EFFECT OF INTERLEUKIN-10 PATHWAY GENES AND DIET ON BEHCET'S DISEASE

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… to my father Mehmet ARPAZ

ABSTRACT

EFFECT OF INTERLEUKIN-10 PATHWAY GENES AND DIET ON BEHCET'S DISEASE

Behcet's disease (BD) is an inflammatory disease characterized by recurrent oral and genital aphthae with unknown etiology. The disease is most prevalent along the Silk Road populations. BD is a complex disease influenced by genetic and environmental factors. Identification of contribution of these factors to BD is an active research question.

The first aim of the thesis is to determine the biological pathways in the etiopathology of BD by a comprehensive literature review of published genetic research. The second aim of the thesis is to investigate the genetic changes and gene expression in IL-10, an anti-inflammatory pathway cytokine, and its primary receptor IL-10R1 in BD. The third aim of the thesis is to discover potential novel functional foods that can benefit patients with BD.

241 variants from 119 genes were identified to be associated with BD. Frequency distribution of the 241 variants among world populations was rather different. IL-10 was identified to be the most significantly associated with BD and differentiated high BD risk populations from the rest based on principal component analyses. Sequence analyses of IL-10 and IL-10R1 identified rs3024498 and rs9610 variants, respectively, in Turkish BD patients. Rs3024498 was not associated with BD risk; however, IL-10R1 rs9610 variant showed a marginally significant relationship with BD. IL-10 gene expression was 9.6 fold higher in BD compared to normal controls.

As an anti-inflammatory IL-10 pathway is identified to influence BD, novel food supplements with high anti-inflammatory ingredients need to be developed to benefit patients with BD.

ÖZET

İNTERLÖKİN-10 YOLAĞI GENLERİNİN VE DİYETİN BEHÇET HASTALIĞI'NA ETKİSİ

Behçet Hastalığı (BH) 1937 yılında Hulusi Behçet tarafından tanısı konan enflamatuvar bir hastalıktır. Hastalık ağız ve genital bölgede tekrarlayan aftlarla ortaya çıkar ve diğer organ ve sistemleri de etkiler. İpek Yolu üzerindeki ülkelerde daha çok görüldüğü için "İpek Yolu Hastalığı" da denilmektedir. En çok görüldüğü ülkeler sırasıyla Japonya, Kore, Çin, İran ve Türkiye'dir. Hastalığın nedeni tam olarak bilinmemekle birlikte genetik ve çevresel faktörlerin etkileşimine dayanan karmaşık bir hastalık olduğu kabul edilmektedir. Bu faktörler hastalığın aydınlatılmasında önemlidir.

Tezin ilk amacı, BH etyopatolojisinde yer alan biyolojik yolları yayınlanmış genetik çalışmalar ile tespit etmekti. Tezin ikinci amacı, IL-10 ve birincil reseptörü IL-10R1'deki genetik değişiklikleri ve gen ekspresyonunu araştırmaktı. Üçüncü amaç ise hastalar için anti-enflamatuar gıdaları bir araya getiren fonksiyonel gıda fikirleri ortaya koymaktı.

BH ile ilişkili olarak 119 genden 241 varyant tespit edildi. Bu 241 varyantın dünya popülasyonları arasındaki frekans dağılımı oldukça farklıydı. IL-10 geninin BH ile en anlamlı ilişkiye sahip olduğu ve ana bileşen analizlerine göre yüksek riskli Behçet popülasyonlarını diğerlerinden ayırt edebildiği tespit edildi. Türk Behçet hastalarında IL-10 ve IL-10R1'in dizi analizleri sırasıyla rs3024498 ve rs9610 varyantlarını tanımladı. Bu çalışmada IL-10 rs3024498 varyantı BH ile ilişkili değildi. Bununla birlikte, IL-10R1 rs9610 varyantı, BH ile çok az anlamlı bir ilişki gösterdi. Behçet hastalarında IL-10 gen ekspresyonu kontrollere göre 9,6 kat daha yüksekti.

Behçet hastalarına fayda sağlamak için, yüksek anti-enflamatuar içerikli yeni besin takviyelerinin geliştirilmesi gerekmektedir.

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CHAPTER 1

INTRODUCTION

1.1. Behcet's Disease

Behcet's disease is an inflammatory disease of unknown etiology which is mainly characterized by oral and genital ulcers, uveitis and skin lesions. It affects on vascular, gastrointestinal, and neurological systems also joints.[1]

Hulusi Behçet is a Turkish dermatologist, described three symptoms with oral and genital ulcerations and hypopyon uveitis in 1937.[2] However back in the 1930's Greek Benediktos Adamantiades recognized similar clinical features. Even so he did not classify them as a new disease.[3]

Even going back as early as the 5th century BC the father of medicine Hippocrates in fact mentioned patients with clinical features which we may call today as BD. But Hulusi Behçet was the first international recognized doctor to classify is a new disease in the literature.[1]

1.2. Epidemiology

BD is mostly seen along the Silk Road which is an ancient trading route between the Mediterranean and East Asia.[4]

The highest prevalence is seen in Japan, Korea, China, Iran and Turkey. However, because of immigration, the prevalence has increased in the other parts of the world. The represented prevelances are in Germany 4.2, in France 7.2, and in the US 8.6 per 100 000 inhabitants. Besides that, BD has the highest prevalence in Turkey from 80 to 420, and in Iran from 80 to 100, in Japan 13.5, in China 14 per 100 000 inhabitants.[5-6] Distribution of the highest cases of BD in Turkey is shown in Figure 1.1.

The age of onset is 20-40 in adulthood and is rarely seen in childhood. The ratio of women and men is almost the same.[7]

In different studies conducted in Turkey, it has been shown that early age and male sex are associated with more severe disease course. Although mostly seen in women in Korea, a more severe disease course is observed in males.[8]

Figure 1.1. Distribution of the highest cases of BD in Turkey

1.3. Pathogenesis

The etiology of BD is still obscure; however, it seems to be a complex disease based on the interaction between the genetic background and the environment.[9]

As a genetic background, BD has MHC class I associations. HLA-B51 is the most strongly associated known genetic factor to BD. However, even in familial cases, it accounts for less than 20% of the genetic risk, indicating that other genetic factors continue to be discovered.[10]

In recent years, there have been intense opinions about the efficacy of infectious agents as an environmental factor in triggering and developing the disease. Herpes simplex type I virus, some streptococcus strains (*S. pyogenes, S. oralis, S. sanguis, S. faecalis, S. salivarus*), hepatitis A, B, C, E viruses, *Helicobacter pylori*, parvovirus B19, borelia burgdorgferi, mycobacteria are some of the most prominent infectious agents. The common feature of these infectious agents is the similarity of their antigenic structures. Although infectious agents have been shown to be histopathologically and statistically involved in the pathogenesis of BD, none of these infectious agents have been isolated and proven to be the cause of BD. The general view today is that BD is

not a direct disease caused by infection. However, it may be due to immune dysregulation caused by viral or bacterial antigens.[8, 11]

1.4. Clinic

Clinical manifestations are oral aphtha, genital aphthae, skin lesions, pathergy test, ocular, musculoskeletal system, central nervous system, vascular lesions, gastrointestinal system.[12-13]

1.4.1. Oral Aphtha

Oral aphtha is the most frequent symptom. It is found in almost every patient. Aphthae are often the first symptom of the disease. BD begins with aphthous ulcers with recurrence in the oral mucosa in 99% of cases. Aphthae can usually repeat once or several times a month. It is frequently seen in the buccal mucosa, tongue, gum, and soft palate.[13]

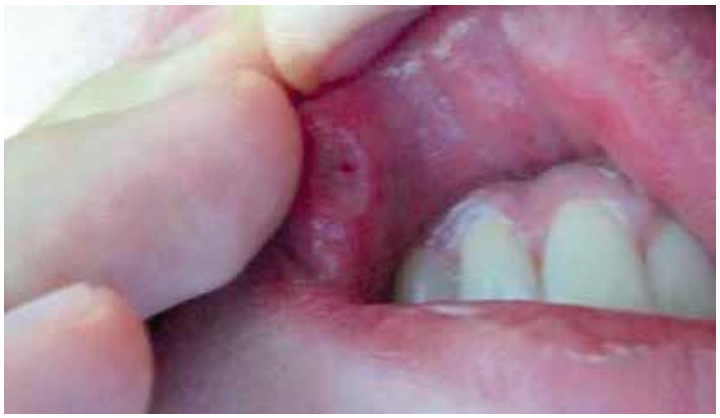

Figure 1.2. Oral aphtha (Source: Wozniacka et al.[4])

1.4.2. Genital Aphthae

Genital aphthae are seen in 60-90% of cases and are a very frequent symptom of BD. They are localized in men on the scrotum, less frequently on the penis or in the

urethra and in women on the vulva and vagina where they can be extensive and painful.[14]

They are morphologically similar to oral ulcers, but are usually larger and deeper, heal with scarring and wounds are specific to BD. [2, 8]

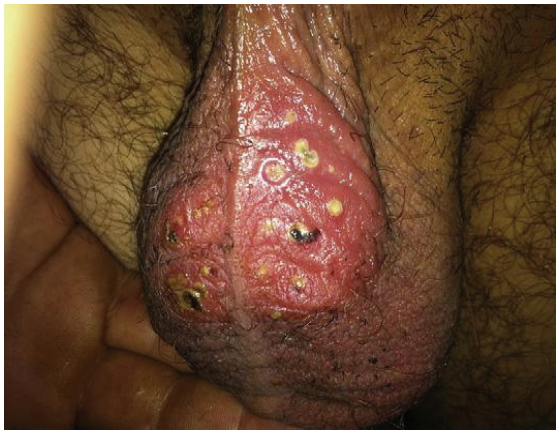

Figure 1.3. Genital apthea (Source: Hatemi et al.[15])

1.4.3. Skin Lesions

The most common skin manifestations are pseudofoliculitis and erythema nodosum-like lesions. Unlike acne vulgaris, pseudopholliculitis and acneiform nodules can occur all over the body and are not always associated with hair follicle.[2]

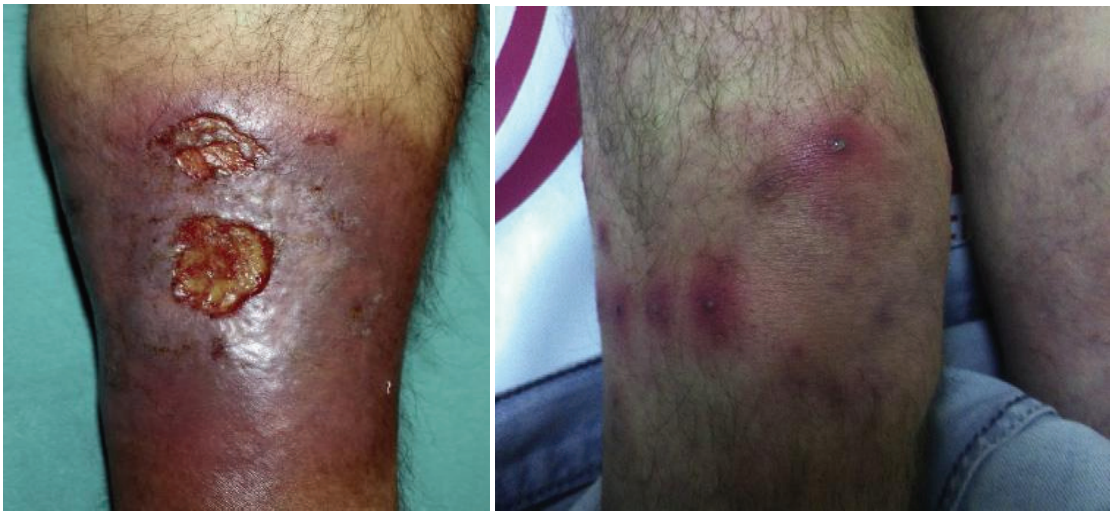

Figure 1.4. Deep wound on the leg (Sources: Hatemi et al. and Mat et al.[15-16])

1.4.4. Pathergy Test

Another important finding of Behcet's disease is the pathergy phenomenon. A positive pathergy test is considered to be the only diagnostic test currently available for BD. It is an important component of many of the 16 classification criteria used to diagnose BD.[4]

It is applied to the hairless area of forearm skin. Twenty gauge needles are placed obliquely along the dermis. After 48 hours, the development of papules and pustules is considered a positive result, are shown in Figure 1.5.

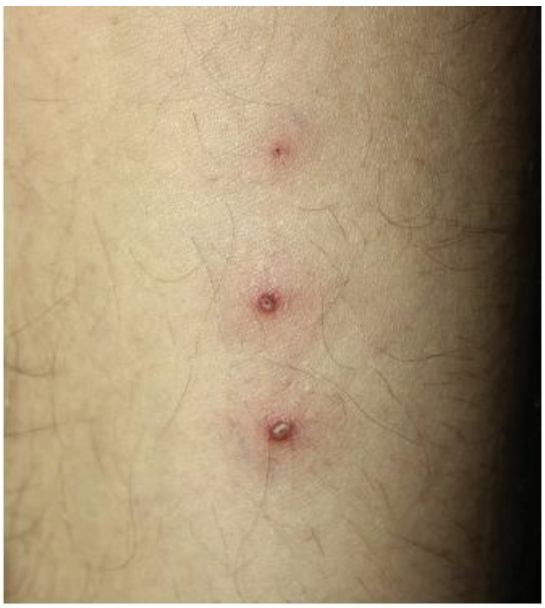

Figure 1.5. Pathergy phenomenon (Sources: Mat et al.[16])

The rate and intensity of pathergy positivity in young male Behçet's patients can be high.[16] Pathergy positivity is observed around 60% of Turkish and Middle East cases and in 44% of Japanese cases, but it is not seen as frequently in the cases living in England and America.[13]

1.4.5. Ocular

Ocular disease is the first symptom in approximately 20% of cases. It can be seen in 28-80% of all patients with BD.[4] Male patients are more likely to develop eye

disease at younger ages and have a higher risk of visual loss in long-term follow-up. Eye involvement in BD includes a broad spectrum of symptoms. In most cases, ocular symptoms follow oral and genital ulcers by 3-4 years.[17]

1.4.6. Musculoskeletal System

Arthritis and arthralgias are seen in half of the patients as a joint involvement and are common in male patients. These arthritis attacks typically resolve spontaneously within a few weeks. The knees are the most commonly affected joints, followed by the ankle, wrist, elbow, and hip.[18]

Patients with Behçet's disease and arthritis also have more acne lesions. Fibromyalgia may be associated with Behçet's disease, especially in female patients. Local and generalized myositis is rare in Behçet's disease. Another rare manifestation is aseptic necrosis of the bones.[16]

1.4.7. Vascular Lesions

Vascular involvement is important because of severe morbidity and increased mortality. Vasculitis of small and large vessels may cause various symptoms depending on the location of the lesions. The arterial disease mainly affects males and rarely occurs in women.[4] Studies performed in the last years confirmed that chronic and multisystemic vasculitis play a key role in BD pathogenesis. It was confirmed by elevated serum levels of several cytokines, such as IL-1, IL-4, IL-6, and TNF-α, which are responsible for the inflammatory reaction.[19]

1.4.8. Central Nervous System

It is usually found in male patients at early ages and in 10-20% of cases. Meningitis, meningoencephalitis, cranial nerve palsies and neurologic symptoms can be seen. Stressful life and psychiatric problems both increase exacerbations and facilitate the development of other symptoms. [8]

1.4.9. Gastrointestinal System

Gastrointestinal involvement in BD can be seen in all regions from the mouth to the anus. Gastrointestinal involvement is most frequently observed in ileocecal region and colon. The incidence rate is different in different countries. While gastrointestinal involvement occurs in 50-60% of Japanese and 38-50% of British patients, it is seen rarely (0-5%) in Turkey, Saudi Arabia, and Lebanon.[20]

1.5. Other Manifestations

Psychiatric changes and depression can be observed in at least 50% of cases, especially during active periods.[13] BD patients can also have neurologic problems such as fatigue, sleep disorder, anxiety, depression and severe headache which further reduce the quality of life in these patients.[21] Pregnancy does not significantly change the activity of the disease.[22] Pulmonary, cardiac and renal involvement is relatively rare.[4] Mortality is more common in young male patients. Major vasculature problems, neurological involvement, and pulmonary artery aneurysm are the causes of death.[23]

1.6. Diagnosis

There is no definitive method for the diagnosis of BD but it is more clinically diagnosed. One of them is The International Study Group (ISG) criteria for BD which is created in 1990. The recurrent oral ulceration is mandatory, and two of, genital ulcerations, ocular disease, skin lesions, and a positive pathergy test are necessary to classify a patient as having BD.[24]

On the other hand as a result of the weaknesses of the ISG criteria, The International Criteria for Behcet's Disease (ICBD) were presented to the International Conference of Behcet's Disease in Lisbon (Portugal) in 2006.[25] Newly formed criteria included oral aphthosis, genital aphthosis, ocular lesions (anterior uveitis, posterior uveitis, or retinal vasculitis), neurological symptoms, skin lesions (pseudofolliculitis, skin aphthosis, erythema nodosum), and vascular symptoms (arterial thrombosis, large vein thrombosis, phlebitis or superficial phlebitis). While 2 points were given to each of the oral aphthae, genital aphthous and ocular lesions, 1 point was given to each of the

skin lesions, vascular findings and neurological symptoms. A patient who scored 4 points or more was classified as having BD (Table 1.1.).[26]

Table 1.1. International Criteria for Behcet's Disease – point score system: scoring ≥ 4 indicates Behcet's diagnosis

Sign/Symptom	Points
Oral aphthosis	2
Genital aphthosis	2
Ocular lesions	2
Skin lesions	1
Neurological symptoms	1
Vascular symptoms	1
Positive pathergy test	1*

* The Pathergy test is optional and the primary scoring system does not include the pathergy test. However, when a pathergy test is performed, an additional score can be assigned for a positive result.

1.7. Treatment

BD is a condition that typically runs a relapsing and remitting course, and the aim of treatment is to immediately suppress inflammatory exacerbations and recurrences to prevent irreversible organ damage. Immunosuppressives are usually necessary to succeed this. Treatment should be individualized according to age, gender, type and severity of organ involvement and patients' preferences. In patients with BD, skin, mucosa and joint involvement can cause impairment of quality of life but do not cause permanent damage whereas untreated eye, vascular, nervous system and gastrointestinal system involvement can cause serious damage and even death.[27]

1.8. Genetics

The widespread distribution in a particular geographical region, the close association with HLA-B51 in different ethnic groups, and the familial aggregation of BD are strong signs in the genetic background of BD.[28]

1.8.1. Geoepidemiology

Although widespread environmental factors are thought to contribute to BD, it is believed that the development of the disease occurs only in genetically predetermined hosts. The broad disease prevalence observed between different geographical regions is probably the result of differences in both the environment and genetics. Differences in disease prevalence among recent migrants represent a role of the environment compared to those living in their own country, while the prevalence of disease among individuals of different ancestors in the same region reflects the genetic role in disease predisposition.[6]

1.8.2. Familial Aggregation

BD does not have a Mendelian inheritance pattern and usually occurs sporadically. Familial aggregation and a higher prevalence in siblings and parents, and monozygotic twins concordant of BD patients have been observed.[17]

Familial aggregation of BD varies among populations. In Turks 18.2%, Koreans 15.4%, and Jews 13.2% familial aggregation is higher than in the Chinese 2.6%, Japanese 2.2%, and various European populations 0-4.5%.[6]

1.8.3. MHC Region

Major histocompatibility complex (MHC) molecules or human leukocyte antigens (HLA) are the cell surface molecules responsible for antigen presentation and activation of T cells and also that help the immune system recognize foreign substances.[29]

1.8.3.1. HLA-B51

Analysis of the Japanese population in 1973 was the first evidence of BD associated with human leukocyte antigen (HLA) class I (HL-A5) in major histocompatibility complex (MHC). The risk allele was later renamed as HLA-B51.[30]

HLA-B51 is the strongest association finding with BD, and it has been repeated in several different ethnic groups.[31] A meta-analysis study shows that the contribution of HLA-B51 varies from 32% to 52% according to geographical area.[32]

In a Genome-wide association studies (GWAS) conducted in Turkey, 1215 BD patients, and 1278 healthy controls, HLA-B51 variant was found in 59.1% in the BD patients and 29.3% in the control group, thus a strong relationship was demonstrated between HLA-B51 and BD.[33]

1.8.3.2. Other MHC Class I Genes

A study in Turkey evaluated the relationship of HLA class type I with BD and the control group and found that the HLA-B51, -B15, -B27 regions were associated with the risk of developing BD; whereas the HLA-A03 and -B49 regions are associated with a protective role against disease.[34]

The MHC Class I gene-related gene (MICA) is often thought to be one of the candidate genes for the susceptibility towards BD.[35] In the meta-analysis, it was found that the MICA-transmembrane (TM) A6 allele was associated with a susceptibility to disease development among European and Asian populations, whereas MICA-0009 was associated with only the European population, and that MICA alleles are in strong linkage disequilibrium (LD) with HLA-B51 in BD.[36] In another meta-analysis of the MICA-A6 allele, the MICA-A6 allele was more frequently observed in BD than in the control group, especially in Asians and Caucasians. It is also suggested that it may serve as an early diagnostic marker.[37]

1.8.3.3. HLA Association with Disease Manifestations

Studies have reported an association between MHC class I alleles and some clinical manifestations of the disease.[38]

A meta-analysis reported a moderate correlation between HLA-B51/B5 with the male gender, the high prevalence of eye involvement, skin involvement, genital ulcers, and low prevalence of gastrointestinal involvement. This analysis was only found in studies conducted in Asia and Europe, but not the Middle East or North Africa.[39]

Another study reported that in Korean BD patients there is a relationship between HLA-B51 and early-onset uveitis, and high prevalence of the development of posterior uveitis with HLA-A26.[40] On the other hand, another study reported that HLA-A2601 was associated with eye involvement in BD independently of HLA-B5101 and that HLA-A2601 might be a possible predictor of poor visual prognosis in Japanese BD patients.[41]

HLA-A02:07, -A26:01 and -A30:04 were associated with skin lesions and arthritis, with uveitis, and with vascular lesions, genital ulcers, and a positive pathergy test, respectively, by a meta-analysis of the Korean and Japanese populations.[42]

1.8.3.4. Non-MHC Complex Genes

GWAS revealed a significant association between the interleukin (IL)-23R-IL12RB2, IL-10, signal transducer and activator of transcription 4 (STAT-4), chemokine C-C motif receptor 1 and 3 (CCR1-CCR3), killer cell lectin-like receptor K4 (KLRC4), endoplasmic reticulum aminopeptidase 1 (ERAP1), tumor necrosis alpha-induced protein 3 (TNFAIP3), fucosyltransferase 2 (FUT2), the class II major histocompatibility complex transactivator (CIITA), interferon regulatory factor 8 (IRF8), REL, NOD1, GTPase of the immunity-associated protein 1,2,4 (GIMAP1,2,4), nuclear receptor coactivator-5 (NCOA5), forkhead box P3 (FOXP3), psoriasis susceptibility 1 candidate 1 (PSORS1C1), ubiquitin-associated domain containing 2 (UBAC2), small ubiquitin-like modifier 4 (SUMO4), ADO-EGR2, CEBPB-PTPN1, and JRKL/CNTN5 loci and BD. Several GWAS studies in Turkish patients reported that IL-10, IL23R-IL12RB2, CCR1, KLRC4, IL-12A, STAT4, ERAP1, MEF4, NOD2, TLR4, FUT2 were disease susceptibility loci.[43-46]

The genes identified are involved in both innate and adaptive immunity and support the idea that polarization in the Th1 / Th17 pathway plays a critical role in the pathogenesis of BD.[6]

Biological pathways that these genes are functioning is shown in Figure 1.6. MHC/ HLA region is responsible for recognizing the environmental factors such as pathogens and foods. Typically the HLA-B51 gene triggers inflammation. There are several inflammatory pathways involved here. IL-10 is the only anti-inflammatory pathway that can block the initiation of the inflammation.

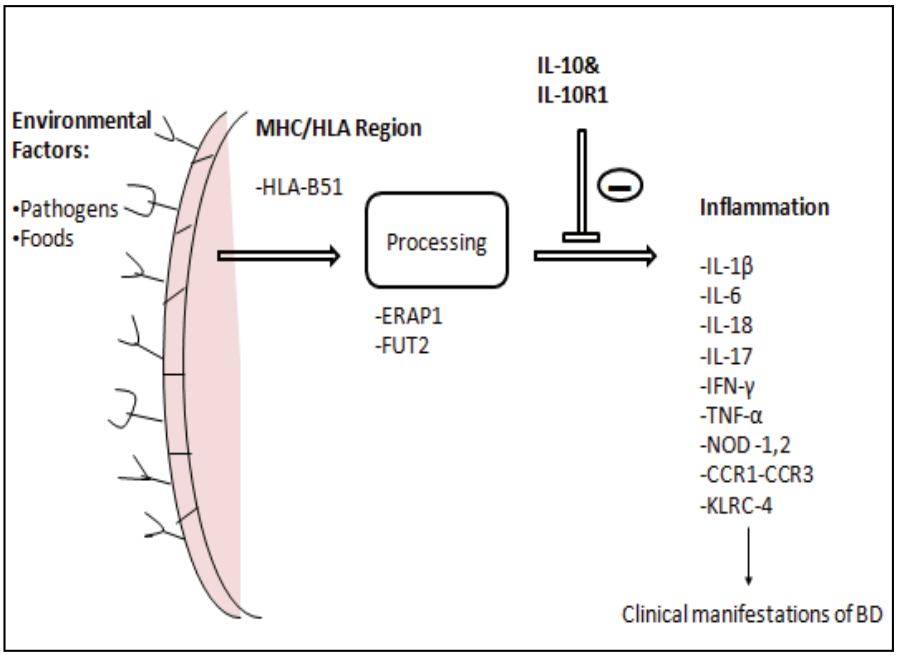

Figure 1.6. Biological pathways of various genes

1.8.4. Cytokines

Cytokines are low molecular weight polypeptides involved in cell communication and function in a number of different immunological mechanisms.[47] Cytokines are involved in almost in all areas of immunity and inflammation; in fact, numerous cytokines have both pro-inflammatory and anti-inflammatory potential.[48] Pro-inflammatory cytokines are IL-1β, IL-6, TNF-α, and IL-17.[49-50] The major anti-inflammatory cytokines are the IL-1 receptor antagonist, IL-4, IL-10, and IL-13.[49] Cytokines play critical roles in the pathogenesis of BD, which were mainly investigated in sera, biologic fluid (e.g., plasma, synovial fluid), or cell supernatants of cultured peripheral blood mononuclear cells from patients with BD.[51]

IL-6 is a key cytokine in BD because it plays a role in the differentiation of $CD4^+$ T cells into Th17 cells. Other cytokines thought to play a role in the pathogenesis of BD are IL-10, a potent suppressor of inflammatory cytokines, IL-12, a potent immune-regulatory cytokine, IL-18, a pro-inflammatory cytokine.[47]

1.8.4.1. IL-10 and IL-10 Receptor

Interleukin-10 (IL-10) is a Type II cytokine and is part of a family of cytokines comprising IL-19, IL-20, IL-22, IL-24, IL-26, IL-28 and IL-29.[48] IL-10 is an anti-inflammatory cytokine that is incorporated in many immune-mediated inflammatory diseases.[52-53]

IL-10 is secreted by a variety of cells, including monocytes, macrophages, dendritic cells, T cells, B cells, granulocytes, epithelial cells, keratinocytes, and mast cells.[54]

IL-10 limits the secretion of pro-inflammatory cytokines, such as TNF-α, IL-1, IL-6 and IL-12, and provides protection against excessive immune responses and tissue damage by controlling pro-inflammatory events. It inhibits the secretion of Th1 cytokines such as IL-2 and interferon- γ (IFN- γ) and controls the differentiation and proliferation of macrophages, T cells and B cells.[55]

In two GWAS study, rs1518111 [33], rs1800872, and rs1800871 [56] were listed as risk genes of BD located in the promoter region of IL-10. The Behçet's disease–associated IL-10 SNP identified in the Turkish population is rs1518111.[33]

IL-10 mediates its anti-inflammatory effects by the signals associated with IL-10R emanating from the cell surface. The IL-10 receptor consists of two subunits, IL-10-R1 and IL-10-R2, which are members of the interferon receptor (IFNR) family. IL-10R1 subunit is unique to IL-10 signaling, but the IL-10R2 subunit is shared by other cytokine receptors, including IL-22, IL-26, and IFN- γ.[57] Whereas IL-10R1 has a dominant role in ligand binding and signal transduction, IL-10R2 is involved in the initiation and transduction of the signal.[58]

Stimulation of IL-10 receptor complex leads to the activation of Janus kinase 1 (JAK1) and tyrosine kinase 2 (Tyk2) and phosphorylation of signal transducer and activator of transcription (STAT) 1, 3, and also 5 which translocate to the nucleus and induce gene expression.[58]

STAT3 is activated by IL-10 receptor signaling and is required for the anti-inflammatory properties of IL-10 and also is critical for IL-10 receptor signaling and could suggest a positive feedback mechanism.[52] STAT3 has also been linked to the regulation of the IL-10 gene through several different signal pathways, including IFN-α.[59]

Interleukin-10 is an anti-inflammatory immunemodulatory cytokine that regulates immune homeostasis especially in the intestine, indicating that the intestine is highly vulnerable to disturbances of immunological balance.[55, 60] The loss of function mutations in the IL-10 or IL-10R gene cause severe early-onset Inflammatory Bowel Disease (IBD) in humans and loss of IL-10 signaling significantly impairs life.[55] Figure 1.7. illustrates suppression of local inflammation in a colon cell.

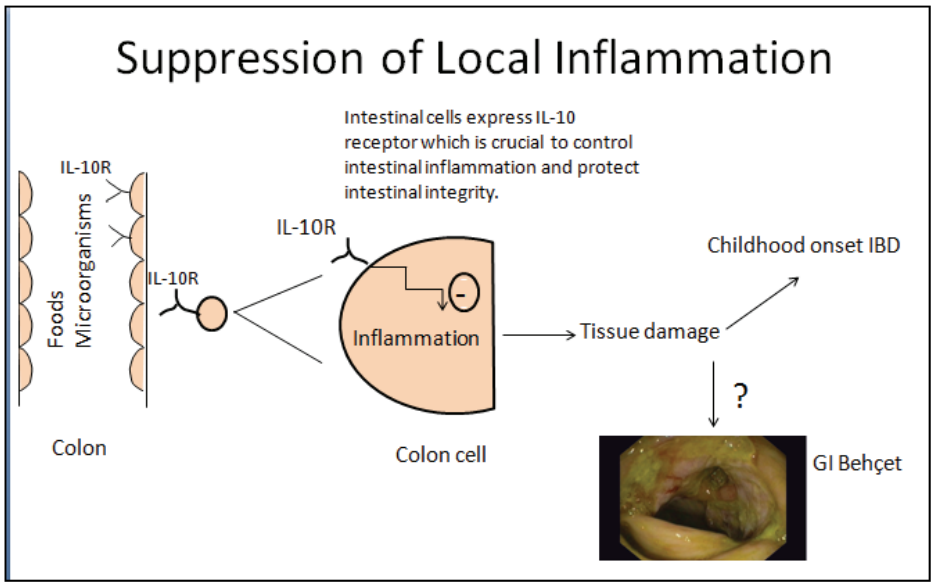

Figure 1.7. Suppression of local inflammation

1.9. Inflammation and Diet

Inflammation is typified by redness, swelling, heat, and pain which are part of the body's immediate response to infection or injury.[61]

Prostaglandins (PG) play an important role in the formation of inflammatory response.[62] Cyclooxygenase (COX) is the key regulatory enzyme of PG biosynthesis, in particular, PGE_2.[63] While COX-1 from two COX isoforms is expressed everywhere and every time in most tissues, COX-2 is generally activated by specific cellular stimuli during inflammation.[50] Inflammation refers to a group of stimuli known to induce COX-2, such as bacterial lipopolysaccharide (LPS), tumor necrosis factor (TNF-α) and cytokines, interleukin-1 (IL-1) and interleukin-2 (IL-2).[63] TNF-α stimulates the production of other pro-inflammatory immune cytokines including IL-1β, IL-6, and INF- γ.[64]

Depending on the cell type in several tissue systems by binding to specific sequences in the genome, the nuclear factor kappa-B (NF-κB) has the capability to firmly regulate and coordinate different changes in gene expression. Components of natural food products inhibit NF-κB activities that coordinate gene expression to advance the inflammatory cascade.[50]

Nitric oxide (NO) can not be precisely defined as an anti-inflammatory or pro-inflammatory molecule but can be considered a true inflammatory agent. The role of inducible nitric oxide synthase (iNOS) in the inflammatory process appears to be dominant.[65]

Reactive oxygen species (ROS) have an important role in responding to damaged lipid membranes, critical cellular proteins, and DNA by activating more stress signals, advancing inflammatory pathways.[50] The antioxidants show their effect by inhibiting the formation of ROS and cleaning the ROS.[66]

Agents derived from plants capable of modulating the expression of pro-inflammatory signals include flavonoids, terpenes, quinones, catechins, alkaloids, anthocyanins, and anthoxanthins, all of which are known to have anti-inflammatory effects.[67]

From ancient times, several natural foods have shown that they can regulate anti-inflammatory responses, and furthermore some clinical studies are carried out to verify the efficacy of these chemical compounds in various natural foods aimed at inflammatory diseases. Besides there are so many natural foods that offer anti-inflammatory actions by elevating antioxidant properties to prevent susceptibility to disease.[50]

1.9.1. Polyphenols

Polyphenols are widespread in plant foods (vegetables, cereals, legumes, fruits, nuts, etc.) and beverages (wine, cider, beer, tea, cocoa, etc.). In general, polyphenols provide a wide variety of anti-inflammatory effects, including antioxidant properties.[68]

1.9.1.1. Flavonoids

The flavonoids, whose numbers are estimated to be over 4000, are abundant in tea, apple, onion, legumes, tomatoes and red wine. Flavonoids have antioxidant properties, also anti-inflammatory, antiviral, antiallergic and antithrombotic properties.[69] Flavonoids show anti-inflammatory properties by inhibition of phospholipase-A_2, cyclooxygenase, lipoxygenase enzymes.[70]

The flavonoids with proven antioxidant effect include green tea, bitter chocolate, red wine, strawberries, raspberries, blackberries and broccoli.[71]

Flavonols:

Isorhamnetin is a dietary flavonoid, found in apples, blackberries, and pears and it is also a major plasma metabolite of quercetin.[72-73] Isorhamnetin has anti-inflammatory and antioxidant properties.[74]

Colorful onion varieties contain more flavonoid than white. External dry shells have been shown to contain quercetin.[70] Quercetin is the most consumed flavonoid and found in fruit, vegetables, cereals, leguminous plants, fruit juices, tea, and wine.[75] Quercetin exhibits a large number of beneficial effects that inhibit NF-κB, COX-2 and ROS. [50]

Animal studies have shown that quercetin is protective in the context of colitis and arthritis varieties.[50, 76] Quercetin inhibits the inflammatory aspects of synovial cell function, neutrophil activation and proliferation of different cancer cell types.[76]

Kaempferol is present in many edible plants such as broccoli, cabbage, kale, beans, endive, leek, tomato, strawberries, and grapes, and in plants or botanical products commonly used in traditional medicine (e.g. *Ginkgo biloba, Tilia spp, Equisetum spp, Moringa oleifera, Sophora japonica*, and propolis).[77] Countless preclinical studies have shown that kaempferol, including, antioxidant, anti-inflammatory, anticancer, antimicrobial, antidiabetic, anti-osteoporotic, estrogenic/antiestrogenic, anxiolytic, analgesic, and antiallergic activities, and cardioprotective, and neuroprotective activities.[78] The anti-inflammatory effects of kaempferol on NF-κB activity and its related gene expressions in the presence of oxidative stress in aged kidney were explained.[79]

Gingerol, shogaol, and other structurally related substances in ginger inhibit prostaglandin and leukotriene biosynthesis by suppression of 5-lipoxygenase or prostaglandin synthetase. In addition, they can inhibit the synthesis of pro-inflammatory

cytokines such as IL-1, TNF-α, and IL-8.[80-81] Shogaol can down-regulate inflammatory iNOS and COX-2 gene expression.[82]

Flavanols (Catechins):

Catechin is present in apples, blueberries, gooseberries, grape seeds, kiwi, strawberries, green tea, red wine, beer, cacao liquor, and chocolate, cocoa.[83] Flavanols are represented by the antioxidants found in tea epigallocatechin (EGC) and epigallocatechin gallate (EGCG).[50] Epigallocatechin gallate (EGCG) which exists in green tea inhibits COX-2 and PGE_2.[84]

Flavanones:

Flavonones are found in tomatoes and certain aromatic plants such as mint, but they are present in high concentrations only in citrus fruit.[75] Flavanones show strong antioxidant and radical scavenging activity and also exhibit antiviral, antimicrobial, and anti-inflammatory activities.[85] Hesperidin inhibit expressions of COX-2 and IL-8 mRNA in hepatic tissue [86] and naringenin downregulates TNF-α, iNOS, and COX-2 too.[87]

Flavones:

Flavones are found in chamomile, parsley, tea, rosemary, oregano, wine, kiwi, spinach, lettuce, broccoli, grapefruit, cereal and legumes.[88] Flavones have anti-inflammatory and anti-microbial activities which by regulate the Toll receptor (TLR)/NF-κB axis. Also, flavones have anti-oxidant activities, based on the ability of compounds to scavenge ROS.[89]

Isoflavones:

Isoflavones are mainly found in soybeans, soy foods, and legumes.[90] Genistein down-regulates cytokine-induced signal transduction events in immune system cells, so that isoflavones are considered an anti-inflammatory agent.[91] Inhibiting the production of IL-1β, IL-6, IL-12, and TNF-α is the main mechanism by which isoflavones exert anti-inflammatory functions.[92]

Anthocyanins:

Anthocyanins are found in colored fruits such as berries, cherries, peaches, grapes, pomegranates, and plums as well as many dark-colored vegetables such as blackcurrant, red onion, red radish, black bean, eggplant, purple corn, red cabbage, and purple sweet potato.[93-94] Anthocyanins have antioxidant, anti-inflammatory, anticarcinogenic and, antimicrobial activity and have properties such as improvement of eye vision, control of diabetes and, prevention of obesity and cardiovascular diseases.[95]

They show antioxidant activities which by scavenging free radicals, downregulation of cell proliferation and apoptosis and thus reducing oxidative stress and lipid peroxidation.[96]

Proanthocyanidins:

Proanthocyanidins are naturally occurring and are frequently seen in fruits, vegetables, nuts, seeds, flowers and tree bark. Proanthocyanidins are associated with a number of biological activities such as anti-inflammatory, antioxidant, anticancer, antimicrobial, and antiallergic, hypertension prevention, asthma prevention and cardioprotective effect.[97]

Proanthocyanidins have anti-inflammatory effects through ROS scavenging and inhibition of the NF-κB pathway. [98]

1.9.1.2. Lignans

The lignans are found in the highest concentrations in flax and sesame seeds, and in lower concentrations in grains, other seeds, fruits, and vegetables (asparagus, grapes, kiwi fruit, lemons, oranges, pineapple) and wine, coffee and tea.[99] Lignans have phytoestrogenic properties, free radical scavenging activities, and antimicrobial and anti-inflammatory effects, and immunosuppressive activities.[100-102] In one study, pinoresinol (PINO) exhibited the strongest anti-inflammatory properties by reducing IL-6, MCP-1, and COX-2–derived PGE_2 secretions in Caco-2 cells.[103]

1.9.1.3. Phenolic Acids

Hydroxycinnamic acids are found in blueberry, kiwi, cherry, plum, aubergine, apple, pear, chicory, artichoke, potato, corn flour, flour (wheat, rice, and oat), cider, and coffee.[75] Caffeic and sinapic acid exhibit immunomodulatory, anti-inflammatory, antimicrobial, anti-carcinogenic, nephroprotective activity against lipid peroxidation and tissue damage.[104-105] Curcumin in turmeric modulates the inflammatory response by down-regulating the activity of COX-2, lipoxygenase, and iNOS enzymes; and also inhibit the production of inflammatory cytokines, TNF-α, IL -1, -2, -6, -8 and -12.[106-107]

Hydroxybenzoic acids are found in blackberry, raspberry, black currant and strawberry.[75] Salicylic acid shows the anti-inflammatory effect through inhibition of

PGE_2 synthesis.[108] Ellagic acid and gallic acid which isolated from pomegranate potentially inhibited LPS-induced NO, PGE_2, and IL-6 production.[109] Additionally, syringic acid exhibits strong antioxidant, antiproliferative, antiendotoxic, antimicrobial, anti-inflammatory, and anticancer effects.[110-111]

1.9.1.4. Stilbenes

Stilbene compounds occur in cocoa, grape, hop, peanut, strawberry, sugar cane, tomato, bilberry, wines, and berries.[112] The anti-inflammatory functions of stilbenes are mediated by COX enzymes as well as Toll-like receptor 4 (TLR4).[113-114] Resveratrol exhibits anti-inflammatory effects via inhibiting enzymes such as COX-1 or COX-2, as well as the inhibitory effect on transcription factors such as NF-κB or AP-1.[115]

Pterostilbene inhibited mitogen-activated protein kinase (MAPK) activation and the production of pro-inflammatory cytokines IL-6 and TNF-α.[116] Both resveratrol and pterostilbene exhibit antioxidant activity through reducing ROS production and scavenging free radicals.[117]

1.9.1.5. Quinones

Quinones show anti-inflammatory and antioxidant effects. Hypericin is found in St. John's wort that inhibits COX- 2 and NF-κB pathway. Anthraquinone also inhibits ROS and COX-2.[50]

1.9.2. Terpenoids

Monoterpenoids

Most of the monoterpenes are volatile in nature and have been found to be more than 1000 in natural products.[118] Aucubin, catalposide, genipin, α-pinene inhibit the activation of the NF-κB system in inflammatory models.[119-122] Genipin also could inhibit the expression of iNOS and NO production.[121]

Sesquiterpenoids

Parthenolide is found in abundance in the medicinal plant feverfew (*Tanacetum parthenium*) which is the herb is a popular remedy for a migraine and some inflammatory diseases, such as arthritis.[123] Parthenolide has shown that anti-inflammatory response through inhibition of NF-κB signaling.[124]

Costunolide isolated from *Magnolia grandiflora* inhibits the basic inflammatory signaling pathway induced by LPS by inhibiting NF-κB activation and downstream gene expression.[125] Sesquiterpenoids are potent NF-κB-dependent anti-inflammatory compounds.[118]

Diterpenoids

Diterpenoids are found in various plants, including rosemary, ginkgo and various Chinese roots.[126] Carnosol shows anticancer, anti-inflammatory and antioxidant activity through inhibition of NF-kB signaling.[127] Kahweol and cafestol isolated from the beans of *Coffea arabica* and they can inhibit inflammatory responses in macrophages.[128-129] Similarly, tanshinone IIA, andalusol, ginkgolides inhibit NF-κB signaling and inflammatory responses.[130-132]

Triterpenoids

Triterpenoids are found in apples, cranberries, rosemary, oregano, prunes, mango, carrot, cucumber, and soybean.[50] Boswellik acid is a potent anti-inflammatory with various effects ranging from COX-2 inhibition to reducing ROS formation.[133] Betulinic acid downregulates NF-κB-dependent gene expression.[134] Lupeol has anti-inflammatory, antimutagenic and antioxidative activities as well as inhibitory potential against prostaglandin (PGE_2) and cytokine production.[135] Ginsenosides being used in inflammatory diseases, cancer and neurodegenerative disorders. Ginseng and ginsenosides directly or indirectly inhibit the NF-κB signal.[136]

Tetraterpenoids (Carotenoids)

Lycopene is found in tomato, watermelon, pink grapefruit, rosehip and papaya and giving them the color is the most important carotenoid.[137] The antioxidant properties of lycopene come from a single oxygen scavenger, scavenging function and hence protecting the cells against oxidative stress.[138] Lycopene also can inhibit nuclear localization and DNA binding of NF-κB complex, as well as reducing macrophage activation.[139]

β-Carotene is present in red palm oil, palm fruits, leafy green vegetables, carrots, sweet potatoes, mature squashes, pumpkins, mangoes, and papayas.[50] β -Carotene has been reported to suppress LPS-induced expression of iNOS, COX-2, TNF-α and IL-1β expression and the DNA binding of NF-κB complex.[140]

Lutein is found in plenty of green vegetables such as spinach, cabbage but also in egg yolks.[97] Lutein is a potent antioxidant and inhibits inflammatory processes including NF-κB activation and subsequent up-regulation of inflammatory molecules.[141]

1.9.3. Alkaloids

The isoquinoline, quinoline and indole alkaloids are the most studied classes for anti-inflammatory activity.[142] Berberine is one of the main components of *Coptis chinensis*, which is often used in Chinese herbal medicines to treat inflammatory reactions.[143] Warifteine is a potential anti-allergic and anti-inflammatory molecule.[144] The quinolizidine alkaloids matrine and oxymatrine exhibited in vitro cyclooxygenase inhibition and antioxidant activity.[145] Indole alkaloids, such as brucine and brucine-N-oxide, showed significant analgesic and anti-inflammatory properties and inhibited the release of PGE_2 in inflammatory tissue.[146]

1.9.4. Organosulfides

Allicin is found in garlic and shows cardio-protective, anti-carcinogenic, antioxidant and anti-inflammatory activity.[64, 147] In a study, allicin not only significantly inhibited the TNF-α, IL-1β, INF-γ, IL-6, and IL-12 but also showed the ability to promote the secretion of IL-4 and IL-10.[64] Sulforaphane is a phytochemical commonly found in broccoli, brussels sprouts, and cabbages.[148] Sulforaphane possesses antiproliferative, anti-inflammatory, antioxidant and anti-cancer activities. Increases in serum TNF-α, IL-6 and IL-10 were significantly reduced in a study after the use of sulforaphane.[149]

1.9.5. Amino Acids

L-carnitine (LC) is an essential compound that is synthesized from lysine and methionine and found in red meat, codfish, avocado, and nuts.[50] LC may have the potential to control inflammation by reducing the main inflammatory cytokines including NF-κB and TNF-α.[150-151] LC can contribute to the antioxidant defenses in different ways such as direct free radical scavenging, chelating transition metal ions such as Fe and Cu, inhibiting ROS-generating enzymes etc.[152]

Glutathione is a tripeptide derived from glutamic acid, cysteine, and glycine and found in avocado, asparagus, broccoli, garlic, and spinach and is a powerful antioxidant.[50, 153]

Melatonin is found in feverfew, almond, cherry, rice, tomato, and ginger.[50] Melatonin has anti-inflammatory and antioxidant activity. Anti-inflammatory actions of melatonin are inhibition of TNF-α release, inhibition of prostaglandins synthesis, down-regulation of COX-2 expression in macrophages, and modulating the NF-κB signaling pathway.[154]

1.9.6. Vitamins and Minerals

The three main carotenoid (A vitamins) compounds found to be anti-inflammatory are lycopene, β-Carotene, and lutein.[50] Vitamin C (ascorbic acid) is present in citrus fruits, papayas, strawberries, cantaloupes, kiwi, bell peppers, broccoli, and cauliflower.[50] In one study, vitamin C was shown to reduce plasma levels of inflammatory mediators of TNF-α and IL-6 by down-regulation of hepatic mRNA expression.[155] Vitamin C indicates that is a potent antioxidant that inhibits ROS.[156] Vitamin E is present in nuts, oils, green vegetables, tomatoes, olives, sweet potato, papayas, pumpkins, and mangoes.[50] Vitamin E shows both anti-inflammatory and antioxidant effect. Vitamin E decreases the production of IL-1β, IL-6, and TNF-α in the colonic tissue and is also an important free radical scavenger and antioxidant that protects cellular membrane lipids from peroxidation.[157]

Anti-inflammatory and antioxidant minerals are boron (apple, banana, bean, peanut), copper (sesame seed, cashew, mushroom, barley), selenium (tuna, cod, poultry, eggs), and zinc (oyster, meat, egg, raisin bran, yogurt).[50] Boron inhibits the TNF-α, IL-

1, and IL-2 from macrophages and is potent inhibitors of both prostaglandin cyclooxygenase and 5'-Lipoxygenase activities of human leukocytes and mouse macrophages.[158] The antioxidant effect of copper is to decrease lipid peroxidation and cell destruction. The amount of antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase decreases in the lack of copper, so the body's antioxidant defense system collapses.[97] Selenium takes part in the antioxidant defense system of the cell and may downregulate the NF-κB pathway by modulating selenoprotein genes expression.[159]

Zinc decreases NF-κB activation and its target genes such as TNF-α, IL-1β.[160] Zinc is an antioxidant which very effective in reducing ROS.[160]

1.10. Objectives of the Thesis

The first objective of the thesis was to identify the biological pathways that are involved in Behcet's disease etiopathology by a thorough literature search of published genetic studies. The genes and their variants with the major contribution to Behcet's disease were identified, and they were categorized by the biological pathways that they function in. Because Behcet's disease is distributed unevenly among the world populations and shows geographic specificity, the distribution of the identified genetic variants were compared between different world populations. After a list of genes with their variants was made, the genetic variants were ranked based on their effect on Behcet's disease, and degree of differentiation between world populations.

Based on the results of the first objective IL-10 gene was chosen for further study because it had a significant effect on Behcet's disease, and was able to differentiate high-risk Behcet populations from others. Moreover, Behcet's disease is an inflammatory disease resulting from an overactive immune response, and IL-10 is the major anti-inflammatory cytokine that (down) regulates the immune system. Therefore the second objective of the thesis was to investigate the genetic changes and gene expression in IL-10 and its primary receptor IL-10R1.

The third aim of the thesis was to discover novel functional foods or ingredients with high anti-inflammatory properties. It was hypothesized that nutrients with anti-inflammatory properties may help alleviate the symptoms of patients with Behcet's

disease. Therefore, anti-inflammatory natural foods were classified according to their chemical compounds and it was aimed to help patients with their diets.

CHAPTER 2

MATERIALS AND METHODS

2.1. Human Samples

Blood samples were collected from 10 healthy controls and 20 patients with Behçet's disease. The diagnosis of Behçet's disease was made by clinical, laboratory, endoscopy and histopathological examination according to the international guidelines (e.g. International Study Group (ISG) [24] and International Team for the Revision of the International Criteria [26] for Behçet's Disease) in Rheumatology Department of Dokuz Eylül University.

All blood samples were collected into EDTA blood collection tubes, and the blood samples were frozen immediately after collection and kept at -20 °C until molecular experiments.

2.2. Identification of Behcet's Disease Associated Genes and Their Variants

A literature search of the genetics of Behcet's disease susceptibility was conducted in Pubmed (https://www.ncbi.nlm.nih.gov/pubmed/) with the keywords "Behcet's disease", "Behcet syndrome", "gene", "SNP", "variant", and "genetics" covering years 1980-2017. Only original research articles where sample size, investigated genes and their variants, and their statistical association with Behcet's disease reported were further evaluated. In total 77 articles were chosen for analyses. BD associated genes were classified based on the pathway, biological process, and protein class. Genetic variants were classified based on the nature of change (i.e. coding, non-coding) and allelic state (ancestral vs. derived). Individual genes, gene groups, and their biological pathways were identified. Population frequencies of BD

associated variants were extracted from the 1000 Genomes database (http://www.internationalgenome.org/).

Statistical analyses compared the distribution of genes among biological processes and pathways (as implemented in Panther Geneontology database (http://www.pantherdb.org/)); allelic states and nature of change of the variants; and geographic and population-specific distribution of variants.

2.3. RNA Isolation

The Total RNA Mini Kit (Blood/Cultured Cell) from Geneaid (Taiwan) company was used for RNA isolation.

2.3.1. RNA Isolation Preparation

Firstly fresh human blood was collected in anticoagulant-treated collection tubes. 1 ml of RBC Lysis Buffer and 300 µl of whole human blood were added to a sterile 1.5 ml microcentrifuge tube and mixed by inversion. Then the tube was incubated on ice for 10 minutes. The supernatant was completely removed after centrifugation at 3,000 x g for 5 minutes. 400 µl of RB Buffer and 4 µl of β-mercaptoethanol (Sigma-Aldrich, St. Louis) were added. The cells were resuspended by pipetting then incubated at the room temperature for 5 minutes. 400 µl of 70 % ethanol (Sigma-Aldrich, St. Louis) prepared in ddH_2O (RNase and DNase-free) was added, then the mixture was shaken, any precipitate was separated by pipetting as much as possible. The RB Column was placed in a 2 ml Collection Tube and 500 µl of the mixture was transferred to the RB Column. It was centrifuged at 16,000 x g for 1 minute then the flow-through was discarded. The remaining mixture was transferred to the same RB Column then centrifuged at 16,000 x g for 1 minute. The flow-through was discarded and the RB Column was placed in a new 2 ml Collection Tube. 400 µl of W1 Buffer was added into the RB Column then centrifuged at 16,000 x g for 30 seconds. The flow-through was discarded then the RB Column was placed back in the 2 ml Collection

Tube. Then 600 µl of Wash Buffer with ethanol was added into the RB Column. It was centrifuged at 16,000 x g for 30 seconds then the flow-through was discarded. The RB Column was placed back in the 2 ml Collection Tube and centrifuged at 16,000 x g for 3 minute to dry the column matrix. The dried RB Column was placed in a clean 1.5 ml microcentrifuge tube. 50 µl of RNase-free Water was added into the center of the column matrix then standed for at least 1 minute to ensure the RNase-free Water was absorbed. Lastly it was centrifuged at 16,000 x g for 1 minute to elute the purified RNA.

2.3.2. Determination of RNA Concentrations

Concentration and purity of isolated RNAs prior to cDNA synthesis was determined by Nanodrop. The absorbance at 260 and 280 nm wavelength was measured. It is expected that the absorbance ratio of A260 / A280 of ideal high purity quality RNA is 1.8-2.0.

2.4. cDNA Synthesis

The iScript cDNA Synthesis Kit from BioRad (USA) company was used for cDNA synthesis. 20 µl reaction mixture consisted of 4 µl 5x iScript Reaction Mix, 1 µl iScript Reverse Transcriptase, 3 µl Nuclease-free water, and 12 µl RNA template (total RNA concentration was adjusted 1000 ng for each sample). Then it was incubated the complete reaction mix in a Thermal Cycler using the following protocol: 25°C for 5 min of priming, 46°C for 20 min of reverse transcription, 95°C for 1 min of RT inactivation and for optional step hold at 4°C. The resulting cDNAs were ready for Real-Time PCR and stored at -20°C.

2.5. PCR

PCR is a sensitive analysis that allows the amplification of a specific DNA fragment from a complex DNA pool. PCR can be performed using DNA from various tissues and organisms including peripheral blood, skin, hair, saliva and microbes.[161]

2.5.1. Primer Design

Gene sequences for human IL-10 (https://www.ncbi.nlm.nih.gov/gene/3586) and IL-10R1 (https://www.ncbi.nlm.nih.gov/gene/3587) was downloaded from NCBI. Primers for the IL-10 and IL-10R1 mRNAs were designed by PRIMER3 (http://primer3.ut.ee/) program. Designed primers were synthesized by Macrogen (Korea) (Table 2.1.).

Table 2.1. Primers for PCR

Genes	**Primer**		**Primer sequence**	**Product Length (bp)**
IL-10	Forward		CTGAGCTTCTCTGTGAACGAT	665
	Reverse		ACTGCAACTTCCATCTCCTG	
IL-10R1	Pair 1	Forward	TAGTGCAGGGTATGTGGGTG	769
		Reverse	CTCTGGGTCTGTAGCTGGAC	
	Pair 2	Forward	GGCCTCAATCTCCCATCTGT	713
		Reverse	TTCCTCAGCAGAACCTCACA	

2.5.2. PCR Preparation

FastStart High Fidelity PCR System, dNTPack from Roche Applied Science (Germany) company was used for PCR. Firstly the reagents were thaw and stored on ice. All reagents were vortexed and centrifuged before setting up the reactions. For each 25 µl reaction, components consisted of 17.75 µl water (ddH_2O), 2.5 µl reaction buffer

(10x), 0.5 µl DMSO, 0.5 µl PCR grade nucleotide mix, 1 µl downstream (forward) primer, 1 µl upstream (reverse) primer, 1.5 µl cDNA, 0.25 µl enzyme blend and they were put to a sterile reaction tube on ice. The reaction was mix thoroughly and each 25 µl reaction put into 0.2 ml PCR tubes. Then analysis was run with the Applied Biosystems SimpliAmp^{TM} Thermal Cycler. The PCR protocol was as follows: 95°C for 2 min of initial denaturation followed by 35 cycles of 30 sec denaturation at 95°C, 30 sec annealing at 56°C, and 50 sec elongation at 72°C, and final elongation step at 72°C for 5 min, and cooling step hold at 4°C. The samples were put in the freezer after cycling.

2.6. Agarose Gel Electrophoresis

Agarose gel electrophoresis is a standard method for the differentiation, identification, purification of DNA molecules. The electrophoretic analysis is based on the principle that the molecules dissolved in the environment migrate according to their electrical charges in an electrical field. Since DNA molecules are negatively charged due to free phosphate groups, they move from cathode to anode on the gel. Large molecules have difficulty walking on the gel, while small molecules can move more quickly and comfortably.

Agarose density: Depending on the size of the PCR sample studied, agarose gel electrophoresis is performed by determining the desired agarose density. Agarose is usually used in concentrations ranging from 0.8% to 1.2%. Recommended agarose gel concentration for the separation of linear DNA molecules was shown in Table 2.2.

Table 2.2. Recommended agarose gel concentration for the separation of linear DNA molecules

% Agarose	DNA size range (bp)
0,75	10.000-15.000
1,00	500-10.000
1,25	300-5000
1,5	200-4000
2,00	100-2500
2,5	50-1000

2.6.1. Buffer Solution Preparation

The most commonly used buffer solutions in agarose gel electrophoresis are Tris-acetate (TAE) and Tris-Borate (TBE). These buffers may be purchased commercially or prepared as concentrated solutions in the laboratory. The 50X TAE to be used in the experiment was purchased commercially. When preparing 1X from a buffer solution in the main stock at 50X; 20 ml of 50X Main Stock is added to 980 ml of pure water.

2.6.2. Agarose Gel Preparation

0.8 % agarose gel was prepared for agarose gel electrophoresis. Firstly 0,8 g agarose was weighed and put in Erlenmeyer. 100 ml 1X TAE buffer solution was added. The prepared mixture was heated in a microwave oven until no particules remain. Then left to cool for a while. 1 µl GelRed® Nucleic Acid Gel Stain dye was added into slightly cooled agarose and mixed.

Note: The dye added at this stage shows the fluorescence effect under UV light and makes the molecule studied visible on the gel. Ethidium bromide is a strong carcinogen and toxic so the GelRed dye is used as an alternative.

The agarose was poured into a gel tank in which the combs are placed. Then allowed to solidify at room temperature. Once solidified, it was placed in the gel box.

2.6.3. Loading Samples and Running an Agarose Gel

1X TAE Buffer solution was used to fill the gel box until the gel was covered. Once the gel was completely solid, the bands were carefully removed and placed in the gel tank. Care was taken that the buffer solution remains at the top of the gel. Then the comb was removed from the gel. 6 µl 100 bp DNA Ladder (Geneaid, Taiwan) was loaded into the first well then 1 µl 6x dye and 5 µl sample were loaded. The gel was run

at 100 V for 70 minutes with Major Science Safeblue Electrophoresis System. At the end of the run, the electric current was closed and the gel was placed under UV light (Uvitec, UK) for visualization.

2.7. Real-time PCR (qPCR)

Quantitative real-time PCR provides information beyond just detection of DNA. Indicates how much of a particular DNA or gene is present in the sample. qPCR allows both the detection and measurement of the PCR product in real-time as it is synthesized.[161]

2.7.1. Primer Design

The primers used for the IL-10, IL-10R1 and ACTB gene regions were specifically designed for Homo sapiens using NCBI and ENSEMBLE gene banks. The specificity of the designed primers was controlled by the BLAST program. Primers were synthesized by Macrogen (Korea).

Table 2.3. The primers used for real-time PCR analysis

Genes	Primer	Primer sequence
IL-10	Forward	TCTCCGAGATGCCTTCA
	Reverse	CATGGCTTTGTAGATGCCTTTC
IL-10R1	Forward	TTCACGTTCACACACAAGAAAGT
	Reverse	CAGAACTCTCCCACTTCTCCA
ACTB	Forward	TCTACAATGAGCTGCGTGTG
	Reverse	GGTCTCAAACATGATCTGGGT

2.7.2. Optimization for Primers

The primers are diluted to 100 µM (i.e. 100 pmol / µl) by adding the required amount of water depending on their molecular mass. Working stock solutions (explained below) were prepared and made ready for Real-Time PCR analysis.

2.7.3. Primer Working Stock Solution Preparation

A 10 µM intermediate stock was prepared from Forward and Reverse primers. For this, 10 µl was taken from 100 µM main stock and 90 µl of water was added.

*When preparing intermediate stocks, the classical formula M1 * V1 = M2 * V2 was used.*

Where M1 and V1 are the molarity and volume of the stock solution, respectively, and M2 and V2 are the molarity and volume of the working solution.

2.7.4. Real-Time PCR (qPCR) Preparation

The synthesized cDNAs were run with the Roche Light Cycler 480 II instrument using the Light Cycler® 480 SYBR Green I Master (Roche Applied Science, Germany) with the primers designed for the indicated gene regions (Table 2.3.). The ACTB gene indicated in the study was taken as the reference (control) gene. Together with the IL-10 and IL-10R1 genes were prepared and loaded into the device. Each 7,5 µl reaction mixture consisted of 1.9 µl water (PCR-grade), 0.3 µl forward primer, 0.3 µl reverse primer, 5 µl enzyme mixture (Light Cycler® 480 SYBR Green I Master).

7,5 µl Reaction Mix + 2,5 µl cDNA = 10 µl Total Reaction Volume

In the reaction tube, each of the components (except cDNA) was added to a single reaction and multiplied by the number of reactions to prepare the reaction mixture. For each reaction, 7.5 µl of the reaction mixture was transferred to the plates.

A 2.5 µl cDNA sample was added to each well to give a final reaction volume of 10 µl. Prepared plates were covered and centrifuged with a plate centrifuge. The study was carried out with the device protocol shown in Table 2.4.

The expression of three genes (IL-10, IL-10R1, ACTB) were analysed in duplicates for all samples via Real-Time PCR (qPCR) analysis.

Table 2.4. Real-Time PCR (qPCR) Protocol

Program Name	**PRE-INCUBATION**	**AMPLIFICATION**			**MELTING CURVE**			**COOLING**
Analysis Mode	None	Quantification Mode			Melting Curve Mode			None
Number of Cycles	1	45			1			1
Target Temperature [°C]	95	95	57	72	95	62	97	40
Time	00:05:00	00:00:10	00:00:15	00:00:10	00:00:05	00:01:00	00:00:00	00:00:30
Temperature increase rate [°C/s]	4,8	4,8	2,5	4,8	4,8	2,5	0,11	2,5
Reading Mode	None	None	None	Single	None	None	Continuous	None

2.7.5. Analysis

The data which contains Ct values were obtained at the end of Real-Time PCR analysis from Roche Light Cycler 480 software using Absolute Quantification and Advanced Relative Quantification analyses methods. ΔΔCt method was used to make Relative Quantification of gene expression in the obtained results. Target gene Ct values were normalized with ACTB by this method. Normalized values were compared with control groups and Fold Change values were found.

ΔΔCt method uses these steps [162] :

Step1: ΔCt values were obtained for both patients and controls.

ΔCt = Ct target – Ct reference

Step 2: ΔΔCt values were obtained.

ΔΔCt values: ΔCt patient sample – ΔCt control sample

Step 3: Fold Change Expression = $2^{-\Delta\Delta CT}$ values were obtained.

Fold change expression is interpreted as follows: If it is greater than 2, then it means significant up-regulation of the target gene. If it is lower than -2, then it means significant down-regulation of the target gene. If it is between -2 and 2, then it means non-significant of the target gene.

2.8. DNA Sequencing

DNA sequencing is based on the chain termination method, where nucleotides in a single-stranded DNA molecule are determined by the complementary synthesis of polynucleotide chains, based on the selective incorporation of chain-terminating dideoxynucleotides driven by the DNA polymerase enzyme.[163]

2.8.1. DNA Sequencing Analysis

Purification of PCR products

The obtained PCR products were purified using EXOSAP. 2 µl of EXOSAP was added to 5 µl of PCR product and kept for 30 minutes at 37 °C and 15 minutes at 85 °C.

Sequencing of purified PCR products

The sequencing PCR will be established from the purified PCR products obtained after purification. A reaction mixture for 1 amplification tube (12 µl) consisted of : 1 µl BigDye Ready Reaction Mix, 0.5 µl primer (3.2pmol/µl), 4 µl distilled water, 2 µl 10x buffer , 2 µl Dye saving, 2.5 µl purified PCR products. The PCR amplification was as follows: 25 cycles of 10 sec at 96 °C, 5 sec at 50 °C, 4 min at 60 °C.

Purification after sequencing PCR

Sequencing PCR products obtained were cleaned with Zymogen DNA Sequencing Clean - Up Kit. Firstly 200 µl of DNA Binding Buffer was added onto 10 µl of PCR product. The prepared mixture was transferred to Zymo-spin column and it was centrifuged at 10,000 x g for 60 sec. The flowing liquid was removed from the tubes and 200 µl of Wash Buffer was added to the column and centrifuged again at 10,000 x g for 60 sec. Finally, the Zymo-spin column was transferred to a new clean tube and 20 µl of distilled water was added and centrifuged at 10,000 x g for 60 sec. The filtered Sequencing PCR product was loaded and run on the ABI Prism 3100.

Analysis of DNA sequence results

Nucleotide sequence chromatograms were visualized, examined, and aligned with Unipro UGENE (http://ugene.net/) [164]. Specifically, ClustalW was used to align DNA sequences.

2.9. Statistical Analysis

Geographic and population-specific distribution of frequencies of Behcet related variants reported in literature among the 1000 Genome database (http://www.internationalgenome.org/) was examined with principal component analysis. Distribution of IL-10 and IL-10R1 genetic variants between Behcet patients and controls were tested with Chi-square test. IL-10 and IL-10R1 gene expression levels were compared between Behcet patients and controls by parametric T-tests, and non-parametric Kruskal-Wallis tests.

All statistical analyses were conducted in R (https://www.r-project.org/). P-values less than or equal to 0.05 were considered statistically significant.

2.10. Project Funding

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CHAPTER 3

RESULTS AND DISCUSSION

3.1. Behçet's Disease Associated Genes, Their Variants, and Related Pathways

Out of 77 articles, 119 genes and 241 variants (SNPs) were reported to be significantly associated with Behcet's disease (Appendix A). Most significantly associated genetic variants were involved in antigen processing and presentation (such as HLA), and interleukin signaling pathways. However, for several genes (such as PSORS1C1, POU5F1, and CCHCR1) that were reported to be significantly associated with Behcet's disease, no biological information was available. Sixty-three percent (153 out of 241) of the variants were reported to increase susceptibility to Behcet's disease.

3.2. Distribution of Behcet's Disease Associated Variants among World Populations

Population frequencies of the 237 variants were calculated in African (7 populations), Ad Mixed American (4 populations), East Asian (5 populations), European (5 populations), and South Asian (5 populations) populations based on 1000 Genome data (Table 3.1, Appendix B).

A principal component analysis was performed on the constructed genetic variant frequency matrix of populations. Differentiation of populations along the most informative top three principal components (PC) was visualized (Figure 3.1 and 3.2).

The first PC differentiated Africans from the rest of the populations. SMARCA, IL23R, SAMD3, EBF2 had the highest loading on the first PC, indicating large frequency differences of genetic variants between African populations and others.

Table 3.1. Country names and abbrevations of the 1000 Genome populations

AFR	**African**
ACB	African Caribbeans in Barbados
ASW	Americans of African Ancestry in SW USA
ESN	Esan in Nigeria
GWD	Gambian in Western Divisions in the Gambia
LWK	Luhya in Webuye, Kenya
MSL	Mende in Sierra Leone
YRI	Yoruba in Ibadan, Nigeria
AMR	**Ad Mixed American**
CLM	Colombians from Medellin, Colombia
MXL	Mexican Ancestry from Los Angeles USA
PEL	Peruvians from Lima, Peru
PUR	Puerto Ricans from Puerto Rico
EAS	**East Asian**
CDX	Chinese Dai in Xishuangbanna, China
CHB	Han Chinese in Bejing, China
CHS	Southern Han Chinese
JPT	Japanese in Tokyo, Japan
KHV	Kinh in Ho Chi Minh City, Vietnam
EUR	**European**
CEU	Utah Residents (CEPH) with Northern and Western European Ancestry
FIN	Finnish in Finland
GBR	British in England and Scotland
IBS	Iberian Population in Spain
TSI	Toscani in Italia
SAS	**South Asian**
BEB	Bengali from Bangladesh
GIH	Gujarati Indian from Houston, Texas
ITU	Indian Telugu from the UK
PJL	Punjabi from Lahore, Pakistan
STU	Sri Lankan Tamil from the UK

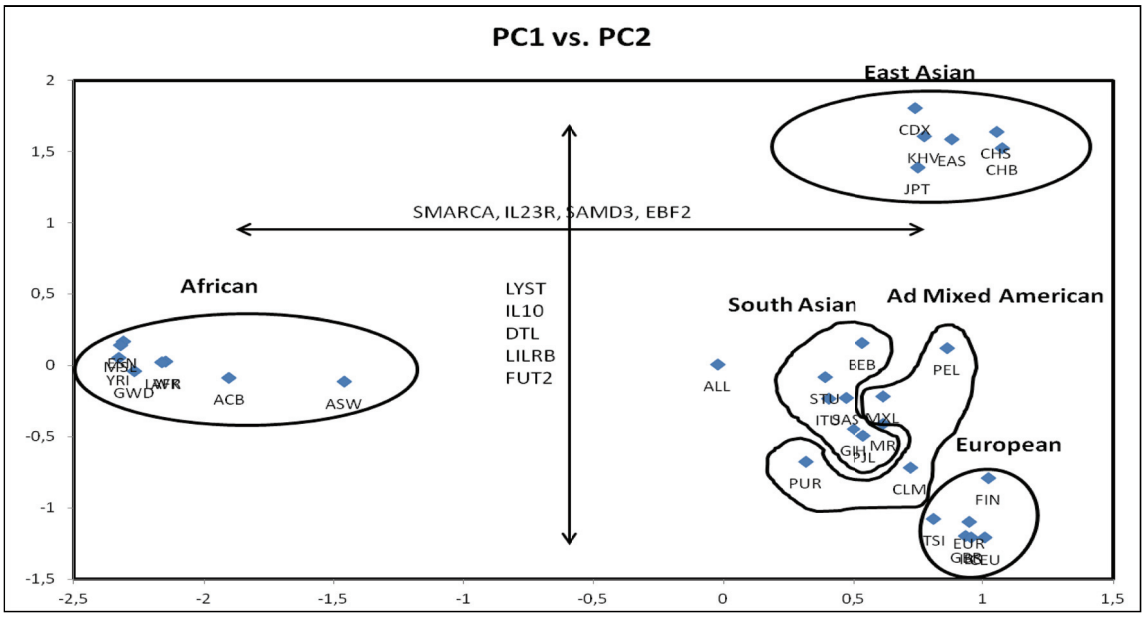

Figure 3.1. Seperation of 1000 Genome populations (Table 3.1) along the top 2 principal components (PC). Genes with the largest contributions on the respective PCs are listed on the axes.

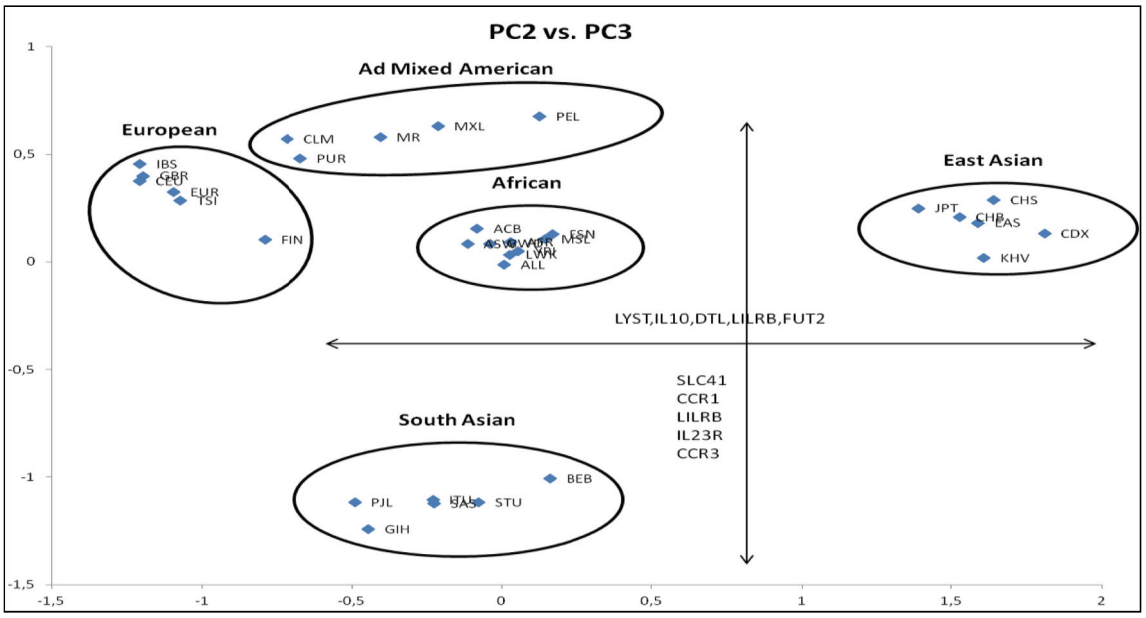

Figure 3.2. Seperation of 1000 Genome populations along PC2 vs. PC3. Genes with the largest contributions on the respective PCs are listed on the axes.

LYST/NID1, IL-10, DTL, LILRB1, FUT2 had the highest loading on the second PC, indicating large frequency differences of genetic variants between East Asians and others. Because Behcet's disease prevalence is high in East Asians, the genetic variants that have the highest loading on the second PC were investigated further (Table 3.1). Of the genes that show high differentiation between East Asians and others, IL-10 was reported to have the most significant association with BD. Moreover, IL-10 was the most thoroughly studied gene in the list and had the most biological pathway related information (Table 3.2).

Therefore rest of the genetic studies of this thesis focused on IL-10, and its primary receptor IL-10R1.

Table 3.2. Genes and variants with high contribution to the second principal component (PC2) that differentiates East Asians from other groups

Biological Pathway	**Gene**	**Variant/SNP**	**Type**	**Behcet Allele**	**Effect on BD**	**OR**	**P Value**	**Loading[a]**
Receptor	LYST/NID1	rs7354999	Up/down	G	Susceptible	1.38	$6.1x10^{-05}$	0.228412
Interleukin signaling	IL-10	rs1554286	Intron	C	Protective	0.62	$8.0x10^{-08}$	0.170559
	DTL	rs1472224	Downstream	G	Protective	0.16	$5.73x10^{-05}$	0.169493
Cellular process	LILRB1	rs798887	Upstream	A	Susceptible	1.83	$2.23x10^{-05}$	0.169396
Biosynthetic process	FUT2	rs681343	Exon	T	Susceptible	1.30	$5.9x10^{-09}$	0.165176
Interleukin signaling	IL-10	rs1518111	Intron	A	Susceptible	1.45	$3.54x10^{-18}$	0.162981
	LINC01499 (API5)	rs420798	Intron	C	Susceptible	1.72	1.79x10-05	0.158447
Interleukin signaling	IL-10	rs1800872	Upstream	A	Susceptible	1.45	$2.1x10^{-14}$	0.157423
Interleukin signaling	IL-10	rs1800871	Upstream	T	Susceptible	1.45	$1x10^{-14}$	0.157417

a. Loading scores of Behcet related genes on the second principal component (PC)

3.3. IL-10 and IL-10R1 Gene Expression Results

Total RNA was isolated from the 30 blood samples. Over 95% of the samples had at least 30 ng/ µl RNA and all samples had high quality (high purity) RNA (Figure 3.3 and 3.4).

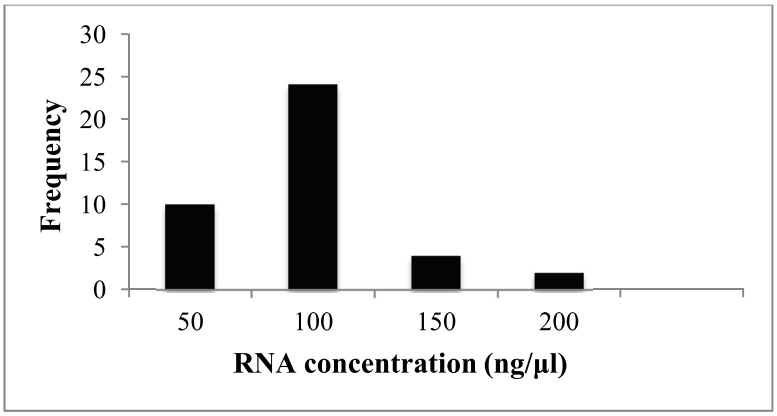

Figure 3.3. RNA concentration of samples

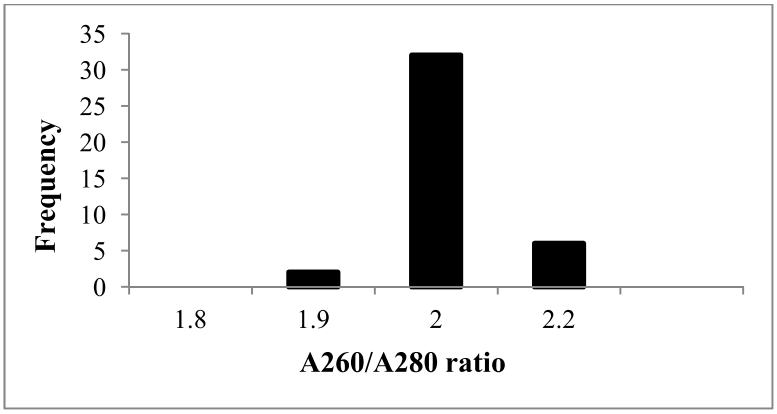

Figure 3.4. Quality of extracted RNA samples

After cDNA construction, IL-10, IL-10R1, and ACTB gene (control gene) expressions were carried out. Successful gene expression was detected for all genes and all samples (Figure 3.5-6-7).

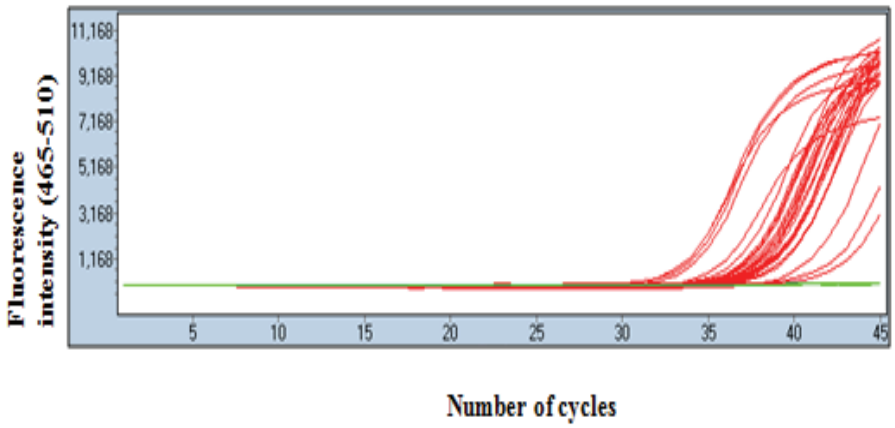

Figure 3.5. Amplification curves of IL-10

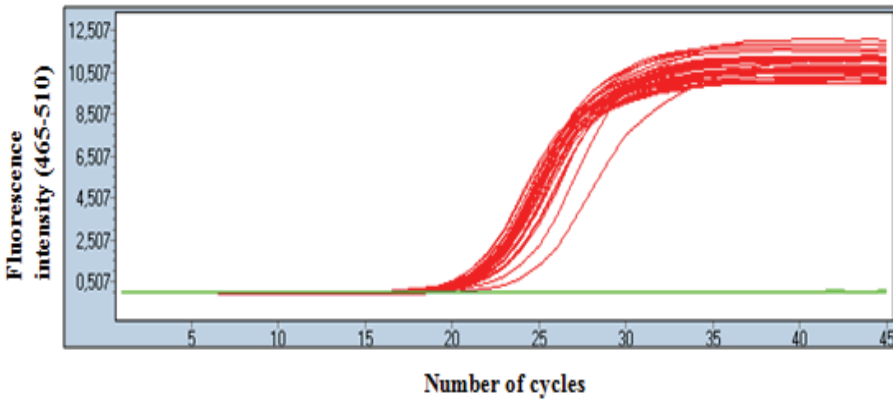

Figure 3.6. Amplification curves of IL-10R1

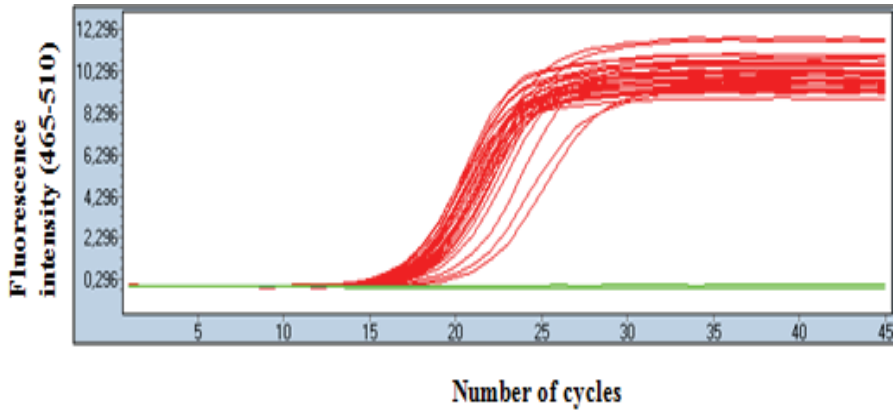

Figure 3.7. Amplification curves of ACTB

IL-10 gene expression was 9.6 fold higher in Behcet patients compared to normal controls (Figure 3.8), whereas IL-10R1 expression was not statistically different between the two groups (means 0.8 vs 0.9, fold change=0.9) (Figure 3.9). Gene expression levels are standardized with respect to the mean of the control group.

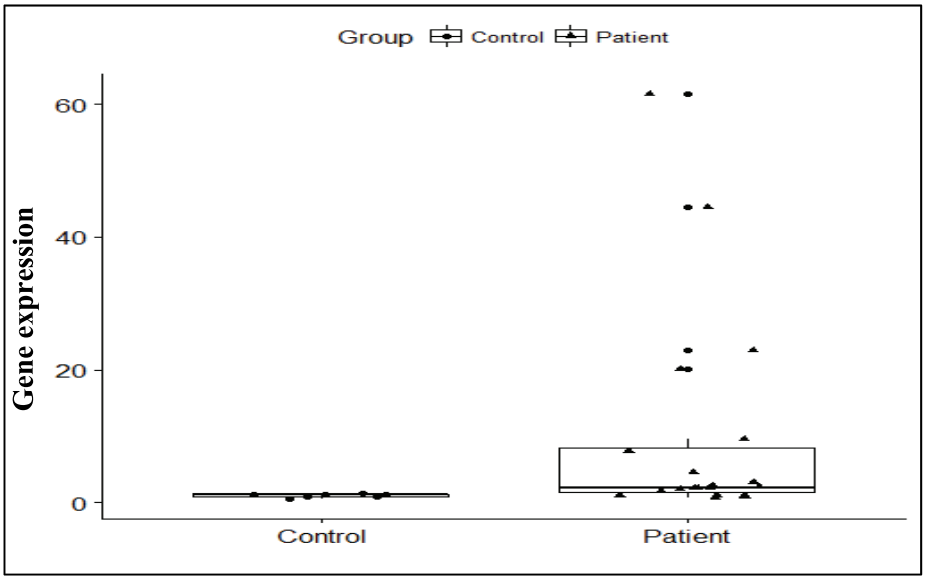

Figure 3.8. Comparison of IL-10 gene expression between Behcet patients and controls

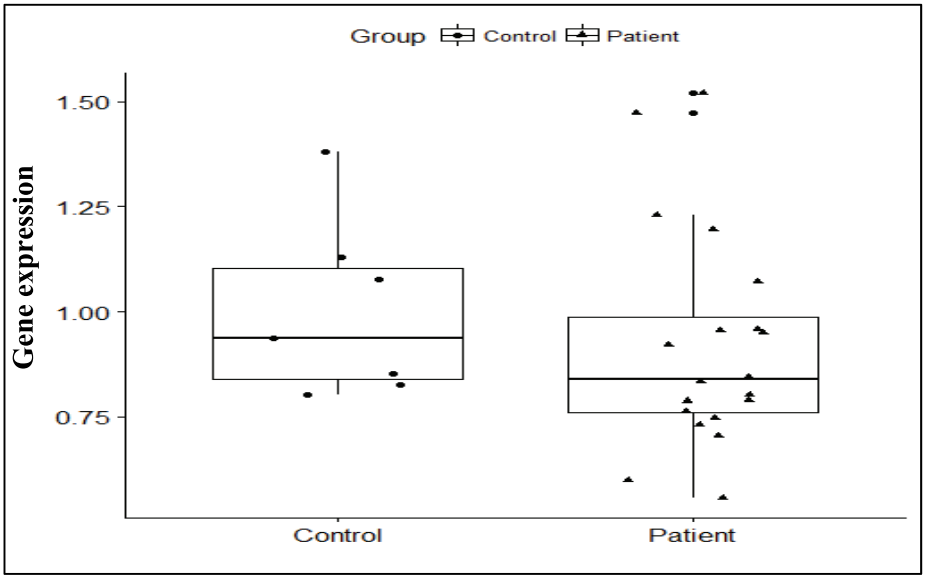

Figure 3.9. Comparison of IL-10R1 gene expression between Behcet patients and controls

3.4. IL-10 and IL-10R1 Gene Sequencing Results

The 800 base-length portion of the 1630 base-length IL-10 mRNA and 1700-base portion of the 3672 base IL-10R1 mRNA were successfully sequenced. Sequence steps and results were further illustrated in Figure 3.10., and Figure 3.11.

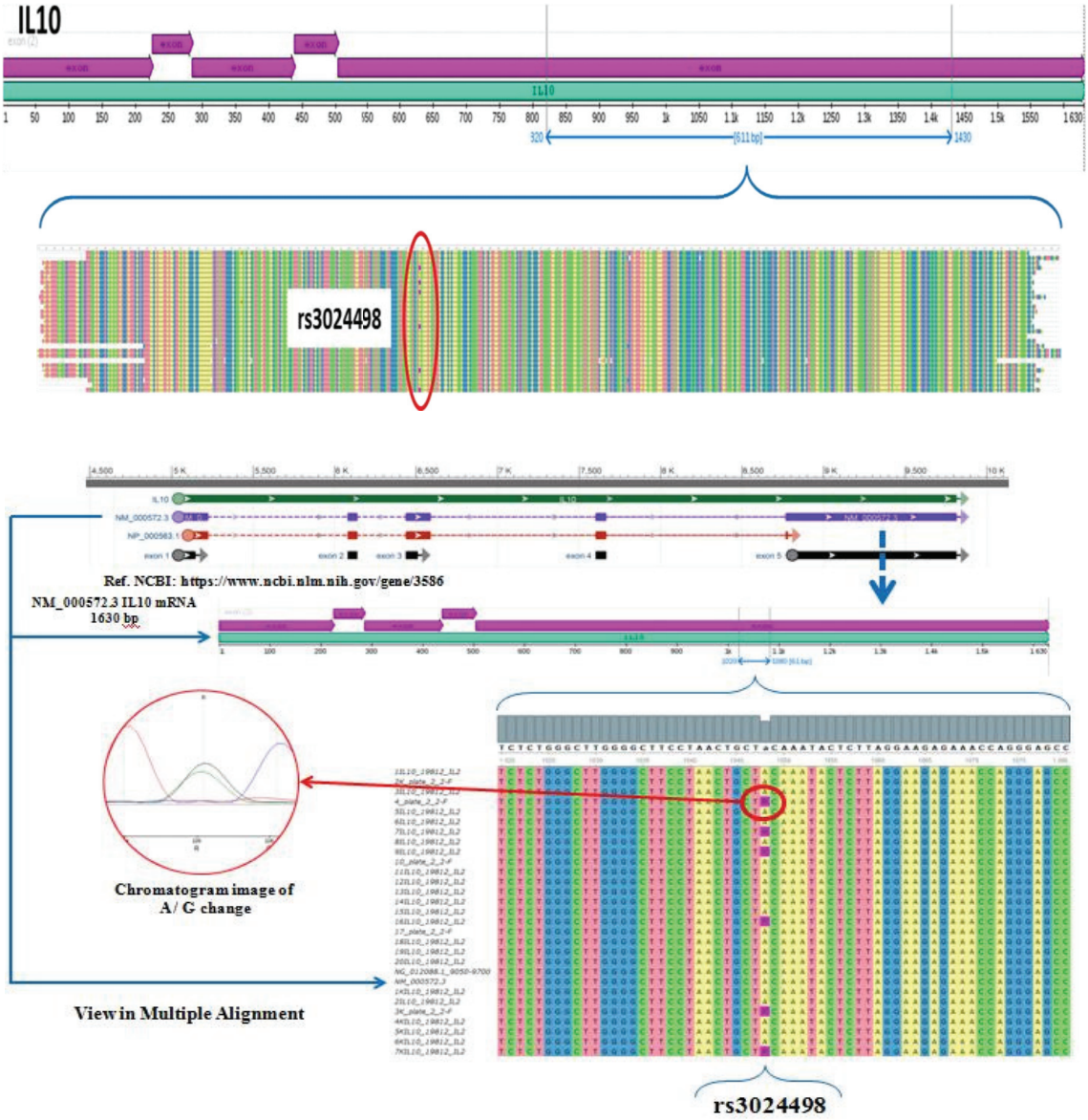

Figure 3.10. Sequencing of the IL-10 gene encoding (exon) portions over the mRNA and results

The IL-10 gene and the mRNA sequence were taken from the NCBI database (NM_000572.3), divided into two regions for mRNA sequencing and primers were

designed. The resulting DNA sequences were aligned with the ClustalW program, and visualized by the UGENE program. The Figure 3.10. shows the final exon portion (exon 5) of IL-10 with rs3024498 SNP.

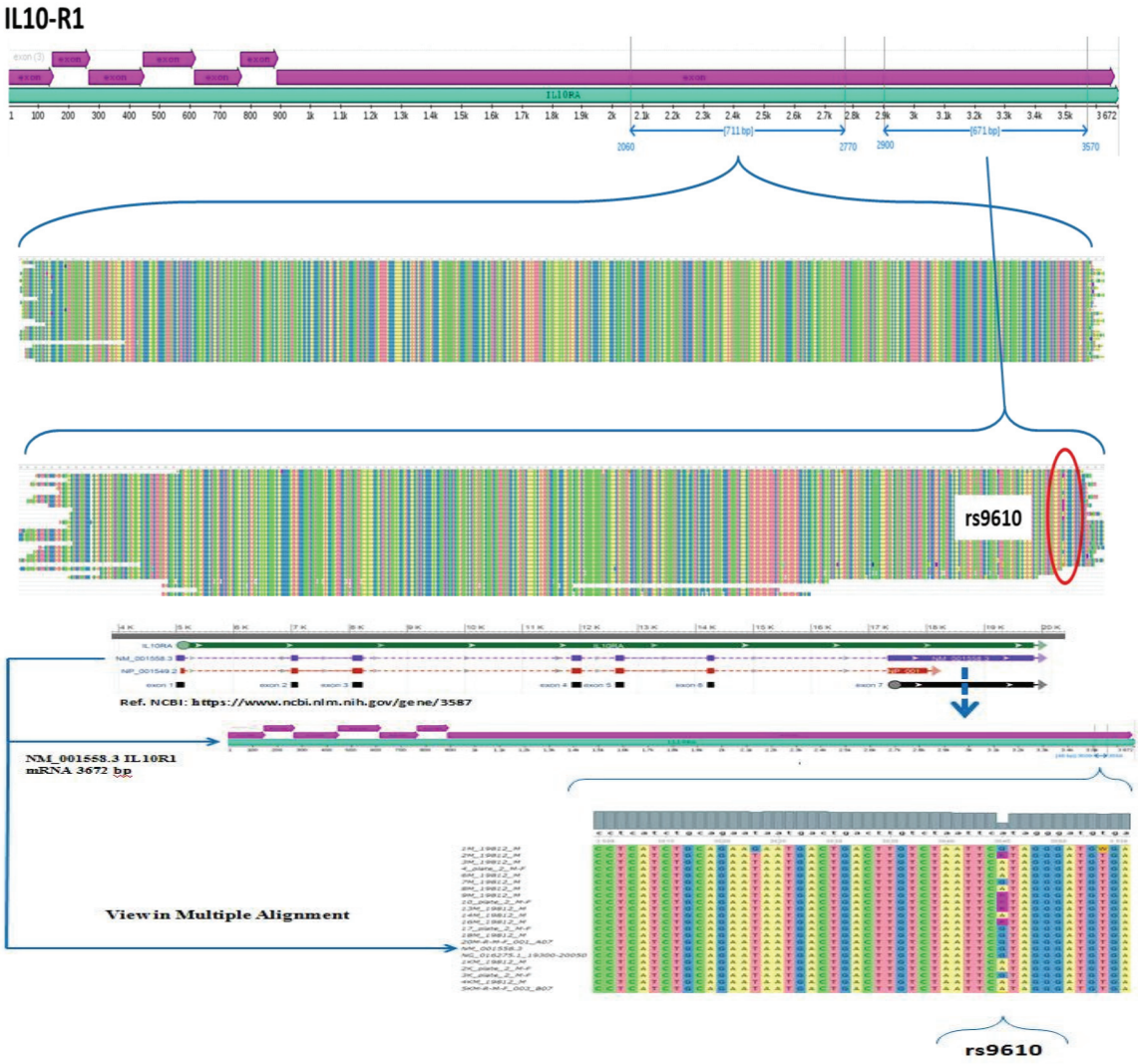

Figure 3.11. Sequencing of the IL-10R1 gene encoding (exon) portions over the mRNA and results

The IL-10R1 gene and the mRNA sequence were taken from the NCBI database (NM_001558.3), divided into five regions for mRNA sequencing and primers were designed. The resulting DNA sequences were aligned with the ClustalW program and visualized by the UGENE program. The Figure 3.11. shows the final exon portion (exon 7) of IL-10R1 with rs9610 SNP.

One polymorphic base was found for both genes as a result of IL-10 and IL-10R1 sequencing. As a result of bioinformatics analysis of the sequences around the

polymorphic bases in the NCBI, dbSNP, 1000 Genome and Ensembl databases, it was determined that the polymorphism in the IL-10 gene was rs3024498 (A / G) and the polymorphism in the IL-10R1 gene was rs9610 (A / G). Table 3.3. shows the distribution frequency of both polymorphisms in patient and control samples. It is a 3 'UTR variation in the last part of the mRNA in both variations and does not cause any amino acid change.

Linkage disequilibrium can confound genetic association signals. Therefore variants that show linkage disequilibrium with the rs30244988 and rs9610 are calculated with the LDproxy program (https://ldlink.nci.nih.gov/?tab=ldproxy).[165] Twelve and five variants that show $R^2 \geq 0.5$ with rs3024498 and rs9610, respectively, using the European populations of the 1000 genomes data were found (Appendix C). Most of these variants were found to be either in upstream or downstream of IL-10 or IL-10R1. Few of them were also in close proximity to other genes such as IL-19 and SMIM35. Follow-up studies can focus on these genes to evaluate their potential effect on BD.

Table 3.3. Distribution frequency of rs3024498 and rs9610 variation in patient and control samples

	IL-10 rs3024498 G allele frequency (%)	IL-10R1 rs9610 G allele frequency (%)
Patient (n=20)	10	50
Control (n=10)	14	18
Total (%)	11	41
P[a]	0.49	0.08

[a]Chi-square (2x2) statistical test result which tests the distribution of alleles in patient and control groups

Although there was no statistically significant difference in the distribution of both polymorphisms between patients and control groups, it was seen that rs9610-G allele was more prevalent in the patient group. A power and sample size calculation showed that in order to show a significant association between rs9610 and BD at alfa 0.05 probability and 80% power, 39 cases and 39 controls are needed. As a result rs9610 variant can be a genetic change that increases the risk of Behçet's disease. Since there were clinical signs of skin and oral aphthae in the patient group, rs9610 may influence the clinical presentations of BD. These findings should be tested with larger sample groups.

Neither the rs3024498, nor the rs9610 variant did not have a significant effect on gene expressions ($p > 0.6$).

3.5. Discussion

There are over 100 genes that were reported to contribute to BD risk from diverse populations. These analyses of distribution of BD associated variants among world populations showed that there is a big population differentiation between the world populations with respect to BD risk alleles where populations with high frequencies of BD, such as the East Asian populations, were rather different in terms of BD risk allele variant frequencies from other world populations. This observation supports the idea that BD has a substantial genetic component and these genetic components can be rather population specific.

IL-10 gene was identified as one of these genetic risk factors that strongly influenced the differentiation of high-risk BD populations from others and these molecular genetic analyses were continued with IL-10 and its primary receptor IL-10R1 in a Turkish BD cohort.

The sequencing results identified only a single variant both in the IL-10 and IL-10R1 genes. The IL-10 rs3024498 variant is not associated with Behcet's disease in this study. This observation is in agreement with Montes-Cano et al., where the allele frequency of IL-10 rs3024498 variant was not significantly different between 304 BD patients, and 313 Spanish matched controls. [166] In another study, Xavier et al. looked at the effect of this variant in 973 Iranian patients with BD and 637 non-BD controls and did not observe a significant effect. [167]

However, this SNP has been found to be associated with active pulmonary tuberculosis in an Indian population [168], colorectal cancer in a US population[169], helminth infection in a Brazilian population [170], gastrointestinal stromal tumours in a US population[171], hepatitis C virus (HCV) clearance in an African American population[172], visceral leishmaniasis in an Indian population [173], systemic lupus erythematosus in a Chinese population [174], motoric cognitive risk syndrome in an Ashkenazi Jewish

population [175], and asthma in Canadian, Australian, US, and Swedish populations [176-177], proliferative vitreoretinopathy across Slovenian and European Subpopulations [178].

The IL-10R1 rs9610 variant showed a marginally significant association with Behcet's disease in this study. Also, Yang et al. reported that IL-10R1 rs9610 polymorphism might contribute to rheumatoid arthritis susceptibility in a Chinese population.[179]

However, this SNP has been found to be associated with cervical squamous cell carcinoma by Hussain et al.[180], non-Hodgkin lymphoma (NHL) overall and B-cell lymphoma by Bi et al.[181], and rubella stimulation by Dhiman et al.[182] in the USA.

There was a significant increase in IL-10 gene expression in Behcet patients compared to the controls in this study. Puccetti et al. [183] also reported a significant increase in IL-10 gene expression in Behcet patients compared to controls in an Italian population.

On the other hand, Alipour et al.[184] and Afkari et al.[185] reported that the expression level of the IL-10 gene was significantly reduced in the Behcet patients group compared to the control group in Iranian population.

Foods and their active anti-inflammatory ingredients were classified according to their effect on the mechanisms of inflammatory processes, such as COX2, NF-κB inhibition (Table 3.4). Very large quantities of foods need to be consumed to deliver the desired effects of their active ingredients. However, this is usually not feasible as the majority of people cannot consume that many vegetables, fruits, nuts or fish. Therefore alternative food supplements need to be developed. Novel food supplements can deliver high quantities of chemical components with anti-inflammatory properties (such as quercetin, boswellic acid, etc.) in a single dosage. Based on their water and oil solubility properties either a tablet or gel capsule formulations can be considered. However, in vitro, in vivo, and controlled clinical trials are necessary to determine the dosage and safe use of the potential supplements.

There are several limitations to the study. Firstly, the patient and control sample size needs to be increased as indicated by the power calculations in the Results section. For gene expression the whole blood was used, however, separate gene expression

analyses of lymphocytes and neutrophils can give a better idea on the role of IL-10 pathway in BD. Finally, only the coding regions of IL-10 and IL-10R1 was sequenced, so the potential influence of regulatory (such as the promoter) and intron region variants were not examined.

Table 3.4. Food ingredients with high anti-inflammatory properties

Active chemical component	**Sources**	**Solubility**	**Mechanism(inhibition)**
Quercetin	Fruit, vegetables, cereals, leguminous plants, fruit juices, tea, wine	It is barely soluble in water. Therefore, it is recommended to consume with bromelain to facilitate absorption.	COX2, NF-κB
Shogaol	Ginger	Soluble in water	COX2, iNOS
Melatonin	Feverfew, almond, cherry, rice, tomato, and ginger	Partially soluble in water and highly soluble in oils.	COX2, TNF-α, NF-κB, PG2
Genipin	The fruit of Gardenia jasminoides Ellis	Soluble in water	iNOS
Boron	Apple, banana, bean, peanut	Soluble in water	COX2, TNF-α, IL-1, IL-2, PG2
Matrine and oxymatrine	*Sophora Flavescens*	Soluble in water	COX2
Hypericin	St. John's wort	Soluble in water	COX- 2, NF-κB
Anthraquinone	Senna fruits, rhubarb root, aloe	Poorly soluble in water	COX2
Resveratrol	Grape, blueberries, peanuts, cranberries, red wines	Soluble in water	COX2, NF-κB

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Table 3.4. (cont.)

Active chemical component	Sources	Solubility	Mechanism(inhibition)
Epigallocatechin gallate (EGCG)	Green tea, hazelnut, strawberry, kiwi, cherry	It is recommended to consume with vitamin C, fish oil, and/or black pepper	COX2, PG2
Stilbenes	Cocoa, grape, hop, peanut, strawberry, sugar cane, tomato, bilberry, wines, and berries.	Soluble in water	COX2 TLR4
Zinc	Oyster, meat, egg, raisin bran, yogurt	Poorly soluble in water	NF-κB, TNF-α, IL-1β
Hesperidin	Tomatoes	Soluble in water	COX2, IL-8
Naringenin	Citrus fruit	Soluble in water	COX2,TNF-α, iNOS
PINO	Sesame, Olive oil	Soluble in oil	COX2, IL-6, PGE_2
Boswellik acid	*B. serrata*	Soluble in water	COX2
Curcumin	Turmeric	Poorly soluble in water	COX2, iNOS, TNF-α, IL -1, -2, -6, -8 and -12
Betulinic acid	Tree bark	Soluble in water	NF-κB
Aucubin, catalposide, genipin, α-pinene	Verbena	Essential oil	NF-κB
Selenium	Tuna, cod, poultry, eggs	Soluble in water	NF-κB

(cont. on next page)

Table 3.4. (cont.)

Active chemical component	Sources	Solubility	Mechanism(inhibition)
β -Carotene	Red palm oil, palm fruits, leafy green vegetables, carrots, sweet potatoes, mature squashes, pumpkins, mangoes, and papayas	When combined with beta carotene E and C vitamins, its effect is further increased.	COX2, iNOS, TNF-α, IL-1β, NF-κB
L-carnitine (LC)	Red meat, codfish, avocado, and nuts	Soluble in water	NF-κB, TNF-α
Ginsenosides	Ginseng	Soluble in water	NF-κB
Lycopene	Tomato, watermelon, pink grapefruit, rosehip and papaya	Consumption of lycopene-containing foods together with oil will allow the body to get better lycopene.	NF-κB
Parthenolide	Feverfew	Soluble in water	NF-κB
Pterostilbene	Blueberries	Poorly soluble in water	TNF-α, IL-6, MAPK
Costunolide and Sesquiterpenoids	*Magnolia grandiflora*	Essential oil	NF-κB
Carnosol	Rosemary, ginkgo and various Chinese roots	Soluble in water	NF-κB
Lutein	Green vegetables such as spinach, cabbage but also in egg yolks	It is may be consumed with resveratrol, omega 3, vitamin C, vitamin E, copper, zinc, selenium.	NF-κB
Tanshinone IIA, andalusol, ginkgolides	Rosemary, ginkgo and various Chinese roots.	Essential oil	NF-κB

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Table 3.4. (cont.)

Active chemical component	Sources	Solubility	Mechanism(inhibition)
Kaempferol	Broccoli, cabbage, kale, beans, endive, leek, tomato, strawberries, and grapes	Poorly soluble in water	NF-κB
Flavones	Chamomile, parsley, tea, rosemary, oregano, wine, kiwi, spinach, lettuce, broccoli, grapefruit, cereal and legumes	Soluble in water	NF-κB TLR4
Proanthocyanidins	Fruits, vegetables, nuts, seeds, flowers and tree bark	Soluble in water	NF-κB
Gingerol, shogaol	Ginger	Soluble in water	PG2, IL-1, TNF-α, IL-8
Indole alkaloids	Marine sources	Soluble in water	PG2
Lupeol	White cabbage, pepper, cucumber, tomato, olive, fig, mango, strawberry, red grapes, American ginseng, Shea butter plant	Poorly soluble in water	PG2
Ellagic acid and gallic acid	Pomegranate	Slightly soluble in water	PG2, IL-6, iNOS
Salicylic acid	Cranberry juice extract	Poorly soluble in water	PG2

(cont. on next page)

Table 3.4. (cont.)

Active chemical component	Sources	Solubility	Mechanism(inhibition)
Isoflavones	Soybeans, soy foods, and legumes	Soluble in water	IL-1β, IL-6, IL-12, and TNF-α
Vitamin E	Nuts, oils, green vegetables, tomatoes, olives, sweet potato, papayas, pumpkins, and mangoes	Soluble in oil	IL-1β, IL-6, and TNF-α
Allicin	Garlic	It is slightly soluble in water	TNF-α, IL-1β, INF-γ, IL-6, and IL-12
Vitamin C	Citrus fruits, papayas, strawberries, cantaloupes, kiwi, bell peppers, broccoli, and cauliflower	Soluble in water	TNF-α, IL-6
Sulforaphane	Broccoli, cabbage, cauliflower, and kale	Soluble in water	TNF-α, IL-6

CHAPTER 4

CONCLUSION

BD is a complex disease where several genetic and non-genetic factors contribute to disease risk. The results suggest that the major anti-inflammatory cytokine IL-10 pathway may be an important player in BD risk. Clearly other genetic and environmental factors also contribute, and possibly interact with IL-10 pathway modifying its role in BD. Further studies with larger sample sizes and more comprehensive genetic and non-genetic data are essential to understand the etiopathogenesis of BD.

Diet regimens in BD are largely unexplored. BD patients may not benefit from so-called anti-inflammatory foods because they have to consume very large amounts to see potential effects. However, functional foods or other products with high amounts of key anti-inflammatory components that are derived from natural sources may be more useful for BD patients.

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APPENDIX A

GENES, VARIANTS, AND BIOLOGICAL PATHWAYS ASSOCIATED WITH BEHCET'S DISEASE REPORTED IN THE LITERATURE

Table A.1. Genes, variants, and biological pathways associated with Behcet's Disease

Gene	Biological Pathway	Variant/SNP	Type	Behcet Allele	Effect on Behcet	OR	P value	Behcet Pop
PSORS1C1		rs4959053	Intron	A	Susceptible	3.18	$1.8x10^{-26}$	Japanese
POU5F1		rs9501063	Exon	G	Susceptible	2.54	$1.2x10^{-23}$	Japanese
CCHCR1		rs2073716	Intron	C	Susceptible	2.57	$1.7x10^{-23}$	Japanese
IL-10	Interleukin signaling	rs1518111	Intron	A	Susceptible	1.45	$3.54x10^{-18}$	Turkish
MUC21		rs2517446	Upstream	C	Susceptible	2.28	$1.5x10^{-17}$	Japanese
LOC285830 (HLA-F antisense RNA1)		rs1610637	Upstream	C	Susceptible	2.17	$8.3x10^{-17}$	Japanese
LOC285830 (HLA-F antisense RNA1)		rs885940	Upstream	A	Susceptible	2.13	$2.4x10^{-16}$	Japanese
HLA-B	Immunoglobulin receptor	rs9266409	Upstream	C	Susceptible	1.92	$2.4x10^{-16}$	Japanese
POU5F1		rs3130501	Intron	A	Protective	0.50	$2.5x10^{-16}$	Japanese
HLA-G	Immunoglobulin receptor	rs2523408	Upstream	G	Susceptible	2.10	$2.7x10^{-16}$	Japanese
LOC285830 (HLA-F antisense RNA1)		rs1633041	Upstream	T	Susceptible	2.15	$6.2x10^{-16}$	Japanese
POU5F1		rs9263804	Intron	C	Protective	0.52	$1.2x10^{-15}$	Japanese
HLA-G	Immunoglobulin receptor	rs1611172	Upstream	G	Susceptible	2.08	$1.4x10^{-15}$	Japanese
HLA-G	Immunoglobulin receptor	rs1736963	Upstream	T	Susceptible	2.08	$1.5x10^{-15}$	Japanese
POU5F1		rs3132524	Intron	A	Protective	0.52	$2x10^{-15}$	Japanese
HLA-B	Immunoglobulin receptor	rs9266406	Upstream	A	Susceptible	1.86	$2.1x10^{-15}$	Japanese
HLA-G	Immunoglobulin receptor	rs753544	Upstream	T	Susceptible	2.08	$3.3x10^{-15}$	Japanese
HLA-B	Immunoglobulin receptor	rs6910516	Upstream	C	Susceptible	1.86	$6x10^{-15}$	Japanese
IL-10	Interleukin signaling	rs1800871	Upstream	T	Susceptible	1.45	$1x10^{-14}$	Japanese
HLA-G	Immunoglobulin receptor	rs407238	Downstream	C	Susceptible	2.01	$1.6x10^{-14}$	Japanese

(cont. on next page)

Table A.1. (cont.)

Gene	Biological Pathway	Variant/SNP	Type	Behcet Allele	Effect on Behcet	OR	P value	Behcet Pop
IL-10	Interleukin signaling	rs1800872	Upstream	A	Susceptible	1.45	$2.1x10^{-14}$	Jap-Turk-Korean
HLA-G	Immunoglobulin receptor	rs1633002	Upstream	A	Susceptible	2.01	$1.1x10^{-13}$	Japanese
HLA-G	Immunoglobulin receptor	rs1632973	Upstream	A	Susceptible	2.00	$1.6x10^{-13}$	Japanese
MUC21		rs2844673	Downstream	A	Susceptible	1.96	$1.7x10^{-13}$	Japanese
MUC21		rs2252926	Downstream	G	Susceptible	1.97	$1.8x10^{-13}$	Japanese
CCR1	Inflammation mediated by chemokine and cytokine signaling	rs7616215	Downstream	T	Protective	0.72	$4.3x10^{-13}$	Turkish-Japanese-Han Chinese
MUC21		rs2517411	Downstream	G	Susceptible	1.95	$4.9x10^{-13}$	Japanese
MEFV		rs61752717	Exon	G	Susceptible	2.65	$1.79x10^{-12}$	Turkish
CCHCR1		rs2240063	Intron	A	Protective	0.55	$2.1x10^{-12}$	Japanese
RNF39		rs9261317	Exon	A	Susceptible	2.25	$3.1x10^{-12}$	Japanese
MUC21		rs1632854	Downstream	T	Susceptible	1.82	$3.2x10^{-12}$	Japanese
MUC21		rs2523915	Downstream	T	Susceptible	1.90	$7.7x10^{-12}$	Japanese
TNFAIP3	Toll receptor signaling	rs9494885	Upstream	T	Protective	0.50	$8.26x10^{-12}$	Han Chinese
HLA-F	Immunoglobulin receptor	rs3116788	Upstream	G	Protective	0.48	$8.4x10^{-12}$	Japanese
IFNγ	Inflammation mediated by chemokine and cytokine signaling		Downstream	A	Susceptible	3.53	$1x10^{-11}$	Turkish
MUC21		rs1634717	Downstream	T	Susceptible	1.80	$1.6x10^{-11}$	Japanese
TCF19		rs2073723	Intron	T	Protective	0.57	$1.9x10^{-11}$	Japanese
MUC21		rs2252925	Downstream	G	Susceptible	1.87	$2.1x10^{-11}$	Japanese
C6orf15		rs1265048	Upstream	A	Protective	0.59	$2.6x10^{-11}$	Japanese
HLA-C	Immunoglobulin receptor	rs3905495	Upstream	C	Protective	0.59	$4.7x10^{-11}$	Japanese

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Table A.1. (cont.)

Gene	Biological Pathway	Variant/SNP	Type	Behcet Allele	Effect on Behcet	OR	P value	Behcet Pop
BTNL2	Cellular defense response	rs2076530	Exon	G	Protective	0.59	$4.7x10^{-11}$	Japanese
ERAP1	Cell-cell signaling	rs17482078	Exon	T	Susceptible	4.56	$4.73x10^{-11}$	Turkish
HLA-F	Immunoglobulin receptor	rs1610584	Upstream	T	Protective	0.51	$6.5x10^{-11}$	Japanese
ZNRD1	RNA metabolic process	rs9261265	Upstream	C	Susceptible	2.04	$7.3x10^{-11}$	Japanese
HLA-F	Immunoglobulin receptor	rs1611388	Upstream	C	Protective	0.52	$7.8x10^{-11}$	Japanese
HLA-DQA1	T cell activation	rs9272346	Upstream	G	Protective	0.60	$8.7x10^{-11}$	Japanese
LOC285830 (HLA-F antisense RNA1)		rs2844845	Intron	A	Susceptible	2.07	$9.5x10^{-11}$	Japanese
HCG9		rs9260954	Downstream	G	Susceptible	2.06	$1.2x10^{-10}$	Japanese
GABBR1	GABA-B receptor II signaling	rs29273	Upstream	G	Susceptible	2.03	$1.4x10^{-10}$	Japanese
MUC21		rs2530710	Upstream	A	Protective	0.53	$3x10^{-10}$	Japanese
HLA-F	Immunoglobulin receptor	rs1610585	Upstream	C	Protective	0.52	$3.3x10^{-10}$	Japanese
HCG9		rs6926792	Downstream	A	Susceptible	1.75	$3.3x10^{-10}$	Japanese
DHFRP2		rs7761068	Exon	T	Protective	0.48	$3.5x10^{-10}$	Japanese
UBD	Proteolysis	rs3025657	Downstream	G	Protective	0.48	$3.8x10^{-10}$	Japanese
HCG27		rs3130944	Downstream	C	Susceptible	1.70	$4.3x10^{-10}$	Japanese
HLA-F	Immunoglobulin receptor	rs1610593	Upstream	T	Protective	0.53	$4.5x10^{-10}$	Japanese
MICA	Immunoglobulin receptor	rs3094584	Downstream	T	Susceptible	1.69	$4.7x10^{-10}$	Japanese
HLA-F	Immunoglobulin receptor	rs1611381	Upstream	T	Protective	0.53	$5.6x10^{-10}$	Japanese
ABCB5	Regulation of biological process	rs2190411	Intron	C	Susceptible	2.51	$8.77x10^{-10}$	Han Chinese
C6orf10		rs574710	Intron	G	Susceptible	1.65	$9.7x10^{-10}$	Japanese
C6orf47		rs2242655	Exon	C	Susceptible	1.70	$1.1x10^{-09}$	Japanese

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Table A.1. (cont.)

Gene	Biological Pathway	Variant/SNP	Type	Behcet Allele	Effect on Behcet	OR	P value	Behcet Pop
KLRC4	Membrane-bound signaling	rs2617170	Exon	C	Protective	0.78	$1.34x10^{-09}$	Turkish-Japanese
SGPP2	Apoptotic process	rs17562982	Intron	T	Susceptible	2.79	$1.91x10^{-09}$	Han Chinese
TRIM31		rs9261376	Downstream	G	Susceptible	1.67	$2.2x10^{-09}$	Japanese
MICA	Immunoglobulin receptor	rs2523467	Upstream	A	Protective	0.59	$2.3x10^{-09}$	Japanese
SUSD1		rs2782932	Intron	T	Susceptible	2.41	$2.47x10^{-09}$	Han Chinese
TRIM31		rs6923832	Downstream	A	Susceptible	2.00	$2.5x10^{-09}$	Japanese
HLA-F	Immunoglobulin receptor	rs1627465	Upstream	C	Protective	0.54	$2.6x10^{-09}$	Japanese
C6orf10		rs544358	Intron	C	Susceptible	1.63	$2.8x10^{-09}$	Japanese
RIMBP2	Cellular process	rs2895135	Intron	A	Susceptible	2.55	$3.35x10^{-09}$	Han Chinese
HLA-F	Immunoglobulin receptor	rs1611356	Upstream	G	Protective	0.55	$3.4x10^{-09}$	Japanese
HLA-DQA1	T cell activation	rs9272723	Intron	T	Protective	0.61	$4.8x10^{-09}$	Japanese
C6orf10		rs926591	Intron	T	Susceptible	1.62	$5.1x10^{-09}$	Japanese
BAG6(BAT3)	Enzyme modulator	rs2077102	Intron	T	Susceptible	1.64	$5.2x10^{-09}$	Japanese
C6orf10		rs539703	Intron	C	Susceptible	1.61	$5.3x10^{-09}$	Japanese
FUT2	Biosynthetic process	rs681343	Exon	T	Susceptible	1.30	$5.9x10^{-09}$	Iranian-Turkish
API5		rs16937370	Upstream	G	Susceptible	2.46	$6.01x10^{-09}$	Han Chinese
TRIM31		rs9261389	Downstream	G	Susceptible	1.64	$6.1x10^{-09}$	Japanese
SMG6		rs749240	Exon	T	Susceptible	2.49	$6.43x^{-09}$	Han Chinese
IL23R,IL12RB2	Interleukin signaling	rs924080	down/up	T	Susceptible	1.28	$6.69x10^{-09}$	Japanese-Turkish

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Table A.1. (cont.)

Gene	Biological Pathway	Variant/SNP	Type	Behcet Allele	Effect on Behcet	OR	P value	Behcet Pop
HLA-G	Immunoglobulin receptor	rs1077433	Upstream	A	Susceptible	1.79	$6.9x10^{-09}$	Japanese
C6orf10		rs4959093	Intron	C	Susceptible	1.62	$8.6x10^{-09}$	Japanese
LOC285830 (HLA-F antisense RNA1)		rs9258205	Intron	C	Protective	0.56	$9.5x10^{-09}$	Japanese
SLC44A4	Transporter	rs11965547	Intron	A	Susceptible	1.65	$1x10^{-08}$	Japanese
MOG	Exocytosis	rs3129045	Downstream	T	Susceptible	1.78	$1.2x10^{-08}$	Japanese
ZNRD1	RNA metabolic process	rs9261189	Upstream	T	Susceptible	1.64	$1.4x10^{-08}$	Japanese
HLA-F	Immunoglobulin receptor	rs7741807	Upstream	G	Protective	0.54	$1.5x10^{-08}$	Japanese
HCG9		rs6931776	Downstream	G	Susceptible	1.63	$1.7x10^{-08}$	Japanese
SLC43A3	Amino acid transport	rs549630	Downstream	G	Susceptible	2.27	$2.04x10^{-08}$	Han Chinese
HLA-DQB1	MHC antigen	rs6457617	Upstream	C	Protective	0.63	$2.1x10^{-08}$	Japanese
GALNTL1	Glycosyltransferase	rs12589991	Intron	A	Susceptible	2.51	$2.16x10^{-08}$	Han Chinese
PPP1R11	Cellular process	rs2074482	Exon	T	Susceptible	1.60	$2.2x10^{-08}$	Japanese
HLA-G	Immunoglobulin receptor	rs1736951	Upstream	A	Susceptible	1.75	$2.3x10^{-08}$	Japanese
LOC285830 (HLA-F antisense RNA1)		rs1615251	Upstream	T	Susceptible	1.62	$2.7x10^{-08}$	Japanese
IL23R,IL12RB2	Interleukin signaling	rs12119179	down/up	A	Susceptible	1.55	$2.7x10^{-08}$	Japanese-Turkish
UBD	Proteolysis	rs6933331	Downstream	A	Protective	0.55	$2.8x10^{-08}$	Japanese
ZNRD1	RNA metabolic process	rs3869068	Upstream	A	Susceptible	1.61	$3.3x10^{-08}$	Japanese
SLIT2	Axon guidance mediated by Slit/Robo	rs13435197	Intron	A	Susceptible	2.46	$3.59x10^{-08}$	Han Chinese
HCG9		rs6911737	Downstream	A	Susceptible	1.60	$4.1x10^{-08}$	Japanese

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Table A.1. (cont.)

Gene	Biological Pathway	Variant/SNP	Type	Behcet Allele	Effect on Behcet	OR	P value	Behcet Pop
LOC285830 (HLA-F antisense RNA1)		rs1737031	Upstream	A	Susceptible	1.59	$4.4x10^{-08}$	Japanese
ASB18		rs7561555	Intron	C	Susceptible	2.28	$4.7x10^{-08}$	Han Chinese
IL23R,IL12RB2	Interleukin signaling	rs11209033	down/up	C	Susceptible	1.54	$5.5x10^{-08}$	Japanese-Turkish
GIMAP4	Immune system process	rs1608157	Upstream	C	Susceptible	2.53	$6.01x10^{-08}$	Korean
IL-10	Interleukin signaling	rs1554286	Intron	C	Protective	0.62	$8x10^{-08}$	Chinese
IL23R,IL12RB2	Interleukin signaling	rs12141431	down/up	C	Susceptible	1.52	$1.1x10^{-07}$	Han Chinese
CPLX1	Neurological system process	rs11248047	Upstream	A	Susceptible	1.36	$1.26x10^{-07}$	Turkish
COL12A1	Inflammation mediated by chemokine and cytokine signaling	rs4640857	Downstream	G	Protective	0.65	$1.3x10^{-07}$	Japanese
GIMAP4	Immune system process	rs1916012	Upstream	T	Susceptible	2.38	$2.62x10^{-07}$	Korean
GIMAP4	Immune system process	rs1522596	Upstream	T	Susceptible	2.38	$3.47x10^{-07}$	Korean
DNMT3A		rs1465825	Intron	C	Protective	0.49	$3.83x10^{-07}$	Han Chinese
C10orf11	Cell differentiation	rs1323076	Intron	G	Protective	0.61	$1.2x10^{-06}$	Japanese
PAX8	DNA binding protein	rs11123169	Downstream	C	Susceptible	1.53	$1.3x10^{-06}$	Japanese
MSX2	Mesoderm development	rs10516130	Downstream	A	Protective	0.23	$2.98x10^{-06}$	Han Chinese
SORBS2	Actin family cytoskeletal protein	rs4493590	Intron	G	Susceptible	1.86	$4.88x10^{-06}$	Han Chinese
HIVEP3	Biosynthetic process	rs4660590	Intron	A	Protective	0.69	$5.7x10^{-06}$	Japanese
CEP135	Cell cycle	rs2593082	Intron	T	Susceptible	1.42	$6.2x10^{-06}$	Japanese

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Table A.1. (cont.)

Gene	Biological Pathway	Variant/SNP	Type	Behcet Allele	Effect on Behcet	OR	P value	Behcet Pop
UBAC2	Proteolysis	rs3825427	Upstream	T	Susceptible	1.50	$6.9x10^{-06}$	Chinese
RALGAPA2		rs6082210	Upstream	A	Protective	0.17	7.01x1t0-06	Han Chinese
GIMAP1	Immune system process	rs2286900	Exon	T	Susceptible	1.81	9.22x10-06	Korean
TTLL7	Ligase	rs11163772	Downstream	A	Susceptible	1.52	$9.5x10^{-06}$	Japanese
HMP19		rs1909704	Downstream	A	Susceptible	1.43	$9.5x10^{-06}$	Japanese
TFCP2L1	Biosynthetic process	rs17006292	Intron	A	Protective	0.13	1.03x10-05	Han Chinese
TENM4(ODZ4)	Intracellular signal	rs2156215	Intron	T	Protective	0.69	$1.1x10^{-05}$	Japanese
OSR1	Segment specification	rs4666492	Upstream	G	Protective	0.62	$1.2x10^{-05}$	Japanese
KLRK1	B cell mediated immunity	rs2617151	Intron	A	Protective	0.63	$1.2x10^{-05}$	Japanese
CTNNA2	Wnt signaling	rs4852547	Intron	G	Protective	0.62	$1.3x10^{-05}$	Japanese
IL12A	Inflammation mediated by chemokine and cytokine signaling	rs17810546	Upstream	A	Susceptible	1.66	1.49x10-05	Turkish-mixed
MN1		rs134006	Downstream	C	Susceptible	1.46	$1.6x10^{-05}$	Japanese
CEP135	Cell cycle	rs2611826	Intron	G	Susceptible	1.40	$1.6x10^{-05}$	Japanese
PSMD14	Ubiquitin proteasome	rs6744214	Intron	T	Susceptible	1.76	1.67x10-05	Han Chinese
LINC01499(API5)		rs420798	Intron	C	Susceptible	1.72	1.79x10-05	Han Chinese
C6orf85(LOC100507336)	Anion transport	rs12194547	Intron	C	Protective	0.16	1.91x10-05	Han Chinese
PSMD14	Ubiquitin proteasome	rs6733456	Intron	C	Susceptible	1.75	1.98x10-05	Han Chinese
LTN1(RNF160)	Protein metabolic process	rs2832137	Downstream	T	Protective	0.64	$2.1x10^{-05}$	Japanese
HERPUD2		rs11763983	Downstream	T	Protective	0.66	$2.1x10^{-05}$	Japanese

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Table A.1. (cont.)

Gene	Biological Pathway	Variant/SNP	Type	Behcet Allele	Effect on Behcet	OR	P value	Behcet Pop
LILRA1	Cellular process	rs103294	Upstream	C	Susceptible	1.76	2.19x10-05	Han Chinese
LILRB1	Cellular process	rs798887	Upstream	A	Susceptible	1.83	2.23x10-05	Han Chinese
SAMD3(TMEM200A)	Kinase modulator	rs9483115	Intron	T	Protective	0.72	$2.5x10^{-05}$	Japanese
GALNT10	Polysaccharide metabolic process	rs574750	Intron	A	Susceptible	1.66	$2.5x10^{-05}$	Japanese
GIMAP2	Immune system process	rs10266069	Upstream	A	Susceptible	1.83	2.57x10-05	Korean
KLRK1	B cell mediated immunity	rs2733852	Intron	G	Protective	0.65	$2.8x10^{-05}$	Japanese
DEPDC1	Intracellular signal transduction	rs6692084	Upstream	A	Susceptible	1.89	2.81x10-05	Han Chinese
GIMAP2	Immune system process	rs10256482	Upstream	T	Susceptible	1.83	2.82x10-5	Korean
UBAC2	Proteolysis	rs9517701	Intron	G	Susceptible	1.40	$2.9x10^{-05}$	Chinese
DEPDC1	Intracellular signal transduction	rs12134670	Upstream	C	Susceptible	2.15	3.13x10-05	Han Chinese
SEMA6D	Membrane-bound signaling molecule	rs470151	Downstream	T	Susceptible	1.54	$3.2x10^{-05}$	Japanese
CDH26	Cadherin	rs817277	Downstream	A	Susceptible	1.78	3.24x10-05	Han Chinese
PMFBP1		rs11862324	Upstream	T	Susceptible	1.39	$3.3x10^{-05}$	Japanese
SAMD3	Kinase modulator	rs4897380	Intron	C	Susceptible	1.38	$3.4x10^{-05}$	Japanese
NAV2		rs2707110	Intron	C	Susceptible	1.43	$3.5x10^{-05}$	Japanese
UBAC2	Proteolysis	rs9517668	Intron	T	Susceptible	2.62	3.61x10-05	Turkish-Italy
STK39	Apoptotic process	rs2390639	Intron	A	Susceptible	1.72	3.97x10-05	Han Chinese
TMEM132B		rs4435061	Intron	A	Protective	0.73	$4x10^{-05}$	Japanese

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Table A.1. (cont.)

Gene	Biological Pathway	Variant/SNP	Type	Behcet Allele	Effect on Behcet	OR	P value	Behcet Pop
STX8	SNARE protein	rs1549332	Intron	A	Susceptible	1.59	$4x10^{-05}$	Japanese
SAMD3(TMEM200A)	Kinase modulator	rs4141940	Intron	A	Protective	0.73	$4x10^{-05}$	Japanese
CCDC180		rs2061634	Exon	G	Susceptible	2.04	$4.2x10^{-05}$	Turkish
OVCH1		rs1436321	Downstream	A	Susceptible	1.39	$4.4x10^{-05}$	Japanese
SLC41A2	Cation transporter	rs2731031	Intron	A	Susceptible	1.40	$4.7x10^{-05}$	Japanese
NAV2		rs873764	Intron	G	Susceptible	1.42	$4.7x10^{-05}$	Japanese
HNF4G	Nuclear hormone receptor	rs2980221	Upstream	A	Protective	0.71	$4.8x10^{-05}$	Japanese
IL1		rs1800587	Exon	C	Susceptible	2.90	$5x10^{-05}$	Turkish
SMARCA2	Wnt signaling	rs7033529	Intron	A	Protective	0.73	$5.1x10^{-05}$	Japanese
EBF2		rs4570167	Intron	C	Susceptible	1.47	$5.2x10^{-05}$	Japanese
GAS2	Non-motor actin binding protein	rs10833804	Intron	G	Protective	0.73	$5.4x10^{-05}$	Japanese
PAX8	DNA binding protein	rs10864912	Intron	T	Susceptible	1.47	$5.7x10^{-05}$	Japanese
DTL		rs1472224	Downstream	G	Protective	0.16	$5.73x10^{-05}$	Han Chinese
STAT4	JAK/STAT signaling	rs897200	Intron	A	Susceptible	1.45	$5.88x10^{-05}$	Han Chinese
LYST/NID1	Receptor	rs7354999	Up/down	G	Susceptible	1.38	$6.1x10^{-05}$	Japanese
STK39	Apoptotic process	rs3769393	Intron	G	Susceptible	1.70	$6.17x10^{-05}$	Han Chinese
TMEM132B		rs10846917	Intron	T	Susceptible	1.39	$6.3x10^{-05}$	Japanese
LOC100132252		rs9469615	Intergenic	C	Protective	0.63	$6.3x10^{-05}$	Japanese
CDH26	Cadherin	rs817283	Downstream	A	Susceptible	1.74	$6.42x10^{-05}$	Han Chinese
SAMD3(TMEM200A)	Kinase modulator	rs899276	Intron	A	Protective	0.73	$6.5x10^{-05}$	Japanese
LOC107984355		rs872837	Intron	A	Susceptible	1.46	$6.5x10^{-05}$	Japanese
SACM1L	Phosphatase	rs1969624	Intron	C	Protective	0.67	$6.8x10^{-05}$	Japanese

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Table A.1. (cont.)

Gene	Biological Pathway	Variant/SNP	Type	Behcet Allele	Effect on Behcet	OR	P value	Behcet Pop
IL23R	Defense/immunity protein	rs11209026	Intron	A	Protective	0.68	$6.9x10^{-05}$	Turkish-Japanese
IL23R	Defense/immunity protein	rs76418789	Intron	A	Protective	0.54	$6.9x10^{-05}$	Turkish-Japanese
PLEKHB1		rs591804	Intron	G	Protective	0.72	$7.4x10^{-05}$	Japanese
SAMD3(TMEM200A)	Kinase modulator	rs7758496	Intron	G	Protective	0.73	$7.7x10^{-05}$	Japanese
TMEM132B		rs10846924	Intron	T	Protective	0.74	$8x10^{-05}$	Japanese
ATP8A1	Biological regulation	rs2100766	Upstream	T	Protective	0.62	$8.2x10^{-05}$	Japanese
IL23R,IL12RB2	Interleukin signaling	rs1495965	down/up	G	Susceptible	1.25	$8.4x10^{-05}$	Japanese-Turkish
EBF2		rs4242425	Intron	T	Susceptible	1.44	$8.4x10^{-05}$	Japanese
UBAC2	Proteolysis	rs9554581	Intron	T	Susceptible	2.48	$8.53x10^{-05}$	Turkish-Italy
STAT4	JAK/STAT signaling	rs7574070	Intron	A	Susceptible	1.27	$8.56x10^{-05}$	Turkish-Japanese
CCR1	Inflammation mediated by chemokine and cytokine signaling	rs17282391	Downstream	G	Protective	0.15	$8.66x10^{-05}$	Han Chinese
CCR1	Inflammation mediated by chemokine and cytokine signaling	rs13084057	Downstream	G	Protective	0.15	$8.66x10^{-05}$	Han Chinese
CCR1	Inflammation mediated by chemokine and cytokine signaling	rs7631551	Downstream	A	Protective	0.15	$8.66x10^{-05}$	Han Chinese
C10orf11	Cell differentiation	rs17434565	Intron	G	Protective	0.64	$9x10^{-05}$	Japanese
SAMD3(TMEM200A)	Kinase modulator	rs724324	Intron	G	Protective	0.74	$9.5x10^{-05}$	Japanese
KCNK9	Opioid proopiomelanocortin	rs1961261	Downstream	A	Protective	0.69	$9.5x10^{-05}$	Japanese
STAT4	JAK/STAT signaling	rs7572482	Intron	A	Susceptible	1.68	$9.77x10^{-05}$	Turkish

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Table A.1. (cont.)

Gene	Biological Pathway	Variant/SNP	Type	Behcet Allele	Effect on Behcet	OR	P value	Behcet Pop
CCR3	Inflammation mediated by chemokine and cytokine signaling	rs13075270	Intron	C	Protective	0.13	$9.9x10^{-05}$	Han Chinese
CCR3	Inflammation mediated by chemokine and cytokine signaling	rs13092160	Intron	C	Protective	0.13	$9.9x10^{-05}$	Han Chinese
CCR3	Inflammation mediated by chemokine and cytokine signaling	rs2373156	Intron	T	Protective	0.13	$9.9x10^{-05}$	Han Chinese
CCR3	Inflammation mediated by chemokine and cytokine signaling	rs1542755	Intron	A	Protective	0.13	$9.9x10^{-05}$	Han Chinese
UBAC2	Proteolysis	rs727263	Intron	A	Susceptible	2.45	$1x10^{-04}$	Turkish-Italy
CPVL	Catabolic process	rs317711	Intron	C	Susceptible	2.26	$1x10^{-04}$	Turkish
UBAC2	Proteolysis	rs7332161	Intron	A	Susceptible	2.43	$1.1x10^{-04}$	Turkish-Italy
IL23R	Defense/immunity protein	rs17375018	Intron	G	Susceptible	1.57	$1.11x10^{-04}$	Han Chinese
CCR1	Inflammation mediated by chemokine and cytokine signaling	rs10510749	Downstream	T	Protective	0.16	$1.22x10^{-04}$	Han Chinese
IL23R	Defense/immunity protein	rs11209032	Downstream	A	Susceptible	1.48	$1.58x10^{-04}$	Han Chinese
UBAC2	Proteolysis	rs17575643	Intron	T	Susceptible	2.91	$1.8x10^{-04}$	Turkish-Italy
SUMO4	p53	rs237024	Downstream	C	Susceptible	1.70	$2x10^{-04}$	Han Chinese
IL1		rs16944	Upstream	G	Susceptible	2.19	$2x10^{-04}$	Turkish
CCR3	Inflammation mediated by chemokine and cytokine signaling	rs13067058	Intron	A	Protective	0.14	$2x10^{-04}$	Han Chinese
UBAC2	Proteolysis	rs2892976	Downstream	G	Susceptible	1.96	$2.3x10^{-04}$	Turkish-Italy
LOC100129342		rs11206377	Intergenic	G	Susceptible	1.84	$3x10^{-04}$	Turkish
UBAC2	Proteolysis	rs7999348	Intron	G	Susceptible	1.78	$5.8x10^{-04}$	Turkish-Italy
TNFAIP3	Toll receptor signaling	rs10499194	Upstream	C	Susceptible	1.92	$1x10^{-03}$	Han Chinese
TNFAIP3	Toll receptor signaling	rs7753873	Upstream	C	Susceptible	1.49	$1x10^{-03}$	Han Chinese

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Table A.1. (cont.)

Gene	Biological Pathway	Variant/SNP	Type	Behcet Allele	Effect on Behcet	OR	P value	Behcet Pop
IL6	Interleukin signaling			C			$1x10^{-03}$	Turkish
UBAC2	Proteolysis	rs6491493	Intron	G	Susceptible	1.74	$1.1x10^{-03}$	Turkish-Italy
UBAC2	Proteolysis	rs9554573	Intron	A	Susceptible	1.73	$1.2x10^{-03}$	Turkish-Italy
UBAC2	Proteolysis	rs9517644	Upstream	T	Susceptible	1.72	$1.3x10^{-03}$	Turkish-Italy
CCR3	Inflammation mediated by chemokine and cytokine signaling	rs13092160	Intron	C	Protective	0.13	$1.48x10^{-03}$	Han Chinese
UBASH3B	Metabolic process	rs4936742	Intron	T	Susceptible	1.71	$1.5x10^{-03}$	Turkish
UBAC2	Proteolysis	rs11069357	Upstream	A	Susceptible	1.68	$2x10^{-03}$	Turkish-Italy
TLR4	Toll receptor signaling	rs4986790	Exon	G	Protective	0.64	$3x10^{-03}$	Turkish-Japanese
TLR4	Toll receptor signaling	rs4986791	Exon	T	Protective	0.82	$3x10^{-03}$	Turkish-Japanese
CCR3	Inflammation mediated by chemokine and cytokine signaling	rs9990343	Downstream	G	Protective	0.48	$3.4x10^{-03}$	Han Chinese
CCR3	Inflammation mediated by chemokine and cytokine signaling	rs6803980	Downstream	A	Protective	0.48	$3.4x10^{-03}$	Han Chinese
TNFα	Wnt signaling	rs1799724	Upstream	T	Protective	0.76	$4x10^{-03}$	Turkish
IL12		rs3212227	Downstream	Susceptible	1.84	$4x10^{-03}$	Turkish	
UBAC2	Proteolysis	rs984477	Intron	G	Susceptible	1.65	$4.3x10^{-03}$	Turkish-Italy
UBAC2	Proteolysis	rs9513584	Intron	G	Susceptible	1.61	$5.8x10^{-03}$	Turkish-China
TNFα	Wnt signaling	rs361525	Upstream	A	Susceptible	1.51	$6x10^{-03}$	Turkish
TNFα	Wnt signaling	rs1799964	Upstream	C	Susceptible	1.35	$7x10^{-03}$	Turkish

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Table A.1. (cont.)

Gene	Biological Pathway	Variant/SNP	Type	Behcet Allele	Effect on Behcet	OR	P value	Behcet Pop
UBAC2	Proteolysis	rs912130	Intron	C	Susceptible	1.58	$7.1x10^{-03}$	Turkish-Italy
CCR3	Inflammation mediated by chemokine and cytokine signaling	rs7651539	Intron	T	Protective	0.35	$8x10^{-03}$	Han Chinese
IL18	Interleukin signaling	rs1946518	promoter	C	Susceptible	1.67	$1.01x10^{-02}$	Korean
IL1			Exon	C	Susceptible	2.60	$1.5x10^{-02}$	Turkish
NOD2	Nucleic acid binding	rs2066844	Exon	T	Protective	0.40	$2x10^{-02}$	Turkish-Japanese
NOD2	Nucleic acid binding	rs2066845	Exon	C	Protective	0.66	$2x10^{-02}$	Turkish-Japanese
NOD2	Nucleic acid binding	rs2066847	Exon	ins-C	Protective	0.38	$2x10^{-02}$	Turkish-Japanese
CCR3	Inflammation mediated by chemokine and cytokine signaling	rs7649764	Downstream	C	Protective	0.69	$2.2x10^{-02}$	Han Chinese
IL1		rs1143634	Exon	T	Susceptible	1.74	$2.4x10^{-02}$	Turkish
IL23R	Defense/immunity protein	rs1343151	Intron	T	Protective	0.50	$2.9x10^{-02}$	Han Chinese
TNFAIP3	Toll receptor signaling	rs610604	Intron	A	Protective	0.80	$5.5x10^{-02}$	Han Chinese
IL17F-A126G, Glu126Gly	Interleukin signaling	rs2397084	Exon	T	No data		<0,001	Korean

APPENDIX B

DISTRIBUTION OF BEHCET'S DISEASE ASSOCIATED VARIANTS AMONG WORLD POPULATIONS

Table B.1. Distribution of Behcet's Disease associated variants among African populations

Gene	**Variant/SNP**	**Behcet Allele**	**ALL**	**AFR**	ACB	ASW	ESN	GWD	LWK	MSL	YRI
IL-10	rs1518111	A	0.427	0.434	0.385	0.377	0.449	0.473	0.394	0.471	0.463
IL-10	rs1800871	T	0.435	0.436	0.391	0.377	0.449	0.473	0.389	0.476	0.468
IL-10	rs1800872	A	0.435	0.436	0.391	0.377	0.449	0.473	0.394	0.476	0.468
IL-10	rs1554286	C	0.592	0.569	0.625	0.623	0.556	0.527	0.606	0.529	0.542
IL23R,IL12RB2	rs1495965	G	0.466	0.422	0.422	0.484	0.409	0.363	0.419	0.471	0.426
IL23R,IL12RB2	rs924080	T	0.604	0.495	0.484	0.541	0.530	0.403	0.515	0.547	0.481
IL23R,IL12RB2	rs12119179	A	0.644	0.801	0.797	0.746	0.788	0.876	0.778	0.806	0.787
IL23R,IL12RB2	rs11209033	C	0.644	0.797	0.792	0.746	0.783	0.876	0.773	0.806	0.778
IL23R,IL12RB2	rs12141431	C	0.294	0.023	0.036	0.131	0.005	0.013	0.010	0	0.005
TNFAIP3	rs9494885	T	0.794	0.477	0.536	0.639	0.505	0.363	0.551	0.447	0.384
TNFAIP3	rs10499194	C	0.809	0.870	0.833	0.811	0.838	0.876	0.929	0.841	0.926
TNFAIP3	rs610604	A	0.613	0.318	0.354	0.369	0.384	0.292	0.278	0.247	0.315
TNFAIP3	rs7753873	C	0.191	0.463	0.458	0.295	0.449	0.522	0.409	0.441	0.579
STAT4	rs7574070	A	0.494	0.734	0.688	0.623	0.828	0.704	0.753	0.759	0.750
STAT4	rs897200	A	0.499	0.734	0.688	0.615	0.828	0.704	0.753	0.765	0.750
STAT4	rs7572482	A	0.484	0.697	0.635	0.607	0.763	0.699	0.702	0.735	0.704
CCR1	rs17282391	G	0.093	0.003	0.010	0.016	0	0	0	0	0
CCR1	rs10510749	T	0.122	0.111	0.052	0.082	0.056	0.173	0.141	0.141	0.116
CCR1	rs13084057	G	0.122	0.111	0.052	0.082	0.056	0.173	0.141	0.141	0.116
CCR1	rs7631551	A	0.180	0.307	0.198	0.262	0.232	0.336	0.449	0.365	0.292
CCR1	rs7616215	T	0.652	0.523	0.609	0.574	0.566	0.513	0.369	0.512	0.537
CCR3	rs7649764	C	0.634	0.722	0.609	0.656	0.722	0.792	0.662	0.776	0.801
CCR3	rs9990343	G	0.409	0.523	0.432	0.402	0.470	0.673	0.424	0.606	0.593
CCR3	rs6803980	A	0.418	0.559	0.458	0.467	0.500	0.704	0.465	0.624	0.639
CCR3	rs13075270	C	0.156	0.220	0.255	0.230	0.217	0.168	0.227	0.235	0.222
CCR3	rs13092160	C	0.125	0.124	0.130	0.164	0.076	0.097	0.146	0.141	0.134

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Table B.1. (cont.)

Gene	Variant/SNP	Behcet Allele	ALL	AFR	ACB	ASW	ESN	GWD	LWK	MSL	YRI
CCR3	rs2373156	T	0.195	0.374	0.344	0.311	0.359	0.381	0.399	0.441	0.370
CCR3	rs7651539	T	0.195	0.374	0.344	0.311	0.359	0.381	0.399	0.441	0.370
CCR3	rs1542755	A	0.084	0.003	0.010	0.016	0	0	0	0	0
CCR3	rs13067058	A	0.079	0.003	0.010	0.016	0	0	0	0	0
CCR3	rs13092160	C	0.125	0.124	0.130	0.164	0.076	0.097	0.146	0.141	0.134
KLRC4	rs2617170	C	0.557	0.433	0.474	0.516	0.434	0.341	0.455	0.365	0.477
MEFV	rs61752717	G	0.0002	0	0	0	0	0	0	0	0
ERAP1	rs17482078	T	0.101	0.054	0.073	0.074	0.035	0.031	0.040	0.071	0.065
FUT2	rs681343	T	0.322	0.491	0.516	0.508	0.566	0.469	0.439	0.388	0.542
IL12A	rs17810546	A	0.960	0.998	0.995	0.992	1.000	1.000	1.000	1.000	1.000
IL23R	rs11209026	A	0.023	0.003	0	0.016	0	0	0.005	0	0.005
IL23R	rs76418789	A	0.0112	0.0008	0	0.0082	0	0	0	0	0
IL23R	rs17375018	G	0.694	0.794	0.812	0.795	0.854	0.752	0.692	0.818	0.843
IL23R	rs11209032	A	0.354	0.198	0.198	0.246	0.222	0.124	0.212	0.194	0.218
IL23R	rs1343151	T	0.338	0.728	0.703	0.598	0.788	0.730	0.712	0.771	0.750
TLR4	rs4986790	G	0.060	0.071	0.042	0.057	0.051	0.128	0.096	0.076	0.037
TLR4	rs4986791	T	0.041	0.005	0	0	0.010	0.018	0	0.006	0
NOD2	rs2066844	T	0.014	0.002	0.005	0.016	0	0	0	0	0
NOD2	rs2066845	C	0.005	0	0	0	0	0	0	0	0
NOD2	rs2066847	ins-C	0.006	0.004	0.005	0.033	0	0	0	0	0
IL1	rs1800587	C	0.721	0.596	0.568	0.664	0.641	0.531	0.606	0.641	0.565
IL1	rs1143634	T	0.133	0.123	0.130	0.123	0.126	0.168	0.111	0.088	0.102
IL1	rs16944	G	0.491	0.427	0.464	0.443	0.434	0.478	0.359	0.400	0.412
TNFα	rs1799964	C	0.219	0.149	0.130	0.156	0.076	0.164	0.207	0.188	0.130
TNFα	rs361525	A	0.061	0.038	0.016	0.041	0.010	0.084	0.061	0.047	0.005
TNFα	rs1799724	T	0.099	0.024	0.031	0.049	0.025	0.022	0.010	0.024	0.019

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Table B.1. (cont.)

Gene	Variant/SNP	Behcet Allele	ALL	AFR	ACB	ASW	ESN	GWD	LWK	MSL	YRI
IL12	rs3212227	A	0.641	0.648	0.682	0.713	0.616	0.659	0.591	0.647	0.648
IL18	rs1946518	C	0.592	0.650	0.661	0.672	0.662	0.606	0.657	0.635	0.667
IL17F-A126G	rs2397084	T	0.967	0.997	0.995	0.992	1.000	1.000	0.990	1.000	1.000
LOC100129342	rs11206377	G	0.540	0.274	0.271	0.320	0.308	0.319	0.212	0.271	0.231
CCDC180	rs2061634	G	0.278	0.410	0.411	0.402	0.434	0.420	0.394	0.371	0.426
CPVL	rs317711	C	0.173	0.203	0.177	0.246	0.212	0.146	0.222	0.247	0.199
UBASH3B	rs4936742	T	0.389	0.163	0.203	0.230	0.136	0.124	0.182	0.159	0.144
UBAC2	rs9513584	G	0.532	0.728	0.667	0.656	0.763	0.770	0.697	0.771	0.741
UBAC2	rs9517644	T	0.526	0.705	0.641	0.631	0.758	0.743	0.677	0.753	0.704
UBAC2	rs11069357	A	0.526	0.707	0.641	0.639	0.758	0.748	0.677	0.753	0.704
UBAC2	rs984477	G	0.546	0.712	0.641	0.648	0.753	0.757	0.682	0.759	0.718
UBAC2	rs9554573	A	0.559	0.809	0.745	0.746	0.874	0.810	0.773	0.788	0.894
UBAC2	rs6491493	G	0.533	0.726	0.656	0.656	0.768	0.770	0.697	0.771	0.736
UBAC2	rs9517668	T	0.266	0.404	0.385	0.369	0.545	0.319	0.369	0.424	0.417
UBAC2	rs7999348	G	0.555	0.741	0.672	0.680	0.823	0.717	0.747	0.735	0.782
UBAC2	rs9554581	T	0.192	0.135	0.099	0.139	0.167	0.159	0.111	0.171	0.102
UBAC2	rs17575643	T	0.096	0.048	0.031	0.082	0.056	0.044	0.040	0.059	0.042
UBAC2	rs727263	A	0.188	0.121	0.099	0.115	0.136	0.146	0.131	0.147	0.074
UBAC2	rs7332161	A	0.189	0.121	0.104	0.115	0.131	0.146	0.131	0.147	0.074
UBAC2	rs912130	C	0.527	0.705	0.635	0.631	0.717	0.765	0.712	0.729	0.708
UBAC2	rs2892976	G	0.344	0.467	0.490	0.443	0.490	0.376	0.556	0.465	0.454
UBAC2	rs3825427	T	0.194	0.135	0.104	0.139	0.167	0.159	0.121	0.159	0.102
UBAC2	rs9517701	G	0.190	0.121	0.104	0.115	0.131	0.146	0.131	0.147	0.074
GIMAP4	rs1916012	T	0.506	0.452	0.521	0.410	0.480	0.434	0.530	0.388	0.389
GIMAP4	rs1522596	T	0.530	0.541	0.536	0.459	0.631	0.588	0.581	0.488	0.463
GIMAP4	rs1608157	C	0.505	0.452	0.516	0.410	0.480	0.434	0.530	0.388	0.389

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Table B.1. (cont.)

Gene	Variant/SNP	Behcet Allele	ALL	AFR	ACB	ASW	ESN	GWD	LWK	MSL	YRI
GIMAP2	rs10266069	A	0.412	0.327	0.396	0.352	0.313	0.270	0.359	0.347	0.278
GIMAP2	rs10256482	T	0.501	0.455	0.484	0.418	0.480	0.447	0.470	0.471	0.407
GIMAP1	rs2286900	T	0.123	0.118	0.115	0.066	0.146	0.150	0.126	0.076	0.116
CPLX1	rs11248047	A	0.440	0.424	0.438	0.434	0.485	0.394	0.343	0.359	0.505
DEPDC1	rs6692084	A	0.293	0.495	0.432	0.500	0.515	0.544	0.480	0.535	0.463
DEPDC1	rs12134670	C	0.068	0.012	0.026	0.008	0.005	0.009	0.015	0.012	0.009
DTL	rs1472224	G	0.452	0.592	0.552	0.557	0.662	0.606	0.551	0.553	0.634
DNMT3A	rs1465825	C	0.364	0.405	0.411	0.385	0.308	0.478	0.318	0.500	0.426
TFCP2L1	rs17006292	A	0.048	0.118	0.156	0.090	0.101	0.093	0.172	0.106	0.102
PSMD14	rs6744214	T	0.374	0.368	0.302	0.393	0.414	0.332	0.379	0.412	0.366
PSMD14	rs6733456	C	0.428	0.582	0.542	0.557	0.576	0.593	0.510	0.676	0.616
STK39	rs2390639	A	0.639	0.632	0.661	0.598	0.657	0.522	0.712	0.671	0.616
STK39	rs3769393	G	0.697	0.720	0.734	0.689	0.758	0.664	0.803	0.682	0.704
SGPP2	rs17562982	T	0.368	0.288	0.260	0.320	0.298	0.270	0.359	0.282	0.245
ASB18	rs7561555	C	0.437	0.822	0.781	0.639	0.828	0.863	0.833	0.859	0.875
SLIT2	rs13435197	A	0.311	0.389	0.417	0.385	0.389	0.442	0.369	0.365	0.347
SORBS2	rs4493590	G	0.174	0.038	0.031	0.057	0.030	0.062	0.025	0.041	0.023
MSX2	rs10516130	A	0.268	0.486	0.438	0.467	0.495	0.496	0.510	0.535	0.463
C6orf85(LOC100507336)	rs12194547	C	0.087	0.115	0.115	0.082	0.146	0.106	0.066	0.141	0.139
ABCB5	rs2190411	C	0.235	0.260	0.250	0.303	0.278	0.248	0.116	0.329	0.319
SUSD1	rs2782932	T	0.140	0.009	0.036	0.033	0	0	0	0	0.005
LINC01499(API5)	rs420798	C	0.795	0.913	0.906	0.926	0.929	0.907	0.874	0.912	0.940
API5	rs16937370	G	0.039	0	0	0	0	0	0	0	0
SLC43A3	rs549630	G	0.364	0.579	0.573	0.516	0.611	0.500	0.667	0.624	0.560

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Table B.1. (cont.)

Gene	**Variant/SNP**	**Behcet Allele**	**ALL**	**AFR**	ACB	ASW	ESN	GWD	LWK	MSL	YRI
RIMBP2	rs2895135	A	0.174	0.039	0.052	0.115	0.010	0.058	0.015	0.018	0.028
GALNTL1	rs12589991	A	0.109	0.089	0.109	0.115	0.056	0.049	0.121	0.065	0.120
SMG6	rs749240	T	0.426	0.691	0.641	0.607	0.697	0.699	0.667	0.729	0.764
LILRB1	rs798887	A	0.695	0.825	0.891	0.803	0.788	0.823	0.798	0.835	0.833
LILRA1	rs103294	C	0.782	0.926	0.938	0.885	0.975	0.867	0.934	0.918	0.954
RALGAPA2	rs6082210	A	0.100	0.165	0.125	0.156	0.182	0.181	0.177	0.106	0.208
CDH26	rs817277	A	0.447	0.692	0.661	0.623	0.722	0.743	0.707	0.753	0.616
CDH26	rs817283	A	0.441	0.669	0.620	0.590	0.687	0.726	0.707	0.729	0.597
UBD	rs6933331	A	0.079	0.123	0.099	0.082	0.121	0.150	0.141	0.129	0.120
UBD	rs3025657	G	0.079	0.123	0.099	0.074	0.116	0.146	0.152	0.147	0.111
GABBR1	rs29273	G	0.863	0.864	0.870	0.844	0.859	0.854	0.894	0.871	0.852
MOG	rs3129045	T	0.386	0.580	0.630	0.525	0.525	0.558	0.556	0.606	0.644
HLA-F	rs3116788	G	0.310	0.312	0.292	0.270	0.338	0.323	0.359	0.329	0.259
HLA-F	rs1610584	T	0.310	0.312	0.292	0.270	0.338	0.323	0.359	0.329	0.259
HLA-F	rs1610585	C	0.310	0.312	0.292	0.270	0.338	0.323	0.359	0.329	0.259
HLA-F	rs1610593	T	0.311	0.312	0.292	0.270	0.338	0.323	0.359	0.329	0.264
HLA-F	rs1611356	G	0.689	0.688	0.708	0.730	0.662	0.677	0.641	0.671	0.736
HLA-F	rs1611381	T	0.311	0.312	0.292	0.270	0.338	0.323	0.359	0.329	0.264
HLA-F	rs7741807	G	0.939	0.934	0.958	0.934	0.955	0.867	0.960	0.947	0.931
HLA-F	rs1611388	C	0.310	0.312	0.292	0.270	0.338	0.323	0.354	0.329	0.264
HLA-F	rs1627465	C	0.311	0.312	0.292	0.270	0.338	0.323	0.359	0.329	0.264
LOC285830 (HLA-F antisense RNA1)	rs9258205	C	0.217	0.223	0.229	0.164	0.268	0.204	0.247	0.212	0.218
LOC285830 (HLA-F antisense RNA1)	rs2523386	A	0.088	0.044	0.026	0.082	0.035	0.080	0.051	0.012	0.028
LOC285830 (HLA-F antisense RNA1)	rs2844845	A	0.094	0.063	0.052	0.082	0.056	0.097	0.106	0.012	0.032

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Table B.1. (cont.)

Gene	Variant/SNP	Behcet Allele	ALL	AFR	ACB	ASW	ESN	GWD	LWK	MSL	YRI
LOC285830 (HLA-F antisense RNA1)	rs1633041	T	0.232	0.251	0.240	0.320	0.227	0.265	0.278	0.194	0.250
LOC285830 (HLA-F antisense RNA1)	rs1737031	A	0.329	0.486	0.505	0.500	0.480	0.518	0.404	0.412	0.565
LOC285830 (HLA-F antisense RNA1)	rs885940	A	0.232	0.250	0.240	0.320	0.222	0.265	0.278	0.194	0.250
LOC285830 (HLA-F antisense RNA1)	rs1610637	C	0.232	0.250	0.240	0.320	0.222	0.265	0.278	0.194	0.250
LOC285830 (HLA-F antisense RNA1)	rs1615251	T	0.616	0.402	0.370	0.393	0.439	0.327	0.510	0.429	0.356
HLA-G	rs1633002	A	0.771	0.757	0.781	0.689	0.778	0.735	0.742	0.806	0.755
HLA-G	rs1632973	A	0.232	0.250	0.240	0.320	0.222	0.261	0.278	0.194	0.250
HLA-G	rs1736963	T	0.232	0.250	0.240	0.320	0.222	0.265	0.278	0.194	0.250
HLA-G	rs2523408	G	0.001	0	0	0	0	0	0	0	0
HLA-G	rs1611172	G	0.232	0.250	0.240	0.320	0.222	0.265	0.278	0.194	0.250
HLA-G	rs753544	T	0.232	0.250	0.240	0.320	0.222	0.265	0.278	0.194	0.250
HLA-G	rs1077433	A	0.232	0.250	0.240	0.320	0.222	0.265	0.278	0.194	0.250
HLA-G	rs1736951	A	0.302	0.374	0.375	0.418	0.318	0.438	0.389	0.353	0.333
HLA-G	rs407238	C	0.260	0.241	0.260	0.213	0.222	0.212	0.278	0.206	0.278
HCG9	rs9260954	G	0.041	0.050	0.052	0.041	0.051	0.080	0.061	0.006	0.046
HCG9	rs6911737	A	0.192	0.300	0.286	0.270	0.253	0.345	0.288	0.324	0.315
HCG9	rs6926792	A	0.191	0.299	0.286	0.270	0.253	0.345	0.278	0.324	0.319
HCG9	rs6931776	G	0.191	0.299	0.286	0.270	0.253	0.345	0.278	0.324	0.319
ZNRD1	rs9261189	T	0.192	0.300	0.286	0.270	0.253	0.350	0.278	0.324	0.319
ZNRD1	rs3869068	A	0.191	0.299	0.286	0.270	0.253	0.345	0.278	0.324	0.319
ZNRD1	rs9261265	C	0.041	0.048	0.052	0.041	0.051	0.071	0.061	0.006	0.046
PPP1R11	rs2074482	T	0.191	0.299	0.286	0.270	0.253	0.345	0.278	0.324	0.319
RNF39	rs9261317	A	0.958	0.950	0.948	0.959	0.949	0.920	0.939	0.994	0.954
TRIM31	rs9261376	G	0.317	0.507	0.490	0.434	0.465	0.580	0.449	0.600	0.505
TRIM31	rs9261389	G	0.315	0.503	0.490	0.434	0.460	0.580	0.449	0.600	0.486
TRIM31	rs6923832	A	0.041	0.050	0.052	0.041	0.051	0.080	0.061	0.006	0.046

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Table B.1. (cont.)

Gene	Variant/SNP	Behcet Allele	ALL	AFR	ACB	ASW	ESN	GWD	LWK	MSL	YRI
MUC21	rs2530710	A	0.139	0.021	0.026	0.057	0.010	0.009	0.030	0.035	0
MUC21	rs2517446	C	0.154	0.154	0.172	0.156	0.116	0.146	0.111	0.229	0.157
MUC21	rs2517411	G	0.155	0.154	0.172	0.156	0.116	0.146	0.111	0.229	0.157
MUC21	rs2844673	A	0.173	0.154	0.172	0.156	0.116	0.146	0.111	0.229	0.157
MUC21	rs2252925	G	0.155	0.154	0.172	0.156	0.116	0.146	0.111	0.229	0.157
MUC21	rs2252926	G	0.155	0.154	0.172	0.156	0.116	0.146	0.111	0.229	0.157
MUC21	rs1634717	T	0.305	0.273	0.286	0.246	0.253	0.279	0.268	0.324	0.255
MUC21	rs2523915	T	0.845	0.846	0.828	0.844	0.884	0.854	0.889	0.771	0.843
MUC21	rs1632854	T	0.695	0.727	0.714	0.754	0.747	0.721	0.732	0.676	0.745
C6orf15	rs1265048	A	0.606	0.705	0.661	0.689	0.732	0.642	0.793	0.735	0.690
PSORS1C1	rs4959053	A	0.093	0.012	0.031	0.041	0.005	0	0	0.012	0.009
CCHCR1	rs2240063	A	0.427	0.438	0.469	0.475	0.500	0.420	0.455	0.347	0.407
CCHCR1	rs2073716	C	0.895	0.849	0.854	0.852	0.884	0.854	0.879	0.794	0.819
TCF19	rs2073723	T	0.231	0.131	0.120	0.189	0.106	0.155	0.101	0.129	0.134
POU5F1	rs9501063	G	0.891	0.811	0.844	0.811	0.813	0.810	0.838	0.771	0.787
POU5F1	rs9263804	C	0.237	0.130	0.120	0.189	0.101	0.155	0.101	0.129	0.134
POU5F1	rs3130501	A	0.231	0.130	0.120	0.189	0.101	0.155	0.101	0.129	0.134
POU5F1	rs3132524	A	0.237	0.130	0.120	0.189	0.101	0.155	0.101	0.129	0.134
HCG27	rs3130944	C	0.779	0.862	0.901	0.811	0.879	0.836	0.778	0.912	0.907
HLA-C	rs3905495	C	0.555	0.508	0.432	0.615	0.500	0.544	0.586	0.441	0.468
DHFRP2	rs7761068	T	0.358	0.402	0.401	0.451	0.348	0.491	0.399	0.412	0.329
HLA-B	rs9266406	A	0.296	0.238	0.255	0.148	0.182	0.248	0.207	0.259	0.329
HLA-B	rs9266409	C	0.297	0.240	0.266	0.148	0.182	0.248	0.207	0.259	0.329
HLA-B	rs6910516	C	0.297	0.240	0.266	0.148	0.182	0.248	0.207	0.259	0.329
MICA	rs2523467	A	0.436	0.554	0.536	0.566	0.667	0.447	0.606	0.565	0.514
MICA	rs3094584	T	0.204	0.253	0.276	0.230	0.177	0.283	0.162	0.265	0.361

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Table B.1. (cont.)

Gene	Variant/SNP	Behcet Allele	ALL	AFR	ACB	ASW	ESN	GWD	LWK	MSL	YRI
BAG6(BAT3)	rs2077102	T	0.127	0.076	0.057	0.131	0.040	0.159	0.045	0.076	0.032
C6orf47	rs2242655	C	0.873	0.924	0.943	0.869	0.960	0.841	0.955	0.924	0.968
SLC44A4	rs11965547	A	0.127	0.077	0.052	0.123	0.040	0.133	0.040	0.082	0.079
C6orf10	rs544358	C	0.327	0.135	0.146	0.164	0.081	0.235	0.111	0.135	0.079
C6orf10	rs574710	G	0.337	0.135	0.146	0.164	0.081	0.235	0.111	0.135	0.079
C6orf10	rs539703	C	0.327	0.135	0.146	0.164	0.081	0.235	0.111	0.135	0.079
C6orf10	rs926591	T	0.326	0.135	0.151	0.164	0.086	0.235	0.101	0.135	0.079
C6orf10	rs4959093	C	0.327	0.135	0.151	0.164	0.086	0.235	0.101	0.135	0.079
BTNL2	rs2076530	G	0.387	0.328	0.312	0.311	0.182	0.522	0.192	0.459	0.301
HLA-DQA1	rs9272346	G	0.475	0.533	0.630	0.598	0.530	0.394	0.682	0.329	0.579
HLA-DQB1	rs6457617	C	0.465	0.459	0.568	0.459	0.586	0.274	0.449	0.329	0.551
COL12A1	rs4640857	G	0.318	0.056	0.099	0.156	0.035	0.018	0.061	0.012	0.051
C10orf11	rs1323076	G	0.365	0.348	0.417	0.393	0.318	0.319	0.409	0.288	0.310
C10orf11	rs17434565	G	0.167	0.023	0.057	0.057	0.015	0.004	0.025	0.012	0.005
PAX8	rs11123169	C	0.322	0.378	0.422	0.328	0.303	0.367	0.414	0.459	0.352
PAX8	rs10864912	T	0.384	0.433	0.484	0.434	0.485	0.358	0.409	0.365	0.495
HIVEP3	rs4660590	A	0.536	0.716	0.677	0.672	0.717	0.765	0.692	0.729	0.731
CEP135	rs2593082	T	0.542	0.686	0.693	0.623	0.687	0.655	0.687	0.718	0.722
CEP135	rs2611826	G	0.460	0.357	0.354	0.410	0.348	0.394	0.374	0.329	0.306
HMP19	rs1909704	A	0.538	0.509	0.526	0.557	0.475	0.473	0.535	0.512	0.509
TTLL7	rs11163772	A	0.220	0.354	0.349	0.328	0.359	0.288	0.379	0.400	0.380
TENM4(ODZ4)	rs2156215	T	0.233	0.248	0.240	0.238	0.308	0.195	0.258	0.235	0.264
KLRK1	rs2617151	A	0.176	0.231	0.229	0.221	0.192	0.336	0.172	0.294	0.167
KLRK1	rs2733852	G	0.315	0.540	0.531	0.475	0.500	0.628	0.601	0.588	0.435
OSR1	rs4666492	G	0.312	0.248	0.281	0.303	0.182	0.279	0.268	0.212	0.227
CTNNA2	rs4852547	G	0.384	0.492	0.531	0.385	0.500	0.460	0.475	0.465	0.579

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Table B.1. (cont.)

Gene	Variant/SNP	Behcet Allele	ALL	AFR	ACB	ASW	ESN	GWD	LWK	MSL	YRI
MN1	rs134006	C	0.213	0.315	0.255	0.254	0.409	0.292	0.313	0.365	0.301
LTN1(RNF160)	rs2832137	T	0.340	0.111	0.135	0.164	0.076	0.102	0.136	0.100	0.088
HERPUD2	rs11763983	T	0.294	0.086	0.146	0.131	0.045	0.084	0.096	0.065	0.056
GALNT10	rs574750	A	0.313	0.460	0.396	0.451	0.540	0.456	0.470	0.476	0.431
SAMD3(TMEM200A)	rs9483115	T	0.544	0.878	0.849	0.738	0.889	0.881	0.924	0.912	0.903
SAMD3(TMEM200A)	rs4141940	A	0.518	0.790	0.781	0.680	0.788	0.783	0.818	0.829	0.815
SAMD3(TMEM200A)	rs899276	A	0.514	0.772	0.776	0.672	0.753	0.779	0.808	0.829	0.759
SAMD3(TMEM200A)	rs7758496	G	0.557	0.937	0.880	0.795	0.955	0.978	0.960	0.976	0.958
SAMD3(TMEM200A)	rs724324	G	0.544	0.877	0.854	0.738	0.909	0.903	0.879	0.906	0.894
SAMD3	rs4897380	C	0.567	0.937	0.865	0.803	0.960	0.978	0.965	0.971	0.963
SEMA6D	rs470151	T	0.197	0.257	0.224	0.295	0.303	0.235	0.247	0.247	0.264
PMFBP1	rs11862324	T	0.381	0.542	0.458	0.492	0.561	0.504	0.662	0.500	0.588
NAV2	rs2707110	C	0.433	0.571	0.615	0.557	0.571	0.588	0.571	0.576	0.519
NAV2	rs873764	G	0.518	0.615	0.651	0.648	0.606	0.615	0.591	0.582	0.620
TMEM132B	rs4435061	A	0.444	0.689	0.688	0.541	0.727	0.735	0.672	0.682	0.713
TMEM132B	rs10846917	T	0.472	0.269	0.286	0.336	0.202	0.239	0.268	0.306	0.282
TMEM132B	rs10846924	T	0.330	0.355	0.396	0.328	0.364	0.358	0.338	0.335	0.352
STX8	rs1549332	A	0.135	0.216	0.229	0.172	0.207	0.204	0.308	0.206	0.171
OVCH1	rs1436321	A	0.489	0.747	0.677	0.648	0.813	0.810	0.763	0.782	0.699
SLC41A2	rs2731031	A	0.373	0.238	0.203	0.287	0.192	0.257	0.273	0.253	0.218
HNF4G	rs2980221	A	0.479	0.483	0.469	0.410	0.520	0.558	0.495	0.441	0.449
SMARCA2	rs7033529	A	0.570	0.152	0.193	0.262	0.126	0.133	0.141	0.141	0.116
EBF2	rs4570167	C	0.493	0.825	0.828	0.656	0.838	0.876	0.864	0.794	0.838
EBF2	rs4242425	T	0.495	0.832	0.839	0.656	0.864	0.885	0.864	0.794	0.843
GAS2	rs10833804	G	0.603	0.598	0.615	0.631	0.601	0.650	0.449	0.612	0.634
LYST/NID1	rs7354999	G	0.738	0.762	0.760	0.803	0.798	0.721	0.823	0.682	0.755

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Table B.1. (cont.)

Gene	**Variant/SNP**	**Behcet Allele**	**ALL**	**AFR**	ACB	ASW	ESN	GWD	LWK	MSL	YRI
LOC100132252	rs9469615	C	0.097	0.129	0.083	0.115	0.136	0.195	0.146	0.129	0.083
LOC107984355	rs872837	A	0.293	0.275	0.297	0.246	0.308	0.221	0.263	0.288	0.301
SACM1L	rs1969624	C	0.403	0.421	0.411	0.426	0.414	0.540	0.303	0.447	0.394
PLEKHB1	rs591804	G	0.383	0.489	0.438	0.492	0.535	0.429	0.525	0.524	0.495
ATP8A1	rs2100766	T	0.145	0.294	0.302	0.230	0.354	0.243	0.278	0.294	0.338
KCNK9	rs1961261	A	0.209	0.129	0.078	0.164	0.126	0.119	0.121	0.200	0.116
SUMO4	rs237024	C	0.702	0.970	0.948	0.926	0.990	0.973	0.975	0.982	0.981

Table B.2. Distribution of Behcet's Disease associated variants among Ad Mixed American and East Asian populations

Gene	**Variant/SNP**	**Behcet Allele**	**AMR**	CLM	MXL	PEL	PUR	**EAS**	CDX	CHB	CHS	JPT	KHV
IL-10	rs1518111	A	0.329	0.287	0.422	0.371	0.274	0.676	0.651	0.743	0.686	0.644	0.652
IL-10	rs1800871	T	0.333	0.298	0.422	0.371	0.279	0.676	0.651	0.743	0.686	0.639	0.657
IL-10	rs1800872	A	0.333	0.298	0.422	0.371	0.279	0.676	0.651	0.743	0.686	0.639	0.657
IL-10	rs1554286	C	0.693	0.729	0.594	0.647	0.760	0.339	0.360	0.267	0.338	0.365	0.369
IL23R,IL12RB2	rs1495965	G	0.354	0.378	0.289	0.371	0.361	0.517	0.565	0.510	0.529	0.433	0.556
IL23R,IL12RB2	rs924080	T	0.581	0.521	0.523	0.765	0.519	0.759	0.769	0.791	0.800	0.707	0.727
IL23R,IL12RB2	rs12119179	A	0.769	0.718	0.773	0.806	0.784	0.494	0.430	0.505	0.495	0.587	0.444
IL23R,IL12RB2	rs11209033	C	0.769	0.718	0.773	0.806	0.784	0.499	0.435	0.515	0.500	0.591	0.444
IL23R,IL12RB2	rs12141431	C	0.215	0.277	0.195	0.176	0.202	0.506	0.575	0.490	0.505	0.413	0.556
TNFAIP3	rs9494885	T	0.863	0.846	0.914	0.900	0.817	0.938	0.973	0.922	0.952	0.875	0.975
TNFAIP3	rs10499194	C	0.722	0.750	0.688	0.806	0.649	0.967	0.973	0.981	0.976	0.933	0.975
TNFAIP3	rs610604	A	0.605	0.580	0.617	0.629	0.601	0.900	0.935	0.883	0.890	0.947	0.843
TNFAIP3	rs7753873	C	0.131	0.144	0.086	0.100	0.173	0.066	0.032	0.078	0.057	0.135	0.025
STAT4	rs7574070	A	0.341	0.319	0.336	0.300	0.399	0.612	0.737	0.612	0.605	0.500	0.621
STAT4	rs897200	A	0.344	0.330	0.328	0.300	0.404	0.614	0.737	0.617	0.605	0.500	0.626
STAT4	rs7572482	A	0.334	0.319	0.320	0.282	0.399	0.614	0.737	0.617	0.605	0.500	0.626
CCR1	rs17282391	G	0.049	0.064	0.031	0.053	0.043	0.044	0.027	0.068	0.043	0.048	0.030
CCR1	rs10510749	T	0.059	0.069	0.039	0.065	0.058	0.043	0.027	0.068	0.043	0.043	0.030
CCR1	rs13084057	G	0.059	0.069	0.039	0.065	0.058	0.043	0.027	0.068	0.043	0.043	0.030
CCR1	rs7631551	A	0.095	0.085	0.055	0.076	0.144	0.043	0.027	0.068	0.043	0.043	0.030
CCR1	rs7616215	T	0.736	0.718	0.789	0.818	0.654	0.873	0.914	0.850	0.876	0.822	0.909
CCR3	rs7649764	C	0.666	0.676	0.711	0.571	0.707	0.403	0.317	0.369	0.424	0.486	0.409
CCR3	rs9990343	G	0.378	0.372	0.391	0.318	0.423	0.122	0.075	0.141	0.110	0.202	0.076
CCR3	rs6803980	A	0.382	0.378	0.398	0.318	0.428	0.122	0.075	0.141	0.110	0.202	0.076
CCR3	rs13075270	C	0.091	0.101	0.062	0.059	0.125	0.038	0.016	0.083	0.033	0.029	0.025

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Table B.2. (cont.)

Gene	**Variant/SNP**	**Behcet Allele**	**AMR**	CLM	MXL	PEL	PUR	**EAS**	CDX	CHB	CHS	JPT	KHV
CCR3	rs13092160	C	0.058	0.074	0.031	0.059	0.058	0.038	0.016	0.083	0.033	0.029	0.025
CCR3	rs2373156	T	0.121	0.133	0.086	0.059	0.183	0.038	0.016	0.083	0.033	0.029	0.025
CCR3	rs7651539	T	0.121	0.133	0.086	0.059	0.183	0.038	0.016	0.083	0.033	0.029	0.025
CCR3	rs1542755	A	0.048	0.064	0.039	0.041	0.043	0.038	0.016	0.083	0.033	0.029	0.025
CCR3	rs13067058	A	0.046	0.059	0.039	0.041	0.043	0.036	0.011	0.083	0.033	0.029	0.020
CCR3	rs13092160	C	0.058	0.074	0.031	0.059	0.058	0.038	0.016	0.083	0.033	0.029	0.025
KLRC4	rs2617170	C	0.667	0.707	0.727	0.682	0.582	0.550	0.500	0.549	0.610	0.601	0.480
MEFV	rs61752717	G	0.001	0	0	0.006	0	0	0	0	0	0	0
ERAP1	rs17482078	T	0.124	0.170	0.070	0.053	0.173	0.058	0.054	0.063	0.057	0.072	0.040
FUT2	rs681343	T	0.343	0.388	0.320	0.124	0.495	0.004	0	0.015	0	0	0.005
IL12A	rs17810546	A	0.899	0.899	0.875	0.929	0.889	1.000	1.000	1.000	1.000	1.000	1.000
IL23R	rs11209026	A	0.052	0.053	0.062	0.012	0.077	0	0	0	0	0	0
IL23R	rs76418789	A	0	0	0	0	0	0.0526	0.0376	0.0631	0.0429	0.10	0.0152
IL23R	rs17375018	G	0.504	0.569	0.516	0.265	0.635	0.680	0.715	0.689	0.695	0.644	0.657
IL23R	rs11209032	A	0.229	0.282	0.227	0.188	0.216	0.497	0.570	0.471	0.495	0.409	0.551
IL23R	rs1343151	T	0.277	0.324	0.234	0.082	0.418	0.053	0.038	0.024	0.038	0.101	0.061
TLR4	rs4986790	G	0.037	0.053	0.031	0.006	0.053	0	0	0	0	0	0
TLR4	rs4986791	T	0.036	0.064	0.031	0	0.043	0	0	0	0	0	0
NOD2	rs2066844	T	0.024	0.053	0	0.006	0.029	0	0	0	0	0	0
NOD2	rs2066845	C	0.013	0.021	0.023	0	0.010	0	0	0	0	0	0
NOD2	rs2066847	ins-C	0.016	0.016	0.008	0.006	0.029	0	0	0	0	0	0
IL1	rs1800587	C	0.725	0.691	0.766	0.724	0.731	0.928	0.930	0.937	0.948	0.865	0.960
IL1	rs1143634	T	0.125	0.170	0.086	0.053	0.168	0.023	0.011	0.019	0.010	0.062	0.010
IL1	rs16944	G	0.450	0.548	0.469	0.300	0.471	0.531	0.500	0.549	0.543	0.534	0.525
TNFα	rs1799964	C	0.219	0.181	0.258	0.182	0.260	0.195	0.210	0.218	0.190	0.135	0.227

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Table B.2. (cont.)

Gene	**Variant/SNP**	**Behcet Allele**	**AMR**	CLM	MXL	PEL	PUR	**EAS**	CDX	CHB	CHS	JPT	KHV
TNFα	rs361525	A	0.082	0.059	0.102	0.118	0.062	0.031	0.011	0.034	0.038	0.014	0.056
TNFα	rs1799724	T	0.183	0.170	0.203	0.282	0.101	0.125	0.129	0.141	0.071	0.163	0.121
IL12	rs3212227	A	0.659	0.755	0.602	0.541	0.702	0.499	0.457	0.568	0.486	0.466	0.515
IL18	rs1946518	C	0.509	0.511	0.508	0.471	0.538	0.473	0.489	0.408	0.514	0.394	0.566
IL17F-A126G	rs2397084	T	0.952	0.931	0.945	0.994	0.942	0.996	0.995	0.995	0.995	1.000	0.995
LOC100129342	rs11206377	G	0.633	0.670	0.633	0.753	0.500	0.568	0.575	0.500	0.519	0.688	0.561
CCDC180	rs2061634	G	0.304	0.314	0.266	0.394	0.245	0.184	0.194	0.131	0.248	0.154	0.192
CPVL	rs317711	C	0.147	0.176	0.156	0.059	0.188	0.152	0.134	0.170	0.138	0.082	0.237
UBASH3B	rs4936742	T	0.418	0.452	0.438	0.394	0.394	0.569	0.618	0.539	0.629	0.428	0.641
UBAC2	rs9513584	G	0.504	0.346	0.547	0.700	0.462	0.494	0.602	0.413	0.448	0.538	0.480
UBAC2	rs9517644	T	0.499	0.340	0.539	0.694	0.457	0.494	0.602	0.413	0.448	0.538	0.480
UBAC2	rs11069357	A	0.499	0.340	0.539	0.694	0.457	0.492	0.602	0.408	0.448	0.538	0.475
UBAC2	rs984477	G	0.526	0.372	0.570	0.700	0.495	0.494	0.602	0.413	0.448	0.538	0.480
UBAC2	rs9554573	A	0.509	0.351	0.547	0.706	0.466	0.507	0.618	0.417	0.462	0.548	0.500
UBAC2	rs6491493	G	0.504	0.346	0.547	0.700	0.462	0.493	0.597	0.413	0.448	0.538	0.480
UBAC2	rs9517668	T	0.287	0.170	0.398	0.441	0.197	0.317	0.398	0.267	0.267	0.356	0.308
UBAC2	rs7999348	G	0.507	0.351	0.539	0.712	0.462	0.495	0.597	0.413	0.448	0.538	0.490
UBAC2	rs9554581	T	0.267	0.149	0.383	0.418	0.178	0.320	0.403	0.272	0.267	0.356	0.313
UBAC2	rs17575643	T	0.219	0.144	0.234	0.376	0.149	0.057	0.038	0.102	0.071	0.034	0.035
UBAC2	rs727263	A	0.267	0.154	0.375	0.418	0.178	0.318	0.403	0.277	0.262	0.341	0.318
UBAC2	rs7332161	A	0.268	0.154	0.375	0.424	0.178	0.319	0.403	0.277	0.262	0.346	0.318
UBAC2	rs912130	C	0.504	0.346	0.555	0.694	0.462	0.495	0.602	0.422	0.443	0.534	0.485
UBAC2	rs2892976	G	0.346	0.229	0.414	0.488	0.293	0.349	0.344	0.291	0.319	0.452	0.338
UBAC2	rs3825427	T	0.264	0.149	0.367	0.418	0.178	0.315	0.398	0.267	0.262	0.351	0.308
UBAC2	rs9517701	G	0.271	0.154	0.383	0.429	0.178	0.322	0.409	0.282	0.262	0.351	0.318

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Table B.2. (cont.)

Gene	**Variant/SNP**	**Behcet Allele**	**AMR**	CLM	MXL	PEL	PUR	**EAS**	CDX	CHB	CHS	JPT	KHV
GIMAP4	rs1916012	T	0.463	0.537	0.461	0.335	0.500	0.513	0.570	0.485	0.529	0.490	0.495
GIMAP4	rs1522596	T	0.473	0.548	0.461	0.335	0.524	0.509	0.554	0.485	0.524	0.490	0.495
GIMAP4	rs1608157	C	0.463	0.537	0.461	0.335	0.500	0.513	0.570	0.485	0.529	0.490	0.495
GIMAP2	rs10266069	A	0.408	0.447	0.438	0.271	0.466	0.501	0.548	0.500	0.476	0.457	0.530
GIMAP2	rs10256482	T	0.484	0.553	0.477	0.335	0.548	0.516	0.565	0.515	0.500	0.462	0.545
GIMAP1	rs2286900	T	0.091	0.106	0.109	0.071	0.082	0.213	0.247	0.189	0.205	0.212	0.217
CPLX1	rs11248047	A	0.555	0.516	0.617	0.624	0.495	0.438	0.371	0.461	0.429	0.500	0.419
DEPDC1	rs6692084	A	0.336	0.282	0.305	0.371	0.375	0.138	0.134	0.146	0.190	0.115	0.101
DEPDC1	rs12134670	C	0.032	0.032	0.023	0.012	0.053	0.099	0.097	0.107	0.124	0.091	0.076
DTL	rs1472224	G	0.403	0.431	0.422	0.188	0.543	0.135	0.086	0.141	0.129	0.202	0.111
DNMT3A	rs1465825	C	0.285	0.282	0.297	0.271	0.293	0.381	0.360	0.422	0.376	0.409	0.333
TFCP2L1	rs17006292	A	0.010	0.005	0	0	0.029	0.032	0.022	0.044	0.014	0.058	0.020
PSMD14	rs6744214	T	0.251	0.202	0.273	0.265	0.269	0.488	0.452	0.476	0.514	0.438	0.561
PSMD14	rs6733456	C	0.275	0.245	0.273	0.259	0.317	0.462	0.441	0.461	0.500	0.361	0.551
STK39	rs2390639	A	0.693	0.691	0.695	0.694	0.692	0.420	0.446	0.388	0.386	0.500	0.379
STK39	rs3769393	G	0.723	0.755	0.711	0.694	0.726	0.492	0.543	0.447	0.495	0.534	0.444
SGPP2	rs17562982	T	0.530	0.473	0.617	0.706	0.385	0.200	0.226	0.214	0.186	0.125	0.258
ASB18	rs7561555	C	0.256	0.282	0.211	0.194	0.312	0.242	0.226	0.277	0.257	0.216	0.232
SLIT2	rs13435197	A	0.316	0.335	0.281	0.294	0.337	0.133	0.140	0.121	0.124	0.183	0.096
SORBS2	rs4493590	G	0.137	0.176	0.164	0.071	0.139	0.246	0.237	0.262	0.262	0.250	0.217
MSX2	rs10516130	A	0.274	0.229	0.281	0.312	0.279	0.165	0.215	0.189	0.167	0.101	0.157
C6orf85(LOC100507336)	rs12194547	C	0.035	0.021	0.078	0.012	0.038	0.104	0.048	0.136	0.095	0.188	0.045
ABCB5	rs2190411	C	0.252	0.298	0.211	0.212	0.269	0.192	0.172	0.199	0.152	0.255	0.182
SUSD1	rs2782932	T	0.174	0.207	0.133	0.147	0.192	0.231	0.220	0.252	0.252	0.240	0.187
LINC01499(API5)	rs420798	C	0.703	0.846	0.633	0.506	0.779	0.490	0.473	0.471	0.462	0.505	0.540

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Table B.2. (cont.)

Gene	Variant/SNP	Behcet Allele	AMR	CLM	MXL	PEL	PUR	EAS	CDX	CHB	CHS	JPT	KHV
API5	rs16937370	G	0	0	0	0	0	0.168	0.124	0.136	0.200	0.202	0.172
SLC43A3	rs549630	G	0.255	0.309	0.289	0.059	0.346	0.276	0.306	0.248	0.233	0.332	0.263
RIMBP2	rs2895135	A	0.197	0.261	0.156	0.088	0.255	0.182	0.204	0.155	0.152	0.183	0.217
GALNTL1	rs12589991	A	0.052	0.064	0.039	0.006	0.087	0.162	0.183	0.131	0.186	0.178	0.131
SMG6	rs749240	T	0.357	0.441	0.281	0.229	0.433	0.237	0.242	0.223	0.243	0.216	0.263
LILRB1	rs798887	A	0.571	0.665	0.516	0.353	0.697	0.343	0.618	0.189	0.305	0.188	0.449
LILRA1	rs103294	C	0.756	0.846	0.641	0.712	0.784	0.487	0.855	0.243	0.452	0.260	0.672
RALGAPA2	rs6082210	A	0.049	0.048	0.047	0.059	0.043	0.128	0.086	0.155	0.148	0.139	0.106
CDH26	rs817277	A	0.298	0.277	0.234	0.212	0.428	0.289	0.409	0.204	0.229	0.260	0.359
CDH26	rs817283	A	0.298	0.277	0.234	0.206	0.433	0.286	0.409	0.194	0.229	0.231	0.384
UBD	rs6933331	A	0.042	0.043	0.031	0.024	0.062	0.129	0.070	0.107	0.057	0.216	0.192
UBD	rs3025657	G	0.042	0.043	0.031	0.024	0.062	0.129	0.070	0.107	0.057	0.216	0.192
GABBR1	rs29273	G	0.800	0.782	0.734	0.871	0.798	0.954	0.984	0.956	0.976	0.894	0.965
MOG	rs3129045	T	0.375	0.351	0.500	0.194	0.466	0.231	0.247	0.282	0.252	0.159	0.217
HLA-F	rs3116788	G	0.265	0.287	0.250	0.176	0.327	0.308	0.306	0.330	0.290	0.250	0.364
HLA-F	rs1610584	T	0.265	0.287	0.250	0.176	0.327	0.309	0.306	0.330	0.290	0.255	0.364
HLA-F	rs1610585	C	0.265	0.287	0.250	0.176	0.327	0.309	0.306	0.330	0.290	0.255	0.364
HLA-F	rs1610593	T	0.265	0.287	0.250	0.176	0.327	0.309	0.306	0.330	0.290	0.255	0.364
HLA-F	rs1611356	G	0.735	0.713	0.750	0.824	0.673	0.691	0.694	0.670	0.710	0.745	0.636
HLA-F	rs1611381	T	0.265	0.287	0.250	0.176	0.327	0.309	0.306	0.330	0.290	0.255	0.364
HLA-F	rs7741807	G	0.981	0.979	0.992	0.988	0.971	0.895	0.930	0.903	0.948	0.784	0.914
HLA-F	rs1611388	C	0.265	0.287	0.250	0.176	0.327	0.309	0.306	0.330	0.290	0.255	0.364
HLA-F	rs1627465	C	0.265	0.287	0.250	0.176	0.327	0.309	0.306	0.330	0.290	0.255	0.364
LOC285830 (HLA-F antisense RNA1)	rs9258205	C	0.146	0.106	0.156	0.141	0.178	0.291	0.301	0.291	0.271	0.250	0.343

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Table B.2. (cont.)

Gene	Variant/SNP	Behcet Allele	AMR	CLM	MXL	PEL	PUR	EAS	CDX	CHB	CHS	JPT	KHV
LOC285830 (HLA-F antisense RNA1)	rs2523386	A	0.125	0.154	0.156	0.059	0.135	0.041	0.011	0.039	0.014	0.106	0.030
LOC285830 (HLA-F antisense RNA1)	rs2844845	A	0.128	0.160	0.156	0.059	0.139	0.041	0.011	0.039	0.014	0.106	0.030
LOC285830 (HLA-F antisense RNA1)	rs1633041	T	0.245	0.223	0.281	0.341	0.163	0.109	0.011	0.160	0.057	0.202	0.106
LOC285830 (HLA-F antisense RNA1)	rs1737031	A	0.280	0.271	0.289	0.341	0.231	0.187	0.081	0.238	0.110	0.303	0.192
LOC285830 (HLA-F antisense RNA1)	rs885940	A	0.245	0.223	0.281	0.341	0.163	0.109	0.011	0.160	0.057	0.202	0.106
LOC285830 (HLA-F antisense RNA1)	rs1610637	C	0.245	0.223	0.281	0.341	0.163	0.109	0.011	0.160	0.057	0.202	0.106
LOC285830 (HLA-F antisense RNA1)	rs1615251	T	0.630	0.644	0.609	0.612	0.644	0.805	0.919	0.733	0.890	0.683	0.808
HLA-G	rs1633002	A	0.759	0.777	0.734	0.665	0.837	0.893	0.989	0.850	0.943	0.798	0.894
HLA-G	rs1632973	A	0.245	0.223	0.281	0.341	0.163	0.109	0.011	0.160	0.057	0.202	0.106
HLA-G	rs1736963	T	0.245	0.223	0.281	0.341	0.163	0.109	0.011	0.160	0.057	0.202	0.106
HLA-G	rs2523408	G	0	0	0	0	0	0.001	0	0	0.005	0	0
HLA-G	rs1611172	G	0.245	0.223	0.281	0.341	0.163	0.109	0.011	0.160	0.057	0.202	0.106
HLA-G	rs753544	T	0.245	0.223	0.281	0.341	0.163	0.109	0.011	0.160	0.057	0.202	0.106
HLA-G	rs1077433	A	0.245	0.223	0.281	0.341	0.163	0.109	0.011	0.160	0.057	0.202	0.106
HLA-G	rs1736951	A	0.346	0.319	0.383	0.406	0.298	0.120	0.011	0.199	0.057	0.216	0.106
HLA-G	rs407238	C	0.252	0.293	0.234	0.282	0.202	0.127	0.011	0.175	0.076	0.207	0.157
HCG9	rs9260954	G	0.035	0.037	0.062	0.012	0.034	0.036	0.011	0.029	0.010	0.101	0.025
HCG9	rs6911737	A	0.174	0.165	0.266	0.100	0.188	0.190	0.091	0.194	0.095	0.303	0.263
HCG9	rs6926792	A	0.174	0.165	0.266	0.100	0.188	0.188	0.086	0.194	0.095	0.303	0.258
HCG9	rs6931776	G	0.174	0.165	0.266	0.100	0.188	0.190	0.091	0.194	0.095	0.303	0.263

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Table B.2. (cont.)

Gene	**Variant/SNP**	**Behcet Allele**	**AMR**	CLM	MXL	PEL	PUR	**EAS**	CDX	CHB	CHS	JPT	KHV
ZNRD1	rs9261189	T	0.174	0.165	0.266	0.100	0.188	0.190	0.091	0.194	0.095	0.303	0.263
ZNRD1	rs3869068	A	0.174	0.165	0.266	0.100	0.188	0.190	0.091	0.194	0.095	0.303	0.263
ZNRD1	rs9261265	C	0.040	0.048	0.062	0.018	0.038	0.036	0.011	0.029	0.010	0.101	0.025
PPP1R11	rs2074482	T	0.174	0.165	0.266	0.100	0.188	0.190	0.091	0.194	0.095	0.303	0.263
RNF39	rs9261317	A	0.960	0.952	0.938	0.982	0.962	0.964	0.989	0.971	0.990	0.899	0.975
TRIM31	rs9261376	G	0.256	0.266	0.336	0.141	0.293	0.208	0.091	0.223	0.110	0.303	0.308
TRIM31	rs9261389	G	0.256	0.266	0.336	0.141	0.293	0.208	0.091	0.223	0.110	0.303	0.308
TRIM31	rs6923832	A	0.040	0.048	0.062	0.018	0.038	0.036	0.011	0.029	0.010	0.101	0.025
MUC21	rs2530710	A	0.125	0.112	0.125	0.100	0.159	0.163	0.156	0.126	0.100	0.221	0.212
MUC21	rs2517446	C	0.261	0.250	0.258	0.371	0.183	0.119	0.075	0.155	0.110	0.159	0.091
MUC21	rs2517411	G	0.262	0.250	0.266	0.371	0.183	0.118	0.075	0.155	0.110	0.154	0.091
MUC21	rs2844673	A	0.262	0.250	0.266	0.371	0.183	0.208	0.317	0.189	0.214	0.154	0.177
MUC21	rs2252925	G	0.261	0.245	0.266	0.371	0.183	0.118	0.075	0.155	0.110	0.154	0.091
MUC21	rs2252926	G	0.261	0.245	0.266	0.371	0.183	0.118	0.075	0.155	0.110	0.154	0.091
MUC21	rs1634717	T	0.535	0.500	0.602	0.571	0.495	0.161	0.075	0.233	0.152	0.188	0.146
MUC21	rs2523915	T	0.739	0.755	0.734	0.629	0.817	0.882	0.925	0.845	0.890	0.846	0.909
MUC21	rs1632854	T	0.465	0.500	0.398	0.429	0.505	0.839	0.925	0.767	0.848	0.812	0.854
C6orf15	rs1265048	A	0.520	0.516	0.477	0.382	0.663	0.475	0.263	0.510	0.457	0.606	0.520
PSORS1C1	rs4959053	A	0.091	0.080	0.070	0.147	0.067	0.128	0.172	0.107	0.095	0.082	0.192
CCHCR1	rs2240063	A	0.367	0.367	0.352	0.318	0.418	0.399	0.274	0.437	0.410	0.481	0.379
CCHCR1	rs2073716	C	0.970	0.968	0.961	0.982	0.966	0.817	0.796	0.854	0.814	0.803	0.818
TCF19	rs2073723	T	0.186	0.181	0.195	0.212	0.163	0.323	0.199	0.320	0.338	0.457	0.288
POU5F1	rs9501063	G	0.968	0.952	0.969	0.982	0.971	0.817	0.796	0.854	0.814	0.803	0.818
POU5F1	rs9263804	C	0.192	0.181	0.203	0.218	0.173	0.323	0.199	0.320	0.338	0.457	0.288
POU5F1	rs3130501	A	0.186	0.181	0.195	0.218	0.159	0.323	0.199	0.320	0.338	0.457	0.288

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Table B.2. (cont.)

Gene	**Variant/SNP**	**Behcet Allele**	**AMR**	CLM	MXL	PEL	PUR	**EAS**	CDX	CHB	CHS	JPT	KHV
POU5F1	rs3132524	A	0.192	0.181	0.203	0.218	0.173	0.323	0.199	0.320	0.338	0.457	0.288
HCG27	rs3130944	C	0.780	0.782	0.797	0.718	0.817	0.698	0.597	0.728	0.724	0.707	0.727
HLA-C	rs3905495	C	0.546	0.590	0.594	0.506	0.510	0.594	0.715	0.612	0.629	0.404	0.626
DHFRP2	rs7761068	T	0.304	0.319	0.242	0.171	0.438	0.273	0.242	0.277	0.357	0.216	0.268
HLA-B	rs9266406	A	0.223	0.186	0.273	0.229	0.221	0.391	0.457	0.354	0.357	0.361	0.434
HLA-B	rs9266409	C	0.225	0.191	0.273	0.229	0.221	0.391	0.457	0.354	0.357	0.361	0.434
HLA-B	rs6910516	C	0.225	0.191	0.273	0.229	0.221	0.391	0.457	0.354	0.357	0.361	0.434
MICA	rs2523467	A	0.520	0.590	0.453	0.494	0.519	0.324	0.360	0.301	0.295	0.337	0.333
MICA	rs3094584	T	0.187	0.191	0.164	0.100	0.269	0.119	0.032	0.131	0.048	0.303	0.071
BAG6(BAT3)	rs2077102	T	0.187	0.181	0.148	0.276	0.144	0.130	0.065	0.165	0.105	0.264	0.040
C6orf47	rs2242655	C	0.813	0.819	0.852	0.724	0.856	0.869	0.935	0.830	0.895	0.736	0.960
SLC44A4	rs11965547	A	0.183	0.197	0.180	0.265	0.106	0.148	0.070	0.209	0.100	0.284	0.066
C6orf10	rs544358	C	0.501	0.415	0.539	0.718	0.380	0.361	0.306	0.398	0.410	0.365	0.318
C6orf10	rs574710	G	0.517	0.431	0.570	0.735	0.385	0.382	0.344	0.408	0.433	0.370	0.348
C6orf10	rs539703	C	0.500	0.415	0.531	0.718	0.380	0.361	0.306	0.398	0.410	0.365	0.318
C6orf10	rs926591	T	0.496	0.399	0.531	0.718	0.380	0.360	0.301	0.398	0.410	0.365	0.318
C6orf10	rs4959093	C	0.496	0.399	0.531	0.718	0.380	0.361	0.301	0.398	0.410	0.370	0.318
BTNL2	rs2076530	G	0.484	0.532	0.531	0.435	0.452	0.292	0.231	0.335	0.181	0.519	0.182
HLA-DQA1	rs9272346	G	0.321	0.447	0.289	0.171	0.351	0.492	0.640	0.422	0.452	0.510	0.449
HLA-DQB1	rs6457617	C	0.318	0.372	0.266	0.194	0.404	0.443	0.312	0.476	0.462	0.404	0.556
COL12A1	rs4640857	G	0.313	0.346	0.328	0.259	0.317	0.390	0.376	0.393	0.390	0.365	0.424
C10orf11	rs1323076	G	0.460	0.532	0.367	0.441	0.466	0.188	0.156	0.204	0.176	0.216	0.182
C10orf11	rs17434565	G	0.229	0.250	0.211	0.335	0.135	0.171	0.156	0.175	0.176	0.183	0.162
PAX8	rs11123169	C	0.316	0.426	0.312	0.253	0.269	0.220	0.194	0.214	0.238	0.212	0.242
PAX8	rs10864912	T	0.353	0.452	0.367	0.276	0.317	0.231	0.247	0.228	0.238	0.159	0.288

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Table B.2. (cont.)

Gene	**Variant/SNP**	**Behcet Allele**	**AMR**	CLM	MXL	PEL	PUR	**EAS**	CDX	CHB	CHS	JPT	KHV
HIVEP3	rs4660590	A	0.693	0.707	0.680	0.800	0.601	0.311	0.269	0.296	0.290	0.385	0.308
CEP135	rs2593082	T	0.640	0.601	0.648	0.718	0.606	0.385	0.360	0.374	0.405	0.447	0.333
CEP135	rs2611826	G	0.362	0.394	0.352	0.282	0.404	0.567	0.597	0.597	0.529	0.505	0.616
HMP19	rs1909704	A	0.595	0.644	0.570	0.600	0.562	0.440	0.457	0.447	0.429	0.409	0.465
TTLL7	rs11163772	A	0.146	0.160	0.117	0.076	0.207	0.272	0.263	0.248	0.267	0.255	0.328
TENM4(ODZ4)	rs2156215	T	0.278	0.223	0.289	0.453	0.178	0.376	0.414	0.364	0.390	0.274	0.444
KLRK1	rs2617151	A	0.125	0.138	0.109	0.041	0.192	0.214	0.269	0.155	0.190	0.207	0.258
KLRK1	rs2733852	G	0.228	0.245	0.133	0.071	0.399	0.262	0.344	0.209	0.219	0.226	0.323
OSR1	rs4666492	G	0.343	0.394	0.320	0.224	0.409	0.197	0.215	0.160	0.186	0.183	0.247
CTNNA2	rs4852547	G	0.441	0.457	0.500	0.329	0.481	0.154	0.145	0.194	0.143	0.135	0.152
MN1	rs134006	C	0.190	0.160	0.219	0.288	0.120	0.279	0.349	0.214	0.290	0.260	0.288
LTN1(RNF160)	rs2832137	T	0.418	0.367	0.453	0.476	0.394	0.172	0.151	0.189	0.138	0.202	0.177
HERPUD2	rs11763983	T	0.427	0.463	0.383	0.424	0.423	0.234	0.220	0.272	0.210	0.250	0.217
GALNT10	rs574750	A	0.215	0.261	0.195	0.088	0.288	0.144	0.156	0.131	0.129	0.159	0.146
SAMD3(TMEM200A)	rs9483115	T	0.445	0.415	0.492	0.476	0.418	0.473	0.538	0.364	0.443	0.534	0.495
SAMD3(TMEM200A)	rs4141940	A	0.435	0.399	0.500	0.465	0.404	0.473	0.538	0.364	0.443	0.534	0.495
SAMD3(TMEM200A)	rs899276	A	0.434	0.394	0.500	0.465	0.404	0.474	0.543	0.364	0.443	0.534	0.495
SAMD3(TMEM200A)	rs7758496	G	0.44	0.41	0.508	0.476	0.42	0.47	0.538	0.36	0.44	0.534	0.48
SAMD3(TMEM200A)	rs724324	G	0.445	0.410	0.500	0.476	0.418	0.473	0.538	0.364	0.443	0.534	0.495
SAMD3	rs4897380	C	0.45	0.43	0.523	0.471	0.41	0.48	0.522	0.40	0.45	0.577	0.46
SEMA6D	rs470151	T	0.159	0.133	0.172	0.259	0.091	0.259	0.269	0.248	0.281	0.144	0.359
PMFBP1	rs11862324	T	0.476	0.367	0.484	0.735	0.356	0.455	0.376	0.505	0.529	0.495	0.359
NAV2	rs2707110	C	0.354	0.335	0.336	0.382	0.361	0.338	0.301	0.335	0.329	0.332	0.394
NAV2	rs873764	G	0.500	0.457	0.469	0.624	0.457	0.408	0.376	0.432	0.405	0.394	0.429
TMEM132B	rs4435061	A	0.341	0.372	0.352	0.329	0.317	0.476	0.468	0.490	0.486	0.438	0.500

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Table B.2. (cont.)

Gene	**Variant/SNP**	**Behcet Allele**	**AMR**	CLM	MXL	PEL	PUR	**EAS**	CDX	CHB	CHS	JPT	KHV
TMEM132B	rs10846917	T	0.588	0.574	0.570	0.571	0.625	0.376	0.430	0.364	0.357	0.346	0.389
TMEM132B	rs10846924	T	0.290	0.314	0.328	0.329	0.212	0.476	0.468	0.485	0.486	0.442	0.500
STX8	rs1549332	A	0.104	0.128	0.117	0.035	0.130	0.091	0.070	0.078	0.086	0.149	0.071
OVCH1	rs1436321	A	0.274	0.266	0.188	0.194	0.399	0.465	0.516	0.456	0.467	0.365	0.530
SLC41A2	rs2731031	A	0.284	0.261	0.312	0.259	0.308	0.390	0.414	0.422	0.381	0.322	0.414
HNF4G	rs2980221	A	0.431	0.521	0.391	0.259	0.514	0.343	0.323	0.350	0.338	0.346	0.359
SMARCA2	rs7033529	A	0.761	0.729	0.742	0.700	0.851	0.538	0.527	0.539	0.557	0.510	0.556
EBF2	rs4570167	C	0.363	0.335	0.359	0.253	0.481	0.250	0.290	0.228	0.238	0.202	0.298
EBF2	rs4242425	T	0.362	0.330	0.359	0.253	0.481	0.250	0.290	0.228	0.238	0.202	0.298
GAS2	rs10833804	G	0.715	0.777	0.727	0.618	0.731	0.400	0.387	0.325	0.371	0.486	0.429
LYST/NID1	rs7354999	G	0.885	0.910	0.891	0.824	0.909	0.364	0.371	0.320	0.357	0.404	0.369
LOC100132252	rs9469615	C	0.086	0.069	0.078	0.053	0.135	0.058	0.005	0.053	0.019	0.173	0.030
LOC107984355	rs872837	A	0.370	0.335	0.352	0.441	0.356	0.240	0.290	0.233	0.243	0.197	0.242
SACM1L	rs1969624	C	0.454	0.410	0.445	0.382	0.558	0.265	0.317	0.204	0.224	0.240	0.348
PLEKHB1	rs591804	G	0.329	0.319	0.328	0.306	0.356	0.310	0.306	0.350	0.290	0.317	0.283
ATP8A1	rs2100766	T	0.082	0.085	0.047	0.094	0.091	0.156	0.113	0.170	0.167	0.188	0.136
KCNK9	rs1961261	A	0.226	0.207	0.250	0.218	0.236	0.233	0.253	0.282	0.148	0.216	0.273
SUMO4	rs237024	C	0.615	0.532	0.594	0.700	0.635	0.736	0.753	0.728	0.714	0.726	0.763

Table B.3. Distribution of Behcet's Disease associated variants among European and South Asian populations

Gene	**Variant/SNP**	**Behcet Allele**	**EUR**	CEU	FIN	GBR	IBS	TSI	**SAS**	BEB	GIH	ITU	PJL	STU
IL-10	rs1518111	A	0.221	0.202	0.207	0.176	0.234	0.276	0.443	0.459	0.403	0.436	0.443	0.475
IL-10	rs1800871	T	0.24	0.207	0.237	0.187	0.262	0.294	0.458	0.494	0.408	0.456	0.448	0.49
IL-10	rs1800872	A	0.240	0.207	0.237	0.187	0.262	0.294	0.458	0.494	0.408	0.456	0.448	0.490
IL-10	rs1554286	C	0.815	0.833	0.813	0.841	0.818	0.776	0.582	0.547	0.621	0.574	0.620	0.544
IL23R,IL12RB2	rs1495965	G	0.480	0.424	0.646	0.445	0.439	0.449	0.537	0.599	0.529	0.505	0.484	0.574
IL23R,IL12RB2	rs924080	T	0.553	0.515	0.697	0.555	0.505	0.500	0.661	0.703	0.655	0.598	0.677	0.676
IL23R,IL12RB2	rs12119179	A	0.665	0.697	0.611	0.698	0.664	0.659	0.475	0.407	0.481	0.510	0.536	0.436
IL23R,IL12RB2	rs11209033	C	0.665	0.697	0.611	0.698	0.664	0.659	0.478	0.407	0.485	0.510	0.542	0.436
IL23R,IL12RB2	rs12141431	C	0.304	0.288	0.323	0.275	0.313	0.318	0.488	0.547	0.461	0.471	0.453	0.515
TNFAIP3	rs9494885	T	0.913	0.904	0.960	0.907	0.916	0.879	0.902	0.924	0.917	0.922	0.875	0.873
TNFAIP3	rs10499194	C	0.720	0.727	0.763	0.720	0.654	0.738	0.715	0.797	0.636	0.725	0.682	0.745
TNFAIP3	rs610604	A	0.662	0.601	0.707	0.654	0.650	0.696	0.674	0.715	0.689	0.637	0.661	0.672
TNFAIP3	rs7753873	C	0.087	0.096	0.040	0.093	0.084	0.121	0.101	0.081	0.083	0.078	0.125	0.137
STAT4	rs7574070	A	0.342	0.343	0.313	0.379	0.318	0.360	0.314	0.366	0.291	0.343	0.297	0.279
STAT4	rs897200	A	0.357	0.364	0.313	0.401	0.341	0.369	0.319	0.372	0.301	0.343	0.292	0.294
STAT4	rs7572482	A	0.343	0.343	0.313	0.385	0.318	0.360	0.315	0.360	0.296	0.343	0.292	0.289
CCR1	rs17282391	G	0.094	0.101	0.141	0.099	0.061	0.075	0.293	0.209	0.325	0.275	0.359	0.289
CCR1	rs10510749	T	0.094	0.101	0.141	0.099	0.061	0.075	0.292	0.209	0.325	0.275	0.359	0.284
CCR1	rs13084057	G	0.094	0.101	0.141	0.099	0.061	0.075	0.293	0.209	0.325	0.275	0.359	0.289
CCR1	rs7631551	A	0.100	0.101	0.141	0.099	0.079	0.084	0.293	0.209	0.325	0.275	0.365	0.284
CCR1	rs7616215	T	0.643	0.616	0.616	0.648	0.631	0.701	0.549	0.640	0.519	0.525	0.500	0.574
CCR3	rs7649764	C	0.735	0.753	0.697	0.769	0.785	0.673	0.628	0.570	0.675	0.603	0.656	0.627
CCR3	rs9990343	G	0.507	0.510	0.566	0.571	0.509	0.393	0.472	0.378	0.515	0.490	0.516	0.451
CCR3	rs6803980	A	0.506	0.510	0.566	0.571	0.509	0.388	0.466	0.384	0.515	0.480	0.495	0.446
CCR3	rs13075270	C	0.098	0.101	0.131	0.099	0.070	0.093	0.299	0.221	0.354	0.265	0.370	0.275
CCR3	rs13092160	C	0.092	0.101	0.131	0.099	0.061	0.075	0.299	0.221	0.354	0.265	0.370	0.275

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Table B.3. (cont.)

Gene	Variant/SNP	Behcet Allele	EUR	CEU	FIN	GBR	IBS	TSI	SAS	BEB	GIH	ITU	PJL	STU
CCR3	rs2373156	T	0.089	0.091	0.106	0.077	0.075	0.098	0.276	0.203	0.316	0.240	0.349	0.265
CCR3	rs7651539	T	0.089	0.091	0.106	0.077	0.075	0.098	0.276	0.203	0.316	0.240	0.349	0.265
CCR3	rs1542755	A	0.080	0.091	0.106	0.077	0.051	0.075	0.272	0.215	0.311	0.245	0.312	0.270
CCR3	rs13067058	A	0.078	0.096	0.111	0.071	0.047	0.065	0.253	0.198	0.301	0.211	0.297	0.250
CCR3	rs13092160	C	0.092	0.101	0.131	0.099	0.061	0.075	0.299	0.221	0.354	0.265	0.370	0.275
KLRC4	rs2617170	C	0.663	0.687	0.591	0.720	0.696	0.626	0.544	0.552	0.515	0.515	0.589	0.554
ERAP1	rs17482078	T	0.224	0.263	0.227	0.253	0.182	0.201	0.065	0.058	0.058	0.078	0.068	0.064
FUT2	rs681343	T	0.440	0.535	0.298	0.473	0.425	0.472	0.283	0.238	0.252	0.240	0.427	0.260
IL12A	rs17810546	A	0.906	0.909	0.894	0.885	0.916	0.921	0.967	0.983	0.942	0.966	0.958	0.990
IL23R	rs11209026	A	0.062	0.051	0.030	0.071	0.065	0.089	0.012	0.006	0.010	0.015	0.016	0.015
IL23R	rs76418789	A	0.002	0	0	0.0055	0.0047	0	0	0	0	0	0	0
IL23R	rs17375018	G	0.714	0.717	0.697	0.747	0.664	0.748	0.686	0.733	0.660	0.667	0.714	0.667
IL23R	rs11209032	A	0.334	0.303	0.389	0.297	0.336	0.341	0.525	0.593	0.515	0.495	0.458	0.569
IL23R	rs1343151	T	0.322	0.343	0.207	0.363	0.336	0.360	0.164	0.122	0.155	0.167	0.203	0.167
TLR4	rs4986790	G	0.057	0.040	0.116	0.044	0.037	0.047	0.126	0.134	0.102	0.142	0.109	0.142
TLR4	rs4986791	T	0.058	0.040	0.116	0.038	0.047	0.047	0.117	0.093	0.092	0.147	0.078	0.167
NOD2	rs2066844	T	0.051	0.071	0.030	0.049	0.056	0.047	0.001	0.006	0	0	0	0
NOD2	rs2066845	C	0.010	0.020	0	0.005	0.009	0.014	0.004	0	0	0.005	0.016	0
NOD2	rs2066847	ins-C	0.014	0.030	0	0.022	0.014	0.005	0	0	0	0	0	0
IL1	rs1800587	C	0.713	0.747	0.722	0.637	0.743	0.706	0.685	0.715	0.704	0.642	0.693	0.676
IL1	rs1143634	T	0.248	0.232	0.237	0.313	0.196	0.266	0.147	0.122	0.194	0.132	0.146	0.137
IL1	rs16944	G	0.650	0.652	0.626	0.681	0.673	0.621	0.400	0.401	0.403	0.382	0.438	0.377
TNFα	rs1799964	C	0.210	0.212	0.202	0.220	0.178	0.238	0.348	0.436	0.383	0.373	0.286	0.270
TNFα	rs361525	A	0.064	0.066	0.040	0.077	0.051	0.084	0.105	0.105	0.170	0.132	0.047	0.069
TNFα	rs1799724	T	0.094	0.056	0.066	0.077	0.131	0.136	0.119	0.076	0.107	0.118	0.151	0.137
IL12	rs3212227	A	0.777	0.808	0.813	0.753	0.780	0.734	0.626	0.674	0.655	0.583	0.667	0.559

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Table B.3. (cont.)

Gene	Variant/SNP	Behcet Allele	EUR	CEU	FIN	GBR	IBS	TSI	SAS	BEB	GIH	ITU	PJL	STU
IL18	rs1946518	C	0.577	0.636	0.545	0.621	0.579	0.509	0.712	0.750	0.772	0.691	0.646	0.701
IL17F-A126G	rs2397084	T	0.921	0.924	0.934	0.907	0.935	0.907	0.953	0.953	0.961	0.956	0.938	0.956
LOC100129342	rs11206377	G	0.542	0.596	0.530	0.533	0.500	0.551	0.802	0.756	0.859	0.789	0.766	0.828
CCDC180	rs2061634	G	0.200	0.237	0.121	0.209	0.215	0.215	0.261	0.227	0.223	0.275	0.328	0.250
CPVL	rs317711	C	0.249	0.247	0.247	0.236	0.234	0.276	0.095	0.087	0.034	0.098	0.120	0.137
UBASH3B	rs4936742	T	0.419	0.369	0.328	0.451	0.439	0.505	0.458	0.465	0.485	0.475	0.396	0.466
UBAC2	rs9513584	G	0.273	0.202	0.359	0.258	0.234	0.313	0.593	0.558	0.597	0.627	0.536	0.637
UBAC2	rs9517644	T	0.276	0.202	0.359	0.264	0.238	0.318	0.594	0.552	0.602	0.623	0.552	0.632
UBAC2	rs11069357	A	0.277	0.202	0.359	0.264	0.238	0.322	0.594	0.552	0.602	0.623	0.552	0.632
UBAC2	rs984477	G	0.341	0.308	0.455	0.319	0.290	0.336	0.599	0.570	0.602	0.627	0.547	0.642
UBAC2	rs9554573	A	0.275	0.202	0.364	0.264	0.234	0.313	0.603	0.576	0.597	0.642	0.547	0.647
UBAC2	rs6491493	G	0.273	0.202	0.359	0.258	0.234	0.313	0.599	0.576	0.607	0.627	0.542	0.637
UBAC2	rs9517668	T	0.115	0.096	0.146	0.137	0.075	0.126	0.168	0.174	0.165	0.176	0.151	0.172
UBAC2	rs7999348	G	0.285	0.202	0.364	0.286	0.243	0.332	0.677	0.651	0.650	0.725	0.604	0.745
UBAC2	rs9554581	T	0.114	0.096	0.146	0.137	0.075	0.121	0.166	0.169	0.165	0.176	0.146	0.172
UBAC2	rs17575643	T	0.100	0.091	0.131	0.126	0.070	0.089	0.109	0.110	0.121	0.118	0.062	0.132
UBAC2	rs727263	A	0.114	0.096	0.146	0.137	0.075	0.121	0.163	0.169	0.155	0.172	0.146	0.172
UBAC2	rs7332161	A	0.114	0.096	0.146	0.137	0.075	0.121	0.167	0.174	0.165	0.176	0.146	0.172
UBAC2	rs912130	C	0.274	0.207	0.364	0.258	0.234	0.308	0.595	0.570	0.592	0.627	0.542	0.637
UBAC2	rs2892976	G	0.202	0.162	0.247	0.203	0.150	0.248	0.317	0.250	0.306	0.338	0.292	0.387
UBAC2	rs3825427	T	0.116	0.096	0.146	0.143	0.075	0.126	0.178	0.186	0.175	0.181	0.167	0.181
UBAC2	rs9517701	G	0.115	0.096	0.146	0.137	0.079	0.121	0.167	0.174	0.165	0.176	0.146	0.172
GIMAP4	rs1916012	T	0.554	0.525	0.475	0.637	0.584	0.551	0.551	0.465	0.587	0.529	0.573	0.588
GIMAP4	rs1522596	T	0.555	0.525	0.475	0.637	0.589	0.551	0.551	0.465	0.587	0.529	0.573	0.588
GIMAP4	rs1608157	C	0.554	0.525	0.475	0.637	0.584	0.551	0.551	0.465	0.587	0.529	0.573	0.588
GIMAP2	rs10266069	A	0.494	0.485	0.455	0.489	0.514	0.523	0.356	0.366	0.393	0.324	0.349	0.348

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Table B.3. (cont.)

Gene	Variant/SNP	Behcet Allele	EUR	CEU	FIN	GBR	IBS	TSI	SAS	BEB	GIH	ITU	PJL	STU
GIMAP2	rs10256482	T	0.597	0.556	0.571	0.654	0.603	0.607	0.463	0.430	0.505	0.412	0.500	0.466
GIMAP1	rs2286900	T	0.092	0.096	0.126	0.082	0.070	0.089	0.090	0.064	0.083	0.127	0.099	0.074
CPLX1	rs11248047	A	0.466	0.480	0.500	0.505	0.453	0.402	0.359	0.355	0.427	0.363	0.328	0.319
DEPDC1	rs6692084	A	0.232	0.242	0.308	0.187	0.210	0.210	0.214	0.198	0.214	0.186	0.245	0.225
DEPDC1	rs12134670	C	0.082	0.076	0.126	0.066	0.065	0.075	0.122	0.087	0.112	0.137	0.141	0.127
DTL	rs1472224	G	0.597	0.616	0.465	0.670	0.621	0.617	0.474	0.384	0.481	0.495	0.495	0.505
DNMT3A	rs1465825	C	0.262	0.258	0.227	0.236	0.322	0.262	0.451	0.465	0.413	0.485	0.432	0.461
TFCP2L1	rs17006292	A	0.002	0	0	0	0.005	0.005	0.043	0.070	0.053	0.054	0.010	0.029
PSMD14	rs6744214	T	0.313	0.227	0.414	0.330	0.304	0.294	0.415	0.453	0.403	0.412	0.396	0.417
PSMD14	rs6733456	C	0.317	0.232	0.419	0.330	0.304	0.304	0.406	0.442	0.374	0.412	0.391	0.417
STK39	rs2390639	A	0.790	0.833	0.753	0.808	0.808	0.752	0.681	0.645	0.646	0.740	0.703	0.667
STK39	rs3769393	G	0.818	0.843	0.808	0.808	0.841	0.790	0.734	0.686	0.728	0.765	0.750	0.735
SGPP2	rs17562982	T	0.402	0.384	0.333	0.396	0.388	0.500	0.500	0.442	0.529	0.529	0.443	0.544
ASB18	rs7561555	C	0.304	0.343	0.354	0.247	0.285	0.290	0.383	0.419	0.393	0.348	0.380	0.382
SLIT2	rs13435197	A	0.397	0.419	0.379	0.396	0.355	0.435	0.297	0.262	0.257	0.333	0.354	0.275
SORBS2	rs4493590	G	0.280	0.343	0.323	0.269	0.271	0.201	0.199	0.256	0.218	0.137	0.182	0.211
MSX2	rs10516130	A	0.141	0.126	0.141	0.176	0.131	0.136	0.203	0.215	0.194	0.255	0.198	0.157
C6orf85(LOC100507336)	rs12194547	C	0.062	0.066	0.081	0.082	0.065	0.019	0.096	0.116	0.068	0.064	0.120	0.118
ABCB5	rs2190411	C	0.273	0.283	0.187	0.269	0.262	0.360	0.192	0.169	0.194	0.181	0.219	0.196
SUSD1	rs2782932	T	0.181	0.157	0.192	0.165	0.196	0.192	0.158	0.134	0.146	0.142	0.161	0.206
LINC01499(API5)	rs420798	C	0.925	0.934	0.924	0.923	0.911	0.935	0.882	0.831	0.898	0.892	0.896	0.887
API5	rs16937370	G	0	0	0	0	0	0	0.026	0.047	0.010	0.020	0.036	0.020
SLC43A3	rs549630	G	0.380	0.449	0.253	0.407	0.393	0.397	0.223	0.186	0.228	0.206	0.229	0.260
RIMBP2	rs2895135	A	0.324	0.303	0.384	0.302	0.374	0.257	0.178	0.215	0.136	0.162	0.219	0.167
GALNTL1	rs12589991	A	0.142	0.091	0.202	0.143	0.164	0.112	0.087	0.099	0.117	0.069	0.083	0.069
SMG6	rs749240	T	0.362	0.328	0.338	0.352	0.369	0.416	0.378	0.384	0.413	0.368	0.312	0.412

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Table B.3. (cont.)

Gene	Variant/SNP	Behcet Allele	**EUR**	CEU	FIN	GBR	IBS	TSI	**SAS**	BEB	GIH	ITU	PJL	STU
LILRB1	rs798887	A	0.810	0.823	0.682	0.802	0.836	0.897	0.852	0.767	0.898	0.902	0.818	0.858
LILRA1	rs103294	C	0.820	0.833	0.702	0.824	0.836	0.897	0.872	0.820	0.908	0.917	0.828	0.877
RALGAPA2	rs6082210	A	0.046	0.025	0.141	0.038	0.009	0.019	0.077	0.058	0.092	0.078	0.083	0.069
CDH26	rs817277	A	0.431	0.500	0.409	0.407	0.416	0.425	0.399	0.401	0.383	0.373	0.411	0.426
CDH26	rs817283	A	0.433	0.500	0.424	0.401	0.421	0.421	0.403	0.424	0.388	0.373	0.411	0.422
UBD	rs6933331	A	0.012	0.010	0.005	0	0.023	0.019	0.063	0.093	0.058	0.044	0.057	0.069
UBD	rs3025657	G	0.012	0.010	0.005	0	0.023	0.019	0.063	0.093	0.058	0.044	0.057	0.069
GABBR1	rs29273	G	0.813	0.889	0.894	0.786	0.724	0.780	0.863	0.901	0.850	0.907	0.792	0.868
MOG	rs3129045	T	0.347	0.247	0.212	0.385	0.472	0.407	0.333	0.413	0.286	0.294	0.354	0.333
HLA-F	rs3116788	G	0.304	0.298	0.429	0.291	0.234	0.276	0.349	0.390	0.320	0.328	0.354	0.358
HLA-F	rs1610584	T	0.304	0.298	0.429	0.291	0.234	0.276	0.349	0.390	0.320	0.328	0.354	0.358
HLA-F	rs1610585	C	0.304	0.298	0.429	0.291	0.234	0.276	0.349	0.390	0.320	0.328	0.354	0.358
HLA-F	rs1610593	T	0.304	0.298	0.429	0.291	0.234	0.276	0.350	0.390	0.320	0.333	0.354	0.358
HLA-F	rs1611356	G	0.696	0.702	0.571	0.709	0.766	0.724	0.650	0.610	0.680	0.667	0.646	0.642
HLA-F	rs1611381	T	0.304	0.298	0.429	0.291	0.234	0.276	0.350	0.390	0.320	0.333	0.354	0.358
HLA-F	rs7741807	G	0.978	0.980	0.975	0.978	0.991	0.967	0.921	0.942	0.927	0.931	0.891	0.917
HLA-F	rs1611388	C	0.302	0.298	0.419	0.291	0.234	0.276	0.350	0.390	0.320	0.333	0.354	0.358
HLA-F	rs1627465	C	0.304	0.298	0.429	0.291	0.234	0.276	0.353	0.407	0.320	0.333	0.354	0.358
LOC285830 (HLA-F antisense RNA1)	rs9258205	C	0.115	0.121	0.111	0.159	0.079	0.112	0.287	0.343	0.262	0.279	0.302	0.260
LOC285830 (HLA-F antisense RNA1)	rs2523386	A	0.174	0.096	0.126	0.187	0.234	0.220	0.081	0.041	0.117	0.039	0.130	0.074
LOC285830 (HLA-F antisense RNA1)	rs2844845	A	0.179	0.096	0.126	0.187	0.248	0.229	0.082	0.041	0.117	0.044	0.130	0.074
LOC285830 (HLA-F antisense RNA1)	rs1633041	T	0.255	0.232	0.202	0.275	0.280	0.285	0.299	0.209	0.417	0.304	0.328	0.221

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Table B.3. (cont.)

Gene	Variant/SNP	Behcet Allele	**EUR**	CEU	FIN	GBR	IBS	TSI	**SAS**	BEB	GIH	ITU	PJL	STU
LOC285830 (HLA-F antisense RNA1)	rs1737031	A	0.280	0.258	0.207	0.286	0.313	0.332	0.350	0.262	0.451	0.333	0.401	0.289
LOC285830 (HLA-F antisense RNA1)	rs885940	A	0.255	0.232	0.202	0.275	0.280	0.285	0.301	0.209	0.417	0.314	0.328	0.221
LOC285830 (HLA-F antisense RNA1)	rs1610637	C	0.255	0.232	0.202	0.275	0.280	0.285	0.303	0.215	0.417	0.314	0.333	0.221
LOC285830 (HLA-F antisense RNA1)	rs1615251	T	0.690	0.712	0.783	0.681	0.650	0.631	0.626	0.727	0.524	0.623	0.573	0.696
HLA-G	rs1633002	A	0.745	0.768	0.798	0.725	0.720	0.715	0.700	0.791	0.587	0.686	0.672	0.779
HLA-G	rs1632973	A	0.254	0.232	0.202	0.269	0.280	0.285	0.302	0.209	0.417	0.314	0.333	0.221
HLA-G	rs1736963	T	0.256	0.232	0.202	0.280	0.280	0.285	0.302	0.209	0.417	0.314	0.333	0.221
HLA-G	rs2523408	G	0	0	0	0	0	0	0.005	0.017	0.005	0.005	0	0
HLA-G	rs1611172	G	0.256	0.237	0.202	0.275	0.280	0.285	0.301	0.209	0.417	0.314	0.328	0.221
HLA-G	rs753544	T	0.255	0.232	0.202	0.275	0.280	0.285	0.303	0.215	0.417	0.314	0.328	0.225
HLA-G	rs1077433	A	0.255	0.232	0.202	0.275	0.280	0.285	0.302	0.209	0.417	0.314	0.333	0.221
HLA-G	rs1736951	A	0.303	0.283	0.237	0.324	0.322	0.346	0.362	0.227	0.476	0.431	0.411	0.245
HLA-G	rs407238	C	0.348	0.333	0.424	0.335	0.276	0.374	0.340	0.297	0.417	0.299	0.328	0.353
HCG9	rs9260954	G	0.051	0.030	0.010	0.060	0.070	0.079	0.028	0.017	0.010	0.039	0.016	0.054
HCG9	rs6911737	A	0.095	0.061	0.030	0.082	0.126	0.168	0.158	0.238	0.121	0.123	0.104	0.216
HCG9	rs6926792	A	0.095	0.061	0.030	0.082	0.126	0.168	0.157	0.238	0.121	0.123	0.099	0.216
HCG9	rs6931776	G	0.096	0.061	0.030	0.088	0.126	0.168	0.157	0.238	0.121	0.123	0.099	0.216
ZNRD1	rs9261189	T	0.095	0.061	0.030	0.082	0.126	0.168	0.158	0.238	0.121	0.123	0.099	0.221
ZNRD1	rs3869068	A	0.095	0.061	0.030	0.082	0.126	0.168	0.156	0.238	0.121	0.123	0.099	0.211
ZNRD1	rs9261265	C	0.051	0.030	0.010	0.060	0.070	0.079	0.027	0.017	0.010	0.039	0.016	0.049
PPP1R11	rs2074482	T	0.095	0.061	0.030	0.082	0.126	0.168	0.157	0.238	0.121	0.123	0.099	0.216
RNF39	rs9261317	A	0.949	0.970	0.990	0.940	0.930	0.921	0.972	0.983	0.990	0.961	0.979	0.951

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Table B.3. (cont.)

Gene	Variant/SNP	Behcet Allele	EUR	CEU	FIN	GBR	IBS	TSI	SAS	BEB	GIH	ITU	PJL	STU
TRIM31	rs9261376	G	0.189	0.146	0.061	0.187	0.248	0.290	0.346	0.372	0.398	0.333	0.302	0.324
TRIM31	rs9261389	G	0.189	0.146	0.061	0.187	0.248	0.290	0.345	0.372	0.398	0.333	0.297	0.324
TRIM31	rs6923832	A	0.051	0.030	0.010	0.060	0.070	0.079	0.027	0.017	0.010	0.039	0.016	0.049
MUC21	rs2530710	A	0.182	0.212	0.232	0.176	0.150	0.145	0.237	0.209	0.199	0.240	0.255	0.279
MUC21	rs2517446	C	0.143	0.101	0.086	0.121	0.224	0.173	0.125	0.145	0.073	0.152	0.130	0.127
MUC21	rs2517411	G	0.146	0.101	0.096	0.121	0.224	0.178	0.127	0.151	0.078	0.152	0.130	0.127
MUC21	rs2844673	A	0.146	0.101	0.096	0.121	0.224	0.178	0.127	0.151	0.078	0.152	0.130	0.127
MUC21	rs2252925	G	0.146	0.101	0.096	0.121	0.224	0.178	0.127	0.151	0.078	0.152	0.130	0.127
MUC21	rs2252926	G	0.146	0.101	0.096	0.121	0.224	0.178	0.127	0.151	0.078	0.152	0.130	0.127
MUC21	rs1634717	T	0.405	0.354	0.293	0.423	0.477	0.467	0.232	0.227	0.180	0.289	0.266	0.201
MUC21	rs2523915	T	0.854	0.899	0.904	0.879	0.776	0.822	0.873	0.849	0.922	0.848	0.870	0.873
MUC21	rs1632854	T	0.595	0.646	0.707	0.577	0.523	0.533	0.768	0.773	0.820	0.711	0.734	0.799
C6orf15	rs1265048	A	0.603	0.682	0.510	0.621	0.579	0.626	0.673	0.744	0.684	0.632	0.609	0.701
PSORS1C1	rs4959053	A	0.082	0.086	0.076	0.082	0.079	0.084	0.178	0.221	0.146	0.157	0.250	0.127
CCHCR1	rs2240063	A	0.437	0.439	0.359	0.423	0.495	0.463	0.474	0.535	0.466	0.451	0.458	0.471
CCHCR1	rs2073716	C	0.957	0.965	0.955	0.962	0.939	0.967	0.922	0.953	0.942	0.931	0.901	0.887
TCF19	rs2073723	T	0.216	0.247	0.232	0.253	0.173	0.182	0.317	0.407	0.243	0.284	0.339	0.328
POU5F1	rs9501063	G	0.957	0.965	0.955	0.956	0.949	0.963	0.950	0.977	0.971	0.961	0.943	0.902
POU5F1	rs9263804	C	0.219	0.247	0.232	0.258	0.182	0.182	0.344	0.424	0.272	0.314	0.380	0.343
POU5F1	rs3130501	A	0.217	0.253	0.232	0.253	0.173	0.182	0.318	0.407	0.243	0.289	0.339	0.328
POU5F1	rs3132524	A	0.220	0.247	0.232	0.258	0.182	0.187	0.344	0.424	0.272	0.314	0.380	0.343
HCG27	rs3130944	C	0.763	0.727	0.808	0.731	0.794	0.752	0.767	0.826	0.733	0.735	0.760	0.789
HLA-C	rs3905495	C	0.607	0.641	0.510	0.648	0.626	0.612	0.532	0.651	0.578	0.475	0.490	0.480
DHFRP2	rs7761068	T	0.512	0.641	0.434	0.555	0.542	0.397	0.268	0.250	0.282	0.221	0.271	0.314
HLA-B	rs9266406	A	0.215	0.182	0.202	0.148	0.224	0.304	0.412	0.483	0.393	0.436	0.375	0.382
HLA-B	rs9266409	C	0.215	0.182	0.202	0.148	0.224	0.304	0.412	0.483	0.393	0.436	0.375	0.382

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Table B.3. (cont.)

Gene	Variant/SNP	Behcet Allele	EUR	CEU	FIN	GBR	IBS	TSI	SAS	BEB	GIH	ITU	PJL	STU
HLA-B	rs6910516	C	0.215	0.182	0.202	0.148	0.224	0.304	0.412	0.483	0.393	0.436	0.375	0.382
MICA	rs2523467	A	0.388	0.293	0.369	0.418	0.444	0.411	0.381	0.419	0.456	0.382	0.271	0.377
MICA	rs3094584	T	0.179	0.121	0.051	0.132	0.318	0.252	0.261	0.302	0.223	0.275	0.255	0.255
BAG6(BAT3)	rs2077102	T	0.163	0.146	0.328	0.165	0.093	0.093	0.115	0.110	0.107	0.093	0.099	0.162
C6orf47	rs2242655	C	0.837	0.854	0.672	0.835	0.907	0.907	0.888	0.890	0.898	0.907	0.901	0.843
SLC44A4	rs11965547	A	0.116	0.101	0.212	0.104	0.056	0.112	0.144	0.128	0.126	0.142	0.130	0.191
C6orf10	rs544358	C	0.372	0.414	0.313	0.368	0.350	0.411	0.383	0.355	0.437	0.338	0.401	0.382
C6orf10	rs574710	G	0.379	0.414	0.333	0.368	0.360	0.416	0.395	0.349	0.442	0.343	0.417	0.417
C6orf10	rs539703	C	0.372	0.414	0.313	0.368	0.350	0.411	0.381	0.337	0.437	0.343	0.401	0.382
C6orf10	rs926591	T	0.374	0.414	0.313	0.368	0.350	0.421	0.381	0.343	0.437	0.338	0.401	0.382
C6orf10	rs4959093	C	0.374	0.414	0.313	0.368	0.350	0.421	0.381	0.343	0.437	0.338	0.401	0.382
BTNL2	rs2076530	G	0.447	0.475	0.444	0.478	0.477	0.369	0.435	0.494	0.388	0.471	0.385	0.441
HLA-DQA1	rs9272346	G	0.451	0.434	0.535	0.407	0.444	0.435	0.511	0.541	0.505	0.520	0.495	0.500
HLA-DQB1	rs6457617	C	0.455	0.480	0.369	0.467	0.491	0.467	0.608	0.610	0.549	0.569	0.729	0.593
COL12A1	rs4640857	G	0.414	0.404	0.465	0.379	0.421	0.397	0.505	0.547	0.500	0.554	0.505	0.426
C10orf11	rs1323076	G	0.500	0.510	0.444	0.484	0.500	0.556	0.367	0.401	0.311	0.382	0.385	0.363
C10orf11	rs17434565	G	0.214	0.192	0.298	0.181	0.206	0.192	0.265	0.331	0.199	0.270	0.271	0.265
PAX8	rs11123169	C	0.329	0.374	0.359	0.253	0.322	0.332	0.349	0.401	0.383	0.353	0.323	0.289
PAX8	rs10864912	T	0.456	0.470	0.510	0.456	0.416	0.435	0.420	0.436	0.456	0.387	0.422	0.402
HIVEP3	rs4660590	A	0.472	0.444	0.535	0.533	0.411	0.449	0.481	0.401	0.408	0.554	0.495	0.534
CEP135	rs2593082	T	0.508	0.455	0.515	0.484	0.547	0.533	0.476	0.477	0.471	0.436	0.464	0.534
CEP135	rs2611826	G	0.490	0.545	0.485	0.516	0.444	0.467	0.527	0.535	0.544	0.574	0.531	0.451
HMP19	rs1909704	A	0.670	0.702	0.636	0.665	0.645	0.701	0.501	0.471	0.500	0.510	0.495	0.525
TTLL7	rs11163772	A	0.159	0.187	0.116	0.143	0.168	0.178	0.102	0.122	0.073	0.103	0.083	0.132
TENM4(ODZ4)	rs2156215	T	0.033	0.005	0.086	0.027	0.033	0.014	0.237	0.262	0.214	0.304	0.203	0.206
KLRK1	rs2617151	A	0.183	0.172	0.222	0.137	0.164	0.215	0.090	0.110	0.083	0.078	0.089	0.093

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Table B.3. (cont.)

Gene	Variant/SNP	Behcet Allele	EUR	CEU	FIN	GBR	IBS	TSI	SAS	BEB	GIH	ITU	PJL	STU
KLRK1	rs2733852	G	0.294	0.293	0.308	0.264	0.280	0.322	0.150	0.157	0.150	0.127	0.161	0.157
OSR1	rs4666492	G	0.418	0.404	0.470	0.385	0.402	0.430	0.385	0.343	0.388	0.392	0.396	0.402
CTNNA2	rs4852547	G	0.484	0.455	0.525	0.495	0.467	0.481	0.333	0.390	0.272	0.333	0.359	0.324
MN1	rs134006	C	0.058	0.040	0.076	0.055	0.042	0.075	0.185	0.186	0.155	0.250	0.161	0.172
LTN1(RNF160)	rs2832137	T	0.562	0.571	0.611	0.632	0.486	0.523	0.538	0.523	0.539	0.549	0.557	0.520
HERPUD2	rs11763983	T	0.571	0.601	0.636	0.588	0.533	0.505	0.259	0.262	0.296	0.245	0.240	0.250
GALNT10	rs574750	A	0.293	0.308	0.258	0.302	0.304	0.294	0.379	0.419	0.403	0.314	0.401	0.368
SAMD3(TMEM200A)	rs9483115	T	0.348	0.354	0.348	0.363	0.318	0.360	0.438	0.471	0.413	0.436	0.370	0.500
SAMD3(TMEM200A)	rs4141940	A	0.343	0.343	0.348	0.357	0.313	0.355	0.435	0.471	0.413	0.431	0.370	0.490
SAMD3(TMEM200A)	rs899276	A	0.343	0.343	0.348	0.357	0.313	0.355	0.438	0.471	0.413	0.436	0.370	0.500
SAMD3(TMEM200A)	rs7758496	G	0.34	0.34	0.36	0.35	0.31	0.36	0.42	0.471	0.40	0.43	0.35	0.45
SAMD3(TMEM200A)	rs724324	G	0.349	0.354	0.348	0.363	0.322	0.360	0.439	0.477	0.413	0.436	0.370	0.500
SAMD3	rs4897380	C	0.36	0.37	0.38	0.36	0.33	0.37	0.44	0.471	0.42	0.49	0.37	0.45
SEMA6D	rs470151	T	0.043	0.066	0.035	0.055	0.019	0.042	0.237	0.314	0.165	0.240	0.135	0.338
PMFBP1	rs11862324	T	0.170	0.182	0.232	0.181	0.126	0.136	0.237	0.279	0.218	0.186	0.260	0.250
NAV2	rs2707110	C	0.300	0.348	0.217	0.308	0.304	0.322	0.534	0.541	0.592	0.529	0.448	0.554
NAV2	rs873764	G	0.430	0.470	0.460	0.462	0.360	0.411	0.601	0.599	0.655	0.613	0.526	0.608
TMEM132B	rs4435061	A	0.286	0.263	0.328	0.308	0.257	0.280	0.317	0.337	0.345	0.289	0.297	0.319
TMEM132B	rs10846917	T	0.669	0.662	0.631	0.621	0.720	0.701	0.562	0.541	0.544	0.588	0.620	0.520
TMEM132B	rs10846924	T	0.230	0.227	0.288	0.264	0.192	0.187	0.279	0.314	0.296	0.260	0.240	0.289
STX8	rs1549332	A	0.124	0.126	0.071	0.104	0.168	0.145	0.103	0.134	0.087	0.083	0.120	0.098
OVCH1	rs1436321	A	0.308	0.283	0.374	0.286	0.290	0.308	0.505	0.552	0.529	0.451	0.505	0.495
SLC41A2	rs2731031	A	0.372	0.374	0.455	0.352	0.350	0.332	0.603	0.541	0.607	0.603	0.589	0.667
HNF4G	rs2980221	A	0.586	0.611	0.545	0.566	0.570	0.636	0.537	0.442	0.573	0.510	0.547	0.598
SMARCA2	rs7033529	A	0.849	0.843	0.793	0.896	0.822	0.893	0.747	0.738	0.767	0.750	0.724	0.755
EBF2	rs4570167	C	0.344	0.313	0.343	0.297	0.350	0.407	0.542	0.453	0.495	0.627	0.589	0.534

(cont. on next page)

Table B.3. (cont.)

Gene	**Variant/SNP**	**Behcet Allele**	**EUR**	CEU	FIN	GBR	IBS	TSI	**SAS**	BEB	GIH	ITU	PJL	STU
EBF2	rs4242425	T	0.344	0.313	0.343	0.297	0.350	0.407	0.542	0.453	0.495	0.627	0.589	0.534
GAS2	rs10833804	G	0.664	0.657	0.646	0.687	0.696	0.636	0.677	0.756	0.665	0.647	0.661	0.667
LYST/NID1	rs7354999	G	0.989	1.000	0.960	0.995	0.995	0.995	0.731	0.680	0.791	0.667	0.776	0.735
LOC100132252	rs9469615	C	0.143	0.126	0.136	0.143	0.117	0.192	0.057	0.041	0.068	0.039	0.094	0.044
LOC107984355	rs872837	A	0.363	0.394	0.449	0.324	0.322	0.327	0.244	0.256	0.277	0.172	0.307	0.216
SACM1L	rs1969624	C	0.564	0.520	0.540	0.516	0.584	0.645	0.319	0.250	0.291	0.363	0.391	0.294
PLEKHB1	rs591804	G	0.354	0.354	0.318	0.352	0.355	0.388	0.383	0.331	0.403	0.392	0.396	0.387
ATP8A1	rs2100766	T	0.034	0.025	0.061	0.060	0.009	0.019	0.093	0.081	0.107	0.083	0.094	0.098
KCNK9	rs1961261	A	0.230	0.232	0.263	0.264	0.201	0.196	0.261	0.326	0.252	0.230	0.260	0.245
SUMO4	rs237024	C	0.483	0.490	0.480	0.522	0.481	0.449	0.593	0.628	0.553	0.613	0.562	0.613

APPENDIX C

VARIANTS THAT SHOW LINKAGE DISEQUILIBRIUM ($R^2 \geq 0.5$) WITH RS3024498 AND RS9610

Table C.2. Variants that show linkage disequilibrium ($R^2 \geq 0.5$) with rs3024498 and rs9610

Target variant	RS Number	Chr	Position (GRCh37)	Alleles	Gene	MAF	Distance	D'	R2
IL-10 rs3024498	rs6673928	1	206937245	(G/T)	IL10 (3′ region)	0.2266	4284	1	0.9943
IL-10 rs3024498	rs61815632	1	206938439	(A/G)	IL-10 (3′ region)	0.2266	3090	1	0.9943
IL-10 rs3024498	rs3024492	1	206944112	(T/A)	IL-10 (3′ region)	0.2217	2583	1	0.9774
IL-10 rs3024498	rs6703630	1	206948639	(C/T)	IL-19 / IL-10 (5′ region)	0.2326	7110	0.9943	0.9504
IL-10 rs3024498	rs17015767	1	206951398	(G/C)	IL-19 / IL-10 (5′ region)	0.2068	9869	0.9627	0.8291
IL-10 rs3024498	rs79309463	1	206953392	(CTC/-)	IL-19 / IL-10 (5′ region)	0.2048	11863	0.9624	0.8184
IL-10 rs3024498	rs7539748	1	206925375	(G/A)	LOC105372877	0.1789	16154	0.9354	0.6544
IL-10 rs3024498	rs17015865	1	206958587	(G/A)	IL-19 / IL-10 (5′ region)	0.2038	17058	0.8551	0.6422
IL-10 rs3024498	rs72756948	1	206970443	(A/G)	IL-19 / IL-10 (5′ region)	0.2018	28914	0.8537	0.6322
IL-10 rs3024498	rs6683473	1	206967152	(C/T)	IL-19 / IL-10 (5′ region)	0.2018	25623	0.8537	0.6322
IL-10 rs3024498	rs10494878	1	206915809	(A/G)	intergenic	0.1988	25720	0.8515	0.6174
IL-10 rs3024498	rs61814960	1	206978249	(A/G)	IL-19 / IL-10 (5′ region)	0.2038	36720	0.8236	0.5958
IL-10R1 rs9610	rs4936415	11	117875313	(G/C)	SMIM35 / IL-10R1 (3′ region)	0.4831	3227	1	0.8835
IL-10R1 rs9610	rs4938467	11	117875171	(C/T)	SMIM35 / IL-10R1 (3′ region)	0.4831	3085	1	0.8835
IL-10R1 rs9610	rs2256111	11	117864047	(A/G)	IL-10R1	0.494	8039	0.9733	0.7638
IL-10R1 rs9610	rs947889	11	117874531	(C/T)	SMIM35 / IL-10R1 (3′ region)	0.4602	2445	1	0.7041
IL-10R1 rs9610	rs2508450	11	117863829	(T/C)	IL-10R1	0.4453	8257	0.9506	0.5992