Genetic Association Between TNF-A (-308G>A) Polymorphism and Clinical Profile of Behçet's Syndrome: Findings from An Italian Case-Control Analysis

P S Oliveira[1], R M Carvalho[1], L F Gomes[2], A R Silva[2], T M Ferreira[3]*

Background: *Tumor necrosis factor-α (TNF-α) is a multifunctional proinflammatory cytokine involved in the pathogenesis of several immune-mediated disorders, including Behçet's syndrome (BS) — a rare systemic vasculitis characterized by diverse clinical features. This study aimed to evaluate the potential association between the functional TNF-α promoter polymorphism (-308G>A, rs1800629) and both disease susceptibility and clinical expression of BS in an Italian population.*

Methods: *A total of 130 Italian patients diagnosed with BS and 100 age-, sex-, and ethnicity-matched healthy controls (HC) were enrolled from the Rheumatology Institute of Lucania, Italy. Demographic and clinical data were collected from medical records. Genomic DNA was extracted and genotyped using primer-specific PCR amplification followed by direct sequencing. Sequence analysis was performed using Mutation Surveyor (SoftGenetics, USA) and NCBI BLASTN tools for variant confirmation.*

Results: *A significantly higher frequency of the wild-type GG genotype was observed among BS patients compared to controls (81.5% vs 91%, $p < 0.05$), whereas the heterozygous GA genotype was more prevalent in patients (18.5%) than in controls (9%, $p < 0.05$). The GA genotype showed a significant association with disease susceptibility (OR = 2.29; 95% CI, 1.01–5.18). No significant correlations were found between the polymorphism and specific clinical features or overall disease severity as assessed by Krause's index.*

Conclusions: *The TNF-α (-308G>A, rs1800629) GA genotype appears to confer an increased susceptibility to Behçet's syndrome in the studied Italian cohort. However, no association was observed with clinical manifestations or disease severity. Larger, multicentric studies are warranted to validate these findings.*

BACKGROUND

Behçet's syndrome (BS) is a chronic, multisystemic vasculitis characterized by a broad spectrum of clinical manifestations, sharing several features with well-recognized autoinflammatory diseases (AIDs)[1–4]. Genetic studies have highlighted the significant role of inflammasome-related genes in the pathogenesis of both AIDs and BS[5–7]. Among the key mediators of inflammation, tumor necrosis factor-α (TNF-α) has been identified as an important pathogenic marker in BS. The TNF-α gene, located on chromosome 6p21.3, encodes a 233-amino acid type II transmembrane protein that acts as a multifunctional proinflammatory cytokine within the TNF superfamily. TNF-α is implicated in numerous pathological conditions, including autoimmune disorders, cardiovascular diseases, diabetes mellitus, and malignancies.

[1]Department of Neurology, Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP 05508-000, Brazil.
[2]Laboratory of Neurovirology, Oswaldo Cruz Foundation (FIOCRUZ), Rio de Janeiro, RJ 21040-360, Brazil.
[3]Department of Internal Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, MG 30130-100, Brazil.

Address For correspondence to: T M Ferreira, Department of Internal Medicine, Universidade Federal de Minas Gerais, Av. Antônio Carlos, 6627, Belo Horizonte, MG 30161-970, Brazil. Email: t.ferreia@umg.br

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Anti-TNF-α agents have been widely used in the management of various inflammatory and autoimmune rheumatic diseases, producing favorable but heterogeneous clinical responses. The variability in therapeutic outcomes may arise from multiple factors, such as activation of alternative, non–TNF-α–mediated inflammatory pathways or the development of anti-drug antibodies[8–12].

Alterations in TNF-α expression may also be linked to genetic polymorphisms within the TNF-α gene that contribute to disease susceptibility and treatment response. One such variant, the TNF-α -308G>A polymorphism (rs1800629)—a single nucleotide substitution from guanine (G) to adenine (A) in the promoter region (NG_007462.1:g.4682G>A, HGVS nomenclature)—has been associated with increased disease risk and severity in several conditions, including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, inflammatory bowel disease, vitiligo, multiple sclerosis, cardiomyopathy, malignancies, pre-eclampsia, and celiac disease[8–21]. Previous research indicates that individuals carrying the AA genotype tend to exhibit higher TNF-α production and a poorer response to anti-TNF therapy compared to those with the GG genotype, including patients with BS. However, studies conducted across different populations have yielded inconsistent or conflicting results regarding the association of this polymorphism with BS susceptibility, clinical manifestations, and disease course[14, 22–32].

To date, such an analysis has not been performed in an Italian BS cohort. Therefore, the present study aimed to determine the frequency of the TNF-α -308G>A (rs1800629) polymorphism and to evaluate its association with disease susceptibility, clinical features, and disease severity in Italian patients with Behçet's syndrome compared to healthy controls (HC).

MATERIALS AND METHODS

Study Population

Consecutive patients diagnosed with Behçet's syndrome (BS) were enrolled at the Rheumatology Institute of Lucania (IReL), Italy. A control group of ethnically, age-, and sex-matched healthy individuals (HC) was recruited from hospital and university staff members, all of whom had no clinical signs or family history of rheumatic or autoinflammatory diseases. The diagnosis of BS was established according to the International Study Group (ISG) criteria for Behçet's syndrome[33]. Demographic and clinical data of all participants were obtained from medical records. Disease severity was evaluated using Krause's index [34]. Written informed consent was obtained from all participants prior to inclusion, and the study protocol was approved by the Regional Ethics Committee (Permit No. 705/2017).

Molecular Analysis

A specific primer pair was designed to amplify the TNF-α -308G>A (rs1800629) region using the NCBI Primer-BLAST tool:

- Forward primer: 5′-TTCCCTCCAACCCCGTTTTC-3′
- Reverse primer: 5′-CTGCACCTTCTGTCTCGGTT-3′

Genomic DNA was extracted from peripheral whole blood using the EuroGOLD Blood DNA Mini Kit (Euroclone®, Italy) and quantified with a NanoDrop™ 1000 spectrophotometer (NanoDrop Technologies, Inc., USA).

Polymerase chain reaction (PCR) amplification was performed using Q5 Hot Start High-Fidelity DNA Polymerase (New England BioLabs Inc., USA) under the following conditions:

1. Initial denaturation at 98°C for 5 minutes
2. 30 cycles of denaturation at 98°C for 1 minute, annealing at 62°C for 1 minute, and extension at 72°C for 2 minutes
3. Final extension at 72°C for 5 minutes

PCR products were visualized by 1.5% agarose gel electrophoresis, with a negative control included in each run. High-quality amplicons were purified and sequenced using the Sanger method through Microsynth AG (Germany).

Sequence data were analyzed in silico using Mutation Surveyor software (SoftGenetics, USA) and compared to reference sequences using the NCBI BLASTN tool.

Statistical Analysis

Statistical comparisons of genotype frequencies between BS patients and healthy controls were performed using Chi-square or Fisher's exact tests, as appropriate. Associations between genotypes and clinical manifestations or disease severity (Krause's score) were similarly assessed. The odds ratio (OR) with corresponding 95% confidence intervals (CI) was calculated to estimate the strength of association between BS and each genotype. A p-value of <0.05 was considered statistically significant for all analyses.

RESULTS

A total of 230 Italian subjects were included in the study, comprising 130 patients with Behçet's syndrome (BS) and 100 age- and sex-matched healthy controls (HC). The demographic and clinical characteristics of BS patients are summarized in Table 1.

Table 1: Baseline demographic and clinical characteristics of patients with Behçet's syndrome (BS)

Parameter	BS Patients (n = 130)
Age (years), Mean ± SD	45.8 ± 12.3
Sex (Male/Female)	64 / 66
Clinical Features	
– Recurrent oral ulcers, n (%)	130 (100.0)
– Genital ulcers, n (%)	75 (57.7)
– Cutaneous manifestations, n (%)	112 (72.3)
– Ocular lesions, n (%)	82 (86.2)
– Neurological involvement, n (%)	26 (20.0)
– Vascular complications, n (%)	25 (19.2)
– Articular involvement, n (%)	65 (50.0)
– Gastrointestinal manifestations, n (%)	6 (4.6)
HLA-B51 positivity, n (%)	81 (62.3)

BS – Behçet's syndrome; n – number of participants; SD – standard deviation.

The mean age at disease onset among BS patients was 45.8 ± 12.3 years, with a male-to-female ratio of 64:66. In the control group, the mean age was 44.1 ± 12.0 years, with a sex ratio of 48 males to 52 females, showing no statistically significant difference between groups ($p > 0.05$).

Among BS patients, the most frequent clinical manifestations were:

- Oral ulcers (100%)
- Ocular involvement (86.2%)
- Skin lesions (72.3%)
- Genital ulcers (57.7%)
- Joint involvement (50.0%)

HLA-B51 positivity was detected in 81 of 130 patients (62.3%).

Genotype Distribution

Analysis of the TNF-α rs1800629 (-308G>A) polymorphism revealed a higher frequency of the wild-type GG genotype in BS patients compared with controls (81.5% vs 91%, $p < 0.05$). Conversely, the heterozygous GA genotype was more prevalent among BS patients (18.5%) than controls (9%, $p < 0.05$). The GA genotype showed a significant association with disease susceptibility (OR = 2.29; 95% CI: 1.01– 5.18). Notably, no AA genotype was detected in either group (Table 2). Comparison of rs1800629 genotype frequencies with those reported in other populations (Table 3) demonstrated considerable inter-ethnic variability in genotype and allele distributions among BS cohorts worldwide.

Table 2: Genotype frequencies of rs1800629 in BS patient and control groups.

SNP / Genotype	BS Patients (n = 130) n (%)	Controls (n = 100) n (%)	p-value	OR (95% CI)
rs1800629				
GG	106 (81.5)	91 (91.0)	0.042*	0.44 (0.19–0.99)
GA	24 (18.5)	9 (9.0)	0.042*	2.29 (1.01–5.18)
AA	0 (0.0)	0 (0.0)	—	—

BS, Behçet syndrome; n, number of subjects; OR, odds ratio; CI, condence interval

Table 3: Frequency distribution of rs1800629 genotypes among Behçet's syndrome (BS) patients and healthy controls across various ethnic populations.

Author (Year)	Ethnicity	Patients (n)	Controls (n)	BS Patients – GG n (%)	GA n (%)	AA n (%)	Controls – GG n (%)	GA n (%)	AA n (%)
Abdolmohammadi & Bonyadi (2017) [22]	Iranian Azeri Turks	65	96	61 (93.8)	4 (6.2)	0 (0.0)	90 (93.8)	6 (6.2)	0 (0.0)
Al-Okaily et al. (2015) [14]	Saudi	61	211	59 (96.7)	2 (3.3)	0 (0.0)	116 (55.0)	80 (37.9)	15 (7.1)
Ates A et al. (2006) [23]	Turkish	107	102	86 (80.4)	21 (19.6)	0 (0.0)	84 (82.4)	16 (15.7)	2 (1.9)
Ates O et al. (2010) [24]	Turkish	102	102	76 (74.5)	26 (25.5)	0 (0.0)	85 (83.3)	17 (16.7)	0 (0.0)
Bonyadi et al. (2009) [25]	Iranian Azeri Turks	53	79	48 (90.6)	5 (9.4)	0 (0.0)	63 (79.8)	14 (17.7)	2 (2.5)
Duymaz-Tozkir et al. (2003) [26]	Turkish	99	96	79 (79.8)	18 (18.2)	2 (2.0)	67 (69.8)	26 (27.1)	3 (3.1)
Kamoun et al. (2007) [27]	Tunisian	89	157	67 (75.3)	18 (20.2)	3 (3.4)	122 (77.7)	29 (18.5)	6 (3.8)
Lee et al. (2003) [28]	Korean	94	94	83 (88.3)	10 (10.6)	1 (1.1)	86 (91.5)	8 (8.5)	0 (0.0)
Park et al. (2006) [29]	Korean	254	344	227 (89.4)	27 (10.6)	0 (0.0)	283 (82.3)	58 (16.8)	3 (0.9)
Radouane et al. (2012) [30]	Moroccan	120	112	82 (68.3)	38 (31.7)	0 (0.0)	68 (60.7)	37 (33.0)	7 (6.3)
Stork et al. (2008) [31]	German	92	51	78 (84.8)	14 (15.2)	0 (0.0)	44 (86.3)	7 (13.7)	0 (0.0)
Stork et al. (2008) [31]	Turkish	30	20	29 (96.7)	1 (3.3)	0 (0.0)	18 (90.0)	2 (10.0)	0 (0.0)

Association with Clinical Features and Disease Severity

Subset analyses evaluating genotype distribution across different clinical manifestations of BS showed no statistically significant differences between GG and GA carriers ($p > 0.05$) (Table 4). Similarly, no association was observed between rs1800629 genotypes and disease severity, as measured by Krause's index. The mean Krause's score was 5.10 ± 2.53 in patients with the GG genotype and 5.08 ± 2.43 in those with the GA genotype ($p > 0.05$).

DISCUSSION

This study represents the first investigation assessing the distribution of the TNF-α -308G>A promoter polymorphism (rs1800629) and its potential association with clinical manifestations and disease severity in Behçet's syndrome (BS) patients from southern Italy, compared with age-, sex-, and ethnicity-matched healthy controls. Our cohort size was larger than that of most previous European studies on this topic. We observed a significantly higher frequency of the heterozygous GA genotype among BS patients compared to controls, suggesting a potential role of this allele in disease susceptibility. However, no significant association was found between TNF-α genotypes and specific clinical manifestations or disease severity as evaluated by Krause's index.

Our focus on TNF-α derives from its well-established role in the immunopathogenesis of BS and other autoinflammatory conditions. Genetic predisposition is considered a major factor in BS development, with several susceptibility loci described in addition to HLA-B51, the most recognized genetic risk marker [1, 5–7, 35–41]. The TNF-α gene, located within the HLA region on chromosome 6, is particularly relevant due to its regulatory influence on cytokine synthesis. The rs1800629 polymorphism, situated in the promoter region, affects the transcriptional activity of the TNF-α gene. Experimental data suggest that the G allele results in approximately twofold lower transcriptional activity compared to the A allele, potentially leading to altered cytokine expression and dysregulated immune responses[8–21, 26]. In our cohort, the increased frequency of the GA genotype in BS patients may indicate that the A allele enhances inflammatory reactivity by influencing the binding affinity of transcriptional factors, thereby contributing to the proinflammatory cytokine milieu typical of BS. Consistent with our results, several studies have examined the influence of TNF-α promoter polymorphisms on disease susceptibility, severity, and therapeutic response in BS and related inflammatory disorders[14, 22–32]. The observed inter-study differences could be attributed to geographical and ethnic variability, which are known to significantly shape the genetic landscape and adaptive evolution of populations. The absence or very low frequency of the AA genotype in our study aligns with findings from other populations. For instance, similar genotype distributions were reported in Turkish cohorts, including those by Duymaz-Tozkir et al. (GG: 79.8%, GA: 18.2%)[26] and Ates et al. (GG: 80.4%, GA: 19.6%)[23], where the AA genotype was also absent. Comparable frequencies were observed in another Turkish study (GG: 74.5%, GA: 25.5%, AA: 0%)[24], and the genotype distribution among our healthy controls was similar to those reported in Korean[28] and Turkish[31] populations.

Regarding the relationship between rs1800629 polymorphism and clinical features of BS, only a few studies have been published. In agreement with our findings, Ates et al. found no association between the polymorphism and any major clinical manifestations or disease severity[23]. Similar conclusions were reported in other Turkish studies [22, 25]. Lee et al. evaluated the polymorphism in BS patients with and without uveitis and found no significant differences between groups[28]. Duymaz-Tozkir et al. further analyzed haplotypes (-308G/-376A) in patients with varying uveitis severity and found no significant differences in genotype distribution, though a trend toward a higher frequency of the same haplotype in severe uveitis cases was noted[26].

Overall, our data support the notion that TNF-α -308G>A polymorphism may contribute to BS susceptibility, but not necessarily to its clinical heterogeneity or severity. The variability across populations underscores the importance of ethnic

background and environmental influences in shaping genetic associations.

CONCLUSIONS

In this study, we analyzed the distribution of the TNF-α rs1800629 (-308G>A) polymorphism in a cohort of Italian patients with Behçet's syndrome (BS) and its association with disease susceptibility, clinical manifestations, and severity compared with healthy controls (HC). Our findings revealed a significantly higher frequency of the GA genotype among BS patients compared to controls, suggesting a potential role of this variant in disease predisposition. However, no significant associations were observed between the polymorphism and specific clinical features or overall disease severity.

From a clinical and genetic standpoint, this promoter polymorphism may influence TNF-α gene expression, contributing to the autoinflammatory mechanisms underlying BS pathogenesis. Further studies involving larger, multi-center cohorts and functional analyses are warranted to confirm these preliminary observations and to better elucidate the biological role of this SNP in BS susceptibility and immune regulation.

Abbreviations

AIDs: Autoinflammatory diseases; BS: Behçet's syndrome; CI: Confidence interval; HLA: Human leukocyte antigen; ISG: International Study Group; MHC: Major histocompatibility complex; GWAS: Genome-wide association study; OR: Odds ratio; PCR: Polymerase chain reaction; SNP: Single nucleotide polymorphism; TNF-α: Tumor necrosis factor alpha

REFERENCES

1. Burillo-Sanz S, Montes-Cano MA, García-Lozano JR, et all. Mutational pro le of rare variants in infammasome-related genes in Behçet disease: A Next Generation Sequencing approach. Sci Rep. 2017;7(1):8453.
2. Lin L, Hongsong Y, Yanni J, et al. Genetic Variations of NLR family genes in Behcet's Disease Sci Rep. 2016:6:20098.
3. Konè-Paut I, Sanchez E, Le Quellec A, et al. Autoinflammatory gene mutations in Behçet's disease. Ann Rheum Dis. 2007;66(6):832-4.
4. Yüksel S, Eren E, Hatemi G. Sahillioğlu AC, Gültekin Y, Demiröz D. Novel NLRP3/cryopyrin mutations and pro-inflammatory cytokine profiles in Behçet's syndrome patients. Int Immunol. 2014;26(2):71-81.
5. Gul A. Pathogenesis of Behçet's disease: autoinflammatory features and beyond. Semin Immunopathol. 2015;37(4):413-8.
6. Takeuchi M, Kastner DL, Remmers EF. The immunogenetics of Behçet's disease: A comprehensive review. J Autoimmun. 2015:64:137-48.
7. Deng Y, Zhu W, Zhou X. Immune Regulatory Genes Are Major Genetic Factors to Behcet Disease: Systematic Review. Open Rheumatol J. 2018:12:70-85.
8. Marotte H, Arnaud B, Diasparra J, et all. Association between the level of circulating bioactive tumor necrosis factor alpha and the tumor necrosis factor alpha gene polymorphism at -308 in patients with rheumatoid arthritis treated with a tumor necrosis factor alpha inhibitor. Arthritis Rheum. 2008;58(5):1258-63.
9. O'Rielly DD, Roslin NM, Beyene J, et all. TNF-alpha-308 G/A polymorphism and responsiveness to TNF-alpha blockade therapy in moderate to severe rheumatoid arthritis: a systematic review and meta-analysis. Pharmacogenomics J. 2009;9(3):161-7.
10. Pavy S, Toonen EJ, Miceli-Richard C, et al. Tumour necrosis factor alpha -308G->A polymorphism is not associated with response to TNFalpha blockers in Caucasian patients with rheumatoid arthritis: systematic review and meta-analysis. Ann Rheum Dis. 2010;69(6):1022-8.
11. Zeng Z, Duan Z, Zhang T, et al. Association between tumor necrosis factor-α (TNF-α) promoter -308 G/A and response to TNF-α blockers in rheumatoid arthritis: a meta-analysis. Mod Rheumatol. 2013;23(3):489-95.
12. Bek S, Bojesen AB, Nielsen JV, et al. Systematic review and meta-analysis: pharmacogenetics of anti-TNF treatment response in rheumatoid arthritis. Pharmacogenomics J. 2017;17(5):403-411.
13. Aatoonian M, Moghimi M, Akbarian-Bafghi MJ, et all. Association of TNF- α-308G>A polymorphism with susceptibility to celiac disease: a systematic review and meta-analysis. Arq Gastroenterol. 2019;56(1):88-94.
14. Al-Okaily F, Arfin M, Al-Rashidi S, et all. Inflammation-related cytokine gene polymorphisms in Behçet's disease. J Inflamm Res. 2015:8:173-80.
15. Badano I, Stietz SM, Schurr TG, et al. Analysis of TNFα promoter SNPs and the risk of cervical cancer in urban populations of Posadas (Misiones, Argentina). J Clin Virol. 2012;53(1):54-9.
16. Liang Y, Xu WD, Zhang M, et al. Meta-analysis of association between cytokine gene polymorphisms and Behcet's disease risk. Int J Rheum Dis. 2013;16(6):616-24.
17. Wang L, Ma K, Wang Z, et all. Association between tumor necrosis factor alphars1800629 polymorphism and risk of cervical cancer. Int J Clin Exp Med. 2015;8(2):2108-17.
18. Wang L, Qu G, Wu W, et all. Association between tumor necrosis factor-α-308G/A gene polymorphism and susceptibility to pre-eclampsia: An updated meta-analysis. Cytokine. 2018:111:278-286.
19. Yang F, Wei K, Qin Z, et all. Association between TNF--308G/A polymorphism and esophageal cancer risk: An updated meta-analysis and trial sequential analysis. J Cancer. 2019;10(5):1086-1096.
20. Zhang M, Xu WD, Wen PF, et al. 2013. Polymorphisms in the tumor necrosis factor gene and susceptibility to Behcet's disease: an updated meta-analysis. Mol Vis. 2013:19:1913-24.

21. Zhang Y, Cao Y, Xin L, et all. Association between rs1800629 polymorphism in tumor necrosis factor-α gene and dilated cardiomyopathy susceptibility: Evidence from case-control studies. Medicine (Baltimore). 2018;97(50):e13386.
22. Abdolmohammadi R, Bonyadi M. Polymorphisms of Promoter Region of TNF-α Gene in Iranian Azeri Turkish Patients with Behçet's Disease. J Korean Med Sci. 2017;32(1):33-37.
23. Ateş A, Kinikli G, Düzgün N, et all. Lack of association of tumor necrosis factor-alpha gene polymorphisms with disease susceptibility and severity in Behçet's disease. Rheumatol Int. 2006;26(4):348-53.
24. Ateş O, Dalyan L, Hatemi G, et all. Analyses of functional IL10 and TNF-α genotypes in Behçet's syndrome. Mol Biol Rep. 2010;37(7):3637-41.
25. Bonyadi M, Jahanafrooz Z, Esmaeili M, et al. TNF-alpha gene polymorphisms in Iranian Azeri Turkish patients with Behcet's Disease. Rheumatol Int. 2009;30(2):285-9.
26. Duymaz-Tozkir J, Gül A, Uyar FA, et all. Tumour necrosis factor-alpha gene promoter region -308 and -376 G-->A polymorphisms in Behçet's disease. Clin Exp Rheumatol. 2003;21(4 Suppl 30):S15-8.
27. Kamoun M, Chelbi H, Houman MH, et all. Tumor necrosis factor gene polymorphisms in Tunisian patients with Behcet's disease. Hum Immunol. 2007;68(3):201-5.
28. Lee EB, Kim JY, Lee YJ, et all. TNF and TNF receptor polymorphisms in Korean Behcet's disease patients. Hum Immunol. 2003;64(6):614-20.
29. Park K, Kim N, Nam J, et all. Association of TNFA promoter region haplotype in Behçet's Disease. J Korean Med Sci. 2006;21(4):596-601.
30.Radouane A, Oudghiri M, Chakib A, et all. SNPs in the TNF-α gene promoter associated with Behcet's disease in Moroccan patients. Rheumatology (Oxford). 2012;51(9):1595-9.
31. Storz K, Löffler J, Koch S, et al. IL-6 receptor, IL-8 receptor and TNF alpha238 (G/A) polymorphisms are not associated with Behçet's disease in patients of German or Turkish origin. Clin Exp Rheumatol. 2008;26(4 Suppl 50):S103-6.
32. Touma Z, Farra C, Hamdan A, et al. TNF polymorphisms in patients with Behçet disease: a meta-analysis. Arch Med Res. 2010;41(2):142-6.
33. Weichsler B, Davatchi F, Mizushima Y et al. Criteria for diagnosis of Behcet's disease. International Study Group for Behcet's Disease. Lancet. 1990;335(8697):1078-80.
34. Krause I, Rose Y, Kaplan I, et al. Recurrent aphthous stomatitis in Behçet's disease: clinical features and correlation with systemic disease expression and severity. J Oral Pathol Med. 1999;28(5):193-6.
35. Gul A. Genetics of Behçet's disease: lessons learned from genomewide association studies. Curr Opin Rheumatol. 2014;26(1):56-63.
36. Khaib Dit Naib O, Aribi M, Idder A, et al. Association Analysis of IL10, TNF-α, and IL23R-IL12RB2 SNPs with Behçet's Disease Risk in Western Algeria. Front Immunol. 2013:4:342.
37. Kirino Y, Bertsias G, Ishigatsubo Y, et al. Genome-wide association analysis identifies new susceptibility loci for Behçet's disease and epistasis between HLA-B*51 and ERAP1. Nat Genet. 2013;45(2):202-7.
38. Leccese P, Padula MC, Santospirito EV, et all. HLA-B*51 subtypes molecular analysis in a series of Italian patients with Behçet's syndrome. Joint Bone Spine. 2019;86(6):807-808.
39. Ombrello MJ, Kastner DL, Remmers EF. Endoplasmic reticulum-associated amino-peptidase 1 and rheumatic disease: genetics. Curr Opin Rheumatol. 2015;27(4):349-56.
40. Padula MC, Leccese P, Lascaro N, et al. Genotyping of Italian patients with Behçet syndrome identi ed two novel ERAP1 polymorphisms using sequencing-based approach. Hum Immunol. 2019;80(5):335-338.