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Imputation-based analysis of *MICA* alleles in the susceptibility to ankylosing spondylitis

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Ankylosing spondylitis (AS) susceptibility is strongly correlated with genetic variation within the major histocompatibility complex (MHC), and the class I *HLA-B*27* allele confers the major genetic risk factor to AS.[1] Furthermore, strong evidence for additional alleles in the MHC has been observed which affect susceptibility independently from the *HLA-B*27* allele, either by direct genotyping in candidate gene studies[2] or through large-scale imputation-driven association studies.[3,4] We have previously identified variants in both class I and II which affect susceptibility to AS through imputation of classical HLA alleles.[4]

The *MICA* gene is encoded 46 kbps from *HLA-B* and previous studies have reported genetic variants within this locus to affect susceptibility to AS and other inflammatory diseases.[5] In particular, in Annals of Rheumatic Diseases, Zhou *et al*[6] evaluated the association of *MICA* variants with susceptibility to AS in cohorts from North America and China. This study found that the allele *MICA*007:01* was strongly associated with risk of AS independently of *HLA-B*27*, with an association observed in the *HLA-B27*-negative cohort (US cohort OR=9.12, $p=4.28\times10^{-8}$; Chinese cohort OR=42.2, $p=9.35\times10^{-7}$). Weak protective associations with other *MICA* alleles were noted, likely because of the over-representation of the risk allele *MICA*007:01*.

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Having previously observed extremely strong linkage disequilibrium (LD) between *HLA-B* and *MICA* single nucleotide polymorphisms (SNPs),[1] we sought to independently test this report. We performed imputation of alleles in the *MICA* gene using a large reference panel of 1046 psoriatic arthritis individuals of European ancestry[7] and assessed the evidence of association of *MICA* alleles controlling for susceptibility *HLA-B* alleles. We successfully imputed *HLA-B* and *MICA* alleles in 9429 AS cases and 13 459 controls of European ancestry from the IGAS cohort[3] genotyped using the Illumina Immunochip SNP microarray.[8] Within the *MICA* locus, we observed 14 distinct alleles where *MICA*008:01* was observed to be the most common with an allele frequency of 50%. We performed association analysis at *HLA-B* and *MICA* imputed alleles with logistic regression controlling for the *HLAB*27* allele and 10 principal components from a genome-wide analysis to control for population structure.

In our study, we imputed the *MICA*007* allele with high confidence (imputation performed in batches, all $r^2>0.85$, mean $r^2=0.90$) and genotypes were confirmed by Sanger sequencing of exons 2, 3, 4 and 5 of the *MICA* gene with perfect accuracy in 7 *MICA*007* homozygote individuals and 5 non-carriers of the *MICA*007* allele. We observed no association with *MICA*007* after controlling for the effect of *HLA-B*27* ($p>0.05$). We also observed that the *HLA-B*27* and the *MICA*007* alleles are in high LD ($r^2=0.66$ in controls, $r^2=0.52$ in cases, $r^2=0.53$ in the reference imputation panel).

No association was observed between *MICA*007* and AS in either *HLA-B*27* negative subjects (1669 cases, 12 263 controls) (OR=1.32, p=0.07) or *HLA-B*27* positive subjects (7760 cases, 1196 controls) (OR=1.04, p=0.34), and our study had over 80% power to detect an association with *MICA*007* in both *HLA-B*27* negative and positive analyses given the study sample size and the effect size previously reported for *MICA*007* (OR=9). To assess whether heterogeneity of the different populations could have affected these findings, the analysis was repeated in the relatively homogenous UK population alone (n=4198 cases, 9611 controls). The findings were similar in *HLA-B*27* positive subjects (p=0.89) and in *HLAB*27* negative subjects (p=0.53).

In this study, we found no evidence of association between the *MICA*007* allele and AS susceptibility in a large cohort of European ancestry. Given the sample size in *the HLA-B*27* negative cohort, we had 80% power to identify an independent effect of *MICA*007* with an effect size of at least 1.55. We identified strong LD between *HLA-B*27* and *MICA*007* potentially explaining previously reported associations with this allele.

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