



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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