Chapter

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, Eyerci 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-1α, IL-1β, and IL-1Ra [32]. Interleukin-1α and -1β, 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-1α (-889) C allele is significantly associated with BD risk [35, 36]. Alayli et al. also reported that the frequency of IL-1β (−511) CC genotype is significantly higher in BD patients compared to controls [35]. In another study showed that IL-1Ra mspa1l 1100 CT and IL-1Ra mspa1l 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-1β 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-4Rα (+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-12Rβ1 (encoded by IL-12 RB1) and IL-12Rβ2 (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-λs 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 30 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-1β 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)-κB 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 an 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

IntechOpen

References

[1] Tursen U et al. Pathological and immunological developments in Behcet's disease. Pathology Research International. 2012;**2012**:305780

[2] Ortiz-Fernández L, Sawalha AH. Genetics of Behçet's disease: Functional genetic analysis and estimating disease heritability. Front Med (Lausanne). 2021;**8**:625710

[3] Cakir N et al. Prevalence of Behçet's disease in rural western Turkey: A preliminary report. Clinical and Experimental Rheumatology. 2004;**22**(4 Suppl 34):S53-S55

[4] Zeidan MJ et al. Behçet's disease physiopathology: A contemporary review. Autoimmunity Highlights. 2016;**7**(1):4

[5] Takeuchi M, Kastner DL, Remmers EF. The immunogenetics of Behçet's disease: A comprehensive review. Journal of Autoimmunity. 2015;**64**:137-148

[6] Demirseren DD et al. HLA-B51 subtypes in Turkish patients with Behçet's disease and their correlation with clinical manifestations. Genetics and Molecular Research. 2014;**13**(3):4788-4796

[7] Wieczorek M et al. Major histocompatibility complex (MHC) class I and MHC class II proteins: Conformational plasticity in antigen presentation. Frontiers in Immunology. 2017;**8**:292

[8] Gough SC, Simmonds MJ. The HLA region and autoimmune disease: Associations and mechanisms of action. Current Genomics. 2007;**8**(7):453-465

[9] Salvarani C et al. Association of MICA alleles and HLA-B51 in Italian patients with Behçet's disease. The Journal of Rheumatology. 2001;**28**(8):1867-1870

[10] Paul M et al. Allelic distribution of HLA-B*5 in HLA-B5-positive Israeli patients with Behçet's disease. Tissue Antigens. 2001;**58**(3):185-186

[11] Mizuki N et al. Sequencing-based typing of HLA-B*51 alleles and the significant association of HLA-B*5101 and -B*5108 with Behçet's disease in Greek patients. Tissue Antigens. 2002;**59**(2):118-121

[12] Ortiz-Fernández L, Carmona FD, Montes-Cano MA, García-Lozano JR, Conde-Jaldón M, Ortego-Centeno N, et al. Genetic Analysis with the Immunochip Platform in Behçet Disease. Identification of Residues Associated in the HLA Class I Region and New Susceptibility Loci. PLoS One. 2016;**11**(8):e0161305

[13] Montes-Cano MA et al. HLA and non-HLA genes in Behçet's disease: A multicentric study in the Spanish population. Arthritis Research & Therapy. 2013;**15**(5):R145

[14] Pekiner FN et al. HLA-A, B (class I) and HLA-DR, DQ (class II) antigens in Turkish patients with recurrent aphthous ulceration and Behçet's disease. Medical Principles and Practice. 2013;**22**(5):464-468

[15] Kaburaki T et al. Genetic association of HLA-A*2601 with ocular Behçet's disease in Japanese patients. Clinical and Experimental Rheumatology. 2010; **28**(4 Suppl 60):S39-S44

[16] Ting JP, Trowsdale J. Genetic control of MHC class II expression. Cell. 2002;**109**(Suppl):S21-S33

[17] Kang EH et al. Associations between the HLA-A polymorphism and the clinical manifestations of Behcet's disease. Arthritis Research & Therapy. 2011;**13**(2):R49

[18] Kang EH et al. Genetic and non-genetic factors affecting the visual outcome of ocular Behcet's disease. Human Immunology. 2013;**74**(10):1363-1367

[19] León Machado JA, Steimle V. The MHC Class II Transactivator CIITA: Not (Quite) the Odd-One-Out Anymore among NLR Proteins. International Journal of Molecular Science. 2021;**22**(3)

[20] Nakamura MC. CIITA: A master regulator of adaptive immunity shows its innate side in the bone. Journal of Bone and Mineral Research. 2014;**29**(2):287-289

[21] Li L et al. Genetic variations of NLR family genes in Behcet's disease. Scientific Reports. 2016;**6**:20098

[22] Li L, Batliwala M, Bouvier M. ERAP1 enzyme-mediated trimming and structural analyses of MHC I-bound precursor peptides yield novel insights into antigen processing and presentation. The Journal of Biological Chemistry. 2019;**294**(49):18534-18544

[23] Kirino Y et al. Genome-wide association analysis identifies new susceptibility loci for Behçet's disease and epistasis between HLA-B*51 and ERAP1. Nature Genetics. 2013;**45**(2):202-207

[24] Zhang L et al. Association of ERAP1 gene polymorphisms with Behçet's disease in Han Chinese. Investigative Ophthalmology & Visual Science. 2015;**56**(10):6029-6035

[25] Sousa I et al. Brief report: Association of CCR1, KLRC4, IL12A-AS1, STAT4, and ERAP1 With Behçet's disease in Iranians. Arthritis & Rhematology. 2015;**67**(10):2742-2748

[26] Conde-Jaldón M, Montes-Cano MA, García-Lozano JR, Ortiz-Fernández L, Ortego-Centeno N, González-León R, et al. Epistatic interaction of ERAP1 and HLA-B in Behçet disease: A replication study in the Spanish population. PLoS One. 2014;**9**(7):e102100

[27] Baranwal AK, Mehra NK. Major histocompatibility complex class I chain-related a (MICA) molecules: Relevance in solid organ transplantation. Frontiers in Immunology. 2017;**8**:182

[28] Muñoz-Saá I et al. Allelic diversity and affinity variants of MICA are imbalanced in Spanish patients with Behçet's disease. Scandinavian Journal of Immunology. 2006;**64**(1):77-82

[29] Zhu W et al. MICA*049, not MICA*009, is associated with Behçet's disease in a Chinese population. Scientific Reports. 2019;**9**(1):10856

[30] Eyerci N et al. Association of MICA alleles and human leukocyte antigen B in Turkish patients diagnosed with Behçet's disease. Archives of Rheumatology. 2018;**33**(3):352-357

[31] Wallace GR et al. IL-10 genotype analysis in patients with Behçet's disease. Human Immunology. 2007;**68**(2):122-127

[32] Migliorini P et al. The IL-1 family cytokines and receptors in autoimmune diseases. Autoimmunity Reviews. 2020;**19**(9):102617

[33] Zarrouk-Mahjoub S et al. Pro- and anti-inflammatory cytokines in post-infarction left ventricular remodeling. International Journal of Cardiology. 2016;**221**:632-636

[34] Dayer JM, Oliviero F, Punzi L. A brief history of IL-1 and IL-1 Ra in

rheumatology. Frontiers in Pharmacology. 2017;**8**:293

[35] Alayli G et al. T helper 1 type cytokines polymorphisms: Association with susceptibility to Behçet's disease. Clinical Rheumatology. 2007;**26**(8):1299-1305

[36] Akman A et al. Relationship between periodontal findings and specific polymorphisms of interleukin-1alpha and -1beta in Turkish patients with Behçet's disease. Archives of Dermatological Research. 2008;**300**(1):19-26

[37] Zou J, Guan JL. Interleukin-1-related genes polymorphisms in Turkish patients with Behçet disease: A meta-analysis. Modern Rheumatology. 2014;**24**(2):321-326

[38] Barış S et al. The impact of the IL-1β, IL-1Ra, IL-2, IL-6 and IL-10 gene polymorphisms on the development of Behcet's disease and their association with the phenotype. Medicina Clínica (Barcelona). 2016;**146**(9):379-383

[39] Mitchell RE et al. IL-4 enhances IL-10 production in Th1 cells: Implications for Th1 and Th2 regulation. Scientific Reports. 2017;**7**(1):11315

[40] Inanir A et al. Association of IL-4 gene VNTR variant with deep venous thrombosis in Behçet's disease and its effect on ocular involvement. Molecular Vision. 2013;**19**:675-683

[41] Oral HB et al. Interleukin-4 gene polymorphisms confer Behçet's disease in Turkish population. Scandinavian Journal of Immunology. 2011;**73**(6):594-601

[42] Iyer SS, Cheng G. Role of interleukin 10 transcriptional regulation in inflammation and autoimmune disease. Critical Reviews in Immunology. 2012;**32**(1):23-63

[43] Trifunović J et al. Pathologic patterns of interleukin 10 expression—A review. Biochem Med (Zagreb). 2015;**25**(1):36-48

[44] Akdis M, Burgler S, Crameri R, Eiwegger T, Fujita H, Gomez E, et al. Interleukins, from 1 to 37, and interferon-γ: receptors, functions, and roles in diseases. Journal of Allergy and Clinical Immunology. 2011;**127**(3):701-21.e1-70

[45] Chang JT, Shevach EM, Segal BM. Regulation of interleukin (IL)-12 receptor beta2 subunit expression by endogenous IL-12: A critical step in the differentiation of pathogenic autoreactive T cells. The Journal of Experimental Medicine. 1999;**189**(6):969-978

[46] Kappen JH et al. Genome-wide association study in an admixed case series reveals IL12A as a new candidate in Behçet disease. PLoS One. 2015;**10**(3):e0119085

[47] Afkari B et al. Molecular analysis of interleukin-10 gene polymorphisms in patients with Behçet's disease. Immunology Letters. 2018;**194**:56-61

[48] Yu H et al. Identification of susceptibility SNPs in IL10 and IL23R-IL12RB2 for Behçet's disease in Han Chinese. The Journal of Allergy and Clinical Immunology. 2017;**139**(2):621-627

[49] Jones LL et al. Distinct subunit pairing criteria within the heterodimeric IL-12 cytokine family. Molecular Immunology. 2012;**51**(2):234-244

[50] van de Vosse E et al. IL-12Rβ1 deficiency: Mutation update and description of the IL12RB1 variation database. Human Mutation. 2013;**34**(10):1329-1339

[51] Li X et al. Genetic variations of IL-12B, IL-12Rβ1, IL-12Rβ2 in Behcet's

disease and VKH syndrome. PLoS One. 2014;**9**(5):e98373

[52] Tang C et al. Interleukin-23: As a drug target for autoimmune inflammatory diseases. Immunology. 2012;**135**(2):112-124

[53] Yang J et al. Targeting Th17 cells in autoimmune diseases. Trends in Pharmacological Sciences. 2014;**35**(10): 493-500

[54] Parham C et al. A receptor for the heterodimeric cytokine IL-23 is composed of IL-12Rbeta1 and a novel cytokine receptor subunit, IL-23R. Journal of Immunology. 2002;**168**(11):5699-5708

[55] Remmers EF et al. Genome-wide association study identifies variants in the MHC class I, IL10, and IL23R-IL12RB2 regions associated with Behçet's disease. Nature Genetics. 2010;**42**(8):698-702

[56] Mizuki N et al. Genome-wide association studies identify IL23R-IL12RB2 and IL10 as Behçet's disease susceptibility loci. Nature Genetics. 2010;**42**(8):703-706

[57] Qin X et al. Association study of rs924080 and rs11209032 polymorphisms of IL23R-IL12RB2 in a Northern Chinese Han population with Behcet's disease. Human Immunology. 2016;**77**(12):1284-1290

[58] Kang EH et al. Behçet's disease risk association fine-mapped on the IL23R-IL12RB2 intergenic region in Koreans. Arthritis Research & Therapy. 2017;**19**(1):227

[59] Monin L, Gaffen SL. Interleukin 17 Family Cytokines: Signaling Mechanisms, Biological Activities, and Therapeutic Implications. Cold Spring Harb Perspect Biol. 2018;**10**(4).

[60] Kuwabara T et al. The role of IL-17 and related cytokines in inflammatory autoimmune diseases. Mediators of Inflammation. 2017;**2017**:3908061

[61] Jang WC et al. Interleukin-17F gene polymorphisms in Korean patients with Behçet's disease. Rheumatology International. 2008;**29**(2):173-178

[62] Kim ES et al. Interactions between IL17A, IL23R, and STAT4 polymorphisms confer susceptibility to intestinal Behcet's disease in Korean population. Life Sciences. 2012;**90**(19-20):740-746

[63] Nakamura K et al. Interleukin-17A gene polymorphism with the susceptibility of intestinal symptoms in patients with Behçet's disease. The Journal of Dermatology. 2016;**43**(6):708-709

[64] Lee YJ et al. Interleukin-18 promoter polymorphisms in patients with Behçet's disease. Human Immunology. 2006;**67**(10):812-818

[65] Hazzaa HH, Rashwan WA, Attia EA. IL-18 gene polymorphisms in aphthous stomatitis vs. Behçet's disease in a cohort of Egyptian patients. Journal of Oral Pathology & Medicine. 2014;**43**(10):746-753

[66] Chyuan IT, Tzeng HT, Chen JY. Signaling Pathways of Type I and Type III Interferons and Targeted Therapies in Systemic Lupus Erythematosus. Cells. 2019;**8**(9)

[67] Goel RR, Kotenko SV, Kaplan MJ. Interferon lambda in inflammation and autoimmune rheumatic diseases. Nature Reviews Rheumatology. 2021;**17**(6):349-362

[68] Cakmak Genc G, Karakas Celık S, Kocaaga A, Koca R, Dursun A. Association Between IL28B, IL29 Gene Polymorphisms and Clinical

Manifestations of Behçet's Disease. Immunol Invest. 2021;**50**(8):906-913

[69] Chan BCL et al. IL33: Roles in allergic inflammation and therapeutic perspectives. Frontiers in Immunology. 2019;**10**:364

[70] Liew FY, Girard JP, Turnquist HR. Interleukin-33 in health and disease. Nature Reviews Immunology. 2016; **16**(11):676-689

[71] Koca SS et al. Serum IL-33 level and IL-33 gene polymorphisms in Behçet's disease. Rheumatology International. 2015;**35**(3):471-477

[72] Talei M et al. Interleukin-33 gene expression and rs1342326 polymorphism in Behçet's disease. Immunology Letters. 2019;**212**:120-124

[73] Elemam NM, Hannawi S, Maghazachi AA. Role of chemokines and chemokine receptors in rheumatoid arthritis. ImmunoTargets and Therapy. 2020;**9**:43-56

[74] Chang TT, Chen JW. The Role of Chemokines and Chemokine Receptors in Diabetic Nephropathy. Int J Mol Sci. 2020;**21**(9)

[75] Hou S et al. Two-stage association study in Chinese Han identifies two independent associations in CCR1/ CCR3 locus as candidate for Behçet's disease susceptibility. Human Genetics. 2012;**131**(12):1841-1850

[76] Swainson LA et al. Expression of the autoimmune susceptibility gene FcRL3 on human regulatory T cells is associated with dysfunction and high levels of programmed cell death-1. Journal of Immunology. 2010;**184**(7):3639-3647

[77] Sakaguchi S et al. Regulatory T cells and immune tolerance. Cell. 2008;**133**(5):775-787

[78] Li K et al. Association between polymorphisms of FCRL3, a non-HLA gene, and Behçet's disease in a Chinese population with ophthalmic manifestations. Molecular Vision. 2008;**14**:2136-2142

[79] Shahram F et al. Single nucleotide polymorphisms of FCRL3 in Iranian patients with Behcet's disease. Iranian Journal of Public Health. 2019;**48**(6):1133-1139

[80] Wu Z, Zhang S, Li J, Chen S, Li P, Sun F, et al. Association between MEFV Mutations M694V and M680I and Behçet's Disease: A Meta-Analysis. PLoS One. 2015;**10**(7):e0132704

[81] Touitou I et al. MEFV mutations in Behçet's disease. Human Mutation. 2000;**16**(3):271-272

[82] Kirino Y et al. Targeted resequencing implicates the familial Mediterranean fever gene MEFV and the toll-like receptor 4 gene TLR4 in Behçet disease. Proceedings of the National Academy of Sciences of the United States of America. 2013;**110**(20):8134-8139

[83] Esmaeili M et al. Common MEFV mutations in Iranian Azeri Turkish patients with Behçet's disease. Scandinavian Journal of Rheumatology. 2011;**40**(5):383-386

[84] Tasliyurt T et al. Common MEFV gene mutations in Turkish patients with Behcet's disease. Gene. 2013;**530**(1):100-103

[85] Wietzke-Braun P et al. Interferon regulatory factor-1 promoter polymorphism and the outcome of hepatitis C virus infection. European Journal of Gastroenterology & Hepatology. 2006;**18**(9):991-997

[86] Yang Y et al. Association study between the IL4, IL13, IRF1 and UGRP1

genes in chromosomal 5q31 region and Chinese Graves' disease. Journal of Human Genetics. 2005;**50**(11):574-582

[87] Lee YJ et al. Associations between interferon regulatory factor-1 polymorphisms and Behçet's disease. Human Immunology. 2007;**68**(9):770-778

[88] Holtschke T et al. Immunodeficiency and chronic myelogenous leukemia-like syndrome in mice with a targeted mutation of the ICSBP gene. Cell. 1996;**87**(2):307-317

[89] Ouyang X et al. Transcription factor IRF8 directs a silencing programme for TH17 cell differentiation. Nature Communications. 2011;**2**:314

[90] Jiang Y et al. Two genetic variations in the IRF8 region are associated with Behçet's disease in Han Chinese. Scientific Reports. 2016;**6**:19651

[91] Takeuchi M et al. Dense genotyping of immune-related loci implicates host responses to microbial exposure in Behçet's disease susceptibility. Nature Genetics. 2017;**49**(3):438-443

[92] Boone DL et al. The ubiquitin-modifying enzyme A20 is required for termination of Toll-like receptor responses. Nature Immunology. 2004;**5**(10):1052-1060

[93] Li H et al. TNFAIP3 gene polymorphisms confer risk for Behcet's disease in a Chinese Han population. Human Genetics. 2013;**132**(3):293-300

[94] Akira S, Takeda K, Kaisho T. Toll-like receptors: Critical proteins linking innate and acquired immunity. Nature Immunology. 2001;**2**(8):675-680

[95] Medzhitov R, Preston-Hurlburt P, Janeway CA Jr. A human homologue of the Drosophila Toll protein signals activation of adaptive immunity. Nature. 1997;**388**(6640):394-397

[96] Fang J et al. Association of TLR2 gene polymorphisms with ocular Behcet's disease in a Chinese Han population. Investigative Ophthalmology & Visual Science. 2013;**54**(13):8384-8392

[97] Boiardi L et al. Toll-like receptor 4 (TLR4) gene polymorphisms in Italian patients with Behçet's disease. Clinical and Experimental Rheumatology. 2009;**27**(2 Suppl 53):S43-S47

[98] Du L et al. No association of CTLA-4 polymorphisms with susceptibility to Behçet disease. The British Journal of Ophthalmology. 2009;**93**(10):1378-1381

[99] Horie Y et al. Association of TLR4 polymorphisms with Behcet's disease in a Korean population. Rheumatology (Oxford). 2009;**48**(6):638-642

[100] Meguro A et al. Association of the toll-like receptor 4 gene polymorphisms with Behcet's disease. Annals of the Rheumatic Diseases. 2008;**67**(5):725-727

[101] Ortiz-Fernández L et al. Association of haplotypes of the TLR8 locus with susceptibility to Crohn's and Behçet's diseases. Clinical and Experimental Rheumatology. 2015;**33**(6 Suppl 94): S117-S122

[102] Song GG et al. Toll-like receptor polymorphisms and vasculitis susceptibility: Meta-analysis and systematic review. Molecular Biology Reports. 2013;**40**(2):1315-1323

[103] Hellquist A et al. The human GIMAP5 gene has a common polyadenylation polymorphism increasing risk to systemic lupus erythematosus. Journal of Medical Genetics. 2007;**44**(5):314-321

[104] Ortiz-Fernández L et al. GIMAP and Behçet disease: No association in the European population. Annals of the Rheumatic Diseases. 2014;**73**(7):1433-1434

[105] Strober W et al. Signalling pathways and molecular interactions of NOD1 and NOD2. Nature Reviews Immunology. 2006;**6**(1):9-20

[106] Kocaaga A, Cakmak Genc G, Karakas Celık S, Koca R, Dursun A. Association of NOD1, NOD2, PYDC1 and PYDC2 genes with Behcet's disease susceptibility and clinical manifestations. Ophthalmic Genet. 2021:1-7

[107] Kappen JH et al. Low prevalence of NOD2 SNPs in Behçet's disease suggests protective association in Caucasians. Rheumatology (Oxford). 2009;**48**(11):1375-1377

[108] Burillo-Sanz S et al. Mutational profile of rare variants in inflammasome-related genes in Behçet disease: A next generation sequencing approach. Scientific Reports. 2017;**7**(1):8453

[109] Kim J et al. Imbalance of Th17 to Th1 cells in Behçet's disease. Clinical and Experimental Rheumatology. 2010; **28**(4 Suppl 60):S16-S19

[110] Watford WT et al. Signaling by IL-12 and IL-23 and the immunoregulatory roles of STAT4. Immunological Reviews. 2004;**202**: 139-156

[111] Morinobu A et al. STAT4 serine phosphorylation is critical for IL-12-induced IFN-gamma production but not for cell proliferation. Proceedings of the National Academy of Sciences of the United States of America. 2002;**99**(19):12281-12286

[112] Hou S et al. Identification of a susceptibility locus in STAT4 for Behçet's disease in Han Chinese in a genome-wide association study. Arthritis and Rheumatism. 2012;**64**(12):4104-4113

[113] Hosseini A et al. A single nucleotide polymorphism in the FOXP3 gene associated with Behçet's disease in an Iranian population. Clinical Laboratory. 2015;**61**(12):1897-1903

[114] Abdelmoktader A, Bassyoun RH, Wegdan AA, Talaat RM, Bassyouni IM. Genetic Association of Promoter FOXP3 Gene Polymorphism with Behcet's Disease in Egyptians Patients. Virology & Immunology Journal; 2018;**2**(2):000147

[115] Liao D et al. Copy number variants and genetic polymorphisms in TBX21, GATA3, Rorc, Foxp3 and susceptibility to Behcet's disease and Vogt-Koyanagi-Harada syndrome. Scientific Reports. 2015;**5**:9511

[116] Ferrer-Admetlla A et al. A natural history of FUT2 polymorphism in humans. Molecular Biology and Evolution. 2009;**26**(9):1993-2003

[117] Xavier JM et al. FUT2: Filling the gap between genes and environment in Behçet's disease? Annals of the Rheumatic Diseases. 2015;**74**(3):618-624

[118] Yigit S et al. DD genotype of ACE gene I/D polymorphism is associated with Behcet disease in a Turkish population. Molecular Biology Reports. 2013;**40**(1):365-368

[119] Turgut S et al. Angiotensin-converting enzyme I/D polymorphism in Behçet's disease. Medical Principles and Practice. 2005;**14**(4):213-216

[120] Jabbarpoor Bonyadi MH, Yaseri M, Soheilian M. Tumor necrosis factor (TNF)-308, –1031, and angiotensin-converting enzyme (ACE) DD/II polymorphisms' role in Behcet's

disease with and without uveitis: A meta-analysis. Ophthalmic Genetics. 2020;**41**(3):235-239

[121] Dursun A et al. Angiotensin-converting enzyme gene and endothelial nitric oxide synthase gene polymorphisms in Behçet's disease with or without ocular involvement. Inflammation Research. 2009;**58**(7):401-405

[122] Takahashi H, Shibuya M. The vascular endothelial growth factor (VEGF)/VEGF receptor system and its role under physiological and pathological conditions. Clinical Science (London, England). 2005;**109**(3):227-241

[123] Ferrara N. Vascular endothelial growth factor: Basic science and clinical progress. Endocrine Reviews. 2004;**25**(4):581-611

[124] Salvarani C et al. Vascular endothelial growth factor gene polymorphisms in Behçet's disease. The Journal of Rheumatology. 2004;**31**(9):1785-1789

[125] Fei Y et al. Identification of novel genetic susceptibility loci for Behçet's disease using a genome-wide association study. Arthritis Research & Therapy. 2009;**11**(3):R66

[126] Sawalha AH et al. A putative functional variant within the UBAC2 gene is associated with increased risk of Behçet's disease. Arthritis and Rheumatism. 2011;**63**(11):3607-3612

[127] Hou S et al. Replication study confirms the association between UBAC2 and Behçet's disease in two independent Chinese sets of patients and controls. Arthritis Research & Therapy. 2012;**14**(2):R70

[128] Yamazoe K et al. Comprehensive analysis of the association between UBAC2 polymorphisms and Behçet's disease in a Japanese population. Scientific Reports. 2017;**7**(1):742

[129] Wu P et al. Association of LACC1, CEBPB-PTPN1, RIPK2 and ADO-EGR2 with ocular Behcet's disease in a Chinese Han population. The British Journal of Ophthalmology. 2018;**102**(9):1308-1314

[130] Rallabhandi P et al. Sumoylation of topoisomerase I is involved in its partitioning between nucleoli and nucleoplasm and its clearing from nucleoli in response to camptothecin. The Journal of Biological Chemistry. 2002;**277**(42):40020-40026

[131] Guo D et al. A functional variant of SUMO4, a new I kappa B alpha modifier, is associated with type 1 diabetes. Nature Genetics. 2004;**36**(8):837-841

[132] Hou S et al. SUMO4 gene polymorphisms in Chinese Han patients with Behcet's disease. Clinical Immunology. 2008;**129**(1):170-175

[133] Kamoun M et al. Association of small ubiquitin-like modifier 4 (SUMO4) polymorphisms in a Tunisian population with Behçet's disease. Clinical and Experimental Rheumatology. 2010; **28**(4 Suppl 60):S45-S49

[134] Park G et al. SUMO4 C438T polymorphism is associated with papulopustular skin lesion in Korean patients with Behçet's disease. Rheumatology International. 2012;**32**(10):3031-3037

[135] Amano M, Nakayama M, Kaibuchi K. Rho-kinase/ROCK: A key regulator of the cytoskeleton and cell polarity. Cytoskeleton (Hoboken). 2010;**67**(9):545-554

[136] Yao L et al. The role of RhoA/Rho kinase pathway in endothelial dysfunction. Journal of Cardiovascular Disease Research. 2010;**1**(4):165-170

[137] Oguz E et al. Association of Rho-kinase 1 (ROCK1) gene polymorphisms with Behçet's disease. Molecular Diagnosis & Therapy. 2014;**18**(4):419-426

[138] Oguz E et al. Association between Rho-kinase (ROCK2) gene polymorphisms and Behçet's disease. Translational Research. 2012;**160**(6):428-434

[139] Kaleta B et al. Vitamin D receptor gene BsmI polymorphism in polish patients with systemic lupus erythematosus. ISRN Endocrinology. 2013;**2013**:427818

[140] Joshi S et al. 1,25-dihydroxyvitamin D(3) ameliorates Th17 autoimmunity via transcriptional modulation of interleukin-17A. Molecular and Cellular Biology. 2011;**31**(17):3653-3669

[141] Karray EF et al. Associations of vitamin D receptor gene polymorphisms FokI and BsmI with susceptibility to rheumatoid arthritis and Behçet's disease in Tunisians. Joint, Bone, Spine. 2012;**79**(2):144-148

[142] Dal NE et al. The role of vitamin D receptor gene polymorphisms in the pathogenesis of Behçet's disease: A case-control study in Turkish population. Annals of Human Genetics. 2019;**83**(3):177-186

[143] Mirfeizi Z et al. Associations between vitamin D receptor polymorphisms and susceptibility to Behcet's disease: A meta-analysis. Immunological Investigations. 2018; **47**(4):389-402

[144] Renauer PA, Coit P, Sawalha AH. The DNA methylation signature of human TCRαβ+CD4-CD8- double negative T cells reveals CG demethylation and a unique epigenetic architecture permissive to a broad stimulatory immune response. Clinical Immunology. 2015;**156**(1):19-27

[145] Xu SJ, Hu HT, Li HL, Chang S. The Role of miRNAs in Immune Cell Development, Immune Cell Activation, and Tumor Immunity: With a Focus on Macrophages and Natural Killer Cells. Cells. 2019;**8**(10)

[146] Puccetti A et al. MicroRNA expression profiling in Behçet's disease. Journal of Immunology Research. 2018;**2018**:2405150

[147] Zhou Q et al. Decreased microRNA-155 expression in ocular Behcet's disease but not in Vogt Koyanagi Harada syndrome. Investigative Ophthalmology & Visual Science. 2012;**53**(9):5665-5674

[148] Qi J et al. A functional variant of pre-miRNA-196a2 confers risk for Behcet's disease but not for Vogt-Koyanagi-Harada syndrome or AAU in ankylosing spondylitis. Human Genetics. 2013;**132**(12):1395-1404

[149] Ibrahim W et al. MicroRNA-146a expression and microRNA-146a rs2910164 polymorphism in Behcet's disease patients. Clinical Rheumatology. 2019;**38**(2):397-402

[150] Oner T et al. Association of Pre-miRNA-499 rs3746444 and Pre-miRNA-146a rs2910164 polymorphisms and susceptibility to Behcet's disease. Genetic Testing and Molecular Biomarkers. 2015;**19**(8):424-430

[151] Alipour S et al. Methylation status of interleukin-6 gene promoter in patients with Behçet's disease. Reumatologia Clinica (Engl Ed). 2020;**16**(3):229-234

[152] Huang Y et al. Different methylation of CpG-SNPs in Behcet's disease. BioMed Research International. 2019;**2019**:3489305