Abstract

Objective. To review the progress in the field of MHC-related genetic susceptibility to Behçet’s disease (BD).

Method. Systematic review of the English literature between 1 January 1980 and 31 January 2010 using Medline. Case–control, population-based, observational cohort studies investigating the association between BD and HLA-B*51 subtypes, classical and non-classical HLA alleles and other HLA-related genes were selected. The geographical distribution of BD and these susceptibility genes was also taken into consideration. Case and familial case reports were excluded except for case series with more than two patients.

Results. Ninety articles plus 17 obtained from other sources were included in the systematic review. We have found high evidence that a core component of genetic susceptibility to BD is within the MHC region being primarily related to an HLA-B*51 subtype: HLA-B*5101/B*510101. Moreover, HLA-A*26, HLA-B*15, HLA-B*5701 and TNF-α –7031C were independently associated with BD. Data suggest that other HLA (HLA-C, HLA-DR) and HLA-related [MHC Class I chain-related gene A (MIC-A), TNF-α] genes may play a role in BD co-susceptibility or pathogenesis. Finally, the distinctive geographical distribution of BD suggested an evolutionary selection of HLA-B*51 subtypes as the major susceptibility factors for BD.

Conclusion. Further studies must be addressed to clarify the functional relevance of the different genes found to be associated with disease susceptibility and the potential interactions between genes located within and outside the MHC region.

Key words: Behçet’s disease, Genetics, Immunogenetics and HLA, Major histocompatibility complex, Systematic review.

Introduction

Behçet’s disease (BD) is a chronic relapsing multisystem vasculitis, characterized by recurrent oral and genital aphthosis, ocular involvement and skin lesions [1]. The aetiology of BD is unknown. Evidence of neutrophil, NK and T-lymphocyte hyperactivity with enhanced pro-inflammatory cytokine production highlights an underlying dysregulation in immune response [2–7]. The involvement of both innate and adaptive immune responses raises doubts as to whether BD is auto-inflammatory, autoimmune or possibly both [8]. The most substantiated immunopathogenesis hypothesis speculates that the pathology can be triggered by microbiological factors in genetically susceptible individuals [9].

BD usually appears as a sporadic disease, but a familial aggregation is well known and an increased prevalence has been observed in siblings and parents of paediatric patients [10]. Despite a number of controversial viewpoints about familial inheritance, the existence of a Mendelian autosomal recessive entity in multicase families with an affected paediatric member has been pointed out, suggesting that genetic load might be somewhat higher in children with BD than in adults [11]. The close association of the HLA-B51 allele with BD represents the clearest evidence of a genetic contribution to the disease [12]. Since the identification of this association, considerable effort has been made to understand whether HLA-B51 participates in BD pathogenesis or if it represents a marker for any other predisposing genes in linkage disequilibrium (LD) with it. Candidate
gene approaches, linkage studies and genome-wide association studies have been useful in identifying genetic susceptibility factors in BD, both within and outside the MHC region [13–15]. The human MHC is a highly polymorphic region, located on chromosome 6p21.3, and encompasses ~3600 kb. It includes the Class I, Class III and Class II HLA genes with >200 identified loci [16]. Since ~40% of genes belonging to the MHC region encode constituents of the immune system, MHC contribution appears to be pivotal in any disease having an immune component [16]. Thus, to assess the progress in the field of MHC-related genetic susceptibility to BD, a systematic review of this topic was carried out.

## Methods

Studies investigating the links between BD and genes located within the MHC region were identified through searches of the PubMed Medline database between 1 January 1980 and 31 January 2010 using a combination of the medical subject heading terms BD and HLA (or MHC) or several combinations of text search terms including BD (or Behc¸ et's syndrome) with HLA (or MHC or HLA region or MHC region) and with genetics. Additional papers were obtained by checking the references from the selected studies as well as from review articles and other sources known to the authors including textbooks and conference proceedings (Fig. 1). To be included in the review, a study had to be designed as a case–control, population-based, observational cohort study investigating the geographical distribution and association between BD and HLA-B*51 subtypes, classical and non-classical HLA genes and HLA-related genes. Studies exclusively emphasizing the association between BD and the HLA-B*51 allele were excluded. Only full publications in English were allowed. Whenever papers reported duplicate data, the most recent article was selected. Case and familial case reports were excluded except for case series with more than two patients.

### HLA genes and BD

The geographical distribution and association between BD and HLA-B*51

BD is concentrated in a world area between latitudes 30° N and 45° N spanning from the Mediterranean basin to the Far East (Table 1). BD prevalence is known to be highest in the Middle East (7.6–420/100 000) [17–24] and in the Far East (7.3–30.5/100 000) [25–29]. In Northern Europe and the USA, BD prevalence is lower (0.27–5.2/100 000) [30–35] than that observed in Southern Europe and North Africa (3.8–15/100 000) [36, 37], while in sub-Saharan Africa,
Australasia and among Amerindians the disease is rare or virtually absent [38–41]. In 2005, Papoutsis et al. [42] estimated the prevalence of BD in Berlin to be highest among people of Turkish (77.3/100 000) and Lebanese (101.3/100 000) origin, while the lowest was among Germans (1.4/100 000). This suggests that disease prevalence is heavily dependent on ethnic origin and that genetic susceptibility factors play a primary role in disease precipitation.

The HLA-B51 allele, a split antigen of HLA-B5, is strongly associated with BD. Recently, it has been calculated that the HLA-B51/B5 allele accounts for a 32–52% risk of BD development within various geographical areas [pooled odds ratio (OR) 5.78; 95% CI 5.00, 6.67] [43]. Notably, the strongest correlation between BD and HLA-B51 is seen among populations with a high incidence of this allele, which confers an increased risk of disease development. Where HLA-B51 is rare BD is seldom observed and their association is weak; hence, geographical distribution of HLA-B51 among healthy controls roughly reflects global disease distribution. In consideration of the distinctive BD geographical distribution, Ohno et al. [44] hypothesized that genetic susceptibility factors, closely linked to HLA-B51, were spread by migrant traders or nomadic tribes along the old East–West trade routes across Asia, and therefore BD became known as the Silk Road disease.

However, HLA-B51 alone is neither necessary nor sufficient to determine BD. Sporadic cases of BD, unrelated to HLA-B51, have been reported in the indigenous South African, West African and Afro-Caribbean populations in whom HLA-B51 incidence is very low [39, 40]. Moreover, in some ethnic groups carrying a high allele frequency (AF), such as the indigenous inhabitants of the Americas and Siberia, disease prevalence is virtually absent [41]. Such observations seem in contrast to the Silk Road

### Table 1: Prevalence of BD and its association with HLA-B51 in patients and healthy controls of different world populations, are reported moving along latitude from North to South

<table>
<thead>
<tr>
<th>Latitude</th>
<th>Population (or region)</th>
<th>Prevalence/100,000</th>
<th>HLA-B51 frequency in controls, %</th>
<th>HLA-B51 frequency in patients, %</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>56 N</td>
<td>Scotland</td>
<td>0.27</td>
<td>NR</td>
<td>13(^a)</td>
<td>[30]</td>
</tr>
<tr>
<td>53 N</td>
<td>Yorkshire</td>
<td>0.63</td>
<td>9(^a)</td>
<td>18(^a)</td>
<td>[31]</td>
</tr>
<tr>
<td>52 N</td>
<td>German (West Berlin)</td>
<td>0.55</td>
<td>14</td>
<td>36</td>
<td>[32]</td>
</tr>
<tr>
<td>52 N</td>
<td>Turkish (West Berlin)</td>
<td>20.75</td>
<td>31</td>
<td>75</td>
<td>[32]</td>
</tr>
<tr>
<td>44 N</td>
<td>Reggio Emilia area</td>
<td>3.8</td>
<td>19</td>
<td>57</td>
<td>[36]</td>
</tr>
<tr>
<td>42 N</td>
<td>Chinese (nationwide)</td>
<td>14.0</td>
<td>12</td>
<td>56</td>
<td>[25, 26]</td>
</tr>
<tr>
<td>42 N</td>
<td>Turkey (nationwide)</td>
<td></td>
<td>25</td>
<td>75</td>
<td>[58]</td>
</tr>
<tr>
<td>41 N</td>
<td>Istanbul</td>
<td>420.0</td>
<td>NR</td>
<td>NR</td>
<td>[17]</td>
</tr>
<tr>
<td>41 N</td>
<td>North-eastern rural area</td>
<td>370.0</td>
<td>NR</td>
<td>26(^a)</td>
<td>[18]</td>
</tr>
<tr>
<td>41 N</td>
<td>North-western rural area</td>
<td>20.0</td>
<td>NR</td>
<td>NR</td>
<td>[19]</td>
</tr>
<tr>
<td>40 N</td>
<td>Spanish (nationwide)</td>
<td>7.5</td>
<td>15</td>
<td>37</td>
<td>[37]</td>
</tr>
<tr>
<td>43 N</td>
<td>Hokkaido region</td>
<td>30.5</td>
<td>NR</td>
<td>NR</td>
<td>[27]</td>
</tr>
<tr>
<td>37 N</td>
<td>Japanese (nationwide)</td>
<td>13.5</td>
<td>14</td>
<td>59</td>
<td>[27, 74]</td>
</tr>
<tr>
<td>37 N</td>
<td>Korean (nationwide)</td>
<td>7.3</td>
<td>13</td>
<td>53</td>
<td>[28, 29]</td>
</tr>
<tr>
<td>33 N</td>
<td>Iraqi (nationwide)</td>
<td>17.0</td>
<td>29</td>
<td>62</td>
<td>[20]</td>
</tr>
<tr>
<td>32 N</td>
<td>Nationwide</td>
<td>15.2</td>
<td>NR</td>
<td>NR</td>
<td>[21]</td>
</tr>
<tr>
<td>32 N</td>
<td>Druze – Northern region</td>
<td>146.4</td>
<td>NR</td>
<td>100(^a)</td>
<td>[21]</td>
</tr>
<tr>
<td>32 N</td>
<td>Arab – Northern region</td>
<td>26.2</td>
<td>NR</td>
<td>81(^a)</td>
<td>[21]</td>
</tr>
<tr>
<td>32 N</td>
<td>Jewish – Northern region</td>
<td>8.6</td>
<td>NR</td>
<td>72(^a)</td>
<td>[21]</td>
</tr>
<tr>
<td>32 N</td>
<td>Arab – Taibe city</td>
<td>120.0</td>
<td>NR</td>
<td>83(^a)</td>
<td>[22]</td>
</tr>
<tr>
<td>31 N</td>
<td>Alexandria region</td>
<td>7.6</td>
<td>7</td>
<td>58</td>
<td>[23]</td>
</tr>
<tr>
<td>26 N</td>
<td>Al Quassim region</td>
<td>20.0</td>
<td>26</td>
<td>72</td>
<td>[24]</td>
</tr>
</tbody>
</table>

Percentages are rounded off. \(^a\)B5 AF. NR: not reported.
disease hypothesis and led Verity et al. [45] to speculate that the global distribution of genes potentially associated with BD, such as HLA-B51 or others in LD, might have been propagated by earlier migrations of Homo sapiens. Thus, the presence of HLA-B51 in some Amerindian populations may reflect the early demographic migrations across Asia and Beringia during the last glacial era. It has been clarified that a high level of recombination in the MHC region had occurred in the ancestors of Amerindian and Eskimo populations, suggesting a strong disruption of genetic loci in LD with HLA-B51. Therefore, the virtual absence of BD in those populations carrying a high incidence of HLA-B51 could be explained by the fact that genetic susceptibility to the disease would be secondary either to differentiated HLA-B51 subtypes or to genes close to and in LD with HLA-B51, or both of them [45].

The different contribution of HLA-B*51 subtypes in BD susceptibility

The HLA-B*51 coding sequence has been analysed and single or multiple nucleotide substitutions have been detected permitting the identification of >89 different subtypes of HLA-B*51 [46]. HLA-B*5101 is the major suballele associated with BD in all the populations studied [47–58]. The remaining subtypes are rarer and whether they give susceptibility to BD or not is unknown, because of their low frequency. However, HLA-B*5108 was identified as associated with BD in Middle Eastern, Italian, Spanish, Greek, Turkish and German patients [54–59]. Gonzalez-Escribano et al. [57] offered a double interpretation of the fact that two HLA-B*51 subtypes are associated with BD. They suggested the possibility of direct immunopathogenetic action through a peptide-binding motif shared by the two subtypes, or the possibility of a mutation, occurring in the haplotype defined by HLA-B*5101 before the divergence of B*5108 from the B*5101 allele, causing susceptibility to BD. The latter supports the existence of a susceptibility or co-susceptibility gene in LD with these subtypes. As for the first hypothesis, it is known that B*5101 differs from B*5201, which is a split antigen of HLA-B5 and is not associated with BD, by two amino acids in positions 63 and 67 inside the antigen-binding groove [54]. In addition, it has been suggested that HLA-B*5107 might be negatively associated with BD in the Turkish and German populations. Noteworthy, B*5107 shares a Ser at position 67 with HLA-B*5201 [58]. These residues may be the crucial anchor points for Behçetogenic epitope binding, a hypothetical disease-inducing peptide presented to HLA Class I-restricted T-lymphocytes, and could explain the different immunopathogenetic roles of HLA-B*51 subtypes.

Recently, Takemoto et al. [60] reported the coding region of HLA-B*5101 to be identical among 24 BD patients and 13 healthy controls of Japanese, Turkish, Jordanian and Iranian origin. The authors found that all the patients carried HLA-B*510101 and confirmed that BD susceptibility was conferred by HLA-B*510101 itself and not by other B*51 subtypes. Moreover, phylogenetic analysis suggested that the entire coding sequence of B*510101 was well conserved, including an exon encoding the binding domain of antigenic peptides, implying that a unifying selective pressure might be operated to preserve the HLA-B*510101 structure.

Amerindian populations, known to carry a high frequency of HLA-B*51 but having no BD incidence, such as the Mexican Tarahumaras (AF: 14.7%), Pima from Arizona (AF: 13.5%) and Navajo from New Mexico (AF: 13.4%), have the apparently non-susceptible HLA-B*510201 allele [46]. To date, Amerindians are known to carry the highest frequencies of HLA-B*510201 reported around the world. The frequency of an allele is likely to be higher in the place of origin as well as in the region where selective factors favour it. As it is found in Asian and Amerindian populations, and since these populations share an Eastern Asian common ancestor, the HLA-B*510201 suballele may have evolved before overland migration. Selective pressure by infectious diseases is likely to account for the high level of polymorphism in HLA loci. Therefore, it might be speculated that, in North America, subtypes of HLA-B*51 different from HLA-B*5101/B*510101, and with them a lower susceptibility to BD, have been fixed over the generations due to the absence of a unifying pathogen-driven selective pressure. Such observations could explain why BD is virtually absent in these ethnic groups as an effect of a favourable genetic drift, rather than a lack of exposure to precipitating environmental factors.

Other HLA genes associated with BD

The HLA-A*26 is independently associated with BD in Greek and Japanese patients compared with healthy controls [53, 61]. Itoh et al. [62] confirmed that Japanese BD patients have a strong primary association with HLA-B*5101 and found that the HLA-A*2602 (Pc = 0.130, OR = 4.3) and HLA-B*3901 (Pc = 0.099, OR = 3.5) had a weak association, insufficient to meet significant Bonferroni corrections, in the patient group without HLA-B*51 as compared with the control group without HLA-B*51, hypothesizing that these two alleles might also have some secondary influence on the onset of BD. In Moroccan BD patients, HLA-B*15 is associated with late disease onset in males and more interestingly with disease susceptibility in females (OR 3.1; 95% CI 1.3, 7.6) showing an effect comparable to that observed for HLA-B*51 in males (OR 3.4; 95% CI 1.5, 7.4) [63]. These data suggest that HLA-B effects on disease pathogenesis might be different in men and women; however, they have not been confirmed in other populations. HLA-B*5701 was identified as associated with BD (P = 0.0002; Pc = 0.008; RR 3.0; 95% CI 1.7, 5.5) in Caucasian patients from Great Britain, conferring a relative risk of disease slightly lower than that of HLA-B*51 (P = 1 × 10⁻⁸; RR 4.5; 95% CI 2.7, 7.4) [64]. Given the study size (n > 130, controls > 300), the effect of HLA-B*5701 seems quite strong in these patients and particularly noteworthy considering that Great Britain is...
enclosed in an area with low frequency of HLA-B*51 and low incidence of BD.

Other HLA-B alleles have been described as associated with BD, but because of their low incidence or the small size of investigated populations, significance levels have been weak and achieved in single studies only. As an example, the HLA-B*2702 resulted in weak association with BD in Turkish patients (AF: 2.3%) when compared with healthy controls (AF: 0.3%) suggesting a possible contribution of this allele to BD susceptibility [65]. As another example, the HLA-B*52 allele, is not considered to be associated with BD except for some Israeli populations (RR 2.8) [66]. Finally, the HLA-B*44 (OR 2.8; 95% CI 1.1, 7.7), HLA-B*52 (OR 5.3; 95% CI 1.1, 29.1) and HLA-B*56 (OR 4.2; 95% CI 3.4, 5.2) alleles have been described as associated with BD in 32 Mexican Mestizos patients compared with 99 healthy controls. In contrast to Mexican native populations, in whom BD is virtually absent, the Mexican Mestizos are genetically more heterogeneous and carry a high proportion of alleles acquired by admixture between Mediterraneans or Asians and Amerindians and with it a somewhat higher susceptibility to BD [67].

Interestingly, the majority of these alleles are part of the serologically defined B5 and B35 cross-reactive group (CREG), which includes alleles such as B*15, B*27, B*35, B*51, B*52, B*57 and B*78 [68]. Each one of them shares an amino acid sequence that contributes to the structure of peptide-binding pocket-B and determines the motif of bound peptides. These structural similarities have been evoked to explain the association with BD in the light of the existence of a hypothetical Behçetogenic peptide [69, 70]. Moreover, some of these alleles, such as HLA-B*15, B*2702, B*44, B*51 and B*57, share a specific sequence of amino acids at residues 77–83 in the α helix, the Bw4 motif, which may be causally related to the disease due to its involvement in NK cell recognition and recruitment [65, 70].

The strong LD within the MHC region is a major problem when trying to identify disease susceptibility genes. Nevertheless, several studies support the existence of co-susceptibility locus for BD within the MHC region, suggesting that genes included in extended haplotypes with HLA-B*51 may be partly responsible for genetic susceptibility to BD [71–73]. The Cw1 [48], Cw14 [74], Cw15 [48, 74, 75] and Cw16 [75, 76] alleles have been described to be associated with BD in Turkish, Japanese and Iberian populations, but their effect does not reach significance after statistical correction, most likely because of their significant LD with B*51. Therefore, it has been speculated that the HLA-C gene may functionally act as a co-susceptibility gene [75] or may represent a marker for an HLA-related co-susceptibility gene inherited in extended haplotype with the HLA-C/HLA-B*51 rather than directly contribute to disease onset [76]. Although several studies highlighted a different HLA-DR and HLA-DQ allele frequency in between BD patients and healthy controls, often due to LD with HLA-B*51, to date it has not been clarified whether and which HLA Class II antigens are associated with BD and they are generally not considered to give primary susceptibility to the disease [25, 48, 51, 56, 67, 71, 72, 77–83].

Other MHC-related genes and BD

Single studies failed to show an association of polymorphisms at the HLA-related LMP2 and LMP7 (low-molecular weight polypeptides) [84, 85], ECI (focus that determines susceptibility to alloreactive NK) [86], HSP-70 [64, 87], lymphotixin-α [64] and nuclear factor κ B1 [88] loci with BD susceptibility. Polymorphisms of transporters associated with antigen processing (TAP) loci resulted as not associated with susceptibility to BD in two studies [84, 89]. However, the TAP1 Val-333/Asp-637 polymorphism was completely absent among Spanish BD patients compared with healthy controls (0 vs 12%; P < 0.05; RR 0.06) suggesting that the TAP polymorphisms may have some significance in BD development [90].

In the past years, the attention of researchers has focused on polymorphisms of the non-classical HLA genes, the MHC Class I chain-related (MIC) genes and TNF genes.

The contribution of non-classical HLA genes to BD susceptibility

The non-classical HLA-E, HLA-F and HLA-G molecules modulate the immune system through NK and T-cell regulation [91, 92]. Evidence of involvement of these ligands for the innate and adaptive immune effector cells in BD susceptibility derives from positive and negative associations with HLA-E, HLA-F and HLA-G polymorphisms detected in Korean and Japanese patients [61, 92, 93]. In Japanese BD patients, two polymorphisms were significantly associated with susceptibility to BD as part of the haplotype consisting of HLA-A*26-F*010101-G*010102 (OR 3.08; 95% CI 2.07, 4.58). The authors concluded that the association with HLA-F and HLA-G alleles was due to LD with HLA-A*26, which showed a primary association with BD (OR 2.50; 95% CI 1.73, 3.62) [61]; however, a co-susceptibility role played by these genes cannot be excluded.

The geographical distribution and link between BD and MIC genes

The MHC Class I chain-related gene A (MIC-A) was considered a major candidate for being responsible for BD genetic susceptibility due to its localization [94], 46 kb centromeric to locus B and to its immunological function as a stress-inducible antigen involved in recognition and interaction with NK and γδ T cells [95]. Following the first observation by Mizuki et al. [96], who suggested the possibility of primary association of the six triplet repeat polymorphism (A6 allele) in the transmembrane (TM) region (exon 5) of MIC-A with BD, several studies in different populations have explored the association between BD and MIC-A TM (Table 2). However, the sole independent association observed was the one between HLA-B*51 and BD. Association with MIC-A6 when present was due to its strong LD with HLA-B*51 [97–106]. Park et al. [104] suggested the association between MIC-A6
### Table 2

Studies investigating the phenotype frequencies of MIC-A TM alleles and of HLA-B51/MIC-A6 haplotype in patients with BD and their association with HLA-B*51 among BD patients and healthy controls in populations of different world areas

<table>
<thead>
<tr>
<th>Allele</th>
<th>Europe</th>
<th>Middle East</th>
<th>Far East</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence in normal population [97–106] % (n)</td>
<td>Prevalence in BD [97–106] % (n)</td>
<td>Spain [97 % (n)]</td>
</tr>
<tr>
<td>MIC-A4</td>
<td>21–32 (926)</td>
<td>13–30 (512)</td>
<td>21% (58)</td>
</tr>
<tr>
<td>MIC-A5</td>
<td>20–56 (1108)</td>
<td>10–52 (656)</td>
<td>19% (58)</td>
</tr>
<tr>
<td>MIC-A5.1</td>
<td>14–45 (1058)</td>
<td>6–51 (607)</td>
<td>45% (58)</td>
</tr>
<tr>
<td>MIC-A6</td>
<td>45–62 (1275)</td>
<td>56–95 (817)</td>
<td>71% (58)</td>
</tr>
<tr>
<td>MIC-A9</td>
<td>13–34 (926)</td>
<td>13–27 (512)</td>
<td>17% (58)</td>
</tr>
<tr>
<td>HLA-B51</td>
<td>12–31 (1124)</td>
<td>35–83 (659)</td>
<td>36% (58)</td>
</tr>
<tr>
<td>B51/A6</td>
<td>12–25 (862)</td>
<td>31–70 (496)</td>
<td>34% (58)</td>
</tr>
</tbody>
</table>

Data are reported moving along longitude from West to East. The total number of tested subjects and the range of association between genes and disease are reported for each allele in each population. Numbers are rounded off. Non-Ashkenazi Jew. Allele frequency. *P < 0.05; **P < 0.01; ***P < 0.001: positive association with BD patients. †P < 0.05; ††P < 0.01; †††P < 0.001: negative association with BD patients. (n): number of tested subjects; %: frequency ratio; NR: not reported.

### Table 3

Studies investigating the phenotype frequencies of MIC-A*009 extracellular domain allele and of HLA-B51/MIC-A*009 haplotype in patients with BD and their association with HLA-B*51 among BD patients and healthy controls in populations of different world areas

<table>
<thead>
<tr>
<th>Allele</th>
<th>Europe</th>
<th>Middle East</th>
<th>Far East</th>
<th>South America</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC-A’009</td>
<td>12–31 (738)</td>
<td>30–76 (354)</td>
<td>45% (56)</td>
<td>40% (42)</td>
</tr>
<tr>
<td>HLA-B51</td>
<td>10–29 (738)</td>
<td>40–82 (354)</td>
<td>43% (56)</td>
<td>40% (42)</td>
</tr>
<tr>
<td>B51/A’009</td>
<td>9–21 (738)</td>
<td>27–70 (321)</td>
<td>43% (56)</td>
<td>34% (42)</td>
</tr>
</tbody>
</table>

Data are reported moving along longitude from West to East. The total number of tested subjects and the range of association between genes and disease are reported for each allele in each population. Numbers are rounded off. Caucasian. *P < 0.05; **P < 0.01; ***P < 0.001: positive association with BD patients. (n): number of tested subjects; %: frequency ratio.
and the complicated form of BD, while an Italian study on juvenile BD demonstrated the development of severe gastrointestinal manifestations in homozygous MIC-A6 patients [107].

The relationship between the extracellular domain (exons 2–4) of MIC-A and BD was also investigated. The MIC-A6 TM variant is known to be associated with some extracellular domain alleles, such as MIC-A*003, MIC-A*004, MIC-A*006 and MIC-A*009. Among the 19 different external domain alleles studied, MIC-A*006 was found to be associated with BD in Brazilian patients (OR = 14.59, \( P = 0.00032, \) \( P_c = 0.0057 \)), but after stratification for the possible confounding effect of HLA-B51 the association with MIC-A*006 was not [108]. The MIC-A*009 extracellular domain AF was recognized as higher in patients than in normal controls among Caucasian British, Spanish, Turkish, Jordanian, Palestinian and Japanese populations (Table 3). However, the significant increase in MIC-A*009 in the patient groups was due to a strong LD with HLA-B*51 [50, 102, 109–111].

Hence, the MIC-A6 TM and MIC-A*009 extracellular domain alleles are unlikely to be the primary susceptibility gene for BD but may be a part of an extended susceptibility haplotype or markers for additional risk factors, such as disease severity, having a direct immunological effect implicated in disease pathogenesis.

MIC-B is located \(~140\) kb centromeric from the HLA-B gene, but no MIC-B allele was found significantly associated with BD in two studies conducted on Caucasian British and Japanese patients [111, 112].

The geographical distribution and link between BD and TNF genes

TNF genes \( \alpha \) and \( \beta \), lying between Class I and Class II regions, encode two cytokines with distinct roles and expression patterns: TNF-\( \alpha \) and TNF-\( \beta \). An analysis conducted by Mizuki et al. [86] of two distinct TNF-\( \beta \) gene restriction fragment length polymorphisms (RFLPs), NcoI and EcoRI, showed a different expression of these alleles between patients and healthy controls due to complete LD between some HLA-B alleles and the TNF-\( \beta \) RFLP. They concluded that another gene in the proximity of the TNF-\( \beta \) region was a candidate to be the susceptibility gene for BD.

Evidence suggesting a role of TNF-\( \alpha \) polymorphism is more consistent, RFLP and microsatellite polymorphism analysis carried out around the HLA-B locus indicated its importance in BD susceptibility [86, 87]. Verity et al. [55], investigating genetic risk factors for ocular involvement in Middle Eastern patients, described the strong LD between HLA-B*51 and the TNFB*2 polymorphism at the TNF-\( \alpha \)-308 promoter position. They concluded that both alleles contribute to disease risk and their co-expression leads to severe blinding disease.

At least 12 single nucleotide polymorphisms (SNPs) in the promoter region of the TNF-\( \alpha \) gene have been described so far. Some of them associated with increased TNF-\( \alpha \) gene transcription and serum levels have been analysed in BD (Table 4) [64, 113–124]. In Caucasian patients from Great Britain, the resulting TNF-\( \alpha \) −1031C (OR 2.3; 95% CI 1.5, 3.5) associated with BD both independently and as part of two susceptibility extended HLA haplotypes, one of these containing HLA-B*51, while the second defined by HLA-B*5701. The association of TNF-\( \alpha \) −1031C with BD was partially confirmed in Turkish, Tunisian, Iranian, Korean and Lebanese patients. Controversial results were observed for −238A, −308G and −863A that led to speculate a distinct role for these allele variants in different populations [64, 123]. This is emphasized in view of the reported association with some disease phenotypes, such as ocular involvement or enhanced risk of developing positive skin pathergy test, carried by TNF-\( \alpha \) polymorphisms in certain populations [55, 122]. The susceptibility role of TNF-\( \alpha \) promoter region haplotype was analysed in subjects of different origin, such as British Caucasoid [64], Korean [123] and Iranian Azeri Turkish [124]. Haplotypes containing the −1031C polymorphism give an increased risk of developing BD whereas those carrying the −1031T SNP conferred a decreased risk of BD. These findings suggest a possible co-susceptibility or pathogenetic role of TNF-\( \alpha \) polymorphisms in BD development, with a different impact on those populations settled close to each other.

Conclusion

In conclusion, the review of the international literature confirmed that a key component of genetic susceptibility to BD is within the MHC region, being primarily related to an HLA-B*51 subtype: the HLA-B*5101/B*510101. Moreover, studies with convincing approaches and data showed that the HLA-A*26, HLA-B*15, HLA-B*5701 and TNF-\( \alpha \) −1031C are independently associated with BD. Data obtained from other surveys suggested that other HLA (HLA-C, HLA-DR) and HLA-related genes (MIC-A*009, TNF-\( \alpha \) polymorphisms) may play a role in BD co-susceptibility or pathogenesis independently or as part of extended haplotypes defined by LD with susceptibility genes. Nonetheless, it is noteworthy that the field apparently lacks functional data on the involvement of the different genes found to be associated with disease susceptibility. Since only such data could help distinguish whether the findings of genetic associations are solely statistical or actually play a pathogenic role, future research could be directed this way. Studies conducted among populations with highly homogeneous and preserved MHC haplotype may clarify the specific synergistic role of genes belonging to the MHC region. Moreover, a contributory influence of genetic factors lying outside the MHC is not excluded by these data. Future studies are needed in order to understand the functional relevance of potential interactions between genes located within and outside the MHC region. Finally, the distinctive geographical distribution of BD cannot be easily explained solely by non-homogeneous distribution of triggering environmental factors throughout the planet, but suggests an evolutionary selection of HLA-B*51 subtypes and linked genes as the major susceptibility factors for BD. Further studies on
### Table 4: AFs of TNF-α and TNF-β SNPs among BD patients and healthy controls in populations of different world areas

<table>
<thead>
<tr>
<th>Allele</th>
<th>Prevalence in normal population [55, 64, 113–124] % (n)</th>
<th>Prevalence in BD [55, 64, 113–124] % (n)</th>
<th>Europe</th>
<th>Africa</th>
<th>Middle East</th>
<th>Far East</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Great Britain(^b) [64] % (n)</td>
<td>Germany [121] % (n)</td>
<td>Tunisia [113] % (n)</td>
<td>Turkey [115–119, 121, 122] % (n)</td>
</tr>
<tr>
<td>α -1031C</td>
<td>15–35 (1241)</td>
<td>17–56 (789)</td>
<td>56(^\uparrow) (133)</td>
<td>NE</td>
<td>33(^\uparrow) (89)</td>
<td>24(^\dagger) (99)</td>
</tr>
<tr>
<td>α -1031T</td>
<td>65–86 (1241)</td>
<td>44–83 (789)</td>
<td>44 (133)</td>
<td>NE</td>
<td>67 (89)</td>
<td>76 (99)</td>
</tr>
<tr>
<td>α -863A</td>
<td>14–26 (902)</td>
<td>13–35 (547)</td>
<td>35 (133)</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>α -863C</td>
<td>74–86 (902)</td>
<td>65–87 (547)</td>
<td>65 (133)</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>α -857C</td>
<td>82–87 (902)</td>
<td>84–89 (546)</td>
<td>84 (133)</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>α -857T</td>
<td>13–18 (902)</td>
<td>11–16 (446)</td>
<td>16 (133)</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>α -646A</td>
<td>5 (114)</td>
<td>5 (115)</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>α -646G</td>
<td>95 (114)</td>
<td>95 (115)</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>α -380A</td>
<td>1 (354)</td>
<td>1 (133)</td>
<td>1 (133)</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>α -380G</td>
<td>99 (354)</td>
<td>99 (133)</td>
<td>99 (133)</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>α -376A</td>
<td>0–3 (542)</td>
<td>0–1 (460)</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>α -376G</td>
<td>97–100 (542)</td>
<td>99–100 (460)</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>α -308A</td>
<td>4–34 (1557)</td>
<td>5–30 (988)</td>
<td>30 (133)</td>
<td>NE</td>
<td>14 (89)</td>
<td>10–11 (300)</td>
</tr>
<tr>
<td>α -308G</td>
<td>66–96 (1557)</td>
<td>70–95 (888)</td>
<td>70 (133)</td>
<td>NE</td>
<td>86 (89)</td>
<td>89–90 (300)</td>
</tr>
<tr>
<td>α -238A</td>
<td>3–27 (1179)</td>
<td>2–43 (855)</td>
<td>18 (133)</td>
<td>8 (92)</td>
<td>NE</td>
<td>2–43(^\dagger) (217)</td>
</tr>
<tr>
<td>α -238G</td>
<td>73–97 (1179)</td>
<td>57–98 (855)</td>
<td>82 (133)</td>
<td>92 (82)</td>
<td>NE</td>
<td>57–98 (217)</td>
</tr>
<tr>
<td>β -B1'</td>
<td>32 (121)</td>
<td>25–94 (193)</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>β -B2'</td>
<td>68 (121)</td>
<td>6–75 (193)</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>β +252A</td>
<td>44–62 (251)</td>
<td>42–63 (183)</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>β +252G</td>
<td>38–56 (251)</td>
<td>37–58 (183)</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
</tbody>
</table>

Data are reported moving along longitude from West to East. The total number of tested subjects and the range of association between polymorphisms and disease are reported for each allele in every populations. Numbers are rounded off. \(^a\)Phenotype frequency. \(^b\)Caucasian patients. \(^c\)Iranian Azeri Turkish patients. \(^\dagger\)P < 0.05; \(^\ddagger\)P < 0.01; \(^\ddagger\)P < 0.001: positive association with BD. (n): in round brackets number of tested subjects; %: frequency ratio; NR: not reported; NE: not evaluated.
population genetics are required to shed more light on this concept.

**Rheumatology key messages**

- A core component of genetic susceptibility to BD lies within the MHC region.
- Genes harboured in haplotype with HLA-B*51 may play a role in BD susceptibility.
- BD geographical distribution may be consequential to an evolutionary selection of genetic susceptibility factors.

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