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PW03-010 - MHC complexity in Behçet’s disease

MJ Ombrello1*, Y Kirino2, P de Bakker3,4, F Cosan5, DL Kastner6, A Gu5, EF Remmers6

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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 (pmin=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 (pmin=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.

Authors’ details
1Translational Genetics and Genomics Unit, NIAMS, Bethesda, USA
2Department of Internal Medicine and Clinical Immunology, Yokohama City University, Yokohama City, Japan. 3Division of Genetics, Brigham and Women’s Hospital and Harvard Medical School, Boston, USA. 4Departments of Medical Genetics and of Epidemiology, University Medical Center Utrecht,