

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

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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 help explain why some patients develop renal crisis and others do not.

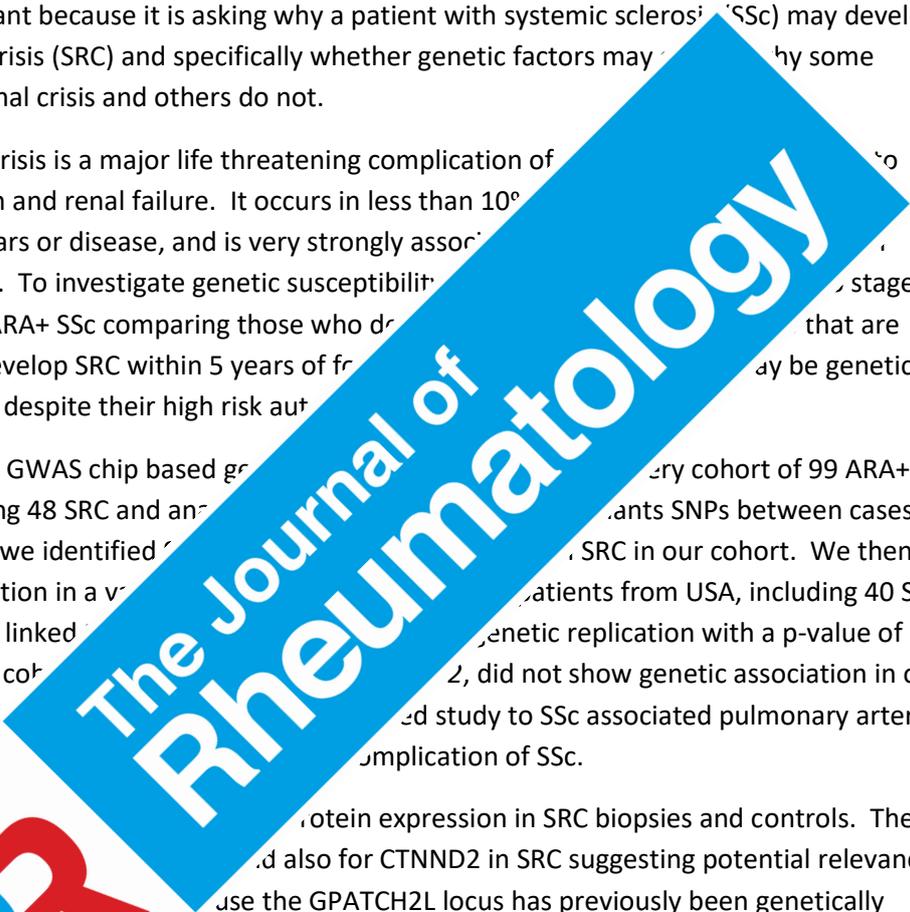
Scleroderma renal crisis is a major life threatening complication of systemic sclerosis (SSc) characterized by severe hypertension and renal failure. It occurs in less than 10% of patients with SSc within the first 3 years of disease, and is very strongly associated with the presence of anti-RNA polymerase III autoantibody (ARA). To investigate genetic susceptibility to SRC, we performed a genome-wide genetic analysis in ARA+ SSc comparing those who developed SRC within 5 years of diagnosis (ARA+ SRC) to those who are ARA+ but did not develop SRC within 5 years of diagnosis (ARA+ no SRC). SRC may be genetically protected from SRC despite their high risk autoantibody.

We used a standard GWAS chip based genome-wide association study in a discovery cohort of 99 ARA+ UK SSc patients including 48 SRC and 51 no SRC patients. We identified 10 candidate SNPs between cases and controls. From this we identified 10 candidate SNPs, 5 of which were associated with SRC in our cohort. We then investigated association in a validation cohort of 100 ARA+ SSc patients from USA, including 40 SRC. One candidate SNP, linked to hypertension, was replicated in the second cohort with a p-value of 0.025 in the second cohort. This SNP, CTNND2, did not show genetic association in our second cohort but has been associated in a previous study to SSc associated pulmonary arterial hypertension (PAH), a common complication of SSc.

For both cohorts we performed immunoblotting to measure protein expression in SRC biopsies and controls. There was overexpression of GPATCH2L in SRC biopsies and also for CTNND2 in SRC suggesting potential relevance to pathogenesis. We also performed immunoblotting to measure the GPATCH2L locus has previously been genetically associated with hypertension in the general population, and because CTNND2 is a negative regulator of Wnt signalling, and because normal Wnt signalling has been implicated in SSc pathogenesis and so could be important.

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 anti-RNA polymerase III 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.



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