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 innate and inflammatory responses [5–7,8*,9**,10]. Among them, HLA-B51 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 B51 genotypes in 4800 patients with Behçet’s syndrome with 16289 healthy controls suggested a 32–52% of population attributable risks for Behçet’s syndrome associated with the HLA-B5/B51 allele [13]. This review discusses the clinical and pathogenetic aspects of HLA-B51 as a hallmark of Behçet’s syndrome.
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 non-endemic 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*].

| Country          | 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-B51 and HLA-A26 are noted as reference findings in possible cases with no strong diagnostic implication [19]. This is contrast to HLA-B27-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-B27-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*].

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

| Country          | Prevalence /100 000 | HLA-B-51 (%) | Patients with Behçet’s syndrome | Control |
|------------------|---------------------|--------------|--------------------------------|---------|
| Japan            | 7.0–14.6            | 58.9         | 13.8                           |
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| Spain            | 5.6–7.5             | 36.2         | 19.6                           |
| German           | 0.6–1.47            | 57.6         | 12.3                           |
The pathogenic role of HLA-B remains unknown. Whether the HLA-B 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 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 itself but not the rs16799036 variant, was primarily associated with Behçet’s syndrome. They further showed that HLA-B, HLA-B/C3, HLA-B/C15, and HLA-A26 were independent risk alleles, whereas HLA-A3 and -B49 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-B52, 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-B51 and B52; Asp at position 63 and Phe at position 67 in HLA-B51 are substituted with Glu and Ser in HLA-B52, 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.

**PATHOGENIC ROLES OF HLA-B51 AND OTHER HLA-CLASS I MOLECULES**

The pathogenic role of HLA-B51 in Behçet’s syndrome remains unknown. Whether the HLA-B51 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-B51 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-B51 itself but not the rs16799036 variant, was primarily associated with Behçet’s syndrome. They further showed that HLA-B15, HLA-B27, HLA-B57, and HLA-A26 were independent risk alleles, whereas HLA-A3 and -B49 were protective against the development of Behçet’s syndrome [9**].

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

| Characteristic clinical presentation | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 | Cluster 5 |
|------------------------------------|----------|----------|----------|----------|----------|
|                                    | Mucocutaneous dominant | Mucocutaneous with arthritis | Ocular involvement | Neurological involvement | 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-B51 is positively associated with ocular involvement but negatively with gastrointestinal lesions [22]. Thus, the strength of association with HLA-B51 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-B51 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-B51 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.
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 ERAP1 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 complimentary 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-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-B51 peptidome [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-B-51-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
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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REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:
- of special interest
- of outstanding interest

1. Sakane T, Takeno M, Suzuki N, Inaba G. Behçet’s disease. New Engl J Med 1999; 341:1284–1291.
2. Yazici H, Seyahi E, Hatemi G, Yazici Y. Behçet syndrome: a contemporary view. Nat Rev Rheumatol 2018; 14:107–119.

This is an excellent review that discusses diversity of clinical presentations, the etiology and the pathogenesis, and current progression of treatment in Behçet’s syndrome.

3. Sunderkotter CH, Zelger B, Chen K-R, et al. Nomenclature of cutaneous vasculitis. Arthritis Rheumatol 2018; 70:171–184.
4. Hatemi G, Christensen R, Bang D, et al. 2018 update of the EULAR recommendations for the management of Behçet’s syndrome. Ann Rheum Dis 2018; 77:808–818.
5. Mizuki N, Meguro A, Ota M, et al. Genome-wide association studies identify IL23R-IL12RB2 and IL10 as Behçet’s disease susceptibility loci. Nat Genet 2010; 42:703–706.
6. Remmers EF, Cosan F, Kirino Y, et al. Genome-wide association study identifies variants in the MHC class I, IL10, and IL23R-IL12RB2 regions associated with Behçet’s disease. Nat Genet 2010; 42:698–702.
7. Kirino Y, Zhou Q, Ishigatsubo Y, et al. Targeted resequencing implicates the familial Mediterranean fever gene MEFV and the toll-like receptor 4 gene TLR4 in Behçet disease. Proc Natl Acad Sci USA 2013; 110:8134–8139.
8. Kirino Y, Bertias G, Ishigatsubo Y, et al. Genome-wide association analysis identifies new susceptibility loci for Behçet’s disease and epitasis between HLA-B*51 and ERAP1. Nat Genet 2013; 45:202–207.

This study first demonstrated epistatic interaction between HLA-B*51 and ERAP1, leading to a novel concept of MHC-lymphopy.
9. Ombrello MJ, Kirino Y, De Bakker PJ, et al. Behçet disease-associated MHC class I residues implicate antigen binding and regulation of cell-mediated cytotoxicity. Proc Natl Acad Sci USA 2014; 111:8867–8872.
10. Ta A, et al. Dense genotyping of immune-related loci implicates host responses to microbial exposure in Behçet’s disease susceptibility. Nat Genet 2017; 49:438–443.
11. Ohno S, Oheuchi M, Hirose S, et al. Close association of HLA-B*51 with Behçet’s disease. Arch Ophthalmol 1982; 100:1455–1458.
12. Verity DH, Marr JE, Ohno S, et al. Behçet’s disease, the Silk Road and HLA-B*51: historical and geographical perspectives. Tissue Antigens 1999; 54:213–220.

This study suggests involvement of HLA-B*51 in the geographic clustering of patients with Behçet’s syndrome.
13. De Menthon M, Lavalley MP, Maldini C, et al. HLA-B*51/DRB1and the risk of Behçet’s disease: a systematic review and meta-analysis of case-control genetic association studies. Arthritis Rheum 2009; 61:1287–1296.
14. Maldini C, Lavalley MP, Cheminant M, et al. Relationships of HLA-B*51 or BS genotype with Behçet’s disease clinical characteristics: systematic review and meta-analyses of observational studies. Rheumatology 2012; 51:887–900.

A meta-analysis shows distinct contribution of HLA-B*51 to each clinical presentation in Behçet’s syndrome.
15. Hirohata T, Kuratsuwe M, Nomura A, Jimi S. Prevalence of Behçet’s syndrome in addition to the HLA-B*51 is a hallmark of Behçet’s disease worldwide, particularly in the Mediterranean basin, Middle Eastern, and Far East Asian countries.
16. 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. Despite extensive studies, the pathogenic roles of HLA-B*51 in Behçet’s syndrome have not yet been elucidated.
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21. 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.
29. Falk K, Ritzschke O, Takiguchi M, et al. Peptide motifs of HLA-B51, -B52 and -B78 molecules, and implications for Behçet’s disease. Int Immunol 1995; 7:223–228.
30. Castano-Nunez A, Montes-Cano MA, Garcia-Lozano JR, et al. Association of functional polymorphisms of KIR3DL1/DS1 with Behçet’s disease. Front Immunol 2019; 10:2755.
31. Takeuchi M, Ombrello MJ, Kirino Y, et al. A single endoplasmic reticulum aminopeptidase-1 protein allotype is a strong risk factor for Behçet’s disease in HLA-B51 carriers. Ann Rheum Dis 2016; 75:2208–2211. This study shows the Behçet’s syndrome-associated ERAP1 variant codes Hap10 allotype that has low trimming activity of the MHC-class I binding peptides.
32. McGonagle D, Aydin SZ, Gul A, et al. ‘MHC-I-opathy’-unified concept for spondyloarthritis and Behçet disease. Nat Rev Rheumatol 2015; 11: 731–740.
33. López De Castro JA. How ERAP1 and ERAP2 shape the peptidomes of disease-associated MHC-I proteins. Front Immunol 2018; 9:3463.
34. Tedeschi V, Paldini G, Paladini F, et al. The impact of the ‘Ms-Peptidome’ on HLA Class I-mediated diseases: contribution of ERAP1 and ERAP2 and effects on the immune response. Int J Mol Sci 2020; 21:9608.
35. Guasp P, Alvarez-Navarro C, Gomez-Molina P, et al. The peptidome of Behçet’s disease-associated HLA-B51:01 includes two subpeptidomes differentially shaped by endoplasmic reticulum aminopeptidase 1. Arthritis Rheumatol 2016; 68:505–515.
36. Guasp P, Barnes E, Gonzalez-Escibano MF, et al. The Behçet’s disease-associated variant of the aminopeptidase ERAP1 shapes a low-affinity HLA-B51 peptide by differential subpeptidome processing. J Biol Chem 2017; 292:9680–9689.
37. Chen L, Shi H, Koftori D, et al. Identification of an unconventional subpeptidome bound to the Behçet’s disease-associated HLA-B51:01 peptide by differential subpeptidome processing. J Biol Chem 2017; 292:9680–9689.
38. Evans DM, Spencer CCA, Pointon JJ, et al., Australo-Anglo-American Spondyloarthritis Consortium (TASC), Welcome Trust Case Control Consortium 2 (WTCCC2). Interaction between ERAP1 and HLA-B27 in ankylosing spondylitis implicates peptide handling in the mechanism for HLA-B27 in disease susceptibility. Nat Genet 2011; 43:761–767.
39. Yasuoka H, Yamaguchi Y, Mizuki N, et al. Preferential activation of circulating CD8+ and gammadelta T cells in patients with active Behçet’s disease and HLA-B51. Clin Exp Rheumatol 2008; 26(Suppl 50):S59–S63.
40. Chen L, Shi H, Koftori D, et al. Identification of an Unconventional Subpeptidome Bound to the Behçet’s Disease-associated HLA-B51:01 peptide by Differential Subpeptidome Processing. J Biol Chem 2017; 292:9680–9689.
41. Takeno M, Kariyone A, Yamashita N, et al. Excessive function of peripheral blood neutrophils from patients with Behçet’s disease and from Hla-b51 transgenic mice. Arthritis Rheum 1995; 38:426–433.