HLA-A 31:01 is not associated with the development of methotrexate pneumonitis in the UK population: results from a genome-wide association study

We read with interest the article by Furukawa et al suggesting an association between HLA-A 31:01 and methotrexate (MTX)-induced interstitial lung disease (ILD) in Japanese patients with rheumatoid arthritis (RA). MTX-ILD or MTX-pneumonitis (MTX-P) is an idiosyncratic hypersensitivity reaction to MTX that usually occurs within the first year of MTX therapy, inducing inflammation, cytokine release and the activation of CD4+ T-lymphocytes within the lung parenchyma, with a reported prevalence of 1% of the Caucasian RA population prescribed MTX.

To investigate this association further, we conducted a genome-wide association study. Rheumatologists working within the National Health Service in the UK identified Caucasian patients with RA, who developed clinician-diagnosed MTX-P (n=65). Caucasian controls, matched for age and gender, were identified from a prospective observational cohort study of patients starting MTX (n=195). In order to be eligible, controls were required to have 1 year of continuous MTX therapy without the development of MTX-R. Assuming HLA-A 31:01 prevalence of 3.6% in the European Caucasian population, this provided 80% power to detect an OR of 3.0. Genotyping was performed using the Illumina Infinium HumanCoreExome 12 BeadChip genome-wide array (Illumina, San Diego, USA); HLA-A 31:01 was imputed using a subset of samples (n=24) were directly genotyped for the allele using an established wet-lab technique described previously.

Following quality control, data for 62 cases and 175 controls remained. HLA-A 31:01 was not associated with MTX-P in this cohort (p=0.21). Wet-lab genotyping of a subset of samples confirmed concordance with in silico imputation (k=1.00). One locus, rs6593803 mapping to an intergenic region between the GJA5 and ACP6 genes, was associated with MTX-P; however, the results did not reach genome-wide significance thresholds for claims of confirmed association (p=1.85×10^-7, OR=3.13). Nonetheless, rs6593803 is known to affect the expression of GJA5. 10 GJA5 is a member of the connexin gene family and the resulting protein is connixin 40.

The connxin 40 protein is a component of gap junctions (GJs) that act at sites of cell–cell contact allowing diffusion of signalling molecules between cells. 11 Transgenic mice deficient GJs have a reduced life span due to lung abnormalities including pulmonary fibrosis, alveolar wall thickening and increased lung fibroblasts, histopathological findings similar to MTX-P. 12

In summary, we have found no evidence of association between HLA-A 31:01 and MTX-P in a European population. Three loci reached suggestive evidence for association with MTX-P (rs6593803 (p=1.85×10^-7, OR=3.13), rs9299346 (p=1.76×10^-6, OR=2.76) and rs1624005 (p=6.54×10^-6, OR=2.59)), but further studies with larger numbers of patients with this rare disease are required to confirm these non-HLA associations with MTX-P.

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Contributors JB recruited patients, NHS sites, co-conducted the GWAS and analysis. S-AO applied to the ethics committee, recruited patients and NHS sites. JM co-conducted the GWAS and analysis. AA co-genotyped the HLA 31:01. MP co-wrote the article. SMMV is PI of the control cohort. AB is the PI of the cases cohort.

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