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 genotyping,⁴ 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 as 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.

Adrian Cortes,¹ Matthew A Brown²

¹Big Data Institute, Li Ka Shing Centre for Health Information and Discovery, University of Oxford, Oxford, UK

²Institute of Health and Biomedical Innovation, School of Biomedical Sciences, Queensland University of Technology (QUT) at Translational Research Institute, Brisbane, Queensland, Australia

Correspondence to Professor Matthew A Brown, Institute of Health and Biomedical Innovation, Queensland University of Technology (QUT) at Translational Research Institute, Brisbane, QLD 4102, Australia; matt.brown@qut.edu.au

Handling editor Josef S Smolen

Contributors AC and MAB wrote, analysed and conceived the study.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

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To cite Cortes A, Brown MA. *Ann Rheum Dis* 2020;**79**:e2.

Received 14 November 2018

Revised 21 November 2018

Accepted 25 November 2018

Published Online First 18 January 2019

► <http://dx.doi.org/10.1136/annrheumdis-2018-214708>

Ann Rheum Dis 2020;**79**:e2. doi:10.1136/annrheumdis-2018-214765

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