OPEN

The association of Behçet's syndrome with HLA-B51 as understood in 2021

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Purpose of review
To discuss clinical and pathogenic roles of HLA-B∗51 in Behçet's syndrome.

Recent findings
HLA-B∗51 remains the most important genetic factor in Behçet's syndrome, despite the recent identification of several susceptibility genes. The prevalence of HLA-B∗51 has been shown to differ among phenotype-based clinical clusters in the same patient population. HLA-B∗51 shows epistatic interaction with the susceptible allele of endoplasmic reticulum aminopeptidase (ERAP)1 encoding the Hap10 allotype, which has the lowest trimming activity of the MHC-Class I binding peptides. Subsequent molecular studies have suggested that the disease-associated Hap10 allotype is implicated in the generation and selection of the disease protective or promoting peptides loading onto HLA-B∗51, although these pathogenic peptides have yet to be identified.

Summary
HLA-B∗51 is a hallmark of Behçet's syndrome but genetic markers are not very useful in the diagnosis of Behçet's syndrome. Rather, it is considered an important factor in determining clinical phenotypes in this heterogeneous condition. The epigenetic interaction of HLA-B∗51 with ERAP1 sheds light on pathogenesis.

Keywords
Behçet's syndrome, epistasis, endoplasmic reticulum aminopeptidase 1, HLA-B∗51, MHC-I-opathy

INTRODUCTION

Behçet's syndrome is a chronic multisystemic inflammatory disorder characterized by relapsing and recurrent oral ulcers, genital ulcers, skin lesions, uveitis, and broader systemic manifestations, such as arthritis, and gastrointestinal or central nervous system involvement [1,2▪] The disease is categorized as a variable vessel vasculitis with multiple lesions in all sizes of arterial and venous vessels [3]. Some readers may be more familiar with the term Behçet's disease than Behçet's syndrome. However, Behçet's disease was replaced with Behçet's syndrome in the 2018 update of European League Against Rheumatism (EULAR) recommendations for management [4].

The cause of Behçet's syndrome remains unknown, although both genetic and environmental factors are considered important in disease pathogenesis. Genome-wide association study and subsequent detail genomic studies have identified multiple susceptibility genes, most of which are involved in the immune and inflammatory responses [5–7,8▪▪,9▪▪,10]. Among them, HLA-B∗51 is responsible for the strongest genetic predisposition. It was first reported by Ohno *et al.* [11] in Japan in 1973, followed by reports in other ethnic groups [12▪,13,14▪]. A meta-analysis of HLA-B5 or B∗51 genotypes in 4800 patients with Behçet's syndrome with 16 289 healthy controls suggested a 32–52% of population attributable risks for Behçet's syndrome associated with the HLA-B5/B∗51 allele [13]. This review discusses the clinical and pathogenetic aspects of HLA-B∗51 as a hallmark of Behçet's syndrome.

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KEY POINTS

- Genetic and environmental factors in Behçet's syndrome.
- Contribution of HLA-B∗51 to the disease phenotypes of Behçet's syndrome.
- Epistasis between HLA-B∗51 and ERAP-1 in Behçet's syndrome as MHC-I-opathy.

ASSOCIATION BETWEEN BEHÇET'S SYNDROME AND HLA-B∗51

Behçet's syndrome is sometimes referred to as 'the Silk Route disease' as it is prevalent in the Mediterranean basin, Middle Eastern, and Far East Asian countries between 30° and 45° latitudes north [12▪]. The unique geographic distribution suggests the involvement of a genetic background and common environmental factors in Behçet's syndrome along the endemic regions. Interestingly, HLA-B∗51 positivity in the general population is higher in these regions compared with the geographies where Behçet's syndrome is not endemic, suggesting that HLA-B∗51 is somehow implicated in the clustering of patients with Behçet's syndrome in these any one region. In contrast, no Behçet's syndrome-related common environmental factors have been shown in these endemic areas [12▪].

The frequency of HLA-B∗51 has been reported in 50–80% of patients with Behçet's syndrome in the endemic geographies (Table 1) [12▪,13,14▪]. The odds ratio has been estimated to be 5–10 in the Behçet's syndrome endemic countries, whereas it was reported to be 2.35 in North America, a nonendemic area. However, and interestingly, in Alaska and Middle Africa, both nonendemic areas, the frequency in HLA-B∗51 exceeds 15% of the general population [12▪].

Table 1. Prevalence of Behçet's syndrome and frequency of HLA-B∗51 in various countries

	Prevalence (/100 000)	HLA-B∗51 (%)	
		Patients with Behçet's syndrome	Control
Japan	7.0–14.6	58.9	13.8
Iran	16.7–80.0	61.9	28.7
Saudi-Arabia	19.5	76.9	22.2
Turkey	80.0–421.0	75.0	24.7
Italy	3.8	57.4	19.2
Spain	5.6–7.5	36.2	19.6
German	0.6–1.47	57.6	12.3

Epidemiological studies of immigrants from endemic to nonendemic areas have also suggested the contribution of environmental factors to the Behçet's syndrome pathogenesis. Only a small number of Japanese immigrants to Hawaii have been reported to develop Behçet's syndrome [15]. Similarly, a study in Berlin showed that the prevalence of Behçet's syndrome was 20-fold higher among the citizens of foreign background with 92% of the patients being of Turkish origin, rather than native German [16]. This study also showed that the frequency of HLA-B∗51 was 42 and 14% in German native patients with Behçet's syndrome and controls, respectively (odds ratio 4.5). On the other hand, it was 75% among patients and 31% among the controls of Turkish ethnicity (odds ratio 6.7) [16]. These findings further support the contribution of genetic factors, including HLA-B∗51, to disease onset. Nevertheless, the prevalence of Behçet's syndrome in patients of Turkish origin was much lower than that reported in Turkey (Table 1). Thus, the implication of environmental factors in the development of Behçet's syndrome in addition to genetic backgrounds is also apparent.

CLINICAL IMPLICATION OF HLA-B∗51

Despite the close association of HLA-B∗51 with Behçet's syndrome, genetic markers are not necessarily helpful in diagnosing Behçet's syndrome. Genetic markers are not listed as criteria in currently used diagnostic criteria sets, including the diagnostic criteria of the International Study Group for Behçet's disease [17] and the International Criteria for Behçet's disease [18]. In the Japanese diagnostic criteria, HLA-B∗51 and HLA-A∗26 are noted as reference findings in possible cases with no strong diagnostic implication [19]. This is contrast to HLA-B∗27-related ankylosing spondylitis, in which the genetic marker provides a strong diagnostic basis. The odds ratio for developing ankylosing spondylitis is estimated to be over 50 in HLA-B∗27-positive individuals [20], whereas it is approximately 5–10 for Behçet's syndrome in HLA-B∗51-positive people.

There is accumulating evidence that HLA-B∗51 positivity differs among the clinical subtypes of Behçet's syndrome [14▪,21,22,23▪]. Maldini *et al.* conducted meta-analyses to determine the relationship of the HLA-B5 or B∗51 genotype with each clinical symptom in patients with Behçet's syndrome [14▪]. The study has shown that HLA-B5/B∗51 is more common in male individuals and is associated with a high prevalence of genital ulcers, ocular and skin manifestations, and a decreased prevalence of gastrointestinal involvement [14▪].

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Table 2. Clinical clusters in Japanese patients with Behçet's syndrome

Characteristic clinical presentation	Cluster 1 Mucocutaneous dominant	Cluster 2 Mucocutaneous with arthritis	Cluster 3 Ocular involvement	Cluster 4 Neurological involvement	Cluster 5 Gastrointestinal involvement
Age at onset (years, mean ± SD)	33.6 ± 10.3	37.4 ± 12.3	40.5 ± 12.8	34.8 ± 10.4	37.4 ± 12.3
Sex (ratio of female) (%)	64.3	75.6	31.5	47.8	57.1
HLA-B∗51 (%)	52.1	50.9	50.0	52,7	33.0

SD, standard deviation.

Our recent epidemiological study using a national registry with more than 3000 Japanese patients with Behçet's syndrome also showed that HLA-B∗51 is positively associated with ocular involvement but negatively with gastrointestinal lesions [22]. Thus, the strength of association with HLA-B∗51 differs among the clinical phenotypes.

Recently, the frequency of HLA-B51 has been declining in Japanese patients with Behçet's syndrome [21,23▪]. This decline has been associated with an increased ratio of female patients, increased gastrointestinal involvement, and decreased ocular disease. Our recent study showed that these epidemiological changes were associated with altered proportions of each clinical cluster in Japanese patients with Behçet's syndrome [23▪]. Our cohort included at least five independent clusters characterized by mucocutaneous dominant, mucocutaneous with arthritis, ocular involvement, neurological involvement, and gastrointestinal involvement. We found frequency of HLA-B∗51 was significantly lower in the last cluster as compared with the other clusters (Table 2) [23▪]. Chronological analysis showed a disproportional expansion of the cluster with gastrointestinal involvement was mainly responsible for most of the recent epidemiological changes, including reduced HLA-B∗51 positivity and increased ratio of female patients [23▪]. Furthermore, as genetic backgrounds are relatively homogenous in Japan, environmental factors, yet to be elucidated, are considered critical in disease mechanisms and epidemiological changes.

PATHOGENIC ROLES OF HLA-B∗51 AND OTHER HLA-CLASS I MOLECULES

The pathogenic role of HLA-B∗51 in Behçet's syndrome remains unknown. Whether the HLA-B∗51 molecule itself is involved in the development of disease or is a mere maker of the true pathogenic gene with linkage disequilibrium has been controversial. Tumor necrosis factor, lymphotoxin, and *major histocompatibility class I chain-related gene A* (*MICA*) genes, all of which are located close to the HLA-B locus, have been discussed as possible candidates [24–27]. Hughes *et al.* [28] showed that the association of HLA-B∗51 with Behçet's syndrome was secondary to that of the rs16799036 variant, which is located between the HLA-B and MICA loci. However, Ombrello *et al.* [9▪▪] disagreed with this finding. A combination analysis of directly obtained and imputed MHC-region single nucleotide polymorphism led to the conclusion that HLA-B∗51 itself but not the rs16799036 variant, was primarily associated with Behçet's syndrome. They further showed that HLA-B∗15, HLA-B∗27, HLA-B∗57, and HLA-A∗26 were independent risk alleles, whereas HLA-A∗3 and -B∗49 were protective against the development of Behçet's syndrome [9▪▪].

It is important to characterize the structure of HLA class I molecules with disease susceptibility. There are 69 amino acid polymorphic residues in HLA-B molecules. HLA-B∗52, a split antigen of HLA-B5, is not associated with Behçet's syndrome. Only two amino acid residues are different in the a1 helix between HLA-B∗51 and B∗52; Asp at position 63 and Phe at position 67 in HLA-B∗51 are substituted with Glu and Ser in HLA-B∗52, respectively [29]. Furthermore, stepwise conditional analysis of the polymorphic amino acid positions of HLA-B revealed that 16 residues were associated with susceptibility to Behçet's syndrome. All 16 amino acid residues are risk types in HLA-B51, whereas B15 and B57 have seven and eight risk types of amino acid residues, respectively [9▪▪]. Of these, Phe at 67, Leu at 116, Thr at 116, and Glu at 152 of the HLA-B molecules are considered critical as these residues located in the MHC-I antigen-binding groove affect the binding of antigenic peptides. Moreover, Phe at 67 and Thr at 116 are involved in the interactions of HLA-B molecules with killer immunoglobulin-like receptors (KIR)3DL1 and KIR3DS1, which regulate the activation of natural killer (NK) cells and CD8+ T cells [30]. Likewise, residues 67 and 116 are considered critical in disease-susceptible HLA-A molecules [9▪▪]. These structural features are implicated in the selection of binding antigens to HLA class I molecules and regulation of T-cell and NK-cell function, leading to the development of Behçet's syndrome.

EPISTATIC INTERACTION BETWEEN HLA-B*51 AND ERAP1

In genetic jargon, the affect of one gene on the function of another gene is called 'epistasis' and Kirino *et al.* [8▪▪] described a recessive model of epistatic interaction between HLA-B*51 and endoplasmic reticulum aminopeptidase (ERAP)1. ERAP1 encodes an enzyme that trims peptides for loading onto MHC class I molecules in the endoplasmic reticulum. The Behçet's syndrome-associated ERAP1 allele encoding p.Asp575Asn and p.Arg725Gln variations is the Hap10 allotype at the protein level [31▪]. The homozygosity but not heterozygosity, significantly increased the risk of Behçet's syndrome with uveitis only in HLA-B*51-positive individuals [8▪▪]. Similarly, epistatic interaction has also been shown between different ERAP 1 allotypes and HLA-B*27 in ankylosing spondylitis, and HLA-C*06 in psoriasis, leading to the proposal of a novel concept, 'MHC-I-opathy' [32]. These diseases are also similar in other susceptibility genes, including the IL-17/23 pathway, distribution of affected organs, and some therapeutic approaches [32]. However, ERAP2, which has complementary and partially redundant effects of ERAP1 on the MHC-class I peptidome, also showed a significant association with ankylosing spondylitis and psoriasis but not with Behçet's syndrome [33,34]. The concept of MHC-I-opathy may be helpful for understanding the pathogenesis of MHC-class I-associated diseases more than in their clinical aspects.

HLA-B*51 PEPTIDOME AND ENDOPLASMIC RETICULUM AMINOPEPTIDASE 1 VARIANTS

ERAP1 variants play a critical role in determining the MHC class I peptidome as trimming activity depends on the allotypes [31▪,33,35–37]. Compared with the other allotypes, the Behçet's syndrome-associated Hap10 allotype has poor peptide trimming activity [31▪], whereas Hap10 is rather protective for ankylosing spondylitis [38]. Thus, the impaired peptide trimming activity of ERAP1 is not necessarily responsible for all MHC-class I-associated diseases. Rather, the disease-associated ERAP1 variants may have an advantage for the generation of disease-promoting peptides or elimination of protective peptides in the susceptible MHC-class I peptidomes of each disease.

Before identifying *ERAP1* as a Behçet's syndrome susceptibility gene, the pathogenic peptides were explored based on the nature of HLA-B*51-binding peptides, which are eight or nine amino acids with Pro and Ala at position 2 and Ile, Val, and Leu at the C terminal. For example, Yasuoka *et al.* have shown that the MICA-derived 9-mer peptide (Ala-Ala-Ala-Ala-Ile-Phe-Val-Ile), which are compatible with typical features of the HLA-B*51-binding peptides, induced an HLA-B51-restricted CD8+ T-cell response in patients with Behçet's syndrome [39].

Recent studies have attempted to determine the effects of Behçet's syndrome-associated Hap10 on the HLA-B51 peptidome using cell lines and in-vitro peptide-priming assays [35,36,40]. These studies have suggested that the Behçet's syndrome-associated Hap10 allotype affects HLA-B*51-binding peptide repertoires. Guasp *et al.* [35] have shown that peptides with Ala at 2 are more sensitive to ERAP1 than those with Pro at 2, the latter of which is not degraded by any type of ERAP1 variant. Significant associations were found between the high activity of the ERAP1 variant and high-affinity peptides with Pro at 2, and between low activity of the variant and low affinity peptides with Ala at 2 in the HLA-B*51peptidome [35]. Thus, the balance of Ala-2 and Pro-2 subpeptidomes depends on ERAP1-trimming activity in HLA-B*51-positive cell lines. In contrast, Chen *et al.* [40] found that unconventional non-Pro/Ala-2 peptides were significantly increased by ERAP1 silencing cells compared with the controls constituting 20% of HLA-B51-binding peptides. As the Hap10 haplotype is considered to mimic the loss-of-function of ERPA1, the results suggest that the non-Pro/Ala-2 subpeptidome expands in HLA-B*51-positive patients with Behçet's syndrome with the susceptibility allotype. These findings suggest that the disease-associated Hap10 allotype is involved in the generation and selection of disease protective or promoting peptides leading to the development of Behçet's syndrome. However, neither protective nor disease-promoting peptides have yet been identified in Behçet's syndrome.

ANIMAL MODELS

Several animal models of Behçet's syndrome have been proposed but none have been established. To determine the direct roles of HLA-B*51 molecules, HLA-B*5101 transgenic mice (C3H/He) were investigated [41]. The transgenic mice did not develop any Behçet's syndrome-related symptoms spontaneously. However, neutrophils from the mice produced excessive superoxides in response to formyl-methionyl-leucyl-phenylalanine, suggesting that circulating neutrophils are already primed to be ready to respond to stimuli. A similar neutrophil hyperactivity was shown in HLA-B*51-positive individuals; however, the mechanism remains unknown. As the transgenic construct contained a heavy chain of HLA-B*5101 without the coupling molecule, human β2 microglobulin, the mice did not completely reproduce the HLA-B51-related molecular structure. Rather, the lack of Behçet's syndrome-related

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manifestations in the HLA-B*51 transgenic mice supports the notion that genetic and environmental factors are essential for the development of Behçet's et's syndrome in addition to the HLA-B*51.

CONCLUSION

HLA-B*51 is a hallmark of Behçet's syndrome. Epidemiological, clinical, and genetic studies have reported the following:

(1) HLA-B*51 is strongly associated with Behçet's syndrome worldwide, particularly in the Mediterranean basin, Middle Eastern, and Far East Asian countries.
(2) HLA-B*51 is not diagnostic of Behçet's syndrome but affects clinical phenotypes.
(3) HLA-B*51 is considered to play a primary role in the development of Behçet's syndrome, but is not a surrogate marker of other susceptible genes.
(4) HLA-B*51 has an epigenetic interaction with ERAP1, which determines the HLA-B*51 peptidome.

Despite extensive studies, the pathogenic roles of HLA-B*51 in Behçet's syndrome have not yet been elucidated.

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Conflicts of interest

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