Analysis of Anti-RNA Polymerase III Antibody-positive Systemic Sclerosis and Altered GPATCH2L and CTNND2 Expression in Scleroderma Renal Crisis

Edward P. Stern, Sandra G. Guerra, Harry Chinque, Vanessa Acquaah, David González-Serna, Markella Ponticos, Javier Martin, Voon H. Ong, Korsa Khan, Svetlana I. Nihtyanova, Mark Harber, Aine Burns, Maureen D. Mayes, Shervin Assassi, Carmen Fonseca, and Christopher P. Denton

The Journal of Rheumatology November 2020DOI: https://doi.org/10.3899/jrheum.190945

Hello, I am Chris Denton from University College London and the Royal Free hospital in UK.

Our study is important because it is asking why a patient with systemic sclerosis (SSc) may develop a scleroderma renal crisis (SRC) and specifically whether genetic factors may explain why some patients develop renal crisis and others do not.

Scleroderma renal crisis is a major life threatening complication of systemic sclerosis leading to severe hypertension and renal failure. It occurs in less than 10% of SSc cases overall, almost always within the first 3 years or disease, and is very strongly associated with anti-RNA polymerase III autoantibody (ARA). To investigate genetic susceptibility to SRC we have performed a two stage genetic analysis in ARA+ SSc comparing those who developed SRC with a control group that are ARA+ but did not develop SRC within 5 years of follow up and so we hypothesise may be genetically protected from SRC despite their high risk autoantibody.

We used a standard GWAS chip based genomic DNA analysis in our discovery cohort of 99 ARA+ UK SSc patients including 48 SRC and analysing differences in common variants SNPs between cases and controls. From this we identified 9 SNPS potentially associated with SRC in our cohort. We then investigated association in a validation cohort of 256 ARA+ SSc patients from USA, including 40 SRC. One candidate SNP, linked to the *GPATCH2L* locus, showed genetic replication with a p-value of 0.025 in the second cohort. Another second SNP, *CTNND2*, did not show genetic association in our second cohort but has been linked in another published study to SSc associated pulmonary arterial hypertension (PAH), another important vascular complication of SSc.

For both candidates we went on to explore protein expression in SRC biopsies and controls. There was overexpression of both GPATCH2L and also for CTNND2 in SRC suggesting potential relevance to pathogenesis. This is interesting because the GPATCH2L locus has previously been genetically associated with diastolic hypertension in the general population, and because CTNND2 is a negative regulator of Wnt signalling. Abnormal Wnt signalling has been implicated in SSc pathogenesis and so could be important in SRC.

This study is novel because it uses unique characteristics of SRC in SSc to perform an enriched cohort analysis and explore genetic association in a subset of patients with the highest SRC risk, and with autoantibody and therefore likely immunogenetic homogeneity.

Our findings suggest that SRC risk may be associated with a gene that gives general susceptibility to diastolic hypertension and also illustrate that common variant SNP association studies may identify pathways or factors that are relevant to pathogenesis but that are not necessarily replicated at a genetic level and this may reflect the complex genetic basis of susceptibility to SSc and its important organ based complications.

If you are interested in our work please visit the Journal of Rheumatology website where you can access the full paper.