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 scleros [illegible] (SSc) may develop a scleroderma renal crisis (SRC) and specifically whether genetic factors may [illegible] hy some patients develop renal crisis and others do not.

Scleroderma renal crisis is a major life threatening complication of [illegible] o severe hypertension and renal failure. It occurs in less than 10 [illegible] ys within the first 3 years or disease, and is very strongly asso [illegible] autoantibody (ARA). To investigate genetic susceptibilit [illegible] stage genetic analysis in ARA+ SSc comparing those who d [illegible] that are ARA+ but did not develop SRC within 5 years of f [illegible] ay be genetically protected from SRC despite their high risk aut [illegible]

We used a standard GWAS chip based g [illegible] ry cohort of 99 ARA+ UK SSc patients including 48 SRC and an [illegible] ants SNPs between cases and controls. From this we identified [illegible] SRC in our cohort. We then investigated association in a v [illegible] atients from USA, including 40 SRC. One candidate SNP, linked [illegible] enetic replication with a p-value of 0.025 in the second co [illegible] 2, did not show genetic association in our second cohort but [illegible] d study to SSc associated pulmonary arterial hypertension (P [illegible] mplication of SSc.

For both c [illegible] rotein expression in SRC biopsies and controls. There was ov [illegible] d also for CTNND2 in SRC suggesting potential relevance to path [illegible] use the GPATCH2L locus has previously been genetically associa [illegible] ion in the general population, and because CTNND2 is a negative regulator [illegible] normal Wnt signalling has been implicated in SSc pathogenesis and so could be impo [illegible]

This study is novel [illegible] ause 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.