Response to: Imputation-based analysis of MICA alleles in the susceptibility to ankylosing spondylitis by Zhou et al

To the Editor,

As Zhou and Reveille note,1 MICA is a functionally enticing candidate gene for ankylosing spondylitis (AS). It is however challenging to study because of the technical difficulty of direct genotyping studies of the locus, its proximity and strong linkage disequilibrium with HLA-B, and the fact that it is subject to major population stratification effects. We recently performed an association study of common MICA alleles with AS susceptibility and observed no evidence of association in either HLA-B*27 positive or negative stratified analyses.2 In this study, we used individuals of European ancestry from the International Genetics of Ankylosing Spondylitis (IGAS) cohort, including 9429 AS cases and 13 459 population controls. We have previously demonstrated the value of imputation to characterise the association of genetic variation to AS susceptibility in the major histocompatibility complex (MHC)3 and these findings have been replicated with cohorts of different ancestry and through direct genotyping4 confirming the accuracy of HLA imputation studies. Validation of MICA allele imputation was performed in a smaller sample set and we observed 100% imputation accuracy. Our analysis demonstrated strong linkage disequilibrium between HLA-B*27 and MICA*007 in the IGAS cohort, in both cases and controls, and in the reference panel cohort used for MICA allele imputation.5 This observation was consistent with other studies.6 No evidence of association was observed when considering higher resolution of MICA allele imputation; in particular, for the five-digit MICA*007:01 allele we observed no association after controlling for the effect of HLA-B*27 (p=0.225). These observations indicate that neither imputation error nor resolution is likely to be the explanation for the difference in findings. In contrast to the study by Zhou et al where population structure was neither assessed nor controlled for, in our study population structure was controlled through principal components analysis of genome-wide single nucleotide polymorphism data, as previously described.7 8 Given that the MHC in which both HLA-B and MICA are encoded is subject to major variation related to ethnic variation among subjects, even those matched broadly by ancestry such among Chinese or North Americans, this is one potential explanation for the difference in results. HLA or MICA genotyping issues are other potential explanations. Further studies to address these potential sources of error would be indicated prior to assigning any functional role to MICA allelic variants in AS.

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