Chapter 15
Genetics of Behçet's Disease

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Keywords Behçet's disease • Familial aggregation • Sibling recurrence risk ratio (λs) • HLA-B51 • MICA • HLA-A26 • Linkage study • Genomewide association study

Behçet's disease (BD) is a systemic inflammatory disorder of unknown etiology. It is generally accepted as a multifactorial disease with a strong genetic background, and the disease manifestations are considered to be triggered by various environmental factors in genetically susceptible individuals [1, 2].

There are several clues supporting involvement of genetic factors in the pathogenesis of BD, which include familial aggregation, distinct geographic distribution, and its association with the HLA-B51 antigen.

Familial Aggregation

Although majority of BD patients are seen as sporadic cases, increased frequency of BD has long been noted among the relatives [3–16]. Varying frequencies of patients with a positive family history for BD were described in large series of patients, with a tendency for higher figures in the Middle Eastern patients compared to the patients from Asian and European countries [16, 17].

Gül and colleagues analyzed the sibling recurrence risk ratio (λs) for quantifying the familial aggregation in BD [17]. They calculated the sibling recurrence rate as 4.2 by taking into account only the immediately older sibling, or if an older sibling is not available, immediately younger sibling for evaluation. By using the prevalence rates of BD in Turkey, λs value was found to be 11.4–52.5 for BD [17].

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This λs value was considered as strongly supporting the contribution of genetics to the multifactorial pathogenesis of BD.

Familial clustering was more frequently observed among juvenile-onset (<16) BD patients [18, 19]. Molinary and colleagues conducted a segregation analysis using the pedigree data of 106 BD cases. They included "possible" BD patients who had only two of the classical disease manifestations into the analysis, and they found a pattern compatible with autosomal recessive inheritance in pediatric BD subgroup, and no Mendelian pattern in adult-onset patients [19]. This study suggested a genetic heterogeneity with a higher impact of genetic load in juvenile BD cases [19].

Frequency of HLA-B51 was found to be higher in familial patients [11, 12]. However, presence of unaffected siblings with risk alleles also showed the complex nature of the disease indicating the contribution of other genes and/or environmental factors [11, 20]. A comparison of related pairs of patients according to their age at onset also supports involvement of both genetic and environmental factors in the pathogenesis [21, 22].

Another study from Turkey documented clues for genetic anticipation in the form of earlier disease onset in the second generation compared with their affected parents in 15 out of 18 familial cases studied [23]. However, no trinucleotide repeat expansion data are yet available to further support this observation.

No large series of twins concordant or discordant for BD were reported so far [24–26]. Therefore, large series of monozygotic and dizygotic twins are being awaited for heritability analysis to assess the relative contribution of genes and environment to the pathogenesis of BD.

Geographic Distribution

Epidemiology of BD has a distinct feature in terms of its geographic distribution. Prevalence of BD is much higher in an area extending from the Mediterranean basin to Japan, between 30° and 45° latitudes North, which overlaps with the ancient Silk Road [27]. There is no known specific environmental factor common along this route, but shared genetic factors may explain the clustering of BD cases. The frequency of BD-related HLA-B51 allele is higher in the healthy population living along this region, and distribution of HLA-B51 allele is suggested to play a role in the disease clustering [27, 28].

HLA-B51 and Other MHC Associations

BD is strongly associated with a class I major histocompatibility complex (MHC) allele, HLA-B51. This association was first reported in Japanese BD patients [28–30]. Association of HLA-B51 with BD was later confirmed in other ethnic groups, including those in which BD is seen very rarely [1, 2, 16, 27, 31–34].

No disease specific differences were observed in the sequence of HLA-B51 alleles between BD patients and healthy controls, neither in the coding region nor in the regulatory sequences [35, 36]. HLA-B51 is a split antigen of HLA-B5, and the other split antigen HLA-B52 has not been associated with BD despite some exceptional reports [37, 38]. HLA-B51 differs from HLA-B52 only by two amino-acids in the α1 helix. Asparagine and phenylalanine at positions 63 and 67 of the HLA-B51 molecule are replaced with glutamic acid and serine in the HLA-B52 at the same positions [39]. These two aminoacids are located at the B pocket of the antigen binding groove (Fig. 15.1). HLA-B51 allele can bind peptides with eight or nine aminoacids and a hydrophobic C-terminus [40]. Later studies suggested that B pocket can be occupied by small aminoacids alanine and proline, and changes in the B pocket can affect the motif of the peptides that can bind to HLA molecule [41]. Isoleucine and valine were identified as dominant anchor residues in the C-terminus of the refined peptide motif which binds to relatively small F pocket, and aminoacids making the F pocket are conserved in all HLA-B51 alleles [41].

HLA-B51 allele has 73 different subtypes (HLA-B*5101–B*5173), and they all share the same aminoacid sequence at the B pocket of the antigen binding groove except for B*5107 and B*5122. HLA-B*5101 is the dominant subtype of the B51 molecule, and molecular HLA-B51 typing in different ethnic groups suggests that HLA-B51 subtypes in BD patients are not different from those in healthy controls, with HLA-B*5101 and -B*5108 as the main subtypes [42–46].

Molecular typing of HLA-B51 molecules suggests that presentation of certain BD-associated peptides with its specific B and F pocket features might be one of

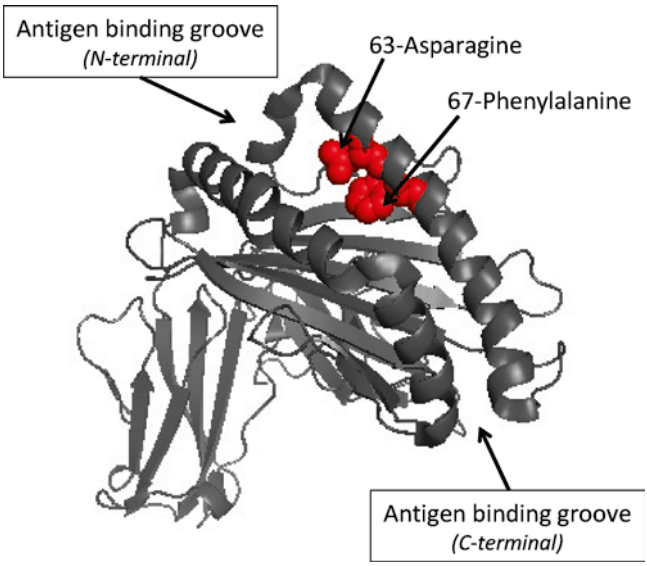

Fig. 15.1 A model of HLA-B51 molecule (1E28) showing the critical asparagine and phenylalanine at positions 63 and 67 in its antigen binding groove (drawn by PyMOL)

the pathogenic mechanisms behind the susceptibility to BD. So far, only major histocompatibility complex class I chain-related gene A (MICA)-derived nonamer peptide (AAAAAIFVI) was shown to induce T cells in less than one-third of active HLA-B51 positive BD patients compared to none of the healthy controls [47].

HLA-B51, as a class I molecule, also interacts with a group of receptors expressed on natural killer (NK) cells, CD8+ and γδ T cells [48]. The killer immunoglobulin-like receptors (KIR), bind to conserved Bw4 epitopes at residues 77–83 of the α1-helix, which are shared by different allellic groups of HLA class I molecules. Engagement of these receptors can result in selective inhibition of NK or T cell mediated cytotoxicity. A relative predispositional effects analysis, conducted to search for weaker HLA-B associations with BD masked by strong HLA-B51 association, revealed a weak association of HLA-B*2702 with BD, which shares the same Bw4 motif with HLA-B51 [49]. Investigation of HLA-B51 interacting KIR3DL1/DS1 polymorphism documented the association of DL1/DL1 genotype with BD in Bw4-motif positive patients [50]. These preliminary studies support an alternative hypothesis that the pathogenic role of HLA-B51 may also include its interaction with KIR3DL1 molecules expressed on inflammatory cells.

HLA-B51-derived peptides can be presented by HLA class II molecules. HLA class I heavy chain misfolding as well as enhanced expression due to up-regulated immune response increase the possibility of class I-derived peptide presentation. Wildner and Thurau identified a polymorphic HLA-B sequence common in HLA-B27, -B51, and several other HLA-B alleles (B27PD), which shares aminoacid homologies with retinal soluble antigen (S-Ag)-derived peptide [51]. Kurhan-Yavuz and colleagues demonstrated increased T cell response against retinal S-Ag, retinal S-Ag derived peptide, and B27PD peptide in BD patients with posterior uveitis compared with those BD patients without eye disease or patients with non-BD anterior uveitis [52].

HLA-B51 is one of the slow folding MHC molecules [53]. However, there is no data showing the role of HLA-B51 folding problems and unfolded protein response in BD pathogenesis similar to the observations on HLA-B27 in ankylosing spondylitis animal models [54].

There is only one HLA-B*5101 heavy chain transgenic mouse model developed so far in investigating the direct role of HLA-B51 molecules in BD [55]. No manifestation typical for BD was observed in these transgenic animals. HLA-B51 transgenic animals showed an increased neutrophil activity following f-Met-Leu-Phe (fMLP) stimulation compared to HLA-B35 and nontransgenic mice [55]. A similar enhanced neutrophil activity was reported in HLA-B51 positive healthy individuals [11, 55, 56]. Extrapolating from the experience with HLA-B27 animal models, it is still needed to have a high heavy chain copy number transgenic animal models with and without human β2-microglobulin in different strains of mice and rats to explore the role of HLA-B51 in BD [57].

In addition to association studies, analysis of 12 multicase families confirmed the genetic linkage of the HLA-B locus to BD by using the transmission disequilibrium test [58]. Contribution of the HLA-B locus to the overall genetic susceptibility

to BD was estimated to be 19% assuming multiplicative interaction between disease susceptibility loci [58]. This result supports the need for studies to look for other susceptibility loci.

Other MHC Associations

Linkage disequilibrium (LD) is high in the MHC, especially in the class I region with larger haplotype blocks [59]. It has long been discussed whether HLA-B51 has a direct role in the BD pathogenesis, or whether this strong association reflects LD with one or more susceptibility genes located close to the HLA-B locus (Fig. 15.2). The tumor necrosis factor (TNF) and lymphotoxin genes, which are located centromeric to HLA-B, were investigated first as possible candidate susceptibility genes. The analysis of the genomic segment between the TNF and HLA-B loci revealed a strong association of MICA gene with BD, which is located 46-kb centromeric to HLA-B [60]. The MICA gene *009 allele and its transmembrane region microsatellite polymorphism A6 allele were found to be significantly increased in BD patients [60–62]. Fine mapping of the region in different ethnic groups revealed HLA-B as the gene providing strongest association with BD, and all other associations including the MICA were resulting from strong LD with HLA-B51 [63]. However, it is still hard to rule out individual contribution of the MICA gene on an HLA-B51 haplotype to the BD susceptibility through its interaction with NK and γδ T cells.

Within the MHC region, no association with class II antigens was observed [64], but HLA-B51-associated LD extends to telomeric part of class I region. Weaker associations with HLA-Cw14, Cw15, and C*16 alleles [65, 66] and a negative association with nonclassical HLA-E*0101 and HLA-G*010101 alleles [67] were reported. Recent studies suggest a second HLA class I region association independent of HLA-B51 [68]. Meguro and colleagues reported the association of HLA-A26 allele and HLA-A*26-F*010101-G*010102 haplotype with BD even in HLA-B51 negative patients in Japan [68]. Association of HLA-A26 allele with BD was also observed in Taiwanese and Greek patients. These observations suggest that contribution of the MHC region to the BD susceptibility includes both HLA-B51 and other classical or nonclassical HLA associations with possible different pathogenic mechanisms.

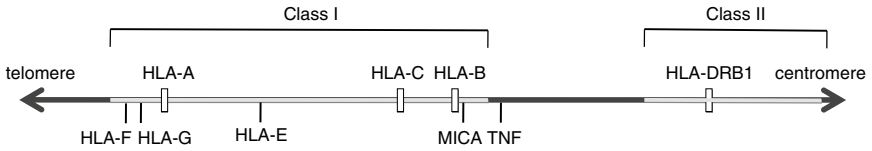

Fig. 15.2 Genetic map of the major histocompatibility complex (MHC) in short arm of chromosome 6 showing the Behçet's disease-associated loci in class I region

Non-HLA Genes and Behçet's Disease

As a complex disease, non-HLA genetic polymorphisms can also contribute to the BD susceptibility. For investigation of these susceptibility genes, a candidate gene approach was frequently preferred by investigators despite no clear evidence for

Table 15.1 List of non-HLA genes reported to be associated with Behçet's disease

Name	Ethnic groups
Cytokines, chemokines and their receptors	
Tumor necrosis factor (TNF)	British Caucasian, Turkish, Korean, Tunisian [69–72]
Interleukin 1 gene cluster	Turkish [73]
Interleukin 6 (IL6)	Korean [74]
Interleukin 8 (IL8/CXCL8)	Korean [75]
Interleukin 10 (IL10)	British Caucasian [76]
Interleukin 12 p40 (IL12B)	Japanese [77]
Interleukin-17F (IL17F)	Korean [78]
Interleukin 18 (IL18)	Korean [79]
Chemokine receptor 5 (CCR5)	Iranian [80]
Other immune response genes	
Natural resistance associated macrophage protein 1 (NRAMP1)	Turkish, Korean [81, 82]
CTLA4	Tunisian, Korean [83, 84]
Mannose binding lectin	Japanese, Korean [85, 86]
Ficolin 2 (FCN2)	Japanese [87]
Small ubiquitin-like modifier 4 (SUMO4)	Chinese [88]
Fc receptor-like 3 gene (FCRL3)	Chinese [89]
CD94/NKG2A	Korean [90]
PTPN22 (negative association)	British Caucasian, Middle Eastern [91]
CD28	Turkish [92]
Pathogen associated molecular pattern receptors	
Toll-like receptor 4 (TLR4)	Japanese, Korean [93, 94]
Autoinflammatory polymorphisms	
Pyrin (MEFV)	Turkish, European, Jewish, Palestinian [95–99]
TNF receptor p55 (TNFRSF1A)	European [100]
Vascular and procoagulant polymorphisms	
Intercellular adhesion molecule-1 (ICAM1)	Palestinian/Jordanian, Italian, Korean, Lebanese [101–104]
Endothelial nitric oxide synthase (eNOS)	Italian, Korean, Turkish, Tunisian [105–108]
Factor V Leiden	Turkish, Arabian [109–111]
Prothrombin	Turkish, Spanish [112, 113]
Manganese superoxide dismutase (SOD)	Japanese [114]
Others	
Cytochrome P450	Turkish, Taiwanese [115, 116]
N-acetyltransferase 2	Turkish [117]

utilizing this method in deciphering the pathogenic mechanisms of BD. Most of these association studies were carried out using small numbers of cases and controls with limited power. The list of non-HLA genes reported to be associated with BD are given in Table 15.1 [69–117]. Among the reported associations, only a few were replicated in different ethnic groups, including polymorphisms in the TNF, MEFV, ICAM1, and eNOS genes. None of these polymorphisms are disease specific, and they are considered to be contributing to a disease-specific inflammatory reaction.

Another approach for investigating complex disease susceptibility genes is screening of whole genome without a priori hypothesis about disease pathogenesis. A genomewide linkage screen using 193 individuals from 28 multicase BD families of Turkish origin with 83 affecteds revealed evidence for linkage to 15 non-HLA chromosomal regions: 1p36, 4p15, 5q12, 5q23, 6q16, 6q25–26, 7p21, 10q24, 12p12–13, 12q13, 16q12, 16q21–23, 17p13, 20q12–13, and Xq26–28 [118]. The linkage peak in the short arm of chromosome 6 (the maximum nonparametric linkage score 3.7) confirmed the strong association of HLA-B locus and also suggested another telomeric susceptibility loci [118, 119]. After the addition of further markers, high maximum nonparametric linkage scores were observed at chromosome 12p12-13 (3.94) and 6q25-26 (3.14).

Linkage studies in families are expected to identify rare, but penetrant genetic variations. However, genomewide association studies (GWAS) in large number of cases and controls can reveal common, but less penetrant polymorphisms affecting the disease susceptibility. A recent GWAS investigated 300 Japanese BD patients and 300 healthy controls with 23,465 microsatellite markers. This study identified six possible genomic regions, including two from the MHC region, one corresponding to HLA-B and the other to HLA-A [68]. Other non-HLA microsatellite markers suggested chromosomal regions 3p12 (D3S0186i), 6q25.1 (536G12Aa), 12p12.1 (D12S0645i), and 22q11.22 (D22S0104im) as possible genomic segments harboring disease susceptibility loci, two of which overlap with the findings of the previous linkage study [68]. Current GWAS approach enables us to analyze thousands of samples using chips for >300,000 single nucleotide polymorphisms in a relatively short time. Results of GWAS from different ethnic groups are eagerly being awaited to clarify the genetics of BD further.

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