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Genetic Evidence in Behcet Disease Pathogensis

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Abstract

Behcets disease (BD) is considered are lapsing multisystem chronic inflammatory disorder. It has a worldwide distribution, but it is more prevalent in Mediterranean countries. The cause of BD remains unknown. Environmental factors, infectious agents, and immune dysregulation, as well as genetic factors, have been studied extensively. The presence of familial cases, the geographic and ethnic distribution of the disease, and the association of BD with the MHC class I antigen HLA-B51 have been cited as evidence of a genetic basis of the disease.

Keywords: Behcets disease; HLA; HLA-B*51; MHC region; Non-HLA genes; TNF gene; MICA gene; ICAM-1; MBL; N-Acetyltransferase; ENOS; VEGF

Behçet's disease (BD) is a chronic relapsing multisystemic chronic relapsing inflammatory disorder characterized by four major symptoms (oral aphthous ulcers, genital ulcers, skin lesions, and ocular lesions) and occasionally by five minor symptoms (arthritis, gastrointestinal ulcers, epididymitis, vascular lesions, and central nervous system) [1]. BD has a worldwide distribution, but it is more prevalent in the regions along the ancient trading route known as "Silk Road," extending from Mediterranean countries such as Turkey to the Far East including Korea and Japan. It starts in the third and fourth decade of life and runs a more severe course in men and in those with a younger age of onset [2].

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Genetic Evidences

Clues from epidemiology: Determining the prevalence of a disease in ethnic populations, who have migrated to parts of the world other than from which they have originated, and comparing it to that in the original area is considered as a good way of determining whether genetic or environmental factors have more influence on the etiology [4].

A survey of BD among Armenians living in Istanbul, showed a prevalence of 110/100000, whereas, the prevalence among Turkish living in Istanbul was 421/100000 [5]. In Berlin, the prevalence of BD among people of Turkish origin was 77.37/100000. This is a higher prevalence compared to the Germans in the same study 1.47/100000, but lower than the prevalence reported by most studies from Turkey [6]. The prevalence of BD in Paris among European, North African, Asian and Turkish varied from 2.4/100000 among Europeans to

17.5/100000 among Asians including Turkish and 34.6/100000 among North Africans [7].

These studies may be interpreted as evidence for genetic aetiology. However, people who migrate to another country usually carry their living and eating habits with them, thereby creating an environment similar to that from which they originated. They live in parts of the city with the most poor living conditions and bad hygiene, for example, Asians and North Africans living in Paris, so the disease may be triggered by environmental factors, such as infectious agents in genetically susceptible individuals [4].

Familial cases of BD: BD does not have a Mendelian inheritance pattern and most cases are sporadic [8]. However, there are a substantial number of familial cases, and monozygotic twins have been reported, which suggested that genetic factors may play a role in the pathogenesis of BD. The familial occurrence has been reported to range from 0% in Greece to 18.2% in patients from endemic areas such as Turkey [9].

Geographic distribution: BD has a worldwide distribution but the highest prevalence of the disease, as well as the associated HLA-B*51, occurs between the latitudes 30 and 45 degrees north, which corresponds to the ancient Silk Route used by traders from the East to Europe [10]. One explanation for the geographical distribution of BD is that a genetic risk factor was propagated through previously isolated communities by traders or nomadic tribes along the Silk Route whose path across Asia [11].

Molecular genetics and the role of HLA-B*51: The close association of the HLA-B*51 allele with BD represents the clearest evidence of a genetic contribution to the disease. Since the identification of this association, considerable effort has been made to understand whether HLA-B*51 participates in BD pathogenesis or if it represents a marker for other predisposing genes in linkage disequilibrium with it [12].

Susceptible Genes

Major histocompatibility complex (MHC) region: The MHC region is located on chromosome 6p21.3 and encompasses a 4000-kb segment. From centromere to telomere, this region is divided into three sub regions, namely, human leukocyte antigen (HLA) class II (1 Mb), class III (1 Mb), and class I (2 Mb) (Figure 1). In addition more than 80 non-HLA genes are expressed in the MHC region. The identification of the gene in this novel susceptibility locus may make a great contribution to more understanding of the pathogenesis of BD, as it may explain the expression of the disease in HLA-B*51 negative individuals, and also the fact that not all HLA-B*51 positive individuals develop the disease. It is likely that the expression of genes other than HLA-B*51, serves as an additional risk factor of developing BD [13].

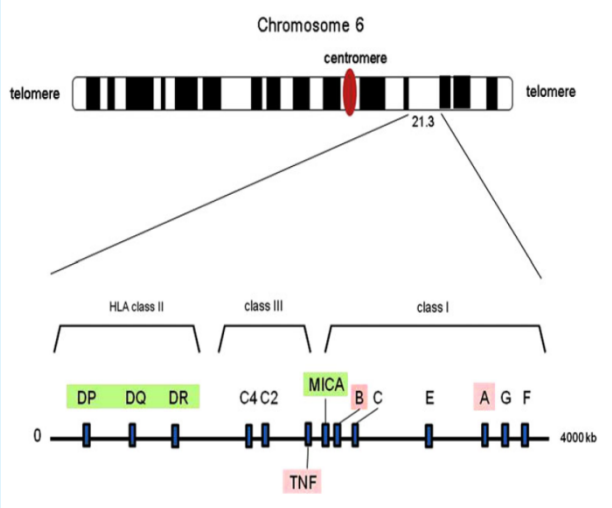

Figure 1: Chromosomal mapping of 6p21.3, which contains the Major Histocompatibility Complex (MHC) region. The MHC region spans a 4000-kb segment and consists of the human leukocyte antigen (HLA) class II, III, and I regions, extending from the centromere to telomere. In addition more than 80 non-HLA genes are expressed in the MHC region examples complement 2 (C2), complement 4 (C4), MHC class I chain-related gene A (MICA) and tumor necrosis factor (TNF).

HLA:

HLA-B*51: HLA-B*51 is one of the split antigens of HLA-B*5. At the present time, 106 amino acids sequence variants for HLAB*51 are known, coded by 132 different alleles, five of which are nulls. Among the HLA-B*51 alleles, HLA-B*51:01 is the most common. The distribution of HLA-B*51 alleles is not different between BD patients and controls, no disease-specific polymorphisms have been found, no exonic sequence difference has yet been found between patients and controls, and intronic/promoter sequence variations were not found to be disease-specific. Therefore, it seems that there are no disease-specific polymorphisms and that HLA-B*51 itself is a risk gene [14]. In 1973 Ono and his colleagues reported a strong association between BD and HLA-B*5 in a Japanese population, the association between BD and HLA-B*51 has been repeatedly demonstrated across different ethnic groups, [10]. The strongest association between HLA-B*51 and BD, confirmed in two Genome-wide association studies

(GWAS), indicating that HLA-B*51 plays a primary role in the development of BD [15].

However, HLA-B*51 has been identified as the genetic marker most strongly associated with BD, it has also been reported that the highest contribution made by the HLA-B locus to overall genetic susceptibility of BD is 19%. This is why other susceptibility genes have been extensively investigated [16]. There are limited evidences for the biological role of HLA-B*51 in the pathogenesis of BD, and several hypotheses have been proposed. The most obvious way to demonstrate the biological function of a given gene would be to build a transgenic (Tg) or knock-out mouse system. Generated HLA-B*51 Tg mice, but these mice failed to develop any BD-related manifestations and only showed neutrophil hyperactivity towards f-Met-Leu-Phe (bacterial chemotactic peptide) as compared with control Tg or non-Tg mice [17]. In humans, a significant correlation was observed between neutrophil hyper function and HLA-B*51 positivity, regardless of the presence of BD. Thus, it appears that HLA-B*51 might be responsible, at least in part, for neutrophil hyperactivity in BD, and the possession of HLA-B*51 is not sufficient to induce clinical disease, and additional genetic or environmental factors are required to trigger disease development [13].

HLA-A region: Although many studies have investigated the HLA class I region in BD patients, only a minority of studies have reported significant results for the HLA-A gene. While HLA-A*26 has been reported to be associated with BD in Taiwan and in Greece, no significant associations have been found in studies conducted in Palestine, Jordan, Iran, Ireland, Italy, or Turkey [18,19]. However, it was clearly demonstrated that HLA-A*26 is a primary susceptibility gene of BD in the Japanese GWAS [20]. An independent association between BD and the HLA-A locus has also been reported in Turkish and Korean studies .Unlike HLA-B*51, HLA-A*26:01 was found to be associated with a poor prognosis for BD-related uveitis in the Japanese study [21].

Non-HLA genes within the MHC region: Although a strong association between BD and HLA-B*51 has long been known, a putative susceptibility gene near HLA-B*51 was extensively sought because of limited evidence of a direct relation between HLA-B*51 and the pathogenesis of BD. In this respect, tumor necrosis factor (TNF) and MICA have been investigated as strong candidate genes [13].

TNF (Tumor Necrosis Factor) gene: TNF is a multifunctional cytokine plays a central role in the initiation and regulation of the immune response. TNF gene is situated in the class III region between HLA-B and HLA-D, the contribution of TNF gene polymorphisms to BD has been an interesting research topic. Of the TNF related polymorphisms, those in the TNF-α promoter gene at positions -238, -308, -857, -863, and -1031 have been studied in various ethnic groups, the polymorphisms at positions -238A, -857T, and -1031C are significantly associated with BD, those at -238A and -1031C increase the risk of BD whereas the one at -857T decreases the risk of BD [22,23].

MICA gene: MHC class I chain-related (MIC-A and MIC-B) genes encode proteins which show homology with classical HLA molecules, but they are not expressed on normal circulating lymphocytes. MIC proteins are expressed on the surface of various cells (gastric epithelium, endothelial cells and fibroblasts) and are ligands for NKG2D; an activating natural killer-cell receptor also found on γδ T cells and αβ CD8 T cells [24]. Because this gene is highly polymorphic and its amino acid sequence shows a similarity with the MHC class I chain, it was once thought that MICA might play a specialized role in antigen presentation or T cell recognition [25].

The MICA gene was proposed as a BD candidate gene who found that MICA-A6 allele is strongly associated with BD. Moreover, a fine mapping study using highly polymorphic microsatellite markers showed that the critical region for BD is the 46-kb segment between the MICA and HLA-B loci [18,25]. However, it was later found that the interaction between MICA molecules and γδ T cells is not restricted by the MICA gene polymorphism and does not require antigen presentation [26]. Despite the lack of a proven genetic association between MICA and BD, the autoreactive CD8+ T cell response to MICA peptide was found to be more frequent in BD patients than in healthy controls, and all responders had HLA-B*51 and active disease state. This finding might suggest that MICA, although not associated with BD at the genetic level, may be involved in the pathogenesis of BD as an effector protein [27].

The regions on chromosome 6 flanking the HLA-B*51 locus including TNF gene and MICA gene, have been studied extensively since TNF exerts a profound effect on the immune response, and MICA has a possible role in non-classical antigen presentation at mucosal surfaces [28]. However, it is becoming apparent that polymorphic areas in these regions, are actually a consequence of linkage disequilibrium with HLA-B*51, and may have little independent contribution to disease in HLA-B*51

negative individuals [29]. It has therefore been proposed that HLA-B is a strong candidate locus responsible for the development of BD and that HLA-B*51 itself is the major disease susceptibility gene for BD [30].

Intercellular adhesion molecule-1 (ICAM-1)

ICAM-1, which is a member of the immunoglobulin superfamily, is expressed on vascular endothelial cells, and elevated plasma [31]. ICAM-1 plays a central role in neutrophil migration into the sites of inflammation and T cell activation [32]. The E469 allele among the Jordanian, Palestinian and Korean populations and the R241 allele among the Italian population have been reported to be associated with a susceptibility to BD [33,34].

Mannose-Binding lectin (MBL)

MBL plays an important role in innate immunity. This protein initiates the lectin complement pathway by binding to mannose containing carbohydrates on bacteria or viruses and also serves as an opsonin for monocytes [35]. Serum concentrations of the MBL are affected significantly by various polymorphic sites located in the promoter and exon 1 regions of the MBL gene. Low MBL levels and the mutant alleles of these polymorphisms are reported to be associated with a susceptibility to recurrent infections and autoimmune rheumatic diseases, such as systemic lupus erythematosus and rheumatoid arthritis [36]. Recently, low levels of MBL have been found in patients with BD when compared with healthy control subjects [37]. In addition, reported that the frequency of codon 54 heterozygotes in exon 1 of the MBL gene was significantly higher in BD patients than in controls [38].

N-Acetyltransferase

Nonacetylated xenobiotics may induce autoimmunity. Polymorphisms in xenobiotic-metabolizing enzymes, such as N-acetyl transferase 2 (NAT2), have been investigated in BD. In a Turkish report, NAT2*5A and NAT2*6A genotypes carried an increased risk of disease, suggesting that the NAT2 slow acetylator status may be determinant in BD susceptibility [39]. In another Turkish research, even if the frequency of the NAT2*5B allele (responsible for slow acetylation) was slightly higher in patients than control [40].

Endothelial nitric oxide synthase (ENOS)

Although the precise pathogenetic mechanism for the vascular lesions in BD remains unclear, endothelial dysfunction is thought to play an important role in the development of these lesions. Recently, brachial artery flow-mediated dilatation has been demonstrated to be impaired in BD [41]. Because flow-mediated dilatation is endothelium-dependent and mediated largely by the release of eNOS, the impairment of endothelium dependent flow-mediated dilatation suggests a decreased endothelial NO activity, which may contribute to vascular lesions in BD [42]. eNOS gene polymorphisms on chromosome 7q35-36 have been shown to be associated with a variety of vascular diseases, which include coronary artery disease, hypertension, stroke, and renal diseases [43]. Investigation about the association between eNOS gene polymorphisms and BD among the Italian and Korean patients with BD has shown that, the Asp298 allele in exon 7 appeared to be susceptibility factor to BD [44].

Vascular endothelial growth factor (VEGF)

VEGF is a potent angiogenic factor exhibiting various endothelial cell effects, including endothelial cell survival, proliferation, migration and tube formation, and also acts as a proinflammatory cytokine by increasing endothelial permeability and inducing adhesion molecules [45]. Increased sera levels of VEGF have been demonstrated in patients with BD, particularly in those with active disease [46]. By performing a molecular genetic study at 3 potentially functional polymorphic sites, which included +936 C/T in 3'untranslated region (UTR), -634 C/G in 5' UTR, and an 18 base pair insertion/deletion (I/D) at -2549 of the promoter of the VEGF gene on chromosome 6p12, carriers of the -634C and I alleles were associated with a susceptibility to BD in the Italian population [47].

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