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Chapter

Genetics of Behçet's Disease

Xiaodong Zhou and Yan Deng

Abstract

Behçet's disease (BD) is a chronic refractory multi-system autoimmune disorder with a strong genetic component. Like many other human complex diseases, multiple genes with polymorphisms have been associated with BD. These genes encode proteins involved mainly in immune regulation and inflammation and some in transcriptional activation and post-translational modification. Understanding the genetic association of these genes with BD may provide insight into the pathogenesis and for development of new, targeted therapies for this human complex disease.

Keywords: Behçet's disease, genetic, HLA region, interleukin family, inflammation and autoimmunity, transcriptional activation

1. Introduction

Behçet's disease (BD) is a chronic inflammatory disorder with unclear etiology. It can affect a variety of organs characterized by refractory ulcers in genitals and mouth, uveitis, skin lesions, and manifestations in joints, gastrointestinal tract, kidneys, lungs, and cardiovascular and central nervous systems [1]. BD has distinctive geographical distribution, and it is found primarily in populations along the ancient Silk Route from the Mediterranean region transiting through Central Asia to East Asia [2]. The reported prevalence of BD varies between Western (0.12–7.5 per 100,000) [3] and Eastern countries (6.3–14 per 100,000) [4]. Turkey has the highest incidence of BD in general population (80–420 per 100,000) [5–7]. A family history of BD significantly increases the risk at a rate of 31.2% [8], which indicates a strong genetic contribution to the disease by comparing to general population. Men are more commonly affected in Middle Eastern countries, but that appears opposite in USA, Brazil, Israel, and Korea [9]. The first reported genetic association of BD was found in the human leukocyte antigen (HLA) region, or the major histocompatibility complex (MHC) on chromosome 6 [10]. HLA-B51 confers the strongest genetic risk to BD [11]. Multiple other genetic factors outside the HLA region have also been identified. The following are the categorized genes associated with BD reported from 1973 to January 2019.

2. HLA and HLA-related genes

2.1 HLA

HLA genes are among the most polymorphic genes in the human genome, and they are associated with almost all autoimmune diseases. HLA-B51 is the strongest risk allele for BD, which has been replicated in almost all studied populations [12–22]. The population attributable risk (PAR) of HLA-B5/B51 was estimated as 52.2% for BD

patients in Southern Europe, 49.9% in Middle East/North Africa, 44.4% in East Asia, and 31.7% in Northern Europe [23]. Other HLA alleles including BD-risk HLA-A02, -A24, -A26, -A31, -B27, -B57, and BD-protective HLA-A03, -B15, -B35, -B49, -B58 were reported in different populations [22, 24–29].

Certain HLA alleles were also associated with clinical outcomes of BD. BD patients carrying HLA-A26:01 have a poor visual prognosis in Japan [30] and a high incidence of posterior uveitis in Korea [31]. Some HLA alleles were associated with lesions of specific organs in the Korean and Japanese patients, such as HLA-A26:01 with uveitis, HLA-A02:07 with skin lesions and arthritis, and -A30:04 with vascular lesions, genital ulcers, and a positive pathergy test [32]. These findings suggest that specific HLA alleles are likely used as genetic markers for subclassification and/or prognostic evaluation of BD patients.

2.2 CIITA

The class II major histocompatibility complex transactivator (CIITA) is a transcriptional activator that acts as a master regulator of the HLA class II genes and some other immune-mediating genes [33, 34]. A single nucleotide polymorphism (SNP) of the CIITA gene rs12932187 with G allele and GG genotype appeared to be a risk factor to Chinese BD, and the GG carriers were correlated with a higher expression of the CIITA gene, and with a lower level of IL-10 protein from the peripheral blood mononuclear cells (PBMC) in response to lipopolysaccharide (LPS) [35].

2.3 ERAP1

Endoplasmic reticulum aminopeptidase 1 (ERAP1) is an essential enzyme to trim peptides in the ER for optimized binding by MHC class I molecules. The association between ERAP1 and BD was first reported in a Turkish population and was replicated in a Chinese cohort, in which the SNPs rs10050860 and rs17482078 of the ERAP1 gene encoding variants of amino acids Asp575Asn and Arg725Gln, respectively, conferred risk to BD [36, 37]. Further analysis of the association indicated that the ERAP1 variant Arg725Gln may interact with the HLA-B51 protein to confer susceptibility to BD [36, 38]. Moreover, the expression of ERAP1 was found to be significantly lower in active BD patients [37], and the patients carrying AA and CC genotype of the ERAP1 SNP rs1065407 and rs10050860, respectively, showed 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 LPS [37, 38].

2.4 MICA

The major histocompatibility complex class I chain-related gene A (MICA), located on the centromeric side of the HLA-B gene on chromosome 6, is highly polymorphic [39]. It functions in immune activation under cellular stress conditions, such as infections, tissue injury, pro-inflammatory signals, and malignant transformation [40]. There have been more than 100 MICA alleles identified according to its overall sequence variations. In addition, the codon 295 of the MICA gene has a tri-nucleotide microsatellite polymorphism (GCT)n that is designated as An (A4, A5, A6, A9) allele, and a five repetition of GCT may coexist with a guanosine insertion that is designated as A5.1 [41].

MICA*009 and *019 alleles were associated with BD in a Spanish population [42], and MICA-A6 allele with Japanese and Korean BD patients [43–45]. The latter appeared to be independent from the potential linkage disequilibrium (LD) effect of HLA-B51 according to the Korean study [45].

On the other hand, MICA-A5.1 demonstrated a negative correlation with ocular lesions and iridocyclitis in BD patients [45, 46]. MICA-A9 was associated with BD patients who had less severe complications including uveitis, thrombosis, and neurological and intestinal involvement [47].

3. Interleukin (IL) family genes

3.1 IL-10

IL-10 is a cytokine with anti-inflammatory properties, which plays critical roles in modulating immune response and preventing inflammatory and autoimmune pathologies [48, 49]. The SNP rs1800871 of the IL10 promoter region was first found in an association with BD in the UK and Middle Eastern (ME) cohorts [50]. The genome-wide association studies (GWAS) revealed multiple BD-associated SNPs (rs1518111, rs1554286, rs1800871, and rs1800872) of the IL-10 in Chinese, Turkey, Japanese, and Korean cohorts [51–53].

3.2 IL-12A, IL-23R, and IL-12RB2

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. IL-35 binds to a heterodimeric IL-12 receptor (IL-12R) that consists of IL-12Rβ1 (encoded by IL-12RB1) and IL-12Rβ2 (encoded by IL-12RB2) [54], and it impacts on activation of NK cells and polarization of the Th1 pathway through differentiation from naïve CD4+ T cells [55, 56]. The association of the IL-12A variants rs1780546 and rs17810458 with BD was found in the Turkish and European cohorts [36, 57].

IL-23 is a member of the IL-12 cytokine family. It plays crucial roles in the development process of the Th17 cells [58]. The receptor for IL-23 is composed of two subunits encoded by the IL-23R and the IL-12RB1 genes [59], and it plays a key role in neutrophil inflammation and in autoimmune diseases [60].

A significant association (reaching a GWAS p value) of the IL-23R gene with BD was found at the SNP rs11209026 (Gly149Arg) in Japanese, and at the SNP rs76418789 (Arg381Gln) in Turkish cohort [61]. The association between BD and the IL-23R/IL-12RB2 genes appeared to be consistent in multiple reports with different populations including Turkey [52], Japanese [53], Han Chinese [62, 63], Iranian [64], Western Algeria [65], and Korean [66].

3.3 IL-33

IL-33 is a member of the IL-1 family that drives production of Th2-associated cytokines [67]. A small Iranian cohort of BD patients showed a significantly higher prevalence of the IL-33 SNP rs1342326 T/G, and this genotype was also associated with higher IL-33 expression in the PBMC of the BD patients [68].

4. Genes involved in inflammation and autoimmunity

4.1 MEFV

The Mediterranean fever (MEFV) protein, also named pyrin is an important regulator of innate immunity [69]. Of noting, familial Mediterranean fever and BD share inflammatory nature and high prevalence in Middle Eastern and

Mediterranean populations. Genetically, the MEFV SNPs rs61752717 Met694Val, rs28940580 Met680Ile, and rs3743930 Glu148Gln confer risk to both diseases [61, 70–74]. Moreover, Met694Val and Met680Ile of the MEFV gene were also associated with greater responsiveness to bacterial products [72, 73].

4.2 IRF8

Interferon regulatory factor (IRF) 8 is a member of the interferon (IFN) regulatory factor (IRF) family, and it acts as a transcription factor to regulate the development and function of a variety of immune cells. In particular, it regulates expression of type I IFN stimulated genes [75], and interacts with the Th17 master transcription factor, ROR-γt to inhibit Th17 cell differentiation [76]. In a study with Chinese cohort, the IRF8 SNPs rs17445836 and rs11642873 were associated with BD, and they appeared to regulate IRF8 expression and corresponding cytokine production [77]. In another study with multiple cohorts including Turkish, Iranian, and Japanese patients, three other BD-associated SNPs (rs11117433, rs142105922 and rs7203487) of the IRF8 gene were reported [78].

4.3 TNFAIP3

TNF-α-induced protein 3 (TNFAIP3) is a ubiquitin-modifying enzyme A20 that regulates inflammation through NF-κB signaling pathway, and it can be induced by TNF, Toll-like receptors (TLRs), IL-1R, and NOD2 signaling [79–82]. The reports of genetic association between TNFAIP3 and BD appeared conflict in studies of Chinese and European populations. In the former, the TNFAIP3 SNPs (rs9494885, rs10499194 and rs7753873) were associated with BD [83], but were not replicated in the latter [84]. On the other hand, a Japanese study of familial BD indicated that a missense mutation C243Y in A20/TNFAIP3 was likely responsible for an increased production of some inflammatory cytokines by reduced suppression of NF-κB activation [85].

4.4 REL

The REL gene encodes for c-Rel, a member of the NF-κB family of transcription factors. It may play important roles in regulation of immune activity [86, 87]. A Chinese study indicated that the REL SNPs rs842647 may confer susceptibility to BD, and the allele C of this SNP was also associated with skin lesions in BD patients [88].

4.5 TLR2 and TLR4

Toll-like receptors (TLR) are transmembrane proteins that mediate innate immunity by recognizing pathogen molecules [89]. TLR2 and TLR4 are two members of the TLR, and they may transduce response to different types of pathogens (e.g., in macrophages, the former mainly for Gram-positive bacteria and the latter for Gram-negative). The TLR2 SNP rs2289318 (C allele and genotype CC) and rs3804099 (CT genotype) were associated with ocular BD in a Chinese cohort [90]. The associations of the TLR4 gene with BD are conflict in different reports. It was found in Japanese [91], Korea [92] and Turkish cohorts [66], but not in Italian [93], Tunisian [94], and Chinese cohorts [95]. Of note, two BD protective TLR4 variants identified in the Turkish cohort, p.Asp299Gly (rs4986790) and p.Thr399Ile (rs4986791) were associated with hyporesponsiveness to endotoxin [96].

4.6 NOD1 and NOD2

Nucleotide-binding oligomerization domain (NOD)-like receptors are intracellular proteins that regulate innate immune response. NOD1 and NOD2 proteins are two members of the NOD family, and they play important roles in initiating inflammation in response to microbial components [97, 98]. In a Chinese report, the minor allele (G) of the NOD1 SNP rs2075818 was protective from BD [35]. Multiple studies indicated that a Crohn's disease-associated polymorphism, Arg702Trp of the NOD2 rs2066844 was also protective from BD [61, 99, 100].

4.7 CCR1 and CCR3

CCR1 and CCR3 proteins are two C-C motif chemokine receptor (CCR) family members. They mediate signal transduction within cells in response to pathogens, and they are critical for the recruitment of effector immune cells to the site of inflammation, and for maintaining homeostasis of the immune system [101]. The CCR1 and 3 genes are clustered together on chromosome 3p. The Several SNPs at CCR1-CCR3 locus were associated with BD including rs7616215 in Turkish [40] and rs13084057, rs13092160 and rs13075270 in Chinese Cohorts [102]. In addition, the CCR1 gene was individually associated with BD in multiple cohorts including Turkish, Japanese, and Iranian cohorts [36, 103]. Functional studies indicated that CCR1 gene expression in primary human monocytes carrying the BD-risk allele was reduced along with a weaker activity of monocyte chemotaxis [36].

4.8 GIMAP

GTPase of the immunity-associated protein (GIMAP) family is a group of newly identified proteins. Although their functions are still poorly characterized, it is believed that they are lymphocyte signaling molecules, and they are also involved in survival and apoptosis of T cells and some other cell types [104, 105]. A GIMAP cluster including SNPs in GIMAP1 (rs2286900), GIMAP2 (rs10266069 and rs10256482), and GIMAP4 (rs1916012, rs1522596, and rs1608157) was associated with BD in a study of Korean and Japanese populations [106], but it failed in a replication study of European cohort [107].

4.9 KLRC4

Killer cell lectin-like receptor subfamily C, member 4 (KLRC4) is a member of NKG2 receptor family that regulates NK cell function. The association of the KLRC4 gene and BD was first suggested in the GWAS of Turkish and Japanese cohorts [36], and then replicated in the independent study of an Iranian cohort [103].

5. Genes involved in transcriptional activation of immune regulation

5.1 STAT4

Signal transducer and activator of transcription-4 (STAT4) is a transcription factor that activates gene expression involved in functional regulation and differentiation of T-helper cells, natural killer (NK) cells, mast cells, and dendritic cells [108]. It modulates differentiation of naïve T cells into Th1 and Th17 cells [56, 109, 110].

The association between the STAT4 gene and BD appeared to be consistent in multiple independent studies including Han Chinese [107], Korean, Turkish, and

Iranians [36, 103]. Functional studies indicated that the risk allele A of the STAT4 SNP rs897200 was correlated with the increased mRNA level of the STAT4 gene, and with the increased gene and protein expression of IL-17, as well as with BD patients who have a higher clinical severity score [111].

5.2 NCOA5

Nuclear receptor coactivator-5 (NCOA5) protein regulates nuclear receptor subfamily 1 group D member 2 (NR1D2) and estrogen receptor 1 and 2 (ESR1 and ESR2) [112, 113]. The NCOA5 gene SNP rs2903908 was associated with BD patients, especially those affected with genital ulceration and uveitis in the Finland and the Turkish cohorts [114].

5.3 FOXP3

FOXP3 (forkhead box P3), also known as scurfin, is a member of the FOX protein family of transcription factors. It regulates the development and function of T regulatory (Treg) cells [115, 116]. The FOXP3 SNP rs3761548 was associated with BD in the North-Western Iranian population [117]. In addition, a low copy number variant (CNV) of the FOXP3 gene was reported to confer risk to female BD patients in a Chinese cohort [118].

6. Other genes

6.1 PSORS1C1

Psoriasis susceptibility 1 candidate 1 (PSORS1C1) is poorly characterized in terms of its biological function. It is initially recognized as a susceptibility locus to psoriasis [119] and psoriatic arthritis [120]. Recent studies indicated that it is also a shared genetic factor, especially with SNP rs12525170, in other autoimmune diseases including systemic sclerosis [121], Crohn's disease [122], and BD [122]. Therefore, it may play important roles in the pathogenesis of autoimmunity [123, 124].

6.2 FUT2

Fucosyltransferase 2 (FUT2) is involved in synthesis of the H antigen, the precursor of the ABO-histo-blood group antigen in body fluids, and on the intestinal mucosa [125]. The association between the FUT2 gene (rs632111, rs601338, rs602662, rs492602, rs681343, and rs281377) and BD was reported in Iranian and Turkish populations [126].

6.3 UBAC2

Ubiquitin-associated domain containing 2 (UBAC2) is another poorly characterized protein, but its gene variants are strongly associated with BD. Limited studies suggest that it may function in protein localization in the endoplasmic reticulum [127]. The association of the UBAC2 gene with BD was found in Turkish, Chinese, Italian, and Japanese populations [128–131]. Functionally, the presence of BD-risk rs9517723 allele was correlated with an increased expression of the UBAC2 gene.

6.4 SUMO4

Small ubiquitin-like modifier 4 (SUMO4) is a member of the SUMO family that post-transcriptionally sumoylates the targeted proteins to regulate their subcellular localization and/or enhance their stability and activity [132]. It is involved in immune regulation by negatively controlling NFκB activity [133]. The genetic association between the SUMO4 (SNPs rs237024, rs237026) and BD was first reported in a Chinese cohort, and that appeared independent from HLA-B51 [134]. The association was replicated in Tunisian and Korean cohorts [135, 136], in which specific polymorphisms were also associated with disease severity, skin lesions, and vascular involvement of BD patients [135, 136].

6.5 LACC1

LACC1 encodes an oxidoreductase that promotes fatty-acid oxidation. It also functions in activation of inflammasome, bactericidal activity of macrophages, and production of mitochondrial and NADPH-oxidase-dependent reactive oxygen species [137]. SNP rs9316059 of the LACC1 was associated with BD in Turkish, Japanese, and Chinese cohorts [78, 138].

6.6 Loci at ADO-EGR2 and CEBPB-PTPN1

Two genetic loci between the ADO and the EGR2 genes and the CEBPB and the PTPN1 genes were associated with BD in the Turkish, Iranian, and Japanese cohorts [78]. The ADO encodes cysteamine (2-aminoethanethiol) dioxygenase that is involved in amino acid metabolism [139]. The EGR2 encodes early growth response protein 2 that is a transcription factor, and highly expressed in a population of migrating neural crest cells [140]. CEBPB encodes CCAAT/enhancer binding protein beta, a member of the CCAAT/enhancer binding protein family of basic leucine zipper transcription factors. It functions in controlling cell differentiation, proliferation, and inflammation [141]. The PTPN1 gene encodes protein tyrosine phosphatase, nonreceptor type 1 that functions as a key regulator of immune homeostasis by inhibiting T-cell receptor signaling and by selectively promoting type I interferon responses after activation of myeloid-cell pattern-recognition receptors [142].

It is worth noting that these BD-linked loci do not directly reflect the association of the corresponding genes, but may be suggestive for further investigation of these genes in terms of their genetic and functional importance to BD.

7. Conclusion

Multiple genes have been associated with BD, and many of them are involved in immune activation and regulation that may suggest their potential biological relevance to chronic inflammatory nature of BD. However, exact pathogenic mechanisms of BD on these genes are still unclear. Like many other immune-regulatory diseases, this multigenic feature of BD underlies complex pathogenesis. Some of the reported associations, for example, TNFAIP3 and TLR4, appeared to be conflict in different study cohorts and/or populations, which suggests that the BD-associated polymorphisms of the genes may be ethnic specific, or sample selection bias may have occurred and further verification may be warranted. In addition, some of the BD-associated genes, for example, HLA-B, ERAP1, MICA, and IL family, have also been reported in other immune-mediated diseases, which supports the shared

genetic effects among these diseases. Moreover, specific gene polymorphisms were associated with clinical presentation of BD, for example, HLA-A02:07 with skin lesions and arthritis, HLA-A*26:01 with uveitis, HLA-A*30:04 with vascular lesions and genital ulcers, MICA-A5.1 with ocular lesions, and MICA-A9 with neurological and intestinal involvement. Thus, these specific genotypes may be further explored as potential biomarkers for diagnostic or prognostic classification of BD patients.

While the genetic studies have supported multigenic contribution to susceptibility to BD, epigenetic alternations including DNA methylation, histone modifications, and microRNAs regulation have also been reported in BD [143]. Furthermore, there is appealing evidence indicating environmental factors, especially that microorganisms may trigger the disease [144]. Understanding the genetics of BD in conjunction with epigenetics and environmental triggers of BD will provide insights into pathogenesis of the disease and an opportunity to interrogate candidate genes in potential diagnostic and therapeutic applications.

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