Behçet's disease: Familial clustering and immunogenetics

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ABSTRACT

Behçet's disease (BD) is a relapsing, multisystemic inflammatory disorder, characterized by major symptoms consisting of recurrent orogenital ulcerations, eye and skin lesions. Other clinical features may include musculoskeletal, vascular, gastrointestinal, renal, cardiopulmonary or neurological involvement. Vasculitis affecting all types and sizes of blood vessels is the main histopathologic process, in a third of cases complicated by thrombosis. The etiopathogenesis is presently unknown, but BD likely represents the result of a peculiar immune response to hitherto unidentified environmental factors in genetically predisposed subjects. The prevalent distribution in a specific geographical area spanning the Mediterranean basin and Asia, the close association with human leukocyte antigen B*51 in different ethnic groups, and the familial clustering of BD are hallmarks accounting for the strong contribution of a genetic background. The BD familial aggregation is characterized by both genetic anticipation and higher prevalence in childhood patients, likely defining a subset with stronger immunogenetic influences. Polymorphisms in genes encoding for host effector molecules may have a supplementary role in disease susceptibility and/or severity. The contribution of prothrombotic mutations and polymorphisms in the pathogenesis of BD thrombosis is controversial. In this paper, the available reports on BD familial clustering and the evidence for the role of immunogenetic predisposing factors are reviewed.

Introduction

Behçet's disease (BD) is a relapsing, multisystemic inflammatory disorder, with a polymorphic clinical picture characterized by major symptoms consisting of recurrent orogenital ulcerations, eye and skin lesions. Osteoskeletal, vascular, gastrointestinal, renal, cardiopulmonary or neurological involvement may variably occur (1, 2). Vasculitis affecting all types and sizes of blood vessels is the main histopathologic process (1, 3), in a third of cases complicated by arterial and, more commonly, venous thrombosis (12% versus 88%) (3). Neurological involvement, major vessel disease and thrombosis account for most of the mortality (3, 4). Lacking pathognomonic symptoms or laboratory findings, the diagnosis is exclusively clinical, according to the International Study Group for BD criteria (5). Although the disease had been described as early as in the 5th century B.C. by Hippocrates (6), its etiopathogenesis is still unknown. The contribution of an antigen-driven immune response in genetically predisposed subjects has been suggested (7). The innate and adaptive immune systems are activated in BD, with evidence of neutrophil hyperfunction (8, 9) and of T helper (Th1-type predominant response (7, 10), likely triggered by either extrinsic [Herpes simplex virus, Streptococcus oralis/sanguis, Saccharomyces cerevisiae, Mycoplasma fermentans, superantigens, microbial heat shock protein (HSP), environmental pollution agents] or intrinsic factors (human HSP, αβ crystallin, retinal-S antigen, endothelial antigens or other organ-specific proteins) (1, 6, 7, 11). Recently, a direct role of TH1 lymphocytes in the mucocutaneous BD lesion development has been suggested (12).

The genetic predisposition to BD is supported by several findings, such as the disease peculiar ethnic distribution, association with human leukocyte antigens (HLA), evidence of the contribution of other immune response controlling genes, and familial clustering (6). As a matter of fact, even though BD may present a worldwide distribution, it endemically affects populations resident in a specific geographic area span-
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ning from the Mediterranean basin to Japan, along the so-called Silk Road (6). The highest BD prevalence (80 to 370 cases/100,000 inhabitants) is observed in the Turkish population (1). The disease frequency ranges from 13.5 to 20 cases/100,000 citizens in Japan, Korea, northern China, Iran and Saudi Arabia (1), and from 2.62 to 0.12/100,000 in southern China (13), Switzerland (14), United Kingdom (UK) (1) and United States of America (USA) (1). BD is sporadic in the indigenous west African or Afro-Caribbean populations (15), and is virtually absent in indigenous Amerindians or among ethnic groups south of the equator (6). BD was likely spread in Asian and Eurasian populations through the migrations of nomadic or Turkish tribes, or even more earlier demographic movements (6, 7, 16). Mitochondrial DNA studies, that indicate trading of genes in populations along the Silk Road, suggest that the peculiar ethnic distribution of BD has a genetic basis (17).

Notably, Turks living in Germany present a disease frequency 18-fold lower than those resident in Anatolia, and Japanese immigrants in Hawaii and California rarely suffer from BD (1, 18). These regional variations in prevalence (19), as well as the observed geographical variability in phenotype, severity and outcome of BD (19-26), may account for the influence of environmental triggering factors, whose intermittent exposure might also explain the recurrent clinical expression of the disease.

BD generally occurs in the third or fourth decade of life, affecting both sexes (1, 2, 19) with a prevalent androgenic status in the eastern Mediterranean area and a gynecocentricism in north European countries (18), that may suggest the modulating interaction between endocrine status and immunogenetic predisposing factors. Moreover, in adult patients, male sex and early onset of symptoms (<25 years) are usually associated with more severe disease (4, 19, 27-31).

Notably, the BD demographic distribution globally overlaps with the prevalence among the healthy populations of the class I HLA-B5, and particularly of its B*51 split (6, 7). B*51 has been hitherto recognized as the strongest genetic marker of BD (1,16, 32, 33), so that HLA typing has been proposed as useful for the diagnosis (1, 34). In B*51-negative patients, the influence of others’ presently undefined genetic factor(s) has been suggested. In addition, polymorphisms in genes controlling the immunomodulatory milieu or the clotting cascade may have a supplementary role in the disease development or severity (6).

The genetic predisposition to BD is further underlined by the familial clustering (35) and concordance in monozygotic twins (36, 37). The familial recurrence of BD has not been clearly associated with a simple Mendelian model (38, 39). However, a recent formal segregation analysis after stratification of affected families into a paediatric and a non-paediatric group provided the evidence of a genetic heterogeneity in BD, focusing the existence of a Mendelian entity (autosomal recessive mode) only in the paediatric subgroup (40).

In this paper, the available reports on BD familial clustering and the evidence for the role of immunogenetic predisposing factors are reviewed, after a detailed search via the PubMed (National Library of Medicine) and Biosis indices. Some familial case descriptions, however, appeared before the International Study Group criteria publication (5).

Familial clustering of Behçet’s disease

Familial clustering is one of the major epidemiological features of BD (35) and is characterized by genetic anticipation, accounting for the earlier disease onset in successive generations (41). The expansion of unstable trinucleotide repeats has been proposed as the genetic basis of the defect in familial cases (41), being the role of the genetic instability further underlined by sister chromatid exchange analyses (42).

The familial aggregation of BD has been observed in different ethnic groups (2, 35-41, 43-84) with a variable frequency. It is higher in Turks (18,25%), Koreans (15,4%) and Jews (13,2%) than in Chinese (2,6%), Japanese (12,2%) and Europeans (1%) (19). The familial clustering is significantly more common in juvenile than adult patients (74-76), reaching 30,7% in a paediatric Moroccan study (81), so that the inclusion of family history has been proposed in the definition of paediatric BD (74). Recurrence mostly occurs between siblings, but also mother/son (35,50,54,64,67,71,76), mother/daughter (35,54,71,76), father/son (35,55,71,76), father/daughter (56,71), cousin/cousin (35) and uncle/nephew (48) cases, and a four-generation BD family (38) have been reported. In Turks, the sibling recurrence risk ratio (S) was estimated to be 11.4-52.5 (76), and these high S values strongly support a hereditary basis for the disease (6,76).

In familial BD, the HLA-B5 (B*51) positivity is much more frequent than in sporadic cases, being 68-83.5% in Turkish studies (61,79) and ranging from 60,9% to 92% in Japanese reports (35,69). The B*51 homozygosity is common in familial cases (79). Two pairs of Turkish monozygotic twins, both HLA-B*51 carriers and concordant for BD, have been reported (36,37). The description of Turkish monozygotic twins, both HLA-B*51-negative and discordant for BD, further supports the role of B*51 as a very close non HLA-gene in the disease susceptibility (85). Among related pairs with a short interval in the disease onset, a great concordance of clinical symptoms was shown, suggesting the contribution of a common environmental trigger (35), whereas the report of 2 brothers brought up in separate homes and concordant for BD, seems to exclude it (53).

A high prevalence of isolated manifestations of the disease, such as recurrent orogenital ulcers or a positive skin pathergy test, was also observed among the patient first degree relatives, probably low-penentant carriers of predisposing genes (76).

Immunogenetics of Behçet’s disease

HLA associations

BD is known to be strongly associated with HLA-B5, and particularly with its split B*51, in various ethnic groups
mainly from the Far East and Mediterranean area (1,6,16). The prevalence of B*51 is up to 81% in Asian patients, whereas is 13% among white patients in western countries (1). This antigen was found to confer an odds ratio of 1.5 to 16 in different populations (11). In an ethnically homogeneous north west European population, such as the Irish people, despite a low B*51 prevalence (25%) in patients, a highly significant association of this antigen with BD was found, and the relative risk was 6.3 (86).

In addition, B*51 positivity has been reported to associate with thrombophlebitis (87, 88) and more severe disease course and outcome (1, 18, 19, 89-92), but the evidence is conflicting (79). However, notwithstanding the relevant role of B*51 itself has been strongly underlined by microsatellite comparative studies performed on Greek, Italian and Japanese patients (32), analyses on Turkish multicase families by the transmission disequilibrium test in affected sibling pairs estimated that its contribution to the overall genetic BD susceptibility was no more than 19% (80).

The exact pathogenic mechanism of the B*51 molecule is still unknown, but it might be primarily involved in the disease development through specific antigen presentation or molecular mimicry with microbial antigens, as well as participate in linkage disequilibrium with a presently unknown susceptibility gene (6, 16). Notably, HLA-B*5101 heavy chain transgenic mice do not develop BD-related manifestations, but show an increased neutrophil activity in response to stimulation, compared to non-transgenic mice (8). Similar neutrophil hyperactivity has been reported in B*51-positive healthy subjects (8).

The HLA-B exonic sequence that encodes the B*51 allele has been proposed to be the real pathogenic factor in BD (93). Among the twenty-four till now described B*51 molecular subtypes (B*5101-B*5124), B*5101 and B*5108 were significantly associated with BD in Spanish (94), Italian (95), Greek (96), German (97), Turkish (97), Iranian (98) and Saudi Arabian (99) patients, whereas Japanese patients were found to express the B*5101, but not B*5108 suballele (100). In a Greek report, the B*5101 subtype was expressed in 80% of patients and in 26% of controls, resulting in positive correlation with a younger disease onset and the development of uveitis nodosum (101). In Israeli patients, HLA-B*51 and B*52 were both primarily associated with BD (102), being B*5101 and B*5201 the prevalent subtypes, while B*5108 and B*5104 were less expressed (103). In Chinese Han patients in Shanghai area, B*5101 predominated, and a novel association between BD and HLA-B*46 was found (104). Interestingly, in Turkish, Jordanian, Iranian and Japanese BD patients the entire nucleotide sequences of HLA-B*510101 genes, including the promoter and intron regions, are completely identical, suggesting that B*510101 may have the same phylogenetic origin (105).

Recently, a selective increase of B*2702 in Turkish BD patients was reported (106). Of note, the two main disease-related suballeles B*5101 and B*5108 share amino-acid residues at positions 63,67 and 77-83 (defining the Bw4 epitope), crucial for the antigen binding and natural killer (NK) cell interactions (7, 97). Moreover, B*2702 is the only HLA-B*27 subtype sharing with B*5101 and B*5108 the same killer immunoglobulin-like receptor (KIR) binding sequence (106). These findings suggest the role of an interaction between HLA molecules and KIRs on NK or T cells in the disease pathogenesis (106). Moreover, in Moroccan BD patients a previously unknown association with HLA-B*15 (107), as well as in UK white Caucasian patients with HLA-B*5701 (108), has been reported. Therefore, the Bw4 motif expressed by HLA-B alleles variably associated with BD, such as B*51, B*27, B*15 and B*57, might be itself causally related to the disease (6). Recently, allelic variants of the HLA-G gene have been associated with BD (109). Indeed, in Korean patients the frequency of the HLA-G haplotype containing 3741*A4 base pair (bp) and 1597*delC was increased more than 2-fold (109). In Japanese patients with refractory ocular attacks, HLA-B*51 and DQw3 alleles, as well as the human complement factor 4 (C4)AQ0 allele were significantly over-expressed (110); similarly, northern Han Chinese patients showed an enhanced frequency of B*51 and C4AQ0 (111). In Italian patients, a significant association between BD and the B51-DR5-DQw3 haplotype was found (112). Moreover, in Turkish patients the B5-DR5 alleles were in a strong positive linkage disequilibrium (113). In Chinese patients, the DR5-DQw1 and DRw8-DQw1 haplotypes were over-expressed (114). In Spanish patients from Andalucia, the DR11 and DQB1*0301 frequency was increased, and the DQBL1*0303 allele was associated with severe uveitis, while the DQ5 expression was reduced particularly in HLA-B*51-positive subjects (89). Iraqi patients, both in sporadic and familial cases, showed a significantly high frequency of B51, DR2 and DQ3 alleles, and the A9,B51(5), Cw1,DR2,DQ3 haplotype was positively associated with BD, whereas the A2,A28,B35,DR12,DQ4 haplotype was negatively related (82). Mexican patients exhibited a markedly enhanced expression of HLA-B*44, B*52, B*56 alleles, as well as of DRB1*01 and DRB1*13 (115).

Moreover, in Turkish patients with uveitis nodosum the HLA-Cw2 frequency was reduced, and patients with genital ulcerations under-expressed the Cw7 allele (88). In Japanese patients, the HLA-Cw*14 and Cw*15 carriage rate was significantly increased, and correlated with B*51 as a result of linkage disequilibrium (116). In patients from southern Spain, a significant association of HLA-Cw*1602 with BD was found, and the B*51-Cw*1602 haplotype was suggested as a new disease susceptibility marker in this population (117).

Tumour necrosis factor gene polymorphisms

The tumour necrosis factor (TNF)-α pathway is likely involved in BD pathophysiology (6,11), and studies have been performed to evaluate the role of polymorphisms in TNF-α, TNF-β, or
TNF receptor superfamily 1A (TNFRSF1A/TNFR1) and 1B (TNFRSF1B/ TNFR2) genes (108, 118-121). In UK white Caucasian patients, the TNF-α gene (TNF) promoter polymorphism -1031C was reported to be strongly associated with BD (108). Moreover, the TNF-1031C allele was strictly related to the disease even in B*51 or B*5701-negative patients. The contribution of TNF-1031C in BD was estimated at 35%. Two extended HLA haplotypes, both containing the TNF-1031C allele along with B*51 or B*5701, positively correlated with BD. A protective effect of the most common haplotype, TFNHI, which does not contain the TNF-1031C allele, was also identified. Furthermore, the TNF-238A variant was associated with the disease (108). These observations have been suggested to provide a crucial link between genetic risk and clinical observations (108).

In Turkish patients compared to controls, no significant difference was detected in the distribution of TNF promoter -308 and -376 polymorphisms, but a decreased frequency of the TNF-308A -378G haplotype was observed in patients with severe eye involvement (118). In patients of Middle Eastern descent, no association between the TNF-308 polymorphism and BD was observed, whereas the TNF-32 allele of the lymphotixin α gene was associated with HLA-B*51 among patients, and positively correlated with a poor visual outcome (119). In Korean BD patients, no differences were found in the distribution of the TNF-308 G/A, TNF-β gene +252 G/A or TNFRSF1B/TNFR2 gene 196 R/M polymorphisms (120). In European BD patients, a high frequency of R92Q mutation in TNFRSF1A/TNFR1 gene was observed, and associated with an increased risk of extracranial venous thrombosis (121).

**Major histocompatibility complex class I chain related gene A polymorphisms**

A strict association between BD and the major histocompatibility complex class I chain-related (MIC) A gene (MICA) A6 allele was demonstrated in Japanese (122). Korean (123, 124), Italian (125), Greek (126), Middle Eastern (127), Israeli Arab (128), but not in Spanish (129), Tunisian (130) and non-Ashkenazi Jewish (128) patients. In an Italian paediatric patient series, A6 homozygous carriers were found to develop a more severe mucosal gut involvement (131). Moreover, in Korean (124), Middle Eastern (127) and Japanese patients (132), the MICA*009 allele was closely related to the disease. However, further stratification and linkage analyses have evidenced that, when exists, the association between BD and MICA alleles is due to a strong linkage disequilibrium with B*51 (127, 132, 133). Similar results were obtained in a comparative analysis of Japanese, Greek and Italian patients (32).

Interestingly, in HLA-B*51-positive Japanese patients with active BD, a specific cytotoxic T lymphocyte (CTL) response was detected to an amino-acid 294-302 sequence containing the HLA-B*51 binding motif in the MICA*009 protein (134) and including part of a triplet-repeat microsatellite polymorphism consisting of a 6 alanine residues, which was reported to be associated with BD (122). This finding suggests the potential involvement of B*51-restricted, MICA-autoreactive CTLs in the pathogenesis of BD (134).

**Transporter associated with antigen processing gene polymorphisms**

In Spanish BD patients compared to healthy controls, the complete absence of the transporter associated with antigen processing (TAP1)C alleles, as well as a linkage disequilibrium between TAP2B and HLA-DQB1*0501 were found (135).

In a Japanese report, the TAP2B/C genotype was absent in the patient group, while the allele frequency of TAP2C was increased in patients with erythema nodosum, and the TAP2C/H genotype was over-expressed in patients with skin involvement, suggesting that in Japanese BD patients TAP polymorphisms may play a role in the skin lesion development (136).

**Interleukin gene polymorphisms**

In Turkish patients, a study on interleukin (IL)-1A, IL-1B, and IL-1 receptor antagonist gene (IL1RN) polymorphisms demonstrated an increase of the IL-1A -889C allele and CC genotype, as well as of the IL-1B +5887T allele and TT genotype (140). Moreover, the IL-1A -889C/IL-1B +5887T haplotype was associated with increased susceptibility, and the IL-1A –889 and IL-1B +5887 CC/TT combined genotype was over-expressed in patients, conferring a 2-fold increased risk of BD. No association was observed for other investigated polymorphisms in IL-1B gene and IL1RN (140). In another Turkish study no difference was found in the genotype or allele frequencies of IL-1A –889, IL-1B -511, and IL1RN between patients and controls, but the susceptibility to BD was increased in patients carrying the IL-1B +3953 T and TT genotype (141).

In Turkish patients, BD was associated with the TT genotype of IL1RN at maspal 11100, whereas the TC genotype was protective (142). In the same cohort, the GG genotype at -330 and
+166 of the IL-2 gene was negatively related to the disease, while the TG genotype significantly confirmed a susceptibility (142).

In Korean patients, the genotype and allele frequencies of polymorphisms in the 3’ flanking region of the IL-6 gene (IL6vnr) significantly differed between patients and controls (143). These differences were particularly evident in both HLA-B51 negative and female patients. Susceptibility to BD was increased in subjects carrying the IL6vnr*C allele, and the IL6vnr*/C/IL6 gene promoter*G haplotype (143).

In Italian patients, the study of single-nucleotide polymorphism at position –607 in the IL-18 gene promoter evidenced that the AA genotype associated with BD, and AA homozygous patients had a significantly higher frequency of central nervous system involvement than patients carrying a C allele (144).

Chemokine and chemokine receptor gene polymorphisms

In UK patients, the CC chemokine ligand (CCL)5 -403 AA genotype was only found in males (145). Similarly, the CCL2/monocyte chemoattractant protein (MCP)-1 genotypes 1/2 were predominant in males, whereas the genotype 4 was significantly associated with BD in females, suggesting that gender-specific polymorphisms affecting chemokine gene functions might influence the disease expression (145).

In different ethnic groups, the CC chemokine receptor 5 (CCR5) Delta32 variant, a deletion mutation in the CCR5 gene, did not correlate with BD (146).

In Korean BD patients, the CCL2/MCP-1 promoter –2518 polymorphism was investigated (147). Serum CCL2/MCP-1 levels were higher and symptoms of severe disease more frequent in G-allele carriers than in AA homozygotes. In addition, mononuclear cells of patients carrying the G-allele, when stimulated, showed a steeper increase in CCL2/MCP-1 production than those from AA homozygotes. However, the G-allele distribution in the patient group did not differ from controls, likely due to its dominance in general Korean population (147).

Mannose binding lectin gene polymorphisms

A study of mannose binding lectin (MBL) gene polymorphisms evidenced that Korean patients carried the ~550*G/G homozygosity in the MBL2 gene promoter more frequently than controls (148). Moreover, the MBL2 HYPA haplotype, which is responsible for high MBL serum levels, positively correlated with both increased risk for the disease and worse prognosis, whereas the LYPA haplotype, which is associated with low MBL values, was negatively related to BD (148).

Japanese patients were found to express a significantly higher frequency of the A/B (wild/mutant) genotype in the codon 54 of MBL exon 1, irrespectively of HLA-B*51 status (149).

N-acetyltransferase gene polymorphism

Nonacetylated xenobiotics may induce autoimmunity (150), and genetic polymorphisms in xenobiotic-metabolizing enzymes, such as the arylamine N-acetyltransferase 2 (NAT2), have been investigated in BD (150, 151). 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 the BD susceptibility (150). Moreover, Japanese patients were found to express a significantly higher frequency of the A/B (wild/mutant) genotype in the codon 54 of MBL exon 1, irrespectively of HLA-B*51 status (149).

Endothelial nitric oxide synthase gene polymorphisms

In Italian BD patients, the Glu-Asp298 polymorphism in exon 7, as well as the 4 a/b polymorphism in intron 4 of the endothelial nitric oxide synthase (eNOS) gene were studied (152). The Asp298 allele frequency positively correlated with the disease, independently of the HLA-B*51 status, whereas the distribution of the 4 a/b genotype in intron 4 did not differ between patients and controls (152). Moreover, in Korean patients suffering from BD or other rheumatic affections with vasculitis, the Asp298 allele was over-represented in comparison with controls (153). In addition, in Turkish patients the Glu-Asp298 polymorphism was found to be a risk factor for BD, owing to the frequencies of Asp/Asp homozygosity and Glu/Asp heterozygosity were both significantly higher than in healthy controls (154).

Other genetic polymorphisms

Glutathione S-transferases (GSTs) are a multi-gene family of enzymes involved in detoxification of xenobiotics and in protection against oxidative stress (155). In Turkish BD patients compared with controls, a higher prevalence of the GSTM1 null genotype was observed, whereas GSTT1 (null) and GSTP1 (val/val) gene polymorphisms were not related to an enhanced risk of developing BD (155).

In Taiwanese BD patients, the manganese superoxide dismutase gene C1183T polymorphism did not differ between patients and controls (156). In the same study, the gene polymorphisms of cytochrome p450 1A1 (CYP1A1), a member of a superfamily of enzymes that catalyze oxidation of various xenobiotics, was evaluated, showing that the frequencies of CYP1A1 4889G and 4887A alleles and CYP1A1 4889A/G and 4887C/A genotypes were significantly higher in patients. In addition, the simultaneous expression of CYP1A1 4889G and 4887A alleles was associated with a marked risk of disease development (156).

HSPs are a group of scavenger proteins expressed under denaturating stress conditions or microbial challenge, and likely implicated in autoimmunity (6, 11). In a Turkish research, the GAT/GAA heterozygote single nucleotide polymorphism in the region 136-150-II of the HSP 60 gene was studied (157). In the same study, the gene polymorphisms of cytochrome p450 1A1 (CYP1A1), a member of a superfamily of enzymes that catalyze oxidation of various xenobiotics, was evaluated, showing that the frequencies of CYP1A1 4889G and 4887A alleles and CYP1A1 4889A/G and 4887C/A genotypes were significantly higher in patients. In addition, the simultaneous expression of CYP1A1 4889G and 4887A alleles was associated with a marked risk of disease development (156).
cant relationships between FcγRIIa allele and arthritis, as well as between FcγRIIH and vascular disease (158).

In a Turkish study, the C/T single nucleotide polymorphism at position 450 in the C5a receptor gene was found to be equally frequent in patients and controls, but was negatively associated with uveitis in the BD group (159).

In Turkish patients compared to controls, the evaluation of the 3DL1/3DS1 polymorphism of the KIR gene demonstrated that the 3DS1 frequency was selectively decreased, especially in B*51-negative patients, suggesting its protective effect (160). In Chinese Han patients of Shanghai area, a negative correlation between BD and both KIR 3DL1 and 2DS genes was observed (161).

In Turkish reports, the distribution of the CTL antigen 4 (CTLA-4) A49G single nucleotide polymorphism did not significantly differ between patients and controls (162, 163). However, the CTLA-4 49A allele and the AA genotype frequencies were selectively increased in patients with ocular involvement and erythema nodosum-like lesions (162), whereas the AG genotype positively correlated with arthritis (163).

In Italian BD patients, the +936C/T polymorphism in the 3' untranslated region (UTR) and the −634C/G polymorphism in the 5' UTR of the vascular endothelial growth factor (VEGF) gene, as well as the 18 bp insertion/deletion (ID) polymorphism at −2549 of the VEGF promoter region were investigated (164). The carriage rates of the −634C and I alleles were significantly higher in patients than in controls. While the distribution of the +936T allele was similar in the two groups, its frequency was significantly enhanced among patients with posterior uveitis/retinal vasculitis. In addition, VEGF levels released by lipopolysaccharide-stimulated peripheral blood mononuclear cells were significantly higher in II homozygous than in DD homozygous individuals (164).

**Procoagulant polymorphisms and mutations**

The contributing role of procoagulant polymorphisms and mutations has been evaluated in BD. In Turkish patients, the methylenetetrahydrofolate reductase (MTHFR) gene C677T mutation (producing a thermolabile and less active variant of the enzyme) did not increase the risk of deep venous thrombosis (DVT) (30, 165). However, plasma homocysteine levels were found significantly higher in patients with DVT history than in those without (165). In an Israeli series of patients with and without thrombosis, no differences either in the prevalence of MTHFR C677T homozygosity or in plasma concentrations of homocysteine were observed (166).

In a Turkish case control study, 37.5% of BD patients with DVT carried a single point mutation (replacement of arginine with glutamine) at nucleotide 1691 in the coagulation factor V (FV) gene, known as the FV Leiden mutation (167). The contributing role of the FV Leiden mutation in BD venous thrombosis was confirmed in some studies (168-170), but not in others (30, 166, 171-174). Moreover, the Leiden mutation seemed to be a risk factor for ocular disease and, in particular, for retinal vascular occlusion among Middle Eastern (175) and Turkish patients (176), but not in UK white patients (177). In Turkish BD patients, the FV 4070G gene mutation did not appear to have a role in the pathogenesis of thrombosis (173).

In Turkish patients with DVT history compared to controls, the 31% of the thrombotic and 3% of the nonthrombotic subjects carried the substitution of gline by adenine at position 20210 (G→A20210) in the 3'-UTR of the prothrombin (PT) gene (phenotypically expressing with an increase of PT plasma levels and hypercoagulability) (178). Moreover, two Italian BD patients with thrombotic events were reported to be heterozygous for the PT G→A20210 mutation (179). A young Spanish BD patient carrying the PT G→A20210 mutation presented right intracardiac thrombosis (180). However, other studies in different populations did not confirm the role of this PT mutation as a risk factor of thrombosis in BD (30, 166, 170, 172, 173).

In an Italian patient cohort, no association between PT G→A20210 and DVT was found, but the frequency of such a mutation was significantly higher in patients with posterior uveitis/retinal vasculitis (174).

In a Turkish patient cohort, the risk of thrombosis was significantly higher in subjects carrying the platelet glycoprotein IIb/IIIa gene (GPIIb/IIIa) in 802CT and 807TT genotypes than in those expressing the 807CC genotype (181).

Notably, in European BD patients the TNFRSF1A R92Q mutation was associated with an increased risk of venous thrombosis, especially in extracranial veins, suggesting the complexity of the thrombosis pathogenesis in BD (121).

**Conclusions**

A complex interaction of multiple factors, such as ethnic background, immunogenetic mechanisms and environmental influences, is likely involved in the BD etiopathogenesis. The strong role of a genetic predisposition is highlighted by the disease peculiar demographic distribution, the close association with HLA-B*51 (especially the B*5101 and B*5108 subtypes) in different ethnic groups, and the familial clustering. Presently, HLA-B*51 is the main BD genetic marker in many populations, likely contributing in the disease development through specific antigen presentation or molecular mimicry with microbial antigens, or participating in linkage disequilibrium with a presently unknown susceptibility gene. In B*51-negative BD patients, the influence of other(s) yet undefined genetic factor(s) is probably involved. HLA-B alleles other than B*51, such as B*27, B*15 and B*57, has been variably associated with BD, and their shared Bw4 motif might be the causally related factor to the disease.

The familial aggregation of BD is characterized by both genetic anticipation and higher prevalence in childhood patients, very likely defining a subset with stronger immunogenetic influences. Notably, in familial cases the HLA-B*51 positivity rate is much higher than in sporadic cases. The reported BD concordance in two pairs of monozygotic twins, all bearing B*51, further
sustains the relevant role of such a genetic association. On the other hand, analyses of a small group of multicase families using the transmission disequilibrium test, even confirming the genetic link between BD and HLA-B locus, estimated that the B*51 contribution to overall genetic predisposition is no greater than 20%.

Polymorphisms in genes encoding for host effector molecules, such as TNF, TAP proteins, ICAM-1, ILs, CCL2/MCP-1, eNOS, VEGF and MBL, may contribute to the disease susceptibility and/or severity. Moreover, gender-specific polymorphisms affecting chemokine gene functions might influence the disease phenotypic expression.

The role of prothrombotic mutations and polymorphisms in the pathogenesis of BD thrombosis is presently controversial. Ultimately, BD is likely a polygenic disease phenotypic expression.

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