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Gut Bacteria Causing Ankylosing Spondylitis Identified Through Mendelian Randomization Studies

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SESSION INFORMATION

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Session Time: 8:30AM-10:30AM

Background/Purpose: There is strong evidence from animal models, human microbiome profiling studies, genetic analyses, and from the model of reactive arthritis, that AS is caused by interaction of the gut mucosal immune system with the gut microbiome. We and others have recently confirmed expansion of CD8 T-lymphocyte clonotypes, in AS patients but not HLA-B27 matched healthy controls, that are also known to be expanded in bacterial-induced reactive arthritis. As disturbance of the gut microbiome can potentially result from either effects of the microbiome on disease or the converse, we sought to examine the causal impact of the gut microbiome on AS using Mendelian randomisation (MR) methodology.

Methods: We utilised MR analysis to investigate potential causal associations between AS genetics and gut microbiome composition. To determine outcome instruments for MR analysis, we used a large-scale GWAS of Caucasian AS cases (n=11,352) vs controls n=35,446). For the exposure instruments, we obtained publicly available data for genomewide significant microbe QTLs as identified by *Kurilshikov A et al*, 2021 (PMID 33462485). Briefly, the study performed GWAS on a meta-analysed population of European host gut microbiomes as determined by 16S ribosomal sequencing.

Results: We identified a significant protective (β=-0.96, FDR=0.011) causal relationship between presence of *Ruminococcus torques* and AS through the rs35866622 variant, which tags the *FUT2* gene determining secretor status, the ability to secrete ABO blood group antigens and other fucosylated mucus glycans in the gastrointestinal mucosa.

Conclusion: Using MR analysis, we demonstrate that the bacterium *Ruminococcus torques* is associated with the gene *FUT2* to influence the risk of developing AS. The observed negative correlation is consistent with previous findings demonstrating reduced carriage of this taxon in the stool microbiome of AS cases (PMID 31377126; 31662318), and with similar Mendelian randomization study findings in inflammatory bowel disease (PMID 33462485). These results support the hypothesis that AS is a gut microbiome driven disease and encourage the evaluation of novel therapeutic approaches targeting the gut microbiome. Correcting the underlying dysbiosis as part of AS clinical management could result in direct improvement for patients, and we hypothesize could be used as a preventative treatment in individuals at high risk of the disease.

Disclosures: N. Harvey, None; **J. Garrido-Mesa**, None; **Z. Li**, None; **D. Evans**, None; **P. Sternes**, None; **M. Brown**, None.

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