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Behçet's Disease as a Canker Sore: MHC-I-Opathy Versus Behcet's Spectrum Disorders

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Abstract

Purpose of Review Behçet's disease is a chronic multisystemic inflammatory disorder characterized by recurrent oral ulcers and a close association with *HLA-B*51*. This review summarizes the clinical and genetic features of Behçet's disease and compares susceptibility genes with those of other HLA class I-associated and stomatitis-related diseases.

Recent Findings In Behçet's disease, recently identified non-HLA susceptibility genes are involved in the innate and acquired immune functions. An epistatic interaction between *HLA-B*51* and *ERAP1* is considered to play a pathogenic role in the disease. Similar findings have been also shown in other HLA class I-associated diseases, leading to a new concept of MHC-I-opathy.

Immune-related non-HLA susceptibility genes are shared among Behçet's disease, recurrent aphthous stomatitis, and periodic fever aphthous stomatitis and adenitis syndrome, leading to another novel concept of Behçet's spectrum disorders.

Summary Recent genetic studies have shown that Behçet's disease has both features of MHC-I-opathy and Behçet's spectrum disorders.

Keywords Behçet's disease · Canker sore · MHC-I-opathy · Behcet's spectrum disorders · *HLA-B*51*

Introduction

Behçet's disease (BD) is a chronic multisystemic inflammatory disorder characterized by recurrent oral ulcer, genital ulcers, skin lesions, and uveitis [1, 2]. It also affects the joints and gastrointestinal, vascular, and central nervous systems [1, 2]. As the disease has a diverse spectrum of clinical presentations, it is also referred to as Behçet's syndrome. When the European League Against Rheumatism (EULAR) recommendations for the management of BD were updated in 2018, the term Behçet's syndrome had been chosen to replace BD [3, 4]. Despite heterogeneous clinical presentations, recurrent oral ulcers are considered a cardinal condition of BD because they commonly appear as an initial symptom and last throughout the clinical course in most patients [1, 2, 5].

The etiology of BD remains unknown, although both genetic and environmental factors are thought to contribute to its development. Human leukocyte antigen (*HLA)-B*51* is known as the strongest genetic predisposition factor, which was first reported by Ohno et al. in Japan [6], followed by reports from other ethnic groups [7••]. Recent genome-wide association studies (GWAS) and subsequent detailed genomic studies have identified several non-HLA susceptibility genes in BD, most of which are involved in the immune and inflammatory systems [8–12].

Genetic studies of other diseases related to HLA class I and recurrent oral ulcers have led to two novel concepts of the disease groups: MHC-I-opathy and Behçet's spectrum disorders [13, 14••, 15••]. These concepts were proposed based on clinical and genetic similarities. MHC-I-opathy includes ankylosing spondylitis, birdshot uveitis, and psoriasis, whereas Behcet's spectrum disorders are clinically characterized by canker sores and consist of BD, recurrent aphthous stomatitis (RAS), and periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome [16, 17].

This review first describes the clinical features and genetic backgrounds of BD and then discusses two novel BD-related disease concepts, MHC-I-opathy and Behcet's spectrum disorders.

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Clinical Manifestations of BD and Classification Criteria

Table 1 shows the frequencies of each symptom in patients with BD from various countries [5, 18, 19, 20•, 21]. Oral and genital ulcers and skin and ocular lesions are common in patients from all countries, although there are some regional differences in the manifestations in other organs. For example, gastrointestinal involvement is more common in countries of the Far East, such as Japan and Korea, whereas vascular involvement is less frequent in these regions [2].

Diagnosis of BD relies on a combination of symptoms owing to a lack of diagnostic biomarkers and because imaging and histological findings are nonspecific. Table 2 shows a comparison of the three sets of criteria currently used for the diagnosis of adult patients [5, 22, 23]. To classify a patient as having BD, the International Study Group (ISG) criteria require two or more of the following: recurrent genital ulcerations, eye lesions, skin lesions, and a positive pathergy test, together with recurrent oral ulcers [24]. In addition to mucocutaneous and ocular lesions, the International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD) criteria include vascular and neurological involvement to avoid diagnostic delay in patients with serious organ lesions as initial manifestations [22, 23], while gastrointestinal involvement is also listed in the Japan criteria that are provided by Behcet's Disease Research Committee of Japan because of its high frequency [5].

Clinical Clustering of Patients With BD

Although the clinical manifestations are heterogeneous in patients with BD, several studies have shown that patients can be stratified according to clinical manifestations [21]. For example, five independent clinical clusters have been identified among patients with BD in Japan, namely, "mucocutaneous," "mucocutaneous with arthritis," "neurological," "gastrointestinal," and "eye" clusters. In addition to the clinical phenotypes, differences in demographic features, therapeutic responses, prognosis, and *HLA-B*51* positivity have been noted between the clusters.

Table 1 Frequency of symptoms in patients with Behçet's disease

Author	Year	Country	Patient number	OU	GU	Eye	Skin	Pathergy	Joint	Epididymitis	GI	CNS	Vessel
				Percentage of patients (%)									
Ideguchi	2010	Japan	412	100	73	65	88	NA	48	6	10	13	8
Soejima	2018	Japan	6754	94	63	35	81	32	49	NA	13	5	2
Zouboulis	1997	Germany	130	98	79	48	73	53	59	32	NA	NA	NA
Dilsen	1993	Turkey	496	100	77	47	78	NA	47	NA	5	8	38
Krause	2007	Israel	112	100	68	53	41	44	70	NA	NA	12	18

OU, oral ulcer; *GU*, genital ulcer; *GI*, gastrointestinal tract; *CNS*, central nervous system

Table 2 Comparison of three sets of criteria for Behçet's disease

	ISG 1990	ITR-ICBD 2014	Japan 1987
Recurrent oral ulcer	mandatory	2	Major
Genital ulcer	○	2	Major
Eye lesion	○	2	Major
Skin lesion	○	1	Major
Arthritis			Minor
Epididymitis			Minor
GI involvement			Minor
CNS involvement		1	Minor
Vascular involvement		1	Minor
Pathergy reaction	○	1	Reference
HLA-B51 (A26)			Reference
Diagnosis or classification	Oral aphtha + more than 2 symptoms	More than score 4	More than 3 major 2 major + 2 minor Eye + one major or 2 minor

Despite a homogeneous genetic background and low immigration rate, epidemiological evolution has been observed in patients with BD in Japan [25]. This evolution is characterized by increased gastrointestinal manifestations, decreased eye involvement, and decreased *HLA-B*51* positivity [25]. Interestingly, this evolution was associated with chronological changes in the cluster proportions, such as an increase in the proportion of the gastrointestinal cluster and a decrease in that of the eye cluster, both of which were associated with a reduced frequency of *HLA-B*51* positivity. Thus, the proportions of individual clusters are considered to determine the epidemiological features. Clustering patterns are likely to differ among different ethnic groups and countries, leading to regional and ethnic differences in the clinical features of patients with BD [26]. However, international comparative studies are yet to be conducted.

Epidemiology of BD

BD is sometimes referred to as "the Silk Route disease" because it is prevalent in the Mediterranean basin and countries of the Middle and Far East (between 30 and 45° latitudes north) [1, 2]. Turkey has the highest prevalence, ranging from 20 to 421 per 100,000 adults (>10–12 years), although childhood onset is rare [27]. The prevalence per 100,000 individuals was reported as 16.7 to 80.0 in Iran [28, 29], 17 in Iraq [30], 30.2 in South Korea [31], and 22 in Japan [31], whereas it was only 0.27 to 7.5 in European countries [18, 28, 32–38], 2.6 in Hong Kong [39], 1.0 in Taiwan [40], and 0.33 in the USA [41].

The unique geographic distribution suggests the involvement of genetic backgrounds and common environmental factors in BD in the prevalent areas. *HLA-B*51* is one such factor because the frequency of *HLA-B*51*-positive individuals in the general population is also higher in the BD-prevalent areas than that in other areas [42].

A family history of BD has been reported in 8–34% of patients from Turkey and the Middle East [43], and a familial study of 170 consecutive unrelated patients with BD in Turkey revealed that the sibling recurrence ratio (λs) ranged from 11.4 to 52.5 [43]. These findings support the implication of genetic factors in BD, although shared environmental factors may partially contribute to this familial clustering.

The involvement of environmental factors can be speculated based on epidemiological studies of immigrants from prevalent to non-prevalent areas; however, the results are not necessarily consistent among the studies. A population-based study in France showed that the prevalence of BD in European, North African, and Asian ancestries was 2.4, 34.6, and 17.5, respectively, indicating that BD is primarily hereditary [28]. In contrast, BD is rare among Japanese immigrants in Hawaii and California [44], suggesting a possible role of environmental factors in disease onset. Studies from Berlin reported that the prevalence of BD in Turkish immigrants was higher than that in German natives but lower than that in Turkish residents, suggesting the involvement of both genetic and environmental factors [18, 28].

In terms of age, BD is more prevalent in people in their 20s to 40s [1, 2, 45]. A regional difference in the sex ratio for prevalence has also been noted [1, 2, 45]. The disease is more common among females in Japan and Korea, whereas it is predominant in males in countries of the Middle East and Europe [1, 2, 31, 45]. Furthermore, early onset and male sex have been identified as independent risk factors for severe manifestations, such as ocular and vascular involvement, regardless of the region and ethnic group [1, 2, 31, 45].

Genetic Backgrounds

BD is a multigenic disease. *HLA-B*51* is known as a hallmark of BD [7••]. The association of other HLA alleles has also been investigated [46]. Besides, *HLA-B*51*, *A*26*, *B*15*, *B*27*, and *B*57* are susceptibility alleles for BD, whereas *A*3* and B*49 are protective alleles [46]. The strong genetic association of HLA class I molecules suggests the involvement of antigen-specific $CD8^+$ T cell responses in the disease process.

On the other hand, the involvement of non-HLA genes had not been determined until two independent GWAS identified *IL10* and *IL12RB2/IL23R* as susceptibility genes for BD in 2010 [8, 9]. These studies represent breakthroughs in the identification of novel susceptibility genes for BD [10–12]. Almost all of the identified genes are involved in innate and acquired immunity (Table 3). These findings suggest that both autoimmune and autoinflammatory abnormalities mediate inflammation in patients with BD. Pathogen-associated molecular pattern (PAMP) sensors, such as *TLR4*, *NOD2*, and *MEFV*, have also been identified as susceptibility genes, indicating that microbial pathogens are also involved in the disease process as environmental factors [10].

MHC-I-Opathy

The identification of susceptibility genes is helpful for understanding the pathophysiology of BD. Of these, *HLA-B*51* and *ERAP1* are disease-specific and interact with each other. The *ERAP1* susceptibility allele significantly enhances the risk of BD only in *HLA-B*51*-positive individuals, but not in those that are *HLA-B*51*-negative [11]. This finding is called an epistatic interaction. *ERAP1* encodes an enzyme that trims peptide antigens to the optimal length for binding to major histocompatibility complex (MHC) class I molecules in the endoplasmic reticulum. Subsequent studies

Table 3 Susceptibility and resistant genes for Behçet's disease

Acquired immune system					
HLA					
Susceptible	*B*51*	*B*15*†*	*B*27*	*B*57*	*A*26*
Resistant	*B*49*	*A*3*			
HLA related	*MICA**	*ERAP1*			
Non-HLA					
Cytokine receptor	*IL23R-IL12RB*	*IL23R*	*EGR2(ADO-EGR2)*		
Signal transduction	*STAT4*	*PTPN1(CEBP-PTPN1)*			
Apoptosis	*GIMAP*				
Innate immune system					
Cytokine	*IL10*†*	*IL12A*†*	*IL1A-IL1B*	*LACC1*	
Chemokine receptor	*CCR1*	*CCR1/CCR3*†*			
DAMPS/PAMPS sensor	*MEFV*	*TLR4*	*NOD2**	*RIPK2**	
Signal transduction	*TNFAIP3*	*IRF8**	*CEBP(CEBP-PTPN1)*		
NK cell receptor	*KLRC4*				
Other	*FUT2*				

*Recurrent aphthous stomatitis

† PFAPA syndrome

have suggested that the disease-associated *ERAP1* allele is involved in the preferential presentation of a pathogenic peptide or in blocking the presentation of a protective peptide onto *HLA-B*51*-encoded molecules [47].

Interestingly, similar epistatic interactions between HLA class I genes and *ERAP1* or *ERAP2* have been demonstrated in *HLA-B*27*-associated ankylosing spondylitis, *HLA-C*06:02*-associated psoriasis, and *HLA-A*29*-associated birdshot uveitis [13, 14••, 15••]. Additionally, these diseases share susceptibility genes in the IL-17 pathway, such as *IL23R*. These findings lead to the novel concept of "MHC-I-opathy" diseases. The detailed immunopathological mechanisms are currently under investigation [13, 14••, 15••].

Behçet's Spectrum Disorders

Recurrent oral aphthous ulcers are a cardinal symptom that appear in almost all patients with BD and last throughout the clinical course, irrespective of the disease phenotype or clinical cluster. The similar canker sore condition is also seen in patients with RAS and PFAPA syndrome, and recent genetic studies have shown similar genetic backgrounds between these three diseases, leading to another new concept of "Behçet's spectrum disorders" [15••, 16].

RAS is a common disease; however, it can also be seen as a symptom of systemic diseases such as cyclic neutropenia, HIV infection, PFAPA syndrome, reactive arthritis, Sweet's syndrome, and mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome, in addition to BD [48]. A GWAS for RAS revealed that this condition was an immune-mediated disorder [16], as 97 disease-associated alleles were identified, most of which were involved in innate and acquired immune functions. Moreover, in silico functional analyses provided evidence for the involvement of T cell regulation in the development of RAS. Interestingly, some susceptibility genes are shared with those of BD, including *IL12A*, *IL10*, *CCR3*, *STAT4*, *MICA*, *RIPK2*, *IRF8*, and *NOD2* (Table 3) [16].

PFAPA syndrome, the most common periodic fever syndrome in children, is characterized by recurrent, regular attacks of high fever associated with pharyngeal inflammation, aphthous stomatitis, and/or cervical lymphadenopathy [49]. It is a non-hereditary autoinflammatory disorder of unknown etiology that is prevalent in children between 1 and

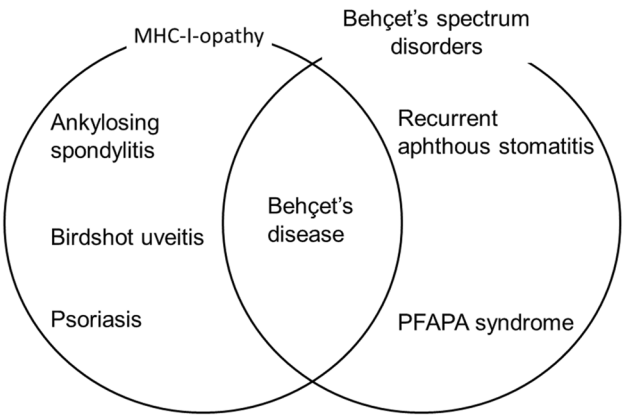

Fig. 1 Behçet's disease has both features of Behcet's spectrum disorders and MHC-I-opathy

5 years of age. Some adults with BD have reported symptoms earlier in childhood that fulfill the diagnostic criteria for PFAPA syndrome [50]. A recent GWAS for PFAPA syndrome revealed that *STAT4*, *IL10*, *IL12A*, and *CCR1-CCR3* are non-HLA susceptibility genes, all of which are observed in BD (Table 3) [15••]. These findings suggest that a common immune mechanism is involved in oral lesions associated with these diseases. Similar therapeutic responses have also been observed. Colchicine and low-dose glucocorticoids, both of which are used to treat the oral manifestations in BD, have some efficacy for RAS [4, 48]. While in PFAPA syndrome, glucocorticoids dramatically suppress the fever attacks, and the prophylactic effects of colchicine have been demonstrated for the treatment of this disease [49].

Although canker sores are a common manifestation, differences in the extraoral organ involvement are apparent among Behçet's spectrum disorders. In principle, RAS presents with no symptoms except for oral lesions, whereas fever, pharyngeal inflammation, and cervical lymphadenopathy are common in PFAPA syndrome. BD, meanwhile, can cause serious symptoms in the ocular, gastrointestinal, central nervous, and vascular systems. Although non-HLA susceptibility genes are shared among these diseases, each disease is associated with different types of HLA, except *HLA-B*15*, which is shared among Behçet's spectrum disorders [15••]. While BD is strongly associated with HLA-B*51:01, RAS are rather associated with HLA class II molecules, HLA-DRB1*01:03. Similarly, PFAPA also showed association with HLA class II including HLA-DRB1*13:01, HLA-DQA1*01:03, and HLADQB1*06:03. Interestingly, the strength of the HLA associations is considered to be related to disease severity. BD shows the strongest HLA association with severe disease, whereas RAS shows a relatively weak association with mild manifestations; PFAPA syndrome appears to have an intermediate association.

Conclusions

BD is a heterogeneous disease with varying phenotypes and severities. The most common symptom is a recurrent oral aphthous ulcer, and the strongest genetic factor is *HLA-B*51*. Recent genetic studies on BD and other diseases have led to the proposal of two novel disease concepts: MHC-I-opathy and Behçet's spectrum disorders. BD has characteristic features of both disease concepts (Fig. 1). To elucidate immune mechanisms of these new concepts will shed light on the pathogenesis of BD.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent Not applicable

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