

## HLA-B51 IN BEHÇET'S DISEASE

F. Davatchi\*, F. Shahram, A. Nadji, S. Soroosh, A. R. Jamshidi, C. Chams, H. Chams, M Akbarian,  
F. Gharibdoost, M. Akhlaghi, B. Sadeghi Abdollahi and N. Ziaie

Department of Rheumatology, Rheumatology Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

**Abstract-** There is some data in the literature on the association of HLA-B5 and some manifestations of Behçet's disease (BD), especially ocular lesions. We studied 433 patients to see if there was any relationship between B51 and the manifestations of the disease. Clinical manifestations of BD were compared in patients having HLA-B51 (155 patients) and those lacking HLA-B51 (278 patients). Oral aphthosis, genital aphthosis, skin manifestations, joint manifestations, gastrointestinal manifestations, phlebitis and neurological manifestations showed no significant difference in patients with and without HLA-B51. Ophthalmologic manifestations were seen in 52% of patients having B51 and in 42% of patients lacking it ( $\chi^2$ : 4.451,  $P = 0.035$ ). Considering different lesions of ocular manifestations separately, no significant difference was found regarding the presence or absence of B51. Pathergy phenomenon was detected in 55% of B51 positive patients and in 45% of B51 negative patients ( $\chi^2$ : 4.111,  $P = 0.043$ ). It seems that HLA-B51 may play a role in the pathogenesis of Behçet's disease, but cannot be used as predictive value for the occurrence of organ involvement, except for the eye.

© 2008 Tehran University of Medical Sciences. All rights reserved.

*Acta Medica Iranica* 2008; 46(6): 507-510.

**Key words:** Behçet's disease, HLA typing, HLA-B5, HLA-B51

### INTRODUCTION

The geographic distribution, the familial forms, and the ethnic origin of patients with Behçet's disease (BD), are many evidence in favor of a genetic background. BD is associated with the B51 subtype (1-2) of HLA-B5 gene, especially the B\*5101 allele (3).

B51 cannot explain by itself the occurrence of BD. There are normal subjects with B51. In familial forms of BD, some members with B51 may not have the disease (4). Therefore, another gene in the region may be involved in the susceptibility to BD, having a high disequilibrium linkage with B51. HLA-Cw14 and Cw15 were found significantly higher in BD patients (5). However detailed analysis showed that

the susceptibility gene may be the MICA gene (MHC class I chain-related gene A) which is the nearest neighbor of HLA-B gene. The A6 allele in MICA was present in all B51 positive patients and in an additional 40% of B51 negative patients. The association of MICA with BD was stronger than the B51 with BD (6). The critical region for BD in the human MHC could be pinpointed to a 46-kb segment between the MIC-A and HLA-B gene. The major susceptibility gene is the HLA-B51 allele itself. The increase of MIC-A009 allele in BD patients is secondary to the strong disequilibrium linkage with B51 (7).

To confirm this finding in Iranian population, HLA class I typing (using the PCR-SSP method) and analyzed eight polymorphic markers distributed within 1100 kb around the HLA-B gene (using automated sequencer and subsequent automated fragment detection by fluorescent-based technology with the DNA samples) was performed in 84 Iranian patients with BD and 87 healthy ethnically matched controls (8). Three microsatellite alleles (MICA-A6,

Received: 22 Jan. 2008, Revised: 27 Jun. 2008, Accepted: 11 Sept. 2008

**\* Corresponding Author:**

Fereidoon Davatchi, Department of Rheumatology, Rheumatology Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran  
Tel: +98 21 88330033  
Fax: +98 21 88026956  
E-mail: fddh@davatchi.net

MIB-348, C1-4-1-217) and HLA-B51 were found to be strongly associated with BD. Of these alleles HLA-B51 is the most strongly associated allele. There were no alleles that were increased in allele frequency at any microsatellite loci centromeric of MICA or telomeric of HLA-B51. Therefore, HLA-B51 was confirmed to be by far the most strongly associated gene with BD in Iranian population.

It is now known that the B51 antigen can be encoded by 21 alleles, B\*5101-B\*5121. To see their distribution in Iranian patients, HLA-B\*51 allele typing as well as HLA class I genotyping was performed in 48 Iranian BD patients (9). The frequency of the B\*51 allele was significantly higher (62.1%) in BD group as compared with the control group (31.8%) ( $P_c = 0.067$ , R.R. = 3.51). In the genotyping of B\*51 alleles, 33 out of the 36 B\*51-positive patients possessed B\*5101 and the remaining 3 carried B\*5108. This study revealed that Iranian patients with BD also had a strong association with HLA-B51. In addition, this significantly high incidence of HLA-B\*51 was found to be caused by an increase in both the HLA-B\*5101 and HLA-B\*5108 alleles. However, there was no significant difference in the HLA-B\*51 allelic distribution between the patient and control groups.

In a cohort of 599 consecutive patients (201 BD and 398 controls) B51 was found in 39% of BD patients and 18% of control patients (patients mimicking BD) by serologic routine typing (10). We extended the study to 433 patients to check our previous results and to see if there was any relationship between the presence of B51 and the disease symptoms.

## MATERIALS AND METHODS

HLA-B51 was checked by serologic routine typing in 433 consecutive patients referring for the first time to the Behçet's Disease Unit. The review board and ethical committee of our institution approved the trial. We obtained informed consent from all participants.

Clinical manifestations of BD and laboratory data were studied prospectively on a predefined protocol comprising 105 items. All the items were compared

in patients having HLA-B51 (155 patients) and those lacking HLA-B51 (278 patients). The comparison was made by Chi square ( $\chi^2$ ) test. Results were adjusted, when necessary, by the Yates formula.

## RESULTS

HLA-B51 was seen in 36% of BD patients. The confidence interval (CI) at 95% was 4.5. Oral aphthosis was seen in 154 of B51 positive group (99%) and in 276 (99%) of B51 negative group.  $\chi^2$  was 0.265, which corresponds to  $P = 0.61$  (the difference is not statistically significant). Genital aphthosis was seen in 111 (72%) patients with B51 and in 191 (69%) patients lacking it ( $\chi^2$ : 0.399,  $P = 0.53$ ). Skin manifestations were seen in 81 (52%) patients with B51 and in 149 (54%) patients without B51 ( $\chi^2$ : 0.072,  $P = 0.79$ ).

Ophthalmologic manifestations were seen in 81 (52%) patients having B51 and in 116 (42%) patients lacking it ( $\chi^2$ : 4.451,  $P = 0.035$ ). Anterior uveitis was seen in 53 patients (34%) with B51 and in 91 (33%) patients without B51 ( $\chi^2$ : 0.096,  $p=0.76$ ). Posterior uveitis was seen in 63 patients (41%) with B51 and in 93 (33%) patients without B51 ( $\chi^2$ : 2.233,  $P = 0.14$ ). Retinal vasculitis was seen in 36 patients (23%) with B51 and in 58 (21%) patients without B51 ( $\chi^2$ : 0.327,  $P = 0.57$ ). Posterior uveitis and retinal vasculitis together was seen in 33 patients (21%) with B51 and in 33 (12%) patients without B51 ( $\chi^2$ : 6.440,  $P = 0.011$ ).

Joint manifestations were seen in 42 (27%) patients with B51 and in 67 (24%) without B51 ( $\chi^2$ : 0.474,  $P = 0.49$ ).

Gastrointestinal manifestations were seen in 9 (5.8%) patients with B51 and in 8 (2.9%) patients without it ( $\chi^2$ : 1.553,  $P = 0.21$ ).

Phlebitis was seen in 3 (1.9%) cases with B51 and in 10 (3.6%) cases without it ( $\chi^2$ : 1.600,  $P = 0.21$ ).

Neurological manifestations were seen in 12 (7.7%) B51 cases and in 14 (5%) negative-B51 cases ( $\chi^2$ : 1.291,  $P = 0.26$ ).

Pathergy phenomenon was detected in 86 (55%) B51 positive patients and in 126 (45%) B51 negative patients ( $\chi^2$ : 4.111,  $P = 0.043$ ).

**Table 1.** Behçet's disease manifestations

	B51+			B51-			$\chi^2$	<i>P</i>
	No.	%	CI	No.	%	CI		
Oral Aphthosis	154	99	1.6	276	99	1.2	0.265	0.61
Genital Aphthosis	111	72	7.1	191	69	5.4	0.399	0.53
Skin Manifestations	81	52	7.9	149	54	5.9	0.072	0.79
Ocular Manifestations	81	52	7.9	116	42	5.8	4.451	0.035
Anterior Uveitis	53	34	7.5	91	33	5.5	0.096	0.76
Posterior Uveitis	63	41	7.7	93	33	5.5	2.233	0.14
Retinal Vasculitis	36	23	6.6	58	21	4.8	0.327	0.57
Joint Manifestations	42	27	7.0	67	24	5.0	0.474	0.49
GI Manifestations	9	5.8	3.7	8	2.9	2.0	1.553	0.21
Neurologic Manifest.	12	7.7	4.3	14	5	2.6	1.291	0.26
Pathergy Phenomenon	86	55	7.8	126	45	5.8	4.111	0.043

Abbreviations: No, number; CI, confidence interval;  $\chi^2$ , chi square test; *P*, *P* value; GI, gastrointestinal.

## DISCUSSION

The frequency of HLA-B51 in this study didn't differ significantly from our previous study (10). However, both results are far from the figure obtained in our first study on 48 consecutive BD patients (9). The large difference (36% versus 64%) may be due to the technique used for the first study (HLA class I typing using the PCR-SSP method).

There was no relationship between HLA-B51 and different manifestations of the disease except for ocular manifestations and the pathergy phenomenon. Both manifestations were seen 10% more frequently in B51 positive patients. However, looking at different lesions of the eye, none of them individually was related to B51, the difference became significant only when all of them were taken together. It is interesting to note that regarding HLA-B5, the difference between the positive and negative patients was highly significant for different eye lesions.

In conclusion, HLA-B51 may play a role in the pathogenesis of Behçet's Disease, but cannot be used as predictive value for the occurrence of organ involvement, except for the eye. In the presence of B51, the risk of eye involvement is superior. However, although the difference is statistically significant between negative and positive patients, it is only of 10%, which is not clinically much important.

## Conflict of interests

The authors declare that they have no competing interests.

## REFERENCES

1. Mizuki N, Inoko H, Mizuki N, Tanaka H, Kera J, Tsuiji K, Ohno S. Human leukocyte antigen serologic and DNA typing of Behçet's disease and its primary association with B51. *Invest Ophthalmol Vis Sci.* 1992 Nov;33(12):3332-3340.
2. Balboni A, Pivetti-Pezzi P, Orlando P, Rubini M, Selvatici R, Accorinti M, Baricordi OR, Gandini E. Serological and molecular HLA typing in Italian Behçet's patients: significant association to B51-DR5-DQw3 haplotype. *Tissue Antigens.* 1992 Mar; 39(3): 141-143.
3. Mizuki N, Nakamura S, Ando H, Inoko H, Ohno S. Molecular genetic studies on Behçet's disease. In: Godeau P, Wechsler B, editors. *Behçet's disease.* Amsterdam: Elsevier Science Publishers B.V.; 1993.
4. Hayasaka S, Kurome H, Noda S. HLA antigens in a Japanese family with Behçet's disease. *Graefes Arch Clin Exp Ophthalmol.* 1994 Oct; 232(10):589-590.
5. Mizuki N, Ohno S, Ando H, Kimura M, Ishihara M, Miyata S, Nakamura S, Mizuki N, Inoko H. HLA-C genotyping of patient with Behçet's disease in the Japanese population. *Hum Immunol.* 1996 Sep 15; 50(1):47-53.

6. Mizuki N, Ota M, Kimura M, Ohno S, Ando H, Katsuyama Y, Yamazaki M, Watanabe K, Goto K, Nakamura S, Bahram S, Inoko H. Triplet repeat polymorphism in the transmembrane region of the MICA gene: a strong association of six GCT repetitions with Behçet disease. *Proc Natl Acad Sci U S A*. 1997 Feb 18;94(4):1298-1303.
7. Mizuki N, Ota M, Yabuki K, Katsuyama Y, Ando H, Palimeris GD, Kaklamani E, Accorinti M, Pivetti-Pezzi P, Ohno S, Inoko H. Localization of the pathogenic gene of Behçet's disease by microsatellite analysis of three different populations. *Invest Ophthalmol Vis Sci*. 2000 Nov; 41(12):3702-3708.
8. Mizuki N, Yabuki K, Ota M, Katsuyama Y, Ando H, Nomura E, Funakoshi K, Davatchi F, Chams H, Nikbin B, Ghaderi AA, Ohno S, Inoko H. Analysis of microsatellite polymorphism around the HLA-B locus in Iranian patients with Behçet's disease. *Tissue Antigens*. 2002 Nov; 60(5):396-399.
9. Mizuki N, Ota M, Katsuyama Y, Yabuki K, Ando H, Yoshida M, Onari K, Nikbin B, Davatchi F, Chams H, Ghaderi AA, Ohno S, Inoko H. HLA class I genotyping including HLA-B\*51 allele typing in the Iranian patients with Behçet's disease. *Tissue Antigens*. 2001 May; 57(5):457-462.
10. Shahram F, Davatchi F, Nadji A, Jamshidi A, Bahar K, Akbarian M, Chams C. HLA-B51 frequency in Iranian patients with Behçet's disease. *Adv Exp Med Biol*. 2003;528:229-230.