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Kugler & Ghedini

HLA ANTIGENS AND BEHÇET'S DISEASE IN ITALY

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The etiology of Behçet's disease (BD) is still unknown, but several items of evidence suggest an autoimmune basis with a genetic background. Indeed, immunogenetic factors controlling susceptibility to the disease are strongly suggested by the association between the HLA-B5 antigen (now subdivided into Bw51 and Bw52) and the disease, first reported by Ohno et al in Japanese patients (1), and subsequently confirmed in different ethnic groups (2-5).

Also the possible associations between HLA-D region antigens and BD has recently been investigated in Japanese patients, showing an increase of DRw52 (MT2) (8-10) and a decrease of DQw1 (6). A similar study in Caucasian patients, suffering from ocular lesions reported an increase of HLA-B 5 and DR 7 antigens (7,8).

In the present study we have investigated the distribution of HLA class I and II antigens in Italian BD patients. HLA typing was performed on 38 (27 male and 11 female) subjects, age range from 18 to 61, all suffering from ocular lesions and diagnosed as complete (n=28) and incomplete (n=10) type according to the clinical criteria proposed by the Behçet's Disease Research Committee of the Japanese Ministry of Health and Welfare (9). HLA typing was performed by conventional two-step complement dependent microlymphocytotoxicity on peripheral blood lymphocytes or enriched B lymphocytes preparation by nylon wool column and prolonged incubation time (120 minutes). Control frequences were obtained from healthy unrelated Italians typed during the VIII and IX Histocompatibility Workshop. The statistical significance of associations was evaluated by Fisher exact P test. Correction of P values for multiple comparisons was performed only for associations not previously reported and when more than one specificity per locus had been formerly described.

The frequencies observed for HLA-A and B locus antigens are shown in Tables 1 and 2.

Thirty-one out of the 38 patients examined showed B51 specificity, with no significant difference between the complete and incomplete types of the disease and presence or absence of particular major or minor symptoms (cutaneous, articular, neurologic, visceral). The antigenic frequency observed showed a significant increase (81.5% vs 21.7% in controls, P = 9, 15 E-15) with an RR of 16.0. No positive significant associations were observed between other HLA A and B determinants and the disease except for A24 (P = 019; Pc = NS). No protective B determinant was found by comparing the observed frequencies with those expected for the compensatory decrease (10). The frequencies observed for the HLA-D region antigens are listed in Table 3. The results showed significant increases for DRw52 (P = 0.045; RR = 2.77) and DQw3 (P = 013; Pc = 039; RR = 2.78) specificities in the patients when compared with controls.

From a clinical standpoint, it is worthwhile noticing that no significant differences in the antigen frequencies were observed between the complete and incomplete types of the disease. The associations between HLA specificities at different loci and the same disease have sometimes been resolved taking into account the linkage disequilibria among HLA alleles (11,12). In this hypothesis a 'primary association' is the result of a linkage disequilibrium between a susceptibility gene (dominant or recessive) and a defined HLA specificity, while the other possible associations are merely due to the 'frozen' HLA haplotypes. The several immunological functions mediated by MHC molecules could however suggest an alternative mechanism, with the direct biological in-

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TABLE 1

Antigen	Control	Patients		
		Complete	Incomplete	Total
A 1	27.0	17.9	20.0	18.4
A 2	41.6	53.6	50.0	52.6
A 3	16.1	21.4	0.0	15.8
A 11	12.1	25.0	0.0	18.4
A 23	4.4	0.0	0.0	0.0
A 24	25.0	39.3	50.0	42.1*
A 25	2.7	0.0	0.0	0.0
A 26	8.8	3.6	10.0	5.3
A 28	8.4	7.1	20.0	10.5
A 29	5.0	0.0	10.0	2.6
A 30/31	12.3	7.1	10.0	7.9
A 32	10.3	14.3	10.0	13.1
A 33	5.9	3.6	0.0	2.6
N	522	28	10	38

* P = 0.019; Pc = NS

TABLE 2

Antigen	Control	Patients		
		Complete	Incomplete	Total
B 7	8.1	3.6	0.0	2.6
B 8	12.1	10.7	0.0	7.9
B 13	8.6	0.0	0.0	0.0
B 14	7.1	0.0	10.0	2.6
B 15	8.1	7.1	0.0	5.2
B 17	8.1	7.1	10.0	7.9
B 18	15.5	0.0	10.0	2.6
B 21	12.5	7.1	20.0	10.5
B 27	4.8	3.6	10.0	5.2
B 35	31.0	3.6	0.0	2.6
B 37	3.3	3.6	0.0	2.6
B 38	6.7	0.0	0.0	0.0
B 39	5.2	7.1	10.0	7.9
Bw41	1.2	0.0	0.0	0.0
B 44	15.1	3.6	20.0	7.9
B 45	1.0	3.6	0.0	2.6
Bw47	0.8	0.0	0.0	0.0
Bw48	0.4	0.0	0.0	0.0
B 51	21.7	82.1	80.0	81.6*
Bw52	2.7	0.0	0.0	0.0
Bw53	2.1	3.6	0.0	2.6
Bw55	4.0	0.0	10.0	2.6
Bw56	0.4	0.0	0.0	0.0
N	522	28	10	38

* P = 9.15E-15 RR = 16.0

TABLE 3

Antigen	Control		Patients		
			Complete	Incomplete	Total
DR 1	16.9		7.1	30.0	13.1
DR 2	22.9		17.9	30.0	21.0
DR 3	16.5		21.4	0.0	15.8
DR 4	12.3		10.7	10.0	10.5
DR 5	35.8		46.4	50.0	47.8
DRw 6	6.8		3.6	10.0	5.3
DR 7	24.4		10.7	20.0	13.1
DRw 8	4.8		17.9	0.0	13.1
DRw 9	1.1		0.0	0.0	0.0
DRw10	4.0		3.5	0.0	2.6
DRw52		69.1	84.6	90.0	86.1*
DRw53		33.3	28.6	20.0	26.3
DQw 1		60.3	57.1	70.0	60.5
DQw 2		36.8	21.4	20.0	21.0
DQw 3		41.9	64.3	70.0	65.8**
N	455	68	28	10	38

* P = 0.45; ** P = 0.13 PC = 0.39

volvement of HLA products in the etiopathogenesis of autoimmune and immunopathologically mediated diseases (13-16). Indeed T lymphocytes recognize antigen in the context of membrane products of the MHC. In particular T8+ and T4+ cell subpopulations seem restricted to HLA class I and II, respectively (17).

The restriction of T4+ cell functions to the II class antigens and of T8+ ones to the HLA class I, could support a possible direct role for both B51 and DRw52 antigens in the pathogenesis of BD disease, where imbalance of T subpopulations is reported (18).

Furthermore, a connection between T4/T8 ratio imbalance and DQw3 association in BD could be supposed if one considers the peculiar role recently claimed to be played by DQ molecules in the production of suppressor and/or cytotoxic T cells.

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