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## PW03-010 - MHC complexity in Behçet's disease

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MEETING ABSTRACT

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## PW03-010 - MHC complexity in Behçet's disease

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### Introduction

Family studies support a genetic contribution to Behçet's disease (BD), with a sibling recurrence-risk ratio of 11-52. The class I MHC molecule, *HLA-B\*51* (*B\*51*), is the strongest known genetic risk factor for BD, however the gene immediately centromeric to *HLA-B*, *MICA*, has also been implicated in BD. Because of strong linkage disequilibrium (LD) between *HLA-B* and *MICA*, their respective contributions to BD susceptibility have been debated. A recent report has proposed that *B\*51* is not a BD susceptibility allele, and several studies have identified *B\*51*-independent association signals within the MHC.

### Objectives

To clarify the relationship between *B\*51* and BD, and to test for *B\*51*-independent genetic variation within the MHC that influences BD susceptibility.

### Methods

Using Illumina Human 370CNV SNP genotypes in a Turkish collection of 1244 BD patients and 1303 geographically-matched healthy subjects, we examined SNP haplotypes and LD patterns across the *HLA-B/MICA* region with Haploview. We performed SNP imputation of the MHC using IMPUTE2 and the 1000 Genomes Phase 1 dataset. We inferred classical HLA types and their amino acids using SNP2HLA. Association testing and regression analyses were performed using SNPTEST and SNP & Variation Suite 7.

### Results

We identified a *B\*51*(+) *HLA-B/MICA* haplotype that was strongly associated with BD ( $p=1.22E-46$ , OR 2.8). A *B\*51*(-) version of the same haplotype occurred at equal frequencies in cases and controls, demonstrating that *B\*51* is essential to the risk haplotype. Further, we found that rs2848713, a variant on the *MICA* end of the

haplotype, conferred additional risk of BD in *B\*51*(+) individuals. Through imputation, we generated a set of 32,689 imputed SNPs. The 2 most strongly associated SNPs were 4.8Kb centromeric of *HLA-B* ( $p_{\min}=1.4E-50$ ), but no SNP was more strongly associated with BD than was *B\*51* itself ( $p=1.3E-55$ ). Conditioning on *B\*51* revealed an association near *HLA-A* ( $p_{\min}=5.4E-9$ ), and upon adding a representative *HLA-A* SNP to the regression model, we detected residual association centromeric of *HLA-B* ( $p=1.5E-5$ ). Analysis of imputed HLA types supported these findings. In addition to the association of BD with *B\*51* ( $p=2.2E-55$ ), sequential regression of imputed HLA types identified associations of *HLA-A\*03* ( $p=1E-8$ ), *HLA-C\*0701* ( $p=9.5E-4$ ), and *HLA-B\*15* ( $p=1.2E-4$ ) with BD. Stepwise forward regression of imputed *HLA-B* amino acids identified 6 *HLA-B* residues that together fully accounted for the regional association at *HLA-B*.

### Conclusion

This study affirms *B\*51* as the strongest risk factor of BD. We have provided strong evidence opposing a *B\*51*-independent role for *MICA* variants in BD susceptibility. We have identified significant effects of *HLA-A\*03* and *HLA-C\*0701*, which protect against BD, and *HLA-B\*15*, which confers risk of BD. We have identified a group of *HLA-B* amino acids, most of which reside in the antigen binding groove, that together account for the entire association signal at the *HLA-B* locus.

### Disclosure of interest

None declared.

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