Associations of HLA-B alleles with Behçet's disease in Ireland

Sirs,

Behçet's disease (BD) is a rare type of vasculitis that presents with distinctive clinical manifestations and derives from a complex immunopathogenesis. Epidemiologic and molecular studies suggest that both genetic and environmental factors contribute to disease susceptibility. The human leukocyte antigen (HLA)-B*51, an MHC Class I antigen that belongs to the HLA-B*5/B*35 cross-reacting group, is strongly implicated as an important genetic susceptibility gene in BD (1, 2). The geographic distribution appears to correspond with the global distribution of BD (1, 2). However, despite strong ecological evidence, controversy remains as to the strength of the genetic link between HLA B*51 and BD, as some studies have failed to demonstrate linkage (2-6). Moreover, specific populations known to carry a high frequency of HLA-B*51 including American Indians, do not appear to develop the disease (2). In Ireland, a previous study by Kilmartin *et al*. found a highly significant HLA-B*51 association with BD, which was confined to affected males (7) and extended the observations of Dame Professor Chamberlain in a UK study from Yorkshire (8). These findings contrasted with previous reports which failed to support a HLA-B*51 immunogenetic predisposition among ethnically homogenous Caucasian population from the North West of Europe (2-6).

The aim of this study was to re-evaluate the association of HLA-B alleles including HLA-B*51 in an ethnically homogenous BD population from the Midwest region of Ireland. Patients with BD from our registry were invited to participate and data on clinical characteristics, laboratory indicators and medical therapies were extracted. HLA profiling was conducted using Gen-Probe Lifecodes HLA-SSO Typing kits based on Luminex xMAP technology (9). The frequencies of the HLA-B alleles were determined and results were compared to five thousand geographically-matched adult Caucasian controls previously typed using a sequence-specific oligonucleotide probe method (10).

The cohort included 20 (6 males, 14 females) Caucasian patients of Irish descent that satisfied the International Study Group for Behçet's disease (ISGBD) or the International Criteria for Behçet's disease (ICBD) criteria for the diagnosis for BD and living in the Midwest region (catchment areas of Limerick, North Tipperary and Clare with total population of 385, 172) (11). All 20 patients were HLA-typed. HLA-B*51 allele was found in only one patient (5%) (Table II). In descending order, the HLA alleles with the highest frequency were B*44 (7 patients; 35%), B*57 (6 patients; 30%), B*08 (6 patients; 30%), B*35 (5 patients; 25%), B*15 (4 patients; 20%), B*07 (4 patients; 20%) and B*27 (3 patients; 15%). Surprisingly, we found no association between HLA-B*51 and BD in this Irish cohort. The low frequency of HLA-B*51 in BD patients (5%) was similar to the prevalence of the HLA allele in the general population in Ireland (5.1%) (10). In contrast, we found high frequencies of other HLA-B alleles, namely B*57 (30%), B*35 (25%), B*15 (20%) and B*27 (15%), which were less frequently expressed in the general population (B*57; 7.6%, B*35; 10.9%, B*15; 9% and B*27; 7.5%) (10).

The present work suggests that several additional susceptibility genes from the HLA B family may contribute to genetic risk for BD in Irish patients. While we did not confirm previously reported association of HLA-B*51 in Ireland (7), we unexpectedly did identify four novel HLA alleles B*57, B*35, B*15 and B*27 as potentially important contributors to disease risk. These findings suggest that regional variability may exist in genetic susceptibility even within ethnically homogeneous populations and that multiple HLA-B alleles may contribute to the pathway of risk susceptibility. We do acknowledge inherent limitations of this study, including the relatively small sample size and the regional restriction. However, as our centre is the sole referral centre for BD in the region and the catchment area represents one twelfth of the total Irish population (11), we believe these findings characterise the genetic associations of BD within this geographically-defined region. We advocate for future studies of sufficient size from throughout Ireland to substantiate our findings and determine the influence of these polymorphisms on the risk, progression, and outcomes of this immunologically complex disease.

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Table I. Phenotypic characteristics of patients with Behçet's disease along with distribution of HLA-B alleles.

ID	Sex	Age	Aphthous oral ulcers	Genital ulcers	Ocular features	Skin features	Pathergy reaction	Vascular features	Gastrointestinal features	Otolaryngeal features	HLA-B typing
1	F	35	+	+	-	+	-	-	-	+	15, 44
2	M	53	+	+	+	+	+	-	+	+	07, 35
3	F	35	+	+	-	+	-	-	-	+	35, 44
4	F	24	+	+	-	+	-	-	-	+	27, 35
5	M	50	+	+	+	+	-	+	-	-	14, 51
6	M	57	+	-	+	+	-	-	-	+	08, 57
7	F	39	+	+	-	-	+	-	-	-	08, 44
8	M	35	+	+	-	+	-	-	-	-	15, 27
9	F	39	+	+	-	+	-	-	-	-	15, 57
10	F	53	+	+	-	+	-	+	-	-	08
11	F	83	+	+	+	+	-	-	-	-	37, 44
12	F	68	+	+	-	+	-	-	+	-	07, 57
13	M	47	+	+	-	-	-	+	-	-	07, 57
14	F	39	+	+	-	+	-	-	-	-	15, 35
15	F	23	+	+	-	+	-	-	-	-	35, 57, 58
16	F	25	+	+	-	+	-	-	-	-	44
17	M	64	+	+	-	+	-	-	-	-	08, 44
18	F	38	+	+	-	+	-	-	+	-	07, 08, 42
19	F	24	+	+	+	+	-	-	-	-	08, 27
20	F	19	+	+	+	+	-	-	-	-	44, 57

Table II. HLA-B alleles observed frequencies among BD patients *versus* controls in the Midwest Region of Ireland.

HLA-B alleles	BD patients (%), n=20	Controls (%), n=5000
B*44	35.0	32.0
B*57	30.0	7.6
B*08	30.0	30.8
B*35	25.0	7.5
B*15	20.0	9.0
B*07	20.0	31.2
B*27	15.0	7.5
B*51	5.0	5.1
B*37	5.0	3.5
B*14	5.0	10.3
B*58	5.0	1.0
B*42	5.0	<1.0

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