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EVIDENCE FOR CAVEOLIN-1 (CAV1) AS A NEW SUSCEPTIBILITY GENE REGULATING TISSUE FIBROSIS IN SYSTEMIC SCLEROSIS

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Background and objective Caveolin-1 (CAV1) is an inhibitor of tissue fibrosis and has been implicated in the pathogenesis of systemic sclerosis (SSc). The aim of our study was to analyse the possible association of CAV1 gene single nucleotide polymorphisms (SNPs) with SSc.

Methods The authors studied a total population of 3974 individuals of European Caucasian ancestry (1355 patients with SSc and 2619 healthy controls). Genotype data for 23 SNPs (rs17138756, rs4730742, rs2191498, rs10278782, rs1052990, rs6466579, rs4236601, rs926198, rs3779512, rs10256914, rs3807986, rs959173, rs10270569, rs3807989, rs3779514, rs3815412, rs729949, rs6466587, rs9920, rs1049337, rs6959106, rs7795356, and rs2191502) spanning a region of more than 55 kb in the CAV1-CAV2 gene locus at chromosome 7q31.1 were obtained from a genome-wide scan conducted in a French population (564 SSc patients and 1776 controls). Three CAV1

SNPs (rs926198 T/C, rs959173 T/C, rs9920 T/C) displaying the most significant associations with SSc and/or clinical phenotypes were then genotyped in an Italian population (791 SSc patients and 843 controls). CAV1 protein expression in skin biopsies from SSc patients and controls was investigated by immunohistochemistry and Western blotting.

Results In the French population, the *CAV1* rs959173 C minor allele showed a significant protective association with susceptibility to SSc (OR 0.71, 95% CI 0.59 to 0.86, $p_{\text{adjusted}}=0.009$), and with the subset of patients with limited cutaneous SSc (lcSSc) (OR 0.71, 95% CI 0.56 to 0.89, $p_{\text{adjusted}}=0.018$). This association was replicated in the Italian population and strengthened in the combined populations through Cochran-Mantel-Haenszel meta-analysis (SSc: pooled OR 0.81, 95% CI 0.71 to 0.92, $p=0.0018$; lcSSc: pooled OR 0.80, 95% CI 0.69 to 0.93, $p=0.0053$). A reduction in rs959173 C allele frequency was also observed in patients with dcSSc compared with healthy controls, although this difference did not reach statistical significance. No significant heterogeneity in OR was observed between the French and Italian populations according to the Breslow–Day method. As determined by immunohistochemical analyses, individuals who carried the rs959173 C minor allele displayed higher CAV1 protein expression in different cell types, including keratinocytes, dermal endothelial cells and fibroblasts, than those who did not. Western blotting analysis on skin protein lysates confirmed that CAV1 protein expression levels were significantly higher in both SSc patients and controls carrying the rs959173 C protective allele than in those carrying the rs959173 TT homozygous genotype (both $p<0.01$).

Conclusions Our results add *CAV1* to the list of SSc susceptibility genes and provide evidence through genotype/phenotype correlation for the direct contribution of this pathway regulating the fibrotic process in SSc pathogenesis.