MATERIALS AND METHODS

Subjects

A group of eighty British, Caucasian patients and 100 controls were studied. The patients consisted of eighteen with the mucocutaneous type, seventeen with the arthritic type, ten with the neurological type, and fifteen with the ocular type of BS, as defined previously (Lehner & Batchelor, 1979). There were also twenty patients with ROU.

HLA tests

HLA-A, B, C typing was performed by the lymphocytotoxicity test, using T lymphocytes and antisera to HLA-A, B and C. HLA-DR was tested with well validated antisera and enriched suspensions of B lymphocytes (Welsh & Batchelor, 1978). HLA-DR was determined in sixty-eight of the patients and seventy controls, the latter were selected so as to exclude subjects with a history of ROU. The frequency of HLA-A and B antigens will not be considered in detail, as a larger population has been investigated previously (Lehner *et al.*, 1979a). Nevertheless, the frequency of HLA-B12, B5 and B27 are given (Table 2), as these will be considered in combination with HLA-DR antigens and the Bw4 locus.

Table 1. The prevalence of HLA-DR antigens in the four types (T) of Behcet's syndrome and in recurrent oral ulceration given as number of subjects

		HLA-DR						
	n	1	2	3	4	5	6	7
Controls	70	15	14	25	25	20	15	12
Behcet's syndrome	51	8	11	11	16	7	10	20‡§
Mucocutaneous T	16	4	1	2	8	2	5	5
Arthritic T	14	1	6	3	3	4	1	2
Neurological T	10	3	2	2	1	1	2	6‡
Ocular T	11	1	1	3	3	0	2	7‡§
Recurrent oral ulcers	17	6	8*	2	5	2	3	2

* $P<0.05$.
‡ $P<0.01$.
§ $P<0.05$ with Svejgaard's correction.

Cold precipitable complexes

These were separated from samples of 20 ml of blood which were allowed to clot at 37° and the serum was separated and then kept at 4° for 7 days. The crypoprecipitate was separated by centrifugation and washed six times in phosphate-buffered saline at 4°. The precipitate was dissolved in 0·3 ml of 0·3 M sodium chloride at 37° and then 0·3 ml of distilled water was added and kept at room temperature. IgG, IgA, IgM and C3 components were assayed in the complexes by laser nephelometry, using specific nephelometry grade antisera (Hyland Reagents) as described elsewhere (Lehner *et al.*, 1979b). The results were read from a curve drawn from the relative light scattering given by standards of known antigen concentrations and the results were expressed in mg/100 ml of serum.

RESULTS

The prevalence of HLA-DR antigens are given in Table 1. Fisher's exact test and Svejgaard's correction factor (C) for the seven DR antigens was applied (Svejgaard *et al.*, 1979). Of the seven HLA DR antigens, only DR7 gave a significantly increased frequency in the entire group of BS ($P=0.0039$;

Table 2. The prevalence of HLA-B 12, 5 and 27 antigens in the four types (T) of Behcet's syndrome and in recurrent oral ulceration given as number of subjects

		HLA		
	n	B12	B5	B27
Controls	100	22	12	3
Behcet's syndrome	60	28‡	15*	5
Mucocutaneous T	18	12‡§	0	2
Arthritic T	17	8*	1	3
Neurological T	10	2	2	0
Ocular T	15	4	12§¶	0
Recurrent oral ulcers	20	9*	2	2

* $P<0{\cdot}05$.
‡ $P<0{\cdot}01$.
§ $P<0{\cdot}001$.
¶ $P<0{\cdot}05$ with Svejgaard's correction.

C = 0·0273). DR7 was also significantly increased in the ocular type ($P=0{\cdot}0051$; C = 0·0357) and in the neurological type of BS ($P=0{\cdot}0141$; C = 0·0987). Of the three selected HLA antigens (Table 2), HLA-B12 was significantly increased in BS ($\chi^2=10{\cdot}620$, $P<0{\cdot}01$), the mucocutaneous ($\chi^2=14{\cdot}837$, $P<0{\cdot}001$) and arthritic types ($\chi^2=4{\cdot}7854$, $P<0{\cdot}05$) and in ROU ($\chi^2=4{\cdot}6017$, $P<0{\cdot}05$), the Chi-squared test was used here as the expected values were large enough. B5 was very significantly increased in the ocular type ($\chi^2=36{\cdot}522$, $P<0{\cdot}0001$) but B27 in the arthritic type failed to reach the 5% level of significance ($P=0{\cdot}0782$). A further analysis of B5 into the Bw51 and Bw52 splits showed that all twelve patients with the ocular type of BS and B5 had the Bw51 split. This is consistent with the much greater prevalence of Bw51 (13·9%) than Bw52 (2·9%) in a control Caucasian population (Terasaki, 1980). In our selected control population of seventy subjects 10% had Bw51 and 1·4% Bw52.

Table 3. The prevalence of HLA B12/DR2, B12/DR7 and B5/DR7 in the four types (T) of Behcet's syndrome and in recurrent oral ulceration given as number of subjects

		HLA		
	n	B12/DR2	B12/DR7	B5/DR7
Controls	70	27	25	18
Behcet's syndrome	51	33‡	38§¶	25†
Mucocutaneous T	16	12†	13‡	5
Arthritic T	14	12‡	10‡	3
Neurological T	10	4	6	6**
Ocular T	11	5	9‡	11§¶
Recurrent oral ulcers	17	13‡	8	3

† $P<0{\cdot}02$.
‡ $P<0{\cdot}01$.
§ $P<0{\cdot}001$.
¶ $P<0{\cdot}05$ with Svejgaard's correction.
** $P=0{\cdot}0731$.

The possibility was then considered that the HLA-B12 or B5 alleles might be significantly associated with HLA-DR7 or DR2 alleles. The frequency of HLA B12 and/or DR7, B12 and/or DR2 and B5 and/or DR7 were calculated in the five groups of patients and the control group of seventy subjects (Table 3). A significant increase in frequency of B12 and/or DR7 was found in BS and the four types, with the exception of the neurological type of BS. The frequency of B12 and/or DR2 was significantly increased in BS and the mucocutaneous and arthritic types but not in the neurological and ocular types of BS. The frequency of B5 and/or DR7 was significantly increased in BS and in the ocular type of BS; it should be noted that all the eleven patients had either B5 or DR7 or both antigens. In view of the significant linkage disequilibrium between Bw51 and both DR5 and DR8 (Terasaki, 1980) we were surprised to find no patients with DR5 among the eight patients with B5 (Bw51) and the ocular type of BS. In the neurological type there was also an increase in frequency of B5 and/or DR7 (6/10; $P=0{\cdot}0731$). Patients with ROU showed an increase in DR2 ($P=0{\cdot}0535$) but the combined B12 and/or DR2 allele was more significant ($P=0{\cdot}0103$).

The percentages and the relative risks of the significant HLA-B and DR antigens and their combinations are shown in Fig. 1. This analysis suggests that the increased risk of ROU, mucocutaneous or arthritic type of BS is associated with B12; whereas the ocular or neurological type is associated with DR7. However, B5 is associated only with the ocular type of BS. The results of combined B and/or DR antigen suggest that B12/DR7 is a significant risk factor across the entire spectrum of BS. However, B12/DR2 is associated with ROU and the mucocutaneous and arthritic types of BS, whereas B5/DR7 is associated with the ocular and neurological types. None of the HLA C antigens showed an increased frequency in either BS or ROU, so that this locus has not been analysed.

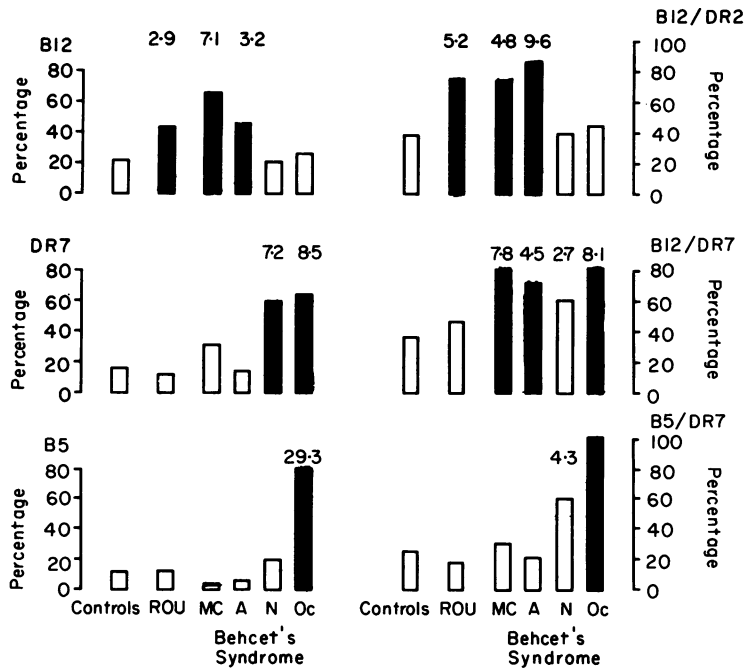

Figure 1. The separate or combined prevalence of HLA-B12, B5, DR7 and DR2 in the four types of Behcet's syndrome and recurrent oral ulcers. Numbers indicate the relative risk. (■) $P<0.05$. MC, mucocutaneous; A, arthritic; N, neurological; Oc, ocular.

Cross-reactive B locus antigens

Cross-reactive group B5, B15, B18, Bw35 (Bw21) (Table 4). A significant increase in frequency of one or more of these antigens was not found in BS, in any of the four types of BS or in ROU when compared with a corresponding control group.

Table 4. The prevalence of two cross-reactive groups within the HLA-B locus in the four types (T) of Behcet's syndrome and in recurrent oral ulceration given as number of subjects

	n	No. (%) HLA-B 5,15,18,w35,w21	No. (%) HLA-B 5,12,27
Controls	70	36 (51)	29 (41)
Behcet's syndrome	60	26 (43)	40 (67)†
Mucocutaneous T	18	5 (28)	13 (72)*
Arthritic T	17	6 (35)	11 (65)
Neurological T	10	3 (30)	3 (30)
Ocular T	15	12 (75)	13 (87)†
Recurrent oral ulcers	20	7 (35)	12 (60)

* $P<0.05$.
† $P<0.01$.

Selected HLA-Bw4 associated antigens B5, B12, B27 (Table 4). A significant increase in frequency of one or more of these antigens was found in BS ($P=0.0067$), in the ocular type ($P=0.0028$) and to a lesser extent the mucocutaneous type of BS ($P=0.0374$). The arthritic type of BS and ROU also showed an increased frequency of these antigens but the 5% level of significance was not reached.

Clusters of HLA-DR alloantigens (supertypic antigens). A significant increase in MT2 ($\chi^2=6.157$; $P<0.02$) and in MT3 ($\chi^2=4.472$; $P<0.05$) was found in the total number of fifty-one patients with BS examined. However, the prevalence of MT2 or MT3 in ROU was less than that found in the controls (Table 5). A significant difference was found between the patients with BS and those with ROU, with both MT2 ($\chi^2=6.157$, $P<0.02$) and with MT3 ($\chi^2=5.9042$; $P<0.02$). Examination of the four types of BS showed a significant increase in MT2 only with the neurological

Table 5. The prevalence of MT2 and MT3 in the four types (T) of Behcet's syndrome and in recurrent oral ulceration

		MT2 (DR3, 5, w6, w8)		MT3 (DR4, 7)	
	n	No.	(%)	No.	(%)
Controls	60	22	(36·7)	28	(46·7)
Behcet's syndrome	51	33	(64·7)* $P<0·01$	34	(66·7)* $P<0·05$
Mucocutaneous T	16	10	(62·5)	12	(75)
Arthritic T	14	9	(64·3)	5	(35·7)
Neurological T	10	9	(90)† $P=0·0041$	7	(70)
Ocular T	11	5	(45)	10	(90·4)† $P=0·0131$
Recurrent oral ulcers	19	6	(31·6)	7	(36·8)

* χ^2 test.
† Fisher exact test.

type ($P=0·0041$) and in MT3 only with the ocular type ($P=0·0131$) by Fisher's exact test.

Cold precipitable complexes

IgG, IgA and the ratio of IgG:IgA was analysed in complexes from thirty-nine patients (Fig. 2). B12 appeared to be dominant in its influence on the immune complexes, so that complexes from patients with B12 or B12 and B5, DR7 or DR2 were plotted with the B12 data. Complexes from patients with B5 and/or DR7 and/or DR2 were plotted separately (Lehner, Welsh & Batchelor, 1981). A significant increase in IgG complexes above an arbitrary level of 0·20 mg/100 ml was found in the B12, as compared with the B5/DR7/DR2 patients ($P=0·0166$). In contrast IgA complexes were significantly increased above 0·20 mg per 100 ml in the B5/DR7/DR2, as compared with the B12 patients ($P=0·0237$). Furthermore, the ratio of IgG:IgA complexes was significantly increased in the B12 patients ($P=0·0127$).

DISCUSSION

The immunogenetic basis of BS and ROU based on the HLA-A and B loci has now been extended to the HLA-DR locus. It seems that B12 is associated with an

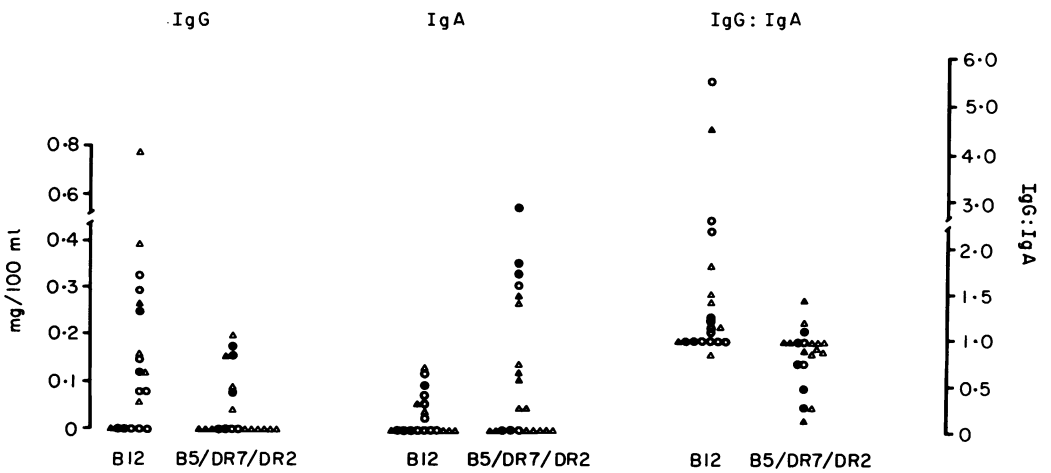

Figure 2. IgG and IgA cold precipitable complexes in patients with HLA-B12 and those with HLA-B5/DR7/DR2 phenotypes. (○) Mucocutaneous type; (●) arthritic type; (▲) neurological type; (△) ocular type.

increase in the relative risk of ROU and the mucocutaneous and arthritic types of BS (Fig. 1), as has been found before (Lehner *et al.*, 1979a). This is, however, further increased with B12 and/or DR2 in ROU and the arthritic type of BS with a relative risk of 5·2 and 9·6, respectively. On the other hand, DR7 shows a high relative risk only for the ocular (8·5) and neurological (7·2) types of BS. A combination of B12 and/or DR7, however, spreads this risk across to the other two types of BS. Indeed, 74·5% of all four types of BS have B12 and/or DR7 and the relative risk is between 4·5 and 8·1 for all except the neurological type. B5 is the most discriminating marker of BS (Ohno *et al.*, 1975), showing a very significant association with the ocular type of BS (Lehner *et al.*, 1979a). Eighty percent (12/15) patients with the ocular type have B5 and this increases to 100% (11/11) if B5 and/or DR7 are considered Fig. 1).

It should be noted that all twelve patients with B5 and the ocular type of BS had the Bw51 split and this agrees with the Japanese group of twenty-three patients with BS in whom 60·9% had the Bw51 and only 8·9% the Bw52 split (Ohno, Asanuma, Sugiura, Wakisaka & Aizawa, 1978). However, a Japanese control population shows 15·9% Bw51 and 20·5% Bw52, unlike a corresponding Caucasian population, with 13·9% Bw51 and only 2·9% of Bw52 (Terasaki, 1980).

Although B5 is also significantly increased in BS in Turkey (Yazici, Akokan, Yalcin & Mutuoglu, 1977), Israel (Haim, Grideoni & Barzilai, 1977) and France (Godeau, Torre, Campinchi, Bloch-Michel, Schmidt, Nunez-Roldan, Hors & Dausset, 1976), an increase in the Bw51 split has been determined only in Turkish patients (Yazici, Chamberlain, Schreuder, Amaro & Muftuoglu, 1980). The significant association between HLA-B5 (or the Bw51 split) and BS among different ethnic groups strengthens the relationship between BS and HLA-B5 to that found between ankylosing spondylitis and HLA-B27. Whether HLA-DR7 is similarly associated with BS in different ethnic groups will need to be determined, but it should be noted that DR7 is not found in Japanese people. The observation that 15/15 patients with the ocular form of BS have either Bw51 and/or DR7, is consistent with the view that DR7 may also be a significant marker of the ocular type of BS. The possibility that a Bw51 and DR7 haplotype is associated with the ocular form will be investigated in families.

These results suggest that certain HLA-B and/or DR antigens discriminate between the spectrum of tissue involvement, with ROU and the mucocutaneous type of BS at one end and the ocular type of BS at the other end of the spectrum. An attractive hypothesis to account for these findings is that HLA phenotypes might be associated with tissue localization by cross-reactions between a specific HLA antigen and the offending antigen. Alternatively, the HLA antigen may have a receptor for the microbial or other antigen. Thus, B5 might have a specific relationship to the uveal tract, whereas DR7 might be associated with both the uveal tract and brain tissue. B12 is less discriminating and is associated with oral, genital and skin epithelia, as well as joints and this is enhanced with B12/DR2. Since B12 appears to be related to the mucocutaneous and arthritic types and DR7 to the neurological and ocular types, it is perhaps not surprising that B12/DR7 is associated with all four types of BS.

The possibility that the 'public' cross-reactive group of B antigens (B5, 15, 18, W35 and W21) might correlate better with BS than the individual antigens (Schwartz *et al.*, 1980), has been tested and has failed to show a significant relationship. However, a corresponding analysis of some of the HLA-BW4 associated antigens (B5, 12, 27) (Lehner & Batchelor, 1979), showed a very significant increase in BS and the ocular type ($P < 0{\cdot}01$) and to a lesser extent the mucocutaneous type ($P < 0{\cdot}05$) of BS. These Bw4 associated antigens suggest a relationship between the mucocutaneous (B12), ocular (B5) and arthritic (B27) types of BS. B27 was not significantly increased in this series of seventeen patients with the arthritic type of BS in which only three patients had B27, unlike in a smaller group of 3/11 positive patients examined previously (Lehner *et al.*, 1979a). The importance of B27 in the arthritic type will have to be pursued in a larger series, but clearly it is not associated with anterior uveitis in BS, as compared with anterior uveitis not associated with BS (Perkins, 1976).

A significant increase in the prevalence of MT2 in BS was suggested in Japanese populations by Sasazuki, Ohguchi, Matsuda, Wakisaka & Aizawa (1982) and Ohno *et al.* (1982) and was also found in our Caucasian, British population (Table 5). The overall MT2 frequency in both our controls and patients are lower than those reported in Japanese populations. However, this might be due to a lack of standardized MT antisera. In addition, MT3 was also increased significantly in BS and both MT2 and MT3 were significantly increased in BS as compared with ROU (Table 5). It seems then that the MT, B cell alloantigen

system (Park, Teraski, Nakata & Aoki, 1980) may also be involved in BS. However, it is of particular interest that in a further analysis of the types of BS, MT2 was increased significantly only in the neurological type and MT3 in the ocular type (Table 5). In view of a computer based analysis of immune complexes which revealed two cross-reactive groups, one of which was represented predominantly by the ocular type and the other by the neurological type of BS (Burton-Kee, Mowbray & Lehner, 1981), this raised the possibility that MT3 or some closely associated antigen might represent the cross-reactive ocular antigen, whereas MT2 the corresponding neurological antigen.

An alternative interpretation to the direct hypothesis, linking HLA with the offending antigen, is one that postulates an association between HLA and genes determining the isotype response to antigen stimulation, with the resulting complexes showing specific localization patterns (Lehner *et al.*, 1981). Patients with HLA-B12 have a significantly greater proportion of IgG to IgA immune complexes, as compared with B5 and/or DR7 and/or DR2 patients (Fig. 2). This suggests that in the B5/DR7/DR2 patients the greater proportion of IgA complexes may block chemotaxis and phagocytosis (Van Epps & Williams, 1976; Van Epps, Reed & Williams, 1978; Abdulla & Lehner, 1979), resulting in failure of clearance of the IgG complexes and thereby contributing to the potential damage induced by the complexes.

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