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Evaluation of HLA-B51 frequency and its relationship with clinical findings in patients with Behçet's disease: 4-year analysis in a single center

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Abstract

Background The clinical findings of Behçet's disease (BD) differ according to the country and race investigated. The most important genetic factor known in the pathogenesis of BD is HLA-B51, and this positivity is high in countries on the "Silk Road" where BD is as frequent as it is in Turkey. Although the positivity of HLA B51 is proven to be high in Turkey, there are no studies in the area of the western Black sea demonstrating its relation to the demographic. We aimed to investigate the association of HLA-B51 positivity in Turkish patients diagnosed as having BD and the relationship between the demographic and clinical findings of the patients.

Results In this descriptive, cross-sectional study, a convenience sample of adults with BD was obtained from an outpatient clinic of a university hospital in Turkey between January 2018 and January 2022. Patients were diagnosed as having BD according to the criteria of the International BD Study Group, and the patients' sociodemographic and clinical characteristics were recorded retrospectively. Demographic data and the frequency of clinical findings were compared between patients who were HLA-B51-positive and HLA-B51-negative. Sixty patients (55.6%) were HLA-B51-positive. Oral ulceration, genital ulceration, thrombophlebitis, and family history of BD were found to be higher in patients who were HLA-B51-positive. Erythema nodosum, papulopustular eruption, pathergy positivity, arthritis, and ocular involvement were less frequent in patients with HLA-B51 positivity. However, there were no statistically significant differences according to the frequency of clinical findings between the HLA-B51-positive and HLA-B51-negative groups.

Conclusions HLA B51 positivity is not diagnostic of BD; however, it may affect clinical phenotypes. Although oral and genital ulcerations, thrombophlebitis, and positive family history of BD were found to be common in patients with HLA-B51 positivity, this relationship could not reach statistical significance.

Keywords Behçet disease, Clinical manifestations, HLA-B51, Turkey

Background

Behçet's disease (BD) is a chronic immune-mediated disease, and many different organ systems can be affected. BD has recurrent oral and genital ulcers as a prominent feature and usually follows a relapsing–remitting course [1]. The etiopathogenesis of BD is still unknown, but it is a multifactorial chronic disease triggered by environmental, microbiologic, and immunologic factors in

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individuals with a genetic predisposition such as human leukocyte antigen (HLA-B51). Although BD generally affects the Middle East, Mediterranean, and East Asian societies on the ancient Silk Road, it can be seen all over the world due to migration. Turkey has the highest prevalence of BD [2–6]. Our study aimed to investigate the association of HLA-B51 positivity in Turkish patients who were diagnosed as having BD and the relationship between the demographic and clinical findings of the patients.

Methods

Study design

This study was cross-sectional and descriptive. The study setting was an outpatient clinic in a tertiary hospital in Turkey.

Ethical statement

The Clinical Research Ethics Committee of the university school of medicine approved the study protocol (Decision no: 2022/109; date: June 6, 2022). All procedures performed in studies with human participants met the ethical standards of the Institutional Research Commission and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

Patient selection

Patients who were diagnosed as having BD according to the criteria of the International Study Group for Behçet Disease (IBSG) had HLA-B51 genetic results [5, 6] and were followed up between January 2018 and January 2022 were included in the study. The electronic records and registration forms of the patients were retrospectively reviewed in the hospital automation system. The exclusion criteria were as follows: (i) age under 18 years and patients with incomplete medical records or follow-ups; (ii) concomitant autoimmune, neurologic, and endocrinologic disease; (iii) patients with malignancy and active infection; (iv) duplicate registration; and (v) patients without HLA-B51 genetic results.

Data collection procedure

The patients' demographic characteristics (sex, age, family history), clinical features (oral aphthae, genital ulcers, papulopustular lesion, erythema nodosum, thrombophlebitis, pathergy response), and systemic involvement were recorded. Systemic involvement findings were evaluated as mucocutaneous, ocular, musculoskeletal, vascular, neurologic, gastrointestinal system, genitourinary system, cardiac, and pulmonary involvement. Systemic involvements of patients were diagnosed by specialists of the related clinics such as dermatology, ophthalmology, cardiovascular surgery, neurology, gastroenterology, and cardiology as a result of the consultations requested. Findings not related to BD were not recorded. Mucocutaneous findings were clinically evaluated by a dermatologist and patients who had more than three oral ulcers per year during their examinations or in their medical history were regarded as positive for oral ulcers. Patients with active genital ulcers or ulcer scars that were identified by dermatologists were regarded as positive for genital ulcers. Erythema nodosum was diagnosed after clinical evaluation. Pseudo-folliculitis and acneiform lesions detected in patients who were not on steroid treatment were defined clinically as papulopustular lesions by a dermatologist.

Pathergy skin tests indicate hyperactivity of the skin to trauma and are performed using a 20-gauge needle on the antecubital region and evaluated by a dermatologist 48 h later. The presence of papules or pustules is considered positive. In our study, pathergy skin test results were recorded in the files of the patients. Patients with swelling or/and pain around the joints were described as having joint involvement and evaluated using magnetic resonance imaging. Vascular system involvement was diagnosed through clinical observation and Doppler ultrasonography.

Statistical analysis

The sample size was calculated using the G*power program(V3.1.9.2), with a minimum sample size of 64 participants at an $\alpha = 0.05$ and a power of 80% [7, 8]. The data were analyzed using the IBM SPSS Ver. 23 software package. The compliance of the data to normal distribution was tested using the Kolmogorov–Smirnov test. As descriptive statistics, mean ± standard deviation for numerical variables, min–max, and number and percentage (%) values for categorical variables are given. Student's *t*-test was used to compare the two groups. $P \leq 0.05$ was considered statistically significant.

Results

The participant recruitment scheme for the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) study is shown in Fig. 1.

A total of 108 patients who were followed up in the department of physical and rehabilitation outpatient clinic with BD and whose files included HLA-B51 results were included in the study. Of the 108 patients, 74 (68.5%) were female and 34 (31.5%) were male. The patient's sociodemographic and clinical characteristics are shown in Table 1. The mean age of the patients at the time of diagnosis was 38.53 ± 12.73 years. HLA-B51 was positive in 60 patients and negative in 48 patients. Demographic data and clinical findings were compared between patients who were HLA-B51-positive and

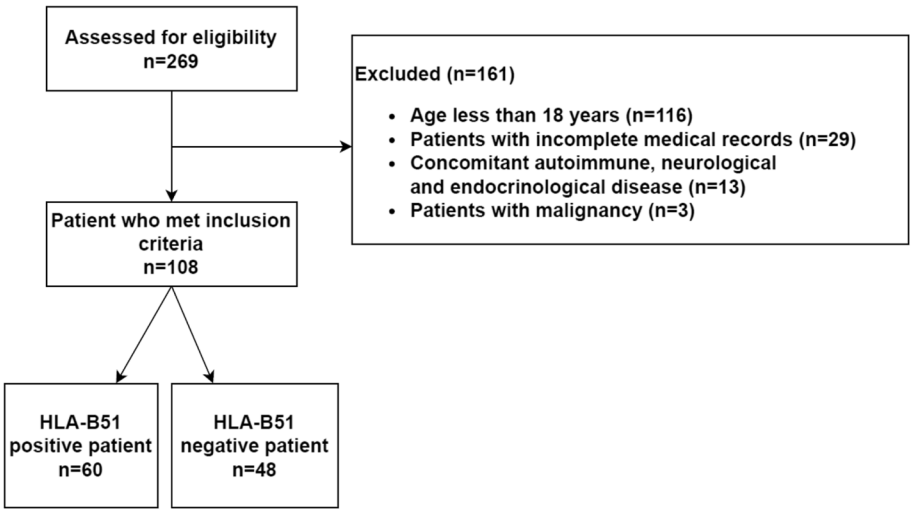

Fig. 1 The participant recruitment scheme

Table 1 Demographic and clinical profiles of the Behçet's patients

		Number	Percent
Gender	Female	74	68.8
	Male	34	31.5
Family history		30	27.8
Oral ulceration		108	100
Genital ulceration		14	13
Positive pathergy test		8	7.4
Erythema nodosum		10	9.3
Papulopustular eruption		21	19.4
Arthritis		28	25.9
Ocular involvement		21	19.4
Vascular involvement		11	10.2

Table 2 Gender distribution and mean age of the Behçet patients

HLA-B51	Gender	Mean ± SD	Age, min–max	Number	*p*
Positive	Female	40.55 ± 13.41	18–68	38	0.170
	Male	36.5 ± 12.04	18–55	22	
Negative	Female	40.5 ± 15.81	18–78	36	0.578
	Male	36.17 ± 17.28	18–62	12	

Abbreviations: *SD*, standard deviation; *min*, minimum; *max*, maximum

HLA-B51-negative. There was no statistically significant difference in the mean age and sex distribution of the patients in the groups (Table 2).

The clinical features of BD according to HLA-B51 positivity are presented in Table 3. The frequency of oral ulceration, genital ulceration, and thrombophlebitis was found to be higher in patients who were HLA-B51-positive than in those who were HLA-B51-negative, and there were no significant differences between the groups in terms of clinical features. Family history of BD was more frequent in patients who were HLA-B51-positive. The frequency of erythema nodosum, papulopustular eruption, arthritis, and ocular involvement was higher in patients with HLA-B51 negativity; however, the difference between the two groups was not significant. None of the patients had neurologic, gastrointestinal, genitourinary, cardiac, or pulmonary involvement. Pathergy positivity was more common in patients who were HLA-B51-negative than in those who were HLA-B51-positive, but no statistically significant difference was found between the two groups (Table 3).

Discussion

BD is an inflammatory disease characterized by recurrent oral aphthous ulcers and various systemic manifestations. BD is more common along the ancient Silk Road, which extends from eastern Asia to the Mediterranean, but is most common in Turkey. The etiopathogenesis is unknown, but it is a multifactorial disease triggered by environmental, microbiologic, and immunologic factors in individuals with a genetic predisposition such as HLA-B51. BD is strongly associated with HLA-B51 in the Turkish population [9]. The present study aimed to investigate the association of HLA-B51 positivity in Turkish patients with BD and the relationship with the demographic and clinical findings. In our study, the frequency of HLA-B51 was 55.6%. Oral and genital ulceration, vascular involvement, and family history were more common in patients with BD with HLA-B51positivity. Erythema nodosum,

Table 3 The clinical differences between HLA-B51 positive and negative groups

		HLA-B51				*p*-value
		Positive (*n* = 60)		Negative (*n* = 48)		
		n	%	*n*	%	
Gender	Female	38	63.33	36	75	0.483
	Male	22	36.67	12	25	
Oral ulceration	Present	60	100	48	100	-
	Absent	0	0	0	0	
Genital ulceration	Present	11	18.3	3	6.3	0.083
	Absent	49	81.7	45	93.7	
Positive pathergy test	Present	4	6.7	4	8.3	0.710
	Absent	56	93.3	44	91.7	
Erythema nodosum	Present	4	6.7	6	12.5	0.159
	Absent	56	93.3	42	87.5	
Papulopustular eruption	Present	7	11.7	14	29.2	0.083
	Absent	53	88.3	34	70.8	
Arthritis	Present	14	23.3	14	29.2	0.399
	Absent	46	66.7	34	70.8	
Ocular involvement	Present	8	13.3	13	27.1	0.159
	Absent	52	86.7	35	72.9	
Vascular involvement	Present	7	11.7	4	8.3	0.371
	Absent	53	88.3	44	91.7	
Family history	Present	19	31.7	11	22.9	0.229
	Absent	41	68.3	37	77.1	

papulopustular eruption, pathergy positivity, arthritis, and ocular involvement were more common in patients who were HLA-B51-negative. However, there were no significant differences according to the frequency of clinical findings between the two groups.

The age of BD onset is often in the range of 24.7–35.2 years; onset after the age of 50 years and before the age of 20 is very rare [10–12]. The disease affects both sexes; however, it is more severe in young men. There are also studies where the number of female patients is higher or equal to the number of male patients [3, 13]. In the present study, the mean age of diagnosis was 38.53 ± 12.73 years, and the male/female ratio was 0.5. The male/female ratio has been reported at different rates according to different geographic regions. In Turkey, the male/female ratio was reported as 1.03 by Türsen et al. [14] and 0.73 by Karıncaoğlu et al. [13]. The ratio can be different according to the geographic region investigated. For example, the male/female ratio was reported as 0.7 in Japan and 1.2 in China [15, 16].

In studies conducted in our country on BD, the prevalence has been reported as 8–42/10,000 [13, 15–19]. Family history has been reported at different rates in patients with BD in Turkey [14, 19, 20]. In our study, family history positivity was 2.7%, and only first-degree relatives were considered positive. Similar to our study, Kalın et al. found family history positivity at 3.9% in their study where only first-degree relatives were considered positive [19].

The etiopathogenesis of BD has not been fully clarified yet, but it is triggered by environmental, microbiologic, and immunologic factors in individuals with a genetic predisposition such as HLA-B51 [21]. There are no pathognomonic laboratory tests to diagnose BD, and as such, the diagnosis is based on clinical criteria. HLA-B51 is known as a genetic marker closely related to BD and is also known to differ between clinical subtypes [22]. In our study, the frequency of HLA-B51 was 55.6%, and there was no difference in terms of HLA-B51 frequency according to age and sex. In the literature, there are conflicting results concerning the association of HLA-B51 with both age and sex. In the Greek population, possession of HLA-B51 alleles carries a high risk for the development of BD, especially at a younger age, and it was reported that men with HLA-B51 were more at risk for BD [23]. In a study conducted on 61 patients with BD from Korea, HLA-B51 status was similar in both sexes, and the patients with HLA-B51 showed significantly

earlier onset compared with those without HLA-B51 [24]. In a study reported from Turkey by Akyürek et al., the results showed that there was no correlation between HLA-B51 positivity and age at sex and onset [25].

The prevalence of HLA-B51 may differ according to the populations investigated. Approximately half of all patients with BD are HLA-B51-negative, and also 15% of healthy individuals are found as HLA-B51 positive but do not develop BD in their lifetime [26, 27]. HLA-B51 gene positivity is frequently seen in areas where Turkish tribes immigrated along the Silk Road, and so the frequency of HLA-B51 may differ according to geographic region and ethnicity. The frequency of HLA-B51 was 54–82% [28] in Turkish patients with BD, 44.5% [15] in Japan, and 48.9% [28, 29] in Iran, and it has been reported as 15% [28] in Northern Europe and America. Moreover, it has been reported in the literature that the relationship between HLA-B51's specific symptoms of BD and the severity of the disease may be different in different ethnic groups [22]. Therefore, the usefulness of HLA-B51 positivity as a diagnostic and prognostic marker in BD remains in doubt [22, 30, 31].

In our study, similar to previous studies, all patients had at least one mucocutaneous finding and the most common was oral ulcers (100%) [32]. Other mucocutaneous findings were papulopustular eruption (19.5%), genital ulcers (13%), and erythema nodosum (10%). Pathergy reaction positivity was present in 7.5%. In a meta-analysis examining the relationship between HLA-B51/B5 clinical features of BD, it was shown that HLA-B51/B5 carriage in BD was associated with increased genital ulcers and ocular and skin symptoms [30]. In the present study, family history, the frequency of oral and genital ulceration, and vascular involvement were found to be more common in patients who were HLA-B51-positive than in those who were HLA-B51-negative. However, there were no statistically significant differences between the groups. The frequency of mucocutaneous findings and ocular and joint involvement was higher in patients with HLA-B51 negativity. Similarly, there were no statistically significant differences between the two groups.

Ocular involvement is an important cause of morbidity in BD. In our study, the frequency of ocular involvement was found as 19.5%, which was lower than reported in the literature [14, 30]. In addition, in the present study, the frequency of ocular involvement was higher in patients who were HLA-B51-negative. The small sample and lack of HLA-B51 subtype analysis may have caused this result. In the literature, it was suggested that patients with the HLA-B51/B5 allele had more ocular or neurologic involvement [30]. However, these observations have not been reported consistently [33], and the discrepancies may have been exacerbated by studies with small sample sizes. In a study conducted in Turkey, Müftüoğlu et al. reported finding no positive or negative association between HLA-B51 and ocular involvement [33]. No association regarding HLAB*51:01 carriage was found with isolated BD manifestations and with ocular involvement in patients with BD from Turkey [28]. Similarly, in an observational study from Turkey, ocular involvement and the type of uveitis showed no correlation with HLA-B51, but it was found that patients who presented with frequent ocular attacks had significantly higher HLA-B51 positivity than patients with rare attacks [34].

In our study, the frequency of vascular involvement was 10.2%, and thrombophlebitis was found more commonly in patients who were HLA-B51-positive. The frequency of vascular involvement was higher in patients who were HLA-B51-positive. However, there were no statistically significant differences between the HLA-B51-positive and HLA-B51-negative groups. Similar to our study, Pamukçu et al. reported vascular involvement at 27% in their study, and they found that the frequency of vascular involvement was higher in patients who were HLA-B51-positive. They also reported that HLA-B51 positivity was not a significant risk factor for vascular involvement [33]. The frequency of arthritis in the present study was 26%. Similar to the literature, the frequency of joint involvement was higher in patients who were HLA-B51-negative, but there were no statistically significant differences according to HLA-B51 status [28, 30, 35].

The present study has some limitations. First, the study was conducted in a single center and had a retrospective design. Second, the impact of HLA-B51 on each clinical manifestation of patients with BD and HLA-B51 subtype analysis could not be examined. Our study is the first to cover the clinical data of a group of patients with BD in the western Black Sea region of Turkey, and we believe that this study will contribute to future larger multicenter studies that will determine whether there are geographic, socioeconomic, and cultural differences across countries, and also investigate the relationship between HLA-B51 and BD in different ethnic groups.

Conclusions

HLA-B51 positivity is not diagnostic of BD; however, it may affect clinical phenotypes. Although oral and genital ulcerations, thrombophlebitis, and positive family history of BD were found to be common in patients with HLA-B51 positivity, this relationship could not reach statistical significance.

Abbreviations

BD	Behçet's disease
CT	Computed tomography
HLA B51	Human leukocyte antigen

IBSG International BD Study Group Criteria

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Authors' contributions
TES, RE, and SA: data collection, writing, and supervision. TES: statistical analyses, supervision, critical analyses, and data collection. The authors read and approved the final manuscript.

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Availability of data and materials
The data sets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Clinical Research Ethics Committee (Decision number: 2022/109, date: 06.06.2022). All procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was given by all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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