235. ABSENCE OF ASSOCIATION FOR DDAH1 POLYMORPHISM, rs17384213, WITH SCLERODERMA RENAL CRISIS HIGHLIGHTS DIVERSITY IN RENAL COMPLICATIONS OF CONNECTIVE TISSUE DISEASE

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Background: SSc is uncommon and pathogenesis is not fully understood, however genetic factors have shown to play a role. SSc has shown evidence of dysregulation of the vascular and immune systems, with end point fibrosis, and fatal vascular complications such as renal crisis. To date, a number of candidate gene studies and Genome-wide association studies (GWAS) have shown the replication of a number of key loci. A variant of rs17384213 SNP in the nitric oxide generating enzyme DDAH1 (Dimethylarginine dimethylaminohydrolase) has previously been reported to be associated with a decline in the renal function during chronic kidney disease. As renal involvement is still a major source of morbidity among SSc patients, we genotyped the previously associated polymorphism in DDAH1 to ascertain if it plays a role in SSc renal crisis.

Methods: 728 SSc cases and 260 healthy controls were genotyped for the polymorphism rs17384213 in DDAH1 as part of a larger genotyping study. All patients and controls were of Caucasian decent and were categorized according to three mutually exclusive autoantibody status: anti-topoisomerase1 (ATA), anticientromere (ACA) and antiRNA-polymerase (ARA). Patients were further classified into sub-phenotypes according to major organ involvement; pulmonary hypertension, pulmonary fibrosis and renal crisis. All genotyping was performed by the KASP system (KBioscience, UK). All genotype data and sub-phenotype analysis was performed using PLINK.

Results: Our cohort consisted of 274 (38%) patients with lung fibrosis, 112 (15%) with pulmonary hypertension and 63 (9%) with renal crisis. 255 (35%) patients were positive for ACA, 155 (21%) patients were positive for ATA, and 140 (19%) patients were positive for ARA. Case control and sub-phenotype analysis were performed using PLINK. No association with SSc or sub-phenotypes were found.

Conclusion: DDAH1 has previously been reported to be associated with chronic kidney disease through increased expression leading to higher levels of asymmetric dimethylarginine (ADMA), this was therefore a good candidate for further investigation in SSc. However we did not find any association with this SNP in SSc or any sub-phenotype. We therefore conclude that there does not appear to be any genetic link between rs17384213 and scleroderma renal disease, which may add additional support to the current hypothesis that mechanisms of renal disease in SSc are distinct from those determining renal decline in other conditions. This is consistent with previous data showing that histological scores of damage that predict outcome in other chronic kidney disease are not useful in SSc. Confirmation of the lack of association of this SNP in an independent cohort is necessary to verify our findings.

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