

Primary association of HLA-B51 with Behçet's disease in Ireland

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Abstract

Aims/background—While a primary association of HLA-B51 with Behçet's disease (BD) in Japanese and Mediterranean patients supports an immunogenetic predisposition, this link is unclear in north western Europe. This study assessed HLA associations with BD, and HLA-B51 with certain clinical characteristics, in the Republic of Ireland, which has an ethnically homogeneous population.

Methods—HLA-A, HLA-B, and HLA-DR typing was performed in 24 BD patients, conforming to International Study Group criteria, and in blood donors, as controls. Patient records were retrospectively reviewed and patients reassessed clinically.

Results—A highly significant HLA-B51 association (corrected exact p value = 0.002, relative risk = 6.3) with BD was determined, despite a low B51 prevalence (25%) in patients. No other HLA type was associated. There was a significant B51 link with male sex in BD patients but no association with age at first manifestation/diagnosis, eye involvement, cyclosporin A therapy, or poor visual acuity was determined.

Conclusions—This study supports a HLA-B51 immunogenetic predisposition, similar to Japanese patients, in Irish BD in an ethnically homogeneous population in north western Europe. However, owing to a low prevalence of B51 positivity in BD patients in Ireland, a multifactorial pathogenesis is suggested.

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Controversy has arisen with regard to the significance of these observations in north western Europe and the USA.^{1 16–22 25–28} No HLA association was found in either US or British patients.^{16–22} Many of these studies were performed before the HLA-B5 antigen was split into its subtypes, with HLA-B51 being strongly associated and not HLA-B52.⁶ HLA typing is not included in the International Study Group Criteria (ISG)²³ for diagnosis, which may be more commonly used in Europe.

Findings from studies in the west may be more difficult to interpret as there is a much lower prevalence and hence smaller study group of patients. There are apparent differences in the spectrum of Behçet's disease in different populations³ and the strength of the HLA-B51 association, emphasising genetic aetiological factors, and its relation with visual prognosis are unclear in north western Europe.

The aim of this study was to investigate whether an immunogenetic predisposition for Behçet's disease is present in an ethnically homogeneous north west European population, that of the Republic of Ireland, and to assess if any relation with visual prognosis exists.

Materials and methods

Twenty four patients were recruited from the ophthalmology departments of university teaching hospitals and by referral from requests to ophthalmologists, rheumatologists, dermatologists, and genitourinary physicians throughout the Republic of Ireland. All were required to satisfy the ISG criteria for diagnosis of Behçet's disease.²³ Hospital charts were reviewed retrospectively and each patient was reassessed by one ophthalmologist (DK) and a blood sample for HLA typing was obtained after informed consent.

HLA typing was carried out by the National Tissue Typing Reference Laboratory of the Blood Transfusion Service Board. HLA-A and HLA-B typing was performed by the standard National Institutes of Health microlymphocytotoxicity method and HLA-DR typing was performed by DNA polymerase chain reaction for both patients and controls. The control group consisted of 96 healthy voluntary blood donors to the Blood Transfusion Service Board, of whom all had HLA-A and HLA-B typing and 84 had HLA-DR typing. Age and sex matched consecutively typed controls were chosen for each patient so that both patient and controls were typed at the same time using

Behçet's disease (BD) is a multisystem vasculitic disorder with frequent devastating ocular manifestations.^{1–3} HLA status in Behçet's disease has supported the idea of an immunogenetic predisposition ever since a strong association with HLA-B5 was first described by Ohno *et al* in Japanese patients in 1973.⁴ Further studies in Japan^{5 6} revealed a primary association with HLA-B51, a split product of HLA-B5, with a calculated relative risk of 7.9.⁶ Several other studies have confirmed this association in Korean, Taiwanese, Kuwaiti, Israeli, Turkish, Greek, and Tunisian patients,^{7–13} where the disease is most common and corresponds to the old Silk Route between the east and the west.¹⁴ HLA typing can aid diagnosis in these patients and HLA-B51 testing is included as a laboratory test in the crite-

the same antisera. There is only one blood donor service in the Republic of Ireland which operates nationally with one central tissue typing laboratory allowing voluntary blood donors to be used as representative of the general population. Antigen frequencies were counted by direct counting. Statistical significance between the relative frequencies of antigens in patients and controls was determined by χ^2 and Fisher's exact tests with Yates's correction. Exact p values were corrected to avoid a type I error, as outlined by Meenken *et al.*,²⁴ for, in a sample of 53 informative comparisons, one may expect to observe, by chance alone, two to three 'significant' HLA associations. The correction is performed by multiplying the exact p value with the number of antigen frequencies tested (a factor of 53 in our study). All p values given are two tailed. Significance was evaluated by 0.05 > p > 0.01 is significant and p < 0.01 is highly significant.

Any HLA-B51 association with certain clinical features, such as sex, age at first manifesta-

tion of disease, age at diagnosis, the presence of eye involvement, visual acuity worse than 6/60 in an affected eye, and requirement for systemic cyclosporin A therapy, was assessed. First manifestation of disease was defined as the first manifestation of one of the ISG diagnostic criteria (including recurrent mouth ulcers). Age at diagnosis was defined as the age at which the ISG criteria for diagnosis were fulfilled. Statistical association with age was assessed using the Mann-Whitney U test for non-parametric data.

Results

Of the 24 patients with Behçet's disease, all had HLA-A and HLA-B typing and 21 underwent HLA-DR typing. There were 14 male and 10 female patients. All patients were white and of ethnic native Irish origin. HLA antigen frequencies of patients and controls are given in Table 1. A remarkably significant HLA association in patients with Behçet's disease in the Republic of Ireland was found with HLA-B51

Table 1 HLA antigen frequencies in 24 Irish patients with Behçet's disease

Antigen	Antigen frequency		χ^2	Relative risk	Exact p value
	Patients (%) (A,B: n=24, DR: n=21)	Controls (%) (A,B: n=96 DR: n=84)			
A1	58.33	45.83	0.8	1.5	0.386
A2	62.50	59.38	0.0	1.1	0.963
A3	16.67	35.42	2.3	0.4	0.128
A9	4.17	3.13	0.2	1.3	1.000
A10	8.33	4.17	0.1	1.7	0.345
A11	20.83	8.33	2.0	2.2	0.133
A19	4.17	6.25	0.0	0.7	1.000
A24	0.00	14.58	2.7	0.0	0.070
A25	0.00	3.13	0.0	0.0	1.000
A26	0.00	2.08	0.0	0.0	1.000
A28	4.17	3.13	0.2	1.3	1.000
A29	8.33	7.29	0.1	1.1	1.000
A31	4.17	1.04	0.0	2.6	0.361
A32	4.17	6.25	0.0	0.7	1.000
A33	4.17	0.00	0.6	5.2	0.200
B5	0.00	3.13	0.0	0.0	1.000
B7	20.83	37.50	7.0	3.7	0.008
B8	37.50	52.08	1.1	0.6	0.294
B12	4.17	0.00	0.6	5.2	0.200
B13	0.00	1.04	0.6	0.0	1.000
B14	16.67	10.42	0.1	1.3	0.517
B15	0.00	2.08	0.0	0.0	1.000
B17	8.33	1.04	1.7	3.5	0.105
B18	0.00	2.08	0.0	0.0	1.000
B22	0.00	1.04	0.6	0.0	1.000
B27	4.17	6.25	0.0	1.3	0.660
B35	4.17	4.17	0.3	1.0	1.000
B37	0.00	5.21	0.3	0.0	0.582
B39	4.17	3.13	0.2	1.3	1.000
B40	8.33	4.17	0.1	1.7	0.345
B44	50.00	34.38	1.4	1.7	0.239
B45	0.00	1.04	0.6	0.0	1.000
B49	0.00	1.04	0.6	0.0	1.000
B50	0.00	1.04	0.6	0.0	1.000
B51	25.00	0.00	20.3	6.3	0.00004
B53	0.00	1.04	0.6	0.0	1.000
B55	0.00	1.04	0.6	0.0	1.000
B57	12.50	5.21	0.7	2.0	0.197
B60	4.17	7.29	0.0	0.6	1.000
B62	0.00	10.42	1.5	0.0	0.209
DR1	23.81	13.10	0.8	1.7	0.305
DR2	33.33	11.90	4.2	2.6	0.041
DR3	38.10	47.62	0.3	0.7	0.590
DR4	19.05	40.48	2.5	0.4	0.116
DR6	14.29	0.00	7.7	5.7	0.007
DR7	28.57	32.14	0.0	0.9	0.958
DR8	0.00	1.19	0.6	0.0	1.000
DR9	0.00	1.19	0.6	0.0	1.000
DR10	0.00	2.38	0.0	0.0	1.000
DR11	4.76	8.33	0.0	0.6	1.000
DR13	19.05	13.10	0.1	1.4	0.494
DR14	9.52	5.95	0.0	1.5	0.625
DR15	4.76	20.24	1.9	0.2	0.114

Table 2 HLA-B51 status and sex in Irish Behçet's disease

Sex	Total (n=24)	HLA-B51 status		Exact p value
		B51 positive (n=6)	B51 negative (n=18)	
Male	14	6	8	0.024
Female	10	0	10	

(exact p value = 0.00004, $\chi^2 = 20.3$, relative risk = 6.3). When the exact p value was corrected for the number of HLA antigens tested (53), this HLA-B51 association remained highly significant (corrected exact p value = 0.002). The HLA-B51 antigen was found in six out of 24 patients (25%) compared with none of the 96 controls.

An increased frequency was observed for HLA-B7 (exact p value = 0.008) in the BD group compared with the control group. We also observed an increased frequency of two HLA class II antigens, HLA-DR6 (exact p value = 0.007, relative risk = 5.7) and HLA-DR2 (exact p value = 0.041), in patients with Behçet's disease compared with controls. However, after correction of the exact p values for the number of antigens tested (53), the observed differences for HLA-B7, HLA-DR6, and HLA-DR2 did not reach a level of significance.

Sex differences in HLA-B51 status are outlined in Table 2. Of patients with the HLA-B51 antigen, all six were male (exact p value = 0.024) with a male sex:HLA-B51 association achieving probable significance. All 10 female patients were negative for the HLA-B51 antigen. Age at first manifestation and at diagnosis of Behçet's disease with respect to HLA-B51 status is given in Table 3. No difference was found within the BD group for age at first manifestation (exact p value = 0.160) between patients who were HLA-B51 antigen positive (mean age 25.5 years (SD 8.12)) and those who were HLA-B51 negative (mean age 19.2 years (7.28)). Mean age at diagnosis of BD was 28.5 years (8.26) in the HLA-B51 positive group compared with 30.0

Table 3 HLA-B51 status and age in Irish Behçet's disease

	HLA-B51 status		Exact p value
	B51 positive (n=6)	B51 negative (n=18)	
	Mean age (years) (SD)	Mean age (years) (SD)	
Age at first manifestation	25.5 (8.12)	19.2 (7.28)	0.160
Age at diagnosis	28.5 (8.26)	30.0 (5.73)	0.867

Table 4 HLA-B51 status and clinical characteristics in Irish Behçet's disease

	Total	HLA-B51 status		Exact p value
		B51 positive	B51 negative	
Eye involvement				
+	19	14	5	1.000
-	5	4	1	
CsA therapy				
+	7	5	2	1.000
-	17	13	4	
Visual acuity < 6/60*				
+	6	4	2	1.000
-	13	10	3	

*Visual acuity of patients with eye involvement (n=19).

years (5.73) in the HLA-B51 negative group with no significant difference (exact p value = 0.867).

Nineteen patients (79.2%) in the BD group had eye involvement with five possessing the HLA-B51 antigen while 14 patients did not. There was no association between HLA-B51 positivity and eye involvement (exact p value = 1.00). No association was seen between the HLA-B51 antigen and requirement for systemic cyclosporin A therapy (exact p value = 1.00) or visual acuity worse than 6/60 in patients with eye involvement (exact p value = 1.00, Table 4). Of six patients with a visual acuity worse than 6/60 in an affected eye, only two possessed the HLA-B51 antigen.

Discussion

The most significant finding in our study is a highly significant association between HLA-B51 and Behçet's disease (corrected exact p value = 0.002) in the Republic of Ireland which has an ethnically homogeneous white population. Mizuki *et al*⁵ has suggested that the same HLA-B51 association exists worldwide and this has been confirmed in many different ethnic groups, but mostly from the Far East and Mediterranean countries.^{4, 7-13} This HLA-B51 association is unclear, however, in white patients from north western Europe and the USA.

Previous older studies from Britain^{18, 19} and the USA^{16, 20} in the 1970s do not show any HLA-B5 association. O'Duffy *et al* found no HLA association in 26 US patients¹⁶ and more recently stated in an editorial in the *New England Journal of Medicine*¹⁷ that no HLA association existed in either US or British patients. In the largest American series of BD patients to date (35 patients), Foster *et al* could not find a HLA-B51 association.²² Previous North American studies in whites have been, however, from ethnically diverse groups.^{16, 22, 23} Lehner *et al*¹⁹ typed 52 white British patients and found no HLA-B5 association, verifying the results of a previous British study,¹⁸ though there was an association (uncorrected p = 0.002) with the 'ocular type' using an unusual classification system. The only previous Irish study on Behçet's disease found no HLA-B5 association in a small group of six typed patients.²⁵ The results of these older studies are difficult to interpret as they were performed before the HLA-B5 complex was differentiated into its subantigens, HLA-B51, B52, and B53. In addition, different and older diagnostic criteria for diagnosis were used before the advent of the ISG criteria, therefore making comparison different. A more recent study in 14 ethnically homogeneous Scottish patients using the ISG criteria found no HLA-B5 proband association.²⁶ However, the HLA-B5 antigen was not subtyped and while only 13% Scottish BD patients were HLA-B5 positive the authors did not report the HLA-B5 frequency in normal Scottish controls precluding statistical comparison.

In Germany, however, two studies reported an increased frequency of HLA-B5 in BD patients of 23% (compared with 14% of

controls)²⁷ and 67%²⁸ using the ISG criteria. Comparison was made of German BD patients with Mediterranean patients and not with normal controls in the latter study.²⁸ Zouboulis *et al*²⁷ reported a statistically significant HLA-B5 association ($p < 0.05$) with a low relative risk of 2.6 but did not correct p values to avoid a type I error²⁴ which would not produce a significant difference between groups.

Both these studies had inappropriate statistical analyses,^{27,28} comparing a small number of patients with a very much greater number of controls.²⁹ Associations between HLA and diseases should be investigated with an equal number of patients and controls for a near optimal estimation of relative risk.³⁰ However, the optimal sampling ratio in our group for a precise estimate of relative risk is a control group four times the number of patients,³⁰ and this increases the power of the test to an optimal level beyond which diminishing power gains will be achieved.³¹

Support for an immunogenetic HLA-B51 predisposition came from Villaneuva *et al*³² in a Mediterranean family from the south of Spain. They described three sisters with BD (ISG criteria) out of six siblings, with all affected siblings possessing identical HLA haplotypes and all siblings possessing the HLA-B51 antigen.

Behçet's disease is relatively rare in north western Europe and the significance of studies on smaller series of European patients is particularly difficult to interpret.³ There are no prevalence data for BD in Ireland and our study is the largest Irish series to date. Assuming a roughly similar prevalence to Yorkshire¹⁸ of 0.6/100 000 population, one would expect there to be 21 or 22 patients with BD in the Republic of Ireland from current census data.³³ Our study on 24 patients has probably recruited the vast majority of BD patients in the Republic of Ireland. Despite HLA-B51 being present in only 25% of Irish BD patients, when compared with B51 positivity in none of the controls, this produces a relative risk of 6.3. While the proportion of HLA-B51 in BD patients is much higher in Japan^{4,5} and Turkey,^{34,35} 57% and 82% with relative risks of 7.9 and 14 respectively, the high relative risk in our study is similar. While our study reports a highly significant HLA-B51 association and strong immunogenetic predisposition for BD in those who possess the HLA-B51 antigen, 75% of Irish BD patients were HLA-B51 negative and indicates a multifactorial pathogenesis for BD. This is supported by the Spanish familial study,³² and another Japanese family with BD,³⁶ where all affected and unaffected siblings possessed the HLA-B51 antigen. The B51 antigen has been recently subdivided into three alleles, HLA-B*5101, HLA-B*5102, and HLA-B*5103, with all B51 positive patients in a Japanese study³⁷ possessing HLA-B*5101. This allele differs from the other two by a single amino acid substitution in each case, and this would merit further study in our B51 positive Irish patients.

In support of previous studies of BD,^{19,27} we have found a significant association of HLA-

B51 positivity with male sex (exact p value = 0.024). However, with respect to other clinical associations, such as age at first presentation/diagnosis, eye involvement, and severity of ocular disease/poor visual acuity, we found no HLA-B51 association, in common with many other studies from the Far East and Europe.^{27,38-41} Wechsler *et al* have questioned whether the HLA-B51 antigen is relevant for the severity of Behçet's disease.⁴² We would suggest that it is not, and we attribute particular importance to the distinct lack of HLA-B51 association with severity of ocular disease found in this study. Two recent studies from Japan³⁹ and Korea⁴¹ also could not find a HLA-B51 association with poor visual prognosis.

In conclusion, our study found a highly significant HLA-B51 association with BD in Ireland, with a high relative risk. A positive HLA-B51:male sex association and no association with visual prognosis in Behçet's disease was confirmed. This study supports a HLA-B51 immunogenetic predisposition in an ethnically homogeneous white population in north western Europe, far from the Silk Route.

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