RESEARCH ARTICLE

ERAP1 polymorphisms interactions and their association with Behçet’s disease susceptibility: Application of Model-Based Multifactor Dimension Reduction Algorithm (MB-MDR)

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Abstract

Background

Behçet’s disease (BD) is a chronic multi-systemic vasculitis with a considerable prevalence in Asian countries. There are many genes associated with a higher risk of developing BD, one of which is endoplasmic reticulum aminopeptidase-1 (ERAP1). In this study, we aimed to investigate the interactions of ERAP1 single nucleotide polymorphisms (SNPs) using a novel data mining method called Model-based multifactor dimensionality reduction (MB-MDR).

Methods

We have included 748 BD patients and 776 healthy controls. A peripheral blood sample was collected, and eleven SNPs were assessed. Furthermore, we have applied the MB-MDR method to evaluate the interactions of ERAP1 gene polymorphisms.

Results

The TT genotype of rs1065407 had a synergistic effect on BD susceptibility, considering the significant main effect. In the second order of interactions, CC genotype of rs2287987 and GG genotype of rs1065407 had the most prominent synergistic effect ($\beta = 12.74$). The mentioned genotypes also had significant interactions with CC genotype of rs26653 and TT genotype of rs30187 in the third-order ($\beta = 12.74$ and $\beta = 12.73$, respectively).

Conclusion

To the best of our knowledge, this is the first study investigating the interaction of a particular gene’s SNPs in BD patients by applying a novel data mining method. However, future studies investigating the interactions of various genes could clarify this issue.
Introduction

Behçet’s disease (BD) is a chronic vasculitis presented with multi-systemic signs and symptoms; however, it is majorly separated from other autoimmune diseases by characteristic bilateral aphthosis [1]. With a wide range of prevalence worldwide (from 0.64 per 100,000 in the UK to 420 per 100,000 in Turkey), BD is mostly distributed in countries alongside the Silk Road [2]. According to the considerable prevalence and morbidity of BD in Asian countries, understanding BD’s pathophysiology might lead to new therapeutic options and increasing patients’ quality of life. Years of research have proven that similar to many other rheumatic disorders, genetic factors have a significant role in BD’s course [3].

HLA region has been proven to have a pivotal contribution to the genetic component of BD [4]. BD’s association with \textit{HLA-B}^{*}51 is proved by several influential studies, including a meta-analysis on 4800 patients that has shown individuals with this allele have an odds ratio of 5.78 for developing BD [5]. In addition to \textit{HLA-B}^{*}51, studies have suggested a link between BD and other genes such as \textit{interleukin 10} (\textit{IL-10}) and \textit{IL-23 receptor} (\textit{IL-23R}), some of which are associated with \textit{HLA-B}^{*}51 [6]. In our previous study, we have shown that the \textit{endoplasmic reticulum aminopeptidase-1} (\textit{ERAP1}) gene polymorphisms are associated with \textit{HLA-B}^{*}51, resulting in higher BD susceptibility [7]. \textit{ERAP1} is an amino-peptidase responsible for the N-terminal trimming of peptides, which is a critical step in peptides processing and their presentation by MHC-I [8].

Furthermore, \textit{ERAP1} takes part in cleaving proinflammatory cytokine receptors such as tumor necrosis factor receptor (\textit{TNFR1}) from the cell membrane [9]. Polymorphisms of \textit{ERAP1} might alternate the activity of the protein and subsequently changing the structure of peptidome available to \textit{HLA-B}^{*}51. However, the association of \textit{ERAP1} single nucleotide polymorphisms (SNPs) and BD susceptibility is not entirely clear, and some studies suggest contradictory findings, which need to assess by more comprehensive studies [7, 10, 11].

Up to now, logistic regression for high dimensional and sparse data, parameter estimation is a costly and non-accurate procedure that introduces significant standard errors because sample sizes are too small compared to the order of interaction size. Also, conventional approaches (e.g., logistic regression) used for the analysis of genomic data are oversimplified and usually cannot consider all possible associations between multiple polymorphisms and gene-gene interactions [12]. Multifactor Dimensionality Reduction (MDR) approach is now a reference in the epistasis and SNPs interactions detection field. However, MDR suffers from some significant drawbacks, including that crucial interactions could be missed owing to pooling too many cells together or that proposed MDR analysis will only reveal at most one significant epistasis model, the selection being based on computationally demanding cross-validation and permutation strategies. To overcome the aforementioned hurdles, model-based multifactor dimensionality reduction (MB-MDR) is a flexible framework to detect gene-gene or SNP-SNP interactions. MB-MDR is a non-parametric data mining method that has sufficient power and is capable of investigating the interaction of the unlimited number of genes and polymorphisms [13]. Therefore, we aimed to use the MB-MDR method to identify the interactions of \textit{ERAP1} polymorphisms and their association with BD susceptibility.

Methods

Study participants

The present study included 748 BD patients who were referred to the outpatient BD clinic in the Rheumatology Research Center, Shariati Hospital, Tehran, Iran. The International Criteria confirmed patients’ diagnosis for Behçet’s Disease (ICBD), and patients who were less than 16
years old or related to each other were excluded from the study [14, 15]. For the control group, we have included 776 healthy individuals with no clinical presentation or family history of any rheumatic disorders or autoimmune diseases, who were matched for sex, age, and ethnicity [16]. Written informed consent was obtained from all individuals themselves or their parents in cases with the age of under 18. The ethical committee of Tehran University of Medical Sciences approved the study protocol, and the relevant university guidelines did all experiments.

### DNA preparation and SNP genotyping

A peripheral blood sample was collected from all participants into EDTA-anticoagulated tubes using venipuncture. Genomic DNA was extracted using the standard phenol/chloroform method, and the extracted DNA samples were stored at −20 °C. Approximately 20 ng of the genomic DNA in each sample was used for genotyping. We assessed 10 common missense SNPs from our previous study [7] that were identified in the super-population of the 1000 Genomes project and had a minor allele frequency of more than one percent (Table 1). We have also included an intronic SNP (rs1065407) that has been associated with BD in another study [17]. MGB-TaqMan Allelic Discrimination technique was used for SNP genotyping (Applied Biosystems, Foster City, CA, USA). Ten μl of reaction volumes, containing 0.25 μl of distilled water, 4.5 μl of genomic DNA, 0.25 μl of TaqMan genotyping assay mix, and 5 μl of the TaqMan genotyping master mix was used for amplification. The StepOnePlus Real-Time PCR System (Applied Biosystems) and the manufacturer’s protocol were used for genotyping the patients and healthy individuals’ samples. The allelic call was done using SDS v.1.4 software (Applied Biosystems) and the analysis of allelic discrimination plots. Finally, the genetic makeup of SNPs for each subject was considered as the genotype of that SNP.

### Statistical methods

The continuous variables were indicated as mean ± SD. Allelic and genotypic frequencies of the ERAP1 SNPs were mentioned as N (%). The genotype distributions of SNPs were tested for deviation from Hardy-Weinberg equilibrium (HWE) in the control group. P-values were corrected for multiple comparisons by the Benjamini-Hochberg approach [18]. Since calculations of the main effect of ERAP1 SNPs were not available by the model-based multifactor dimensionality reduction (MB-MDR), multiple logistic regression has been used to obtain the main effects of ERAP1 SNPs, simultaneity. To adjust for main effects, main effects should be
calculated. MB-MDR has been proposed by Calle et al. as a dimension reduction method for exploring SNP-SNP interactions with disease susceptibility in case-control association studies [19]. MB-MDR method has proven to be more potent than multifactor dimensionality reduction (MDR) in the presence of genetic heterogeneity [20]. MB-MDR can unify the best of both nonparametric and parametric machine learning algorithms.

On the other hand, characterization, and identification SNP-SNP interactions lack performance in the absence of proper statistical methods and large sample sizes. Logistic regression, as a standard tool for modeling effects and interactions with binary response data, lacks power in the identification of gene interactions in high-order levels due to sparsity and separation [21]. Thus, in this study, SNP-SNP interactions were calculated by the MB-MDR algorithm. MB-MDR shows high power in the presence of all types of noises, such as missing data, genotyping error, genetic heterogeneity, and low sample size [22]. This algorithm was performed by “mbmdr” R package version 3.5.1. To assess the significance in MB-MDR, permutation test with 1000 replications has been done, which corrects for multiple testing (overall marker pairs) and adequately controls the family-wise error rate at $\alpha = 0.05$.

Results

In this case-control study, 748 patients and 776 age-, sex-, and ethnicity-matched healthy controls were included according to the inclusion and exclusion criteria [16]. In BD patients, the mean age was 40.26 ± 10.88 years, and in the control group was 38.88 ± 11.54 years (P-value = 0.076). Out of 748 patients and 776 healthy individuals, 448 (59.9%) and 476 (61.3%) were male, respectively (P-value = 0.599). Based on the results of assessing the main effects of \textit{ERAP1} SNPs, the TT genotype of rs1065407 SNP ($\beta = 0.23$, and adjusted P-value = 0.034) had a significant synergistic effect on BD. The synergistic effect of an allele is described as the allele increasing the disease risk, and the antagonistic effect is described as the allele having a protective effect regarding the disease susceptibility. In contrast, TT genotype of rs30187 SNP ($\beta = -0.26$ and adjusted P-value = 0.041) and AA genotype of rs469876 SNP ($\beta = -0.20$ and adjusted P-value = 0.046) had significant antagonistic effects on BD (Table 2). Other \textit{ERAP1} SNPs do not have significant main effects concerning BD susceptibility.

Table 2 summarizes the results of SNP-SNP interactions for six important SNPs (rs1065407, rs30187, rs469876, rs2287987, rs17482078, and rs26653). Based on the results of second-order interaction effects, there were only six significant 2-locus models. For instance, CC genotype of rs2287987 and GG genotype of rs1065407 ($\beta = 12.74$ and adjusted P-value = $2.12 \times 10^{-10}$) had a significant synergistic effect on BD susceptibility. rs30187 and rs1065407, CT, and TT genotype ($\beta = -0.39$ and adjusted P-value of $1.98 \times 10^{-3}$) had a significant antagonistic effect on BD. Synergistic effects of rs469876 (AA and GG) genotypes with rs1065407 (GG and GT) genotypes were significant as well ($\beta = 0.32$, adjusted P-value = $4.73 \times 10^{-3}$). Effects of rs30187 and rs469876 (CC vs. AA) and (TT vs. AG) were also significantly synergistic ($\beta = 0.32$ adjusted P-value = $2.39 \times 10^{-2}$). rs26653 (CC) with rs1065407 (GG) had a significant synergistic effect on BD ($\beta = 0.76$, adjusted P-value = $2.49 \times 10^{-3}$). However, the results of rs26653 (CT) and rs469876 (AG) showed a significant negative association with BD susceptibility ($\beta = -0.42$, adjusted P-value = $7.38 \times 10^{-2}$).

Considering third-order interaction effects, we had five 3-locus models for SNP-SNP interactions of \textit{ERAP1} SNPs. For example, the GG genotype of rs1065407, CC genotype of rs2287987, and CC genotype of rs26653 had a significant synergistic effect on BD by a 3-locus model ($\beta = 12.74$, adjusted P-value = $2.13 \times 10^{-10}$). However, the 3-locus model (rs1065407, rs2287987, rs26653) did not have any significant antagonistic effect on BD. Considering rs1065407, rs2287987, and rs30187, results reveal that the synergistic effect of (GG, CC, and
TT) genotypes and the antagonistic effect of (TT, CT and CT) genotypes on BD, were significant as well. Besides, rs1065407 (TT), rs30187 (CT) and rs469876 (AG) had a significant antagonistic effect on BD ($\beta = -0.67$, adjusted P-value = $1.26 \times 10^{-3}$). In addition, rs1065407 (TT), rs2287987 (CT) and rs469876 (AG) interaction had a significant antagonistic effect on BD ($\beta = -0.92$, adjusted P-value = $3.18 \times 10^{-2}$). In contrast, (rs1065407: GG, rs30187: TT, rs469876: AG), (rs1065407: GG, rs2287987: CC, rs469876: GG), and (rs30187: CC, rs1065407: GG, rs17482078: CC) had significant synergistic effects on BD. More details are shown in the third-order interaction section of Table 2.

Results of fourth-order interaction effects indicated that (rs1065407: GG, rs2287987: CC, rs30187: CT, rs26653: GG) and (rs1065407: TT, rs287987: TT, rs30187: CT, rs26653: GG) had significant synergistic effects on BD. In contrast, (rs1065407: TT, rs287987: TT, rs30187: CT, rs26653: GG) and (rs1065407: TT, rs287987: TT, rs26653: CG, rs469876: AG) had significant antagonistic effects on BD. Based on the results of five-order interaction effects, (rs1065407: GT, rs2287987: TT, rs30187: CC, rs26653: CC, rs17482078: TT) had a significant synergistic effect on BD ($\beta = 0.32$, adjusted P-value = $3.93 \times 10^{-1}$). However, (rs1065407: TT, rs287987: CT, rs30187: CT, rs26653: GG, rs17482078: CT) had a significant antagonistic effect on BD ($\beta = -0.89$, adjusted P-value = $7.25 \times 10^{-3}$). In six-order interaction effects, no significant effects were observed (Table 2).

### Table 2. Model-based multifactor dimensionality reduction algorithm for assessing the main and interaction effects of 11 ERAP1 SNPs on Behçet's disease risk (748 Iranian BD patients and 776 healthy individuals).

| Order     | Significant Effects | Synergistic Effect | Antagonism Effect | Permutation Test |
|-----------|---------------------|--------------------|-------------------|------------------|
|           | N. levels | Genotypes | Coefficient | Adj. P-value | N. levels | Genotypes | Coefficient | Adj. P-value | Perm. P-value |
| Main Effects | rs1065407 | 1 | TT | 0.23 | 0.034 | 0 | NA | NA | NA | 0.019 |
|           | rs30187 | 0 | NA | NA | NA | 1 | TT | -0.26 | 0.041 | 0.18 |
|           | rs469876 | 0 | NA | NA | NA | 1 | AA | -0.20 | 0.046 | 0.054 |
| #2 order interactions | rs2287987+rs1065407 | 1 | CC+GG | 12.74 | $1.21 \times 10^{-10}$ | 0 | NA | NA | NA | 0.065 |
|           | rs30187+rs1065407 | 0 | NA | NA | NA | 1 | CT+TT | -0.39 | 1.98 $\times 10^{-3}$ | 0.053 |
|           | rs469876+rs1065407 | 2 | AA+GG | GG+GT | 0.32 | $4.73 \times 10^{-3}$ | 0 | NA | NA | NA | 0.181 |
|           | rs30187+rs469876 | 2 | CC+AA | TT+AG | 0.32 | $2.39 \times 10^{-2}$ | 0 | NA | NA | NA | 0.091 |
|           | rs26653+rs1065407 | 1 | CC+GG | 0.76 | $2.49 \times 10^{-2}$ | 0 | NA | NA | NA | 0.210 |
|           | rs26653+rs469876 | 2 | CC+AA | GG+AG | 0.54 | $2.83 \times 10^{-2}$ | 1 | CT+AG | -0.42 | 7.38 $\times 10^{-2}$ | 0.193 |
| #3 order Interaction | rs1065407+rs2287987+rs26653 | 1 | GG+CC+CC | 12.74 | $2.13 \times 10^{-10}$ | 0 | NA | NA | NA | 0.243 |
|           | rs1065407+rs2287987+rs30187 | 1 | GG+CC+TT | 12.73 | $2.15 \times 10^{-10}$ | 1 | TT+CT+CT | -0.39 | 5.95 $\times 10^{-2}$ | 0.230 |
|           | rs1065407+rs30187+rs469876 | 3 | GG+TT+AG| GT+TT+AA | 0.43 | $2.87 \times 10^{-2}$ | 1 | TT+CT+AG | -0.67 | 1.26 $\times 10^{-3}$ | 0.169 |
|           | rs30187+rs1065407+rs26653 | 4 | CC+GG+CC| TT+GT+GG | 0.77 | $2.36 \times 10^{-2}$ | 0 | NA | NA | NA | 0.137 |
|           | rs1065407+rs2287987+rs469876 | 2 | GG+CC+GG| GT+TT+AA | 0.04 | $9.77 \times 10^{-1}$ | 1 | TT+CT+AG | -0.92 | 3.18 $\times 10^{-2}$ | 0.229 |
| #4 order Interaction | rs1065407+rs2287987+rs30187+rs26653 | 7 | GG+CC+CC| GG+CG| CT+TG | 0.53 | $1.94 \times 10^{-1}$ | 2 | TT+TT+CT+GG | -0.88 | 7.50 $\times 10^{-3}$ | 0.184 |
|           | rs1065407+rs2287987+rs26653+rs469876 | 5 | GG+CC+CC| GG+CG| GT+TT+AA | 0.66 | $4.49 \times 10^{-1}$ | 2 | TT+TT+CG+AG | -0.65 | 1.18 $\times 10^{-2}$ | 0.219 |
| #5 order Interaction | rs1065407+rs2287987+rs30187+rs26653+rs17482078 | 11 | GT+TT+CC+CC | 0.32 | $3.93 \times 10^{-1}$ | 2 | TT+CT+CT+GG | -0.89 | 7.25 $\times 10^{-3}$ | 0.032 |

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More details of the results of 11 ERAP1 SNP-SNP interactions are presented in the supplementary Table. Also, the entropy-based interaction network of 11 ERAP1 SNPs was shown in Fig 1 by using MDR. To assess the sensitivity and cross-validity of the results of MB-MDR, permutation results are shown in the last column of Table 2.

Discussion

In this study, we aimed to investigate the interactions of the ERAP1 gene polymorphisms and their associations with BD susceptibility in an Iranian cohort. Using the MB-MDR package, we have found plenty of synergistic and antagonistic significant interactions between ERAP1 polymorphisms and BD development. Considering the main effects, the TT genotype of rs1065407 had a synergistic effect on BD susceptibility. In the second-order interactions, CC genotype of rs2287987 and GG genotype of rs1065407 had the most prominent synergistic effect ($\beta = 12.74$). Furthermore, the mentioned genotypes also had significant interactions with CC genotype of rs26653 and TT genotype of rs30187 in the third-order ($\beta = 12.74$ and $\beta = 12.73$, respectively). Hence, we propose that the genotypes, as mentioned earlier of rs2287987, rs1065407, rs26653, and rs30187, could have prominent interactions resulting in a higher risk of developing BD.

ERAP1 gene is located in the 5q15 chromosome, and its expression has been observed in many tissues [23]. There are two main processes that ERAP1 is proposed to have a role in them. First, this amino-peptidase is involved in optimizing the length of peptides to bind with MHC-class I molecules by trimming their N-terminal in the endoplasmic reticulum (ER) [23]. Moreover, ERAP1 is involved in the cleavage process of various cytokine receptors such as TNFR1, Interleukin 1 receptor II (IL-1RII), and Interleukin 6 receptor α (IL-6 α), which results in receptor shedding [24, 25]. Previous studies have shown that the ERAP1 gene is associated with other autoimmune disorders such as ankylosing spondylitis (AS) and psoriasis [26, 27]. Homozygosity of ERAP1 polymorphisms is proposed to be correlated with a lower risk of AS and psoriasis, whereas it might be associated with a higher risk of developing BD [28, 29].
These differences could be justified by the fact that loading different peptides on MHC-class I molecules can alter the subsequent immune response.

Our results indicated that the homozygous genotypes of minor alleles of rs2287987, rs1065407, rs26653, and rs30187 had the most prominent interactions causing BD susceptibility. In this regard, it has been demonstrated that the frequencies of the homozygous alleles of the ERAP1 gene are higher among BD patients [11]. As it was shown in further studies, these combinations of homozygote ERAP1 SNPs could result in alternations in the surface electrostatic potential of the protein [30]. These changes might alter the trimming activity of ERAP1, resulting in an altered composition of peptidome that is available for binding to HLA-B*51. This claim could support the higher risk of developing BD observed in individuals carrying the mentioned genotypes. Furthermore, some SNPs such as rs30187 (Arg528Lys) are placed proximal to the entrance pocket of the protein [28]. Amino acid changes in such positions could modify the ideal structure of the protein and alter the enzyme activity.

Although several studies have investigated the association of ERAP1 polymorphisms and BD, there have been some contradictory findings that motivated us to utilize a more complex statistical method for addressing this issue. Zhang et al. evaluated 930 Chinese patients and proposed that rs1065407 and rs10050860 might be associated with increased risk of BD [17]. Sousa and colleagues studied another Iranian cohort and proposed that rs10050860 and rs13154629 might contribute to the genetic susceptibility of BD [15]. Moreover, Conde-Jaldón et al. found that homozygous genotypes for the minor alleles of rs27044, rs10050860, rs30187, and rs2287987 could be considered as risk factors for BD [10]. Takeuchi and colleagues found a haplotype consisting of 10 SNPs (five of which were non-ancestral), which was associated with a higher risk of developing BD, especially in those individuals who carry HLA-B*51 [30]. Interestingly, our results indicated that homozygous genotypes of minor alleles of rs30187 and rs2287987 are associated with a higher risk of BD. rs30187 and rs2287987 are among those five SNPs that their non-ancestral alleles were mentioned in Takeuchi’s study. Finally, the previous study by our team and the study on the Turkish population revealed that ERAP1 polymorphisms have epistatic interactions with HLA-B*51 contributing to BD risk [7, 30].

In conclusion, this is the first study investigating the interaction of a particular gene’s SNPs in BD patients by applying a novel data mining method (MB-MDR package). Model-Based MDR as a flexible framework and a reference method to detect gene–gene or SNP-SNP interactions has adequate power even the presence of genotyping errors, missing genotypes, and genetic heterogeneity in this study compare with traditional methods (e.g., logistics regression). Finally, a significant interaction between minor genotypes of ERAP1 polymorphisms was observed in BD patients in comparison to healthy individuals. rs2287987, rs1065407, rs26653, and rs30187 interactions had the strongest association with developing BD in our study population. Taken together, these findings imply the contribution of ERAP1 polymorphisms in BD pathogenesis. However, further studies investigating the interactions of different genes could shed more light on this issue.

Supporting information
S1 Table. Model-based multifactor dimensionality reduction algorithm for assessing the main and interaction effects of 11 ERAP1 SNPs on Behçet’s disease risk (748 Iranian BD patients and 776 healthy individuals).

(DOCX)

S1 File.

(RAR)
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References
1. Davatchi F, Shahram F, Chams-Davatchi C, Shams H, Abdolahi BS, Nadj A, et al. Behcet's disease in Iran: Analysis of 7641 cases. Modern rheumatology. 2018;1–8. Epub 2018/12/18. https://doi.org/10.1080/14397595.2018.1558752 PMID: 30557064.
2. Davatchi F, Chams-Davatchi C, Shams H, Shahram F, Nadj A, Akhlaghi M, et al. Behcet's disease: epidemiology, clinical manifestations, and diagnosis. Expert review of clinical immunology. 2017;13 (1):57–65. Epub 2016/06/29. https://doi.org/10.1080/1744666X.2016.1205486 PMID: 27351485.
3. Tong B, Liu X, Xiao J, Su G. Immunopathogenesis of Behcet’s Disease. Frontiers in immunology. 2019; 10:665. Epub 2019/04/16. https://doi.org/10.3389/fimmu.2019.00665 PMID: 30984205; PubMed Central PMCID: PMC6449449.
4. Yazici H, Fresko I, Yurdakul S. Behcet's syndrome: disease manifestations, management, and advances in treatment. Nature clinical practice Rheumatology. 2007; 3(3):148–55. Epub 2007/03/06. https://doi.org/10.1038/ncprheum0436 PMID: 17334337.
5. de Menthon M, Lavalley MP, Maldini C, Guillevin L, Mahr A. HLA-B51/B5 and the risk of Behcet's disease: a systematic review and meta-analysis of case-control genetic association studies. Arthritis and rheumatism. 2009; 61(10):1287–96. Epub 2009/10/01. https://doi.org/10.1002/art.24642 PMID: 19790126; PubMed Central PMCID: PMC3867978.
6. Remmers EF, Cosan F, Kirino Y, Ombrello MJ, Abaci N, Satorius C, et al. Genome-wide association study identifies variants in the MHC class I, IL10, and IL23R-IL12RB2 regions associated with Behcet’s disease. Nature genetics. 2010; 42(8):698–702. Epub 2010/07/14. https://doi.org/10.1038/ng.625 PMID: 20622878; PubMed Central PMCID: PMC2923807.
7. Mahmoudi M, Ashraf-Ganjouei A, Javinani A, Shahram F. Epistatic Interaction of ERAP1 and HLA-B*51 in Iranian Patients with Behcet’s Disease. 2018; 8(1):17612. https://doi.org/10.1038/s41598-018-35700-0 PMID: 30514861.
8. Saric T, Chang SC, Hattori A, York IA, Markant S, Rock KL, et al. An IFN-gamma-induced aminopeptidase in the ER, ERAP1, trims precursors to MHC class I-presented peptides. Nature immunology. 2002; 3(12):1169–76. Epub 2002/11/19. https://doi.org/10.1038/nii859 PMID: 12436109.
9. Cui X, Hawari F, Alsaa I, Lawrence M, Combs CA, Geng W, et al. Identification of ARTS-1 as a novel TNFR1-binding protein that promotes TNFR1 ectodomain shedding. The Journal of clinical investigation. 2002; 110(4):515–26. Epub 2002/08/22. https://doi.org/10.1172/JCI13847 PMID: 12189246; PubMed Central PMCID: PMC150410.
10. Conde-Jaldon M, Montes-Cano MA, Garcia-Lozano JR, Ortiz-Fernandez L, Ortego-Centeno N, Gonzalez-Leon R, et al. Epistatic interaction of ERAP1 and HLA-B in Behcet disease: a replication study in the Spanish population. PloS one. 2014; 9(7):e102100. Epub 2014/07/16. https://doi.org/10.1371/journal.pone.0102100 PMID: 25019531; PubMed Central PMCID: PMC4098596.
11. Kirino Y, Bertsias G, Ishigatsubo Y, Mizuki N, Tugal-Tutkun I, Seyahi E, et al. Genome-wide association analysis identifies new susceptibility loci for Behcet’s disease and epistasis between HLA-B*51 and ERAP1. Nature genetics. 2013; 45(2):202–7. Epub 2013/01/08. https://doi.org/10.1038/ng.2520 PMID: 23291587; PubMed Central PMCID: PMC3810947.
12. Zuk O, Hechter E, Sunyaev SR, Lander ES. The mystery of missing heritability: Genetic interactions create phantom heritability. Proceedings of the National Academy of Sciences of the United States of America. 2012; 109(4):1193–8. Epub 2012/01/10. https://doi.org/10.1073/pnas.1119675109 PMID: 22223662; PubMed Central PMCID: PMC3268279.

13. Calle ML, Urrea V, Malats N, Van Steen K. nbmnr: an R package for exploring gene-gene interactions associated with binary or quantitative traits. Bioinformatics (Oxford, England). 2010; 26(17):2198–9. Epub 2010/07/03. https://doi.org/10.1093/bioinformatics/btq352 PMID: 20595460.

14. The International Criteria for Behcet’s Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. Journal of the European Academy of Dermatology and Venereology. JADV. 2014; 28(3):338–47. Epub 2013/02/28. https://doi.org/10.1111/jdv.12107 PMID: 23441863.

15. Mahmoudi M, Ashraf-Ganjouei A, Javinani A, Meguro A, Mizuki N, et al. Epistatic Interaction of ERAP1 and HLA-B*51 in Iranian Patients with Behcet’s Disease. Scientific reports. 2018; 8 (1):17612. https://doi.org/10.1038/s41598-018-35700-0 PMID: 30514861

16. Zhang L, Yu H, Cheng M, Li H, Liu Y, Klijnstra A, et al. Association of ERAP1 Gene Polymorphisms With Behcet’s Disease in Han Chinese. Investigative ophthalmology & visual science. 2015; 56(10):6029–35. Epub 2015/09/24. https://doi.org/10.1167/iovs.15-17544 PMID: 26393469.

17. Noble WS. How does multiple testing correction work? Nature biotechnology. 2009; 27(12):1135. https://doi.org/10.1038/nbt1209-1135 PMID: 20010596

18. Calle ML, Urrea Gales V, Malats i Riera N, Van Steen K. MB-MDR: model-based multifactor dimensionality reduction for detecting interactions in high-dimensional genomic data. 2008.

19. Calle ML, Urrea V, Malats N, Van Steen K. MB-MDR: model-based multifactor dimensionality reduction for detecting interactions in high-dimensional genomic data. 2008.

20. Cattaert T, Calle ML, Dudek SM, Mahachie John JM, Van Lishout F, Urrea V, et al. Model-Based Multifactor Dimensionality Reduction to detect epistasis in case-control data in the presence of noise. Annals of human genetics. 2011; 75(1):78–89. https://doi.org/10.1111/j.1469-1809.2010.00604.x PMID: 21158747

21. Park MY, Hastie T. Penalized logistic regression for detecting gene interactions. Biostatistics. 2007; 9 (1):30–50. https://doi.org/10.1093/biostatistics/kxm010 PMID: 17429103

22. John JMM, Van Lishout F, Van Steen K. Model-Based Multifactor Dimensionality Reduction to detect epistasis for quantitative traits in the presence of error-free and noisy data. European Journal of Human Genetics. 2011; 19(6):696. https://doi.org/10.1038/ejhg.2011.17 PMID: 21407267

23. Hammer GE, Gonzalez F, Champsaur M, Cado D, Shastri N. The aminopeptidase ERAAP shapes the peptide repertoire displayed by major histocompatibility complex class I molecules. Nature immunology. 2006; 7(1):103–12. Epub 2005/11/22. https://doi.org/10.1038/nri1286 PMID: 16299505.

24. Cui X, Rouhani FN, Hawari F, Levine SJ. An aminopeptidase, ARTS-1, is required for interleukin-6 receptor shedding. The Journal of biological chemistry. 2003; 278(31):28677–85. Epub 2003/05/16. https://doi.org/10.1074/jbc.M300456200 PMID: 12748171.

25. Mizuki N, Meguro A, Ota M, Ohno S, Shiota T, Kawagoe T, et al. Genome-wide association studies identify IL23R-IL12RB2 and IL10 as Behcet’s disease susceptibility loci. Nature genetics. 2010; 42 (8):703–6. Epub 2010/07/14. https://doi.org/10.1038/ng.624 PMID: 20622879.

26. Burton PR, Clayton DG, Cardon LR, Craddock N, Deloukas P, Duncanson A, et al. Association scan of 14,500 nonsynonymous SNPs in four diseases identifies autoimmune variants. Nature genetics. 2007; 39(11):1329–37. Epub 2007/10/24. https://doi.org/10.1038/ng.2007.17 PMID: 17952073; PubMed Central PMCID: PMC2880141.

27. Cargill M, Schrodi SJ, Chang M, Garcia VE, Brandon R, Callis KP, et al. A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes. American journal of human genetics. 2007; 80(2):273–30. Epub 2007/01/20. https://doi.org/10.1086/511051 PMID: 17236132; PubMed Central PMCID: PMC1785338.

28. Evans DM, Spencer CC, Pointon JJ, Su Z, Harvey D, Kochan G, et al. Interaction between ERAP1 and HLA-B27 in ankylosing spondylitis implicate peptide handling in the mechanism for HLA-B27 disease susceptibility. Nature genetics. 2011; 43(8):761–7. Epub 2011/07/12. https://doi.org/10.1038/ng.873 PMID: 21743469; PubMed Central PMCID: PMC3640413.

29. Strange A, Capon F, Spencer CC, Knight J, Weale ME, Allen MH, et al. A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. Nature genetics. 2010; 42(11):985–90. Epub 2010/10/19. https://doi.org/10.1038/ng.694 PMID: 20953190; PubMed Central PMCID: PMC3749730.
30. Takeuchi M, Ombrello MJ, Kirino Y, Erer B, Tugal-Tutkun I, Seyahi E, et al. A single endoplasmic reticul-um aminopeptidase-1 protein allotype is a strong risk factor for Behcet’s disease in HLA-B*51 carriers. Annals of the rheumatic diseases. 2016; 75(12):2208–11. Epub 2016/05/25. https://doi.org/10.1136/annrheumdis-2015-209059 PMID: 27217550; PubMed Central PMCID: PMC5106293.