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Genetics of Behçet's Disease

Ayca Kocaaga

Abstract

Behçet's disease (BD; MIM 109650) is an autoinflammatory disease characterized by with recurrent oral aphthae, genital ulcers and vasculitis involving the skin, joints, eyes, veins, arteries, nervous and gastrointestinal systems. Although the pathogenesis remains uncertain, genome-wide and validation studies have demonstrated that genetic predisposition is a major factor in disease susceptibility. Several gene polymorphisms that are involved in the response to pathogens and modulate inflammation have been associated with the pathophysiology of BD. Understanding the genetic association with BD may ensure insight into the pathogenesis and for development of targeted therapies for this autoinflammatory disease. This chapter will deal the role of genetic and epigenetic factors as contributing factors in the pathogenesis of BD.

Keywords: autoinflammation, Behçet's disease, epigenetics, genetics, pathogenesis

1. Introduction

Behçet's disease (BD; MIM 109650) is an autoinflammatory disease characterized by with recurrent oral aphthae, genital ulcers and vasculitis involving the skin, joints, eyes, veins, arteries, nervous and gastrointestinal systems [1]. BD is diagnosed worldwide, although its highest prevalence coincides with the countries stretching from Japan to the Mediterranean region along the ancient trading route "Silk Route". Among the affected countries, the prevalence of BD varies between Western (0.12–7.5 per 100,000) and Eastern countries (6.3–14 per 100,000) [2]. The prevalence of BD is the highest in Turkey (80–420 cases per 100,000) [3]. Although the pathogenesis remains uncertain, it is thought that both genetic and environmental factors contribute to the onset and progression of the BD [4]. The first reported susceptibility genetic region for BD was found in the human leukocyte antigen (HLA) region, or the major histocompatibility complex (MHC) on chromosome [5]. HLA-B51 antigen was recognized as the strongest evidence of a BD genetic background [6]. Multiple other putative genes outside the HLA region have also been identified.

2. HLA and HLA-related genes

2.1 HLA

The MHC, also known in humans as the human leukocyte antigen (HLA) region encodes several molecules that play key roles in the immune system [7]. A strong

association was established between the HLA regions and autoimmune disorders. Among them, HLA-B51 has been shown to be the strongest risk allele for BD in multiple studies and in different ethnic populations [6, 8–11]. Several other HLA class I and class II alleles including HLA-A26, HLA-B15, HLA-B5701, HLA-B2702, HLA-B3901, HLA-B52, HLA-B56, HLA-DRB104, and HLA-DRB107 have been also associated with BD in different populations [12–15]. The several HLA alleles including HLA-A03, -B15, -B35, -B49, -B58 were reported BD-protective [1, 16, 17]. In addition to susceptibility, HLA alleles were also associated with reflect clinical outcomes of BD. The HLA-A26:01 was associated with poor visual prognosis and high incidence of posterior uveitis in previous studies [15, 18]. There were significant associations found between clinical manifestations of BD and some HLA alleles such as HLA-A26:01 with uveitis, HLA-A*02:07 with skin lesions and arthritis, and HLA-A*30:04 with vascular lesions, genital ulcers, and positive pathergy test [17]. These findings indicate that HLA alleles may be associated clinical manifestations and prognosis and the specific HLA alleles are can be used as genetic markers for diagnostic or prognostic classification of BD patients.

2.2 CIITA

The HLA class II transactivator gene (CIITA), encodes an important transcription factor that regulates the MHC class II genes, IL-4, IL-10 and other immune-mediating genes [19]. CIITA is implicated in various autoimmune and autoinflammatory diseases [20]. In a recent study of a Chinese Han population, the GG genotype and G allele of the CIITA gene (rs12932187) were correlated with risk factor for BD, and the GG carriers had a higher expression of the CIITA gene [21].

2.3 ERAP1

Endoplasmic reticulum aminopeptidase 1 (ERAP1) is an essential enzyme to optimizing the length of peptides to bind with MHC-class I molecules by trimming their N-terminal in the ER [22]. The association between ERAP1 and BD was first reported in a Turkish population. The rs10050860 and rs17482078 SNPs of the ERAP1 gene were found to confer risk to BD in Turkish population [23]. Zhang et al. reported the rs1065407 and rs10050860 polymorphisms might be associated with increased risk of BD in a Chinese cohort [24]. Sousa et al. studied in an Iranian cohort and reported that rs10050860 and rs13154629 of ERAP1 might contribute to the genetic susceptibility of BD [25]. A functional study indicated that the expression of ERAP1 was found to be significantly lower in active BD patients. The patients carrying AA genotype of rs1065407 and CC genotype of the rs10050860, respectively, were found a higher expression level of the ERAP1 gene than the patients carrying AC or CC and CT or TT genotypes of the SNPs, respectively, in response to lipopolysaccharide stimulation [24, 26].

2.4 MICA

The major histocompatibility complex class I chain related gene A (MICA) is a gene that functions in immune activation under cellular stress conditions, such as infections, tissue injury, pro-inflammatory signals, and malignant transformation [27]. MICA*009 and *019 alleles were found strongly associated with BD in a Spanish population [28]. The MICA-A6 allele has been reported to increase the risk of BD in

Japanese and Korean populations. In a recent study, the MICA*049 allele was found to be significantly higher in BD patients than in controls in a Chinese cohort [29]. On the other hand, Eyerici et al. reported the MICA*006 (MICA-A6) and MICA*009 alleles were associated with BD susceptibility in the HLA-B*51 positive Turkish population. [30]. MICA-A5.1 was indicated a negative correlation with ocular lesions and iridocyclitis in BD patients [31].

3. Interleukin (IL) family genes

3.1 IL-1 gene family

IL-1 gene family is composed of IL-1 α , IL-1 β , and IL-1Ra [32]. Interleukin-1 α and -1 β , are pleiotropic cytokines with primarily proinflammatory effects, which induce acute phase responses, activate endothelial cells, and lead to expression of adhesion molecules and coagulation factors [33]. IL-1Ra acts as an antagonist of IL-1 by blocking the IL-1 receptor [34]. Previous studies have shown that the IL-1 α (-889) C allele is significantly associated with BD risk [35, 36]. Alayli et al. also reported that the frequency of IL-1 β (-511) CC genotype is significantly higher in BD patients compared to controls [35]. In another study showed that IL-1Ra mspa11 1100 CT and IL-1Ra mspa11 1100 TT promoter polymorphisms could be confer susceptibility to BD in Turkish population [37]. Barış et al. found IL-1RN2 gene polymorphism was correlated with the presence of articular involvement and the IL-1 β gene polymorphism was correlated with the presence of an ocular lesion [38].

3.2 IL-4

Interleukin-4 (IL-4) is a key cytokine secreted by Th2 lymphocytes. It has cytotoxic, anti-tumor effects, inhibits induction of nitric oxide synthase, and also has role in chemotaxis, formation of endothelial cell adhesion molecules and hematopoiesis [39]. IL-4 gene 70 bp VNTR polymorphism was first reported to be associated with BD in the Turkey. The P1 allele of the IL-4 gene 70 bp VNTR polymorphism was found to constitute a risk for developing BD in a Turkish population. In the same study, P2P2 genotype was associated deep venous thrombosis and ocular involvement in the BD patients [40]. The IL-4 -1098 G, IL-4 -590 T alleles and IL-4 TTC haplotypes were showed more common in the patients with BD when compared with healthy controls in an another Turkish cohort. They also demonstrated that IL-4R α (+1902) gene polymorphism was associated with the Pathergy test positivity in BD patients [41].

3.3 IL-10

IL-10 is an anti-inflammatory cytokine, which is secreted by T lymphocytes (mainly Th2 subsets), B lymphocytes, NK cells, monocytes, and macrophages, plays critical roles in modulating immune response and preventing inflammatory and autoimmune pathologies [42]. IL-10 may inhibit the antigen-presenting process by downregulating the expression of HLA molecules on the surface of a cell and suppressing the expression of multiple proinflammatory cytokines, such as TNF- α , IL-1, IL-6, and IL-8 [43]. The first reported SNP of the IL10 gene was rs1800871 that found to be an association with BD in the UK and Middle Eastern cohorts [44].

The -1082A > G (rs1800896), -819 T > C (rs1800871), and -592A > C (rs1800872) SNPs of IL-10 gene were found to be association with BD susceptibility in different populations including Chinese, Japanese, Korean and Iranian [45–48].

3.4 IL-12A, IL12B and IL-12RB2/ IL-23R

IL-12A is a gene which encodes for IL-35 that is a subunit of the heterodimeric cytokines IL-12 (encoded by IL-12B) and IL-35 [49]. It binds to a heterodimeric IL-12 receptor (IL-12R) which consists of IL-12R β 1 (encoded by IL-12 RB1) and IL-12R β 2 (encoded by IL-12RB2) [50]. IL-12A gene variants (rs1780546 and rs17810458) were revealed to be associated with BD susceptibility in a Turkish cohort [23]. In a study with a Chinese cohort rs3212227/IL-12B genotype CC and C allele was found involved in the susceptibility to BD [51]. IL-23 is a member of the IL-12 cytokine family that plays important roles in the development process of the Th17 cells [52, 53]. The IL-23 receptor consists of two subunits encoded by the IL-23R and IL-12RB1 genes [54]. A meta-analysis of the association data (including a total of 2430 BD cases and 2660 controls) provided strong evidence for associations of the IL23R/IL12RB2 loci with BD [55]. The IL-23R/IL-12RB2 genes were associated with BD, in multiple reports with different populations including Japanese, Chinese, and Korean [56–58].

3.5 IL-17 and IL-18

IL-17 is a pleiotropic inflammatory cytokine that plays a pivotal role in a variety of pathologic conditions by inducing numerous inflammatory molecules and the recruitment of neutrophils [59]. This cytokine is produced by CD + T helper, hematopoietic cells, Th17 cells and neutrophils and consists of a family of cytokines from IL-17A to IL-17F [60]. Jang et al. reported the allele and genotype frequencies of A126G SNP of IL-17 were significant differences between BD and controls [61]. The another genetic study in a Korean population, the IL17A rs8193036C > T variant was associated with the risk of intestinal BD [62]. In another study, the IL-17A gene rs2275913 polymorphism has been showed it might be associated with intestinal involvement in patients with BD [63]. IL-18 is a proinflammatory cytokine that mediates T-helper (Th)-1-polarized immune responses. Lee et al. found that IL-18 – 607 C/A promoter polymorphism was significantly associated with BD and also age at disease onset [64]. IL-18 gene –607 promoter site polymorphism was associated with patients with BD in Egyptian patients. Moreover, they found GG genotype at position –137 had a higher risk of developing ocular manifestations in patients with BD [65].

3.6 IL-28 and IL-29

IL-29, IL-28A and IL-28B are subgroups of Type III IFNs known as IFN- λ s that induce activation of the Jak/STAT signaling pathway and modulating the Th1/Th2 response [66, 67]. The first relationship between IL-28 and IL-29 and BD was investigated in a study from Turkey. Genc et al. showed that the GG genotype of rs8099917 (IL28 G/T) might be a protective factor against BD. They also found a significant difference between patients with and without central nervous system (CNS) involvement in rs12979860 (IL28 C/T) polymorphism [68].

3.7 IL-33

IL-33 is a member of the IL-1 cytokine family that expressed by various types of immune cells such as mast cells, macrophages and dendritic cells, that drives production of Th2-associated cytokines [69, 70]. The rs7044343 and rs11792633 variants of IL-33 gene were associated with the decreased risk of BD in Turkish patients [71]. Talei et al. showed that a significantly higher prevalence of the IL-33 SNP rs1342326 T/G in BD patients. They showed also this genotype was also associated with increased IL-33 expression in patients with BD compared to healthy controls [72].

4. Genes involved in autoinflammation and autoimmunity

4.1 CCR1 and CCR3

C–C chemokine receptor type 1 (CCR1) and C–C chemokine receptor type 3 (CCR3) encode the chemokine receptor belonging to the G protein-coupled receptor super family. These receptors play an important role in the accumulation and activation of inflammatory cells [73, 74]. The rs7616215 SNP located in the CCR1-CCR3 locus was showed to be associated with BD in a Turkish population [25]. The CCR1 gene was associated to susceptibility with BD in multiple cohorts including Turkish, Japanese, and Iranian cohorts [23, 25]. Hou et al. reported that the CCR1-CCR3 (rs13084057 in the 3' UTR of CCR1; rs13075270 and rs13092160 in the intergenic region between CCR1 and CCR3) polymorphisms also associated with BD in a Chinese population [75].

4.2 FCRL3

The Fc receptor-like (FCRL) family is a recently recognized potential immunoregulatory cell surface molecule. FCRL3 is predominantly expressed in germinal centers of lymphoid organs and has been linked to B cell maturation [76]. FCRL3 may be involved in the mechanisms regulating Treg dysfunction, which may in turn contribute to the loss of self-tolerance and development of autoimmunity [77]. The -110 G allele and CGCG haplotype of FCRL3 were found to be associated with BD, while the ATCG haplotype was found to be protective for BD in a Chinese population [78]. In a study with Iranian BD patients, there was a significant difference demonstrated between groups at position -169 (rs7528684) of FCRL3 gene [79].

4.3 MEFV

The Mediterranean fever (MEFV) protein also named pyrin is an is an significant regulator of innate immunity and the inflammatory response to IL-1 β and IFN- γ . Some clinical findings and geographic distribution of FMF and BD seem to be similar [80]. Touitou et al. who first suggested a possible implication of MEFV mutations in BD, reported higher frequencies of four mutations such as M694V, V726A, E148Q, and L110P mutations [81]. The MEFV SNPs rs61752717 Met694Val, rs28940580 Met680Ile, and rs3743930 Glu148Gln were reported conferred risk to both of FMF and BD [80, 82–84].

4.4 IRF1 and IRF8

IRF-1 is originally identified to be a regulator of the interferon (IFN)- β gene family. It plays an important role in various biologic functions such as innate immunity to viral infection, lymphocyte development, macrophage cytotoxicity, induction of apoptosis and tumor suppression [85, 86]. A study by Lee et al. showed that a significant association between BD and IRF-1 gene polymorphisms (-415 C/A, -410 A/G, and -300 A/G, and 3'-untranslated region (UTR) A/G) [87]. Interferon Regulatory Factor (IRF) 8 is a transcription factor of a member of Interferon (IFN) Regulatory Factor (IRF) family that it regulates expression of type I IFN stimulated genes and the development and function of a variety of immune cells [88, 89]. The rs17445836 and rs11642873 polymorphisms of the IRF8 gene were associated with BD and these SNPs appeared to regulate IRF8 expression and cytokine production in a Chinese cohort [90]. The other SNPs (rs11117433, rs142105922 and rs7203487) of the IRF8 gene were reported BD-associated in multiple cohorts including Turkish, Iranian, and Japanese populations [91].

4.5 TNFAIP3

TNFAIP3 gene encodes A20 protein, which is a key regulator of the nuclear factor (NF)- κ B signaling pathway, toll-like receptor (TLR), interleukin 1 receptor (IL1R), and nucleotide-binding oligomerization domain containing 2 (NOD2) [92]. A genetic linked between the TNFAIP3 gene SNPs (rs9494885, rs10499194 and rs7753873) and BD was reported in Chinese BD patients [93].

4.6 Toll-like receptors

Toll-like receptor (TLR) proteins are a family receptors that recognize pathogen molecules and have a critical role in both innate and adaptive immune systems [94]. TLRs are thought to be one of the links between infection and autoinflammatory or autoimmune disease [95]. The TLR2 rs2289318 CC genotype and rs3804099 CT genotype were significantly associated with ocular BD in a Chinese population [96]. The associations of the TLR4 gene with BD have been found to be contradictory in different studies. It was not found an association between TLR4 gene polymorphisms and BD in Italian and Chinese patients [97, 98]. Horie et al. showed that the TAGCGGTAA haplotype of TLR4 gene was significantly associated with BD susceptibility and BD arthritis in a Korean cohort [99]. A Japanese study indicated that the TLR4 gene may confer susceptibility to BD [100]. Fernández et al. revealed the rs2407992 and the rs5744067 of TLR8 were associated with susceptibility to BD in Spanish patients [101]. An Asian study revealed a significant association between the TLR7 rs5743733 and rs3853839 and BD and it showed also an association of TLR9 rs352140 with BD [102].

4.7 GIMAP

The GIMAP (GTPase of the immune associated nucleotide binding protein) gene family have been suggested as being involved in different aspects of the immune system in different species. These events appear to be associated with cell regeneration and proliferation and apoptosis [103]. The SNPs in GIMAP1 (rs2286900), GIMAP2 (rs10266069 and rs10256482), and GIMAP4 (rs1916012, rs1522596, and rs1608157) were associated with BD in a study of Korean and Japanese populations, but they were not found to be associated in a study with European cohort [104].

4.8 NOD1 and NOD2

Nod-like receptors (NLRs) are a member of pattern-recognition receptor molecules (PRRs) can capable to sense several pathogens or endogenous danger signals [105]. In a Chinese study, the C allele (major) of the NOD1 SNP rs2075818 was associated with BD susceptibility [21]. In a recent study indicated that the CC genotype of rs2075818 (NOD1 G/C) increased the risk of BD by 3.780-fold and the AA genotype of rs2075820 (NOD1 G/A) was increased the risk of cardiovascular involvement in BD 4.286-fold. In addition, they did not find the NOD2 gene variants (R334Q and R334W) in nor the BD patients and neither control groups [106]. Multiple reports have demonstrated that a Crohn's disease-associated polymorphism, Arg702Trp of the NOD2 rs2066844 was protective to BD [107, 108].

5. Other genes

5.1 STAT4

Signal transducer and activator of transcription-4 (STAT4) is a transcription factor that activates gene expression involved in differentiation of naïve T cells into Th1 and Th17 cells, natural killer (NK) cells, mast cells, and dendritic cells [109–111]. The association between the BD and STAT4 gene appears to be consistent in many independent reports including Korean, Turkish, and Iranians [23, 25]. The functional studies have shown that risk allele A of STAT4 rs897200 correlates clinically with BD disease score due to increased mRNA level of STAT4 gene and expression of IL-17 [112].

5.2 FOXP3

FOXP3 is a key transcription factor in the development and function of T(reg) cells. Recent reports have shown the FOXP3 SNPs contribute to the susceptibility to some autoimmune and autoinflammatory disorders. The FOXP3 SNP rs3761548 (-3279 C/A) was significantly associated with BD in the Iranian patients [113]. The FOXP3 (-3279 C/A) A allele has been reported to be associated with neural involvement in BD in Egyptian patients [114]. A low copy number variant of the FOXP3 gene was shown to increase risk in female BD patients in a Chinese cohort [115].

5.3 FUT2

FUT3 (Fucosyltransferase) gene is responsible for the formation of histo-blood group antigens, it might affect the intestinal microbiota composition and modulate innate immune responses [116]. Recent studies indicated that the association between the FUT2 gene variants (rs632111, rs601338, rs602662, rs492602, rs681343, and rs281377) and BD was reported in Iranian and Turkish populations [117].

5.4 ACE and VEGF

The renin-angiotensin system (RAS) is important in vascular tone and inflammatory processes. It has been suggested that DD genotype of ACE gene I/D polymorphism might be a genetic marker for BD in Turkish populations [118, 119]. In the other hand, the ACE gene I/D polymorphism was not associated with BD patients in

a Iranian cohort and in another Turkish population [120, 121]. 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 [122, 123]. The carriers of the -634C (3'untranslated region UTR) and I (insertion/deletion) alleles of VEGF gene were associated with a susceptibility to BD in Italian patients [124].

5.5 UBAC2 and LACC1

Ubiquitin-associated domain containing 2 (UBAC2) encodes an ubiquitination-related structural domain that is implicated in ubiquitination and proteasomal degradation. The association of the UBAC2 gene polymorphisms (rs9513584, rs9517723, rs7999348) with BD were found in multiple cohorts found including Turkish, Chinese Han, Italian, and Japanese populations [125–128]. The LACC1 (Laccase domain-containing 1), also known as multicopper oxidoreductases, encodes an oxidoreductase that promotes fatty-acid oxidation. It known functions in activation of inflammasome, bactericidal activity of macrophages, and production of mitochondrial and NADPH-oxidase-dependent reactive oxygen species. SNP rs9316059 of the LACC1 was associated with BD in all the populations tested including Chinese Han, Turkish, Iranian and Japanese [91, 129].

5.6 SUMO4

Small ubiquitin-like modifier 4 (SUMO4) has been shown to have the potential to down-regulate NF-kappaB signal, leading to decreased transcription of pro-inflammatory cytokines [130, 131]. The association between the SUMO4 gene (rs237024 and rs237026) polymorphisms and BD was first reported in a Chinese cohort, and they showed the GGAC haplotype was protectively associated with BD in HLA-B51 positive patients [132]. The association was replicated in Tunisian and Korean cohorts for the rs237024 and rs237026 polymorphisms of SUMO4 gene. This study also showed this polymorphisms were associated with disease severity and also some clinical manifestations such as skin lesions, and vascular involvement [133, 134].

5.7 ROCK1 and ROCK2

The Rho-kinase (ROCK) family members, consisting of ROCK1 and ROCK2, play significant roles in the actin cytoskeleton organization and regulate a wide range of fundamental cellular functions, such as adhesion, migration, motility, cell proliferation, apoptosis, and multiple inflammatory responses [135, 136]. Oguz et al. showed the SNPs rs73963110, rs112130712, rs111874856, rs112108028 might increase the susceptibility to Behçet's disease, but they failed for the other SNPs such as rs35996865, rs111312709 and rs2271255 [137]. In addition, the ROCK2 gene rs35768389 (Asp601Val) polymorphism was showed to be associated with BD and the C allele was significantly higher in BD patients compared to controls [138].

5.8 VDR gene

The proven role of vitamin D in innate and adaptive immune responses has led to an increase in studies on the relationship between vitamin D and autoinflammatory diseases. The VDR gene encodes the VDR protein, a member of the nuclear receptor

superfamily, that is essential for the biological functions of vitamin D [139, 140]. Karray et al. found that the VDR gene (rs1544410 and rs2228570) polymorphism were associated with BD in Tunisian patients [141]. In a study with a Turkish cohort, the VDR gene rs1544410 A allele and rs2228570 C allele were reported to be a risk factor for BD susceptibility [142]. In a meta-analysis, the role of the four common VDR polymorphisms has been investigated and it was suggested that rs731236 polymorphism might be a risk factor for BD [143].

6. Epigenetic factors

Epigenetics is the study of stable and heritable changes in the function of genes which occur without altering the DNA sequence and include DNA methylation, histone modification, and microRNAs [144]. MicroRNAs (miRNAs) are short noncoding RNAs are crucial in regulating multiple cellular processes, such as development, proliferation and apoptosis [145]. Several miRNAs have been associated with the susceptibility of BD disease, which includes many different inflammatory pathways [146]. Zhou et al. revealed miR155 expression was significantly decreased in dendritic cells from patients with BD with active compared to inactive uveitis [147]. In addition, the many SNPs in miRNA have been showed to be a risk for BD in association studies. Both of the TT genotype and T allele of rs11614913 located at pre-miR196a2 were found had increased frequency in patients with BD [148]. The microRNA-146a rs2910164 was associated with decreased frequency of CC genotype and C allele in patients with BD, whereas GG genotype was significantly increased in an Egyptian cohort [149]. Also, TT genotypes and T allele of rs3746444 miRNA-499 exhibited a significantly higher risk in patients with BD in a study of Turkish population [150]. In a Spanish cohort, the relative promoter methylation level of the IL-6 mRNA was found significantly lower in BD patients compared to controls [151]. The variant in the pre-miRNA region of miR-196a2, rs11614913, was associated with BD susceptibility, as well as BD arthritis [148]. In an Epigenome-wide association study with Chinese BD patients, the genetic variants of 10 CpG-SNPs were not associated with BD susceptibility [152].

7. Conclusion

From a genetic perspective, several molecules involved in the response to pathogens and multiple genes that activate or regulate inflammation appear to be critical in the etiopathogenesis of BD. However, the precise pathogenic mechanisms of these genes on BD are still unclear. In addition, it is unknown how genetic components as well as other associated risk factors such as bacterial and viral pathogens affect the developmental process of BD. Genome-wide association studies (GWAS) have become a very important step in understanding BD pathogenesis. GWASs with satisfactory numbers of subjects in regions where BD is prevalent revealed a strong association between BD and inflammatory cytokines such as IL-1, IL-4, IL-6, IL-10, IL-17, and IL-23–IL-12RB2. Some association studies, for example TNFAIP3, TLRs and miRNAs, appear to be conflict in different study groups and/or populations. The conflicting results of these genes associated with BD suggest that they may be ethnically specific or have occurred due to sample selection bias. In the future, similar studies in different populations with a higher number of patients will provide

significant advances in the etiopathology of BD. We proposed that genetic factors located at loci outside the MHC region (IL1A-IL1R, IL10, CCR1-CCR3, ERAP1, IRF8, RIPK2, FUT2, IL-28, IL-29, NOD1, NOD2, VEGF and etc....) contributed to BD susceptibility by playing a role in host defense and immune responses to pathogens in inflammation pathways. Moreover, specific gene polymorphisms have been linked with clinical presentation of BD such as ocular lesions, neurological and intestinal and cardiovascular involvement. The future direction will guide possible therapeutic approaches by understanding the functional significance of BD-associated gene polymorphisms, as well as insights into the pathogenesis of the disease.

Author details

Ayca Kocaaga

Department of Medical Genetics, Eskisehir City Hospital, Eskisehir, Turkey

*Address all correspondence to: dr.aycacelikmakas@hotmail.com

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