A87 ASSOCIATION BETWEEN THE MMP-12 GENE AND SYSTEMIC SCLEROSIS: ROLE OF RS2276109 FUNCTIONAL POLYMORPHISM IN THE MODULATION OF SKIN AND PULMONARY FIBROSIS

M Manetti,[1,2] L Ibba-Manneschi,[1] C Fatini,[3] S Guiducci,[2] A F Milia,[2] R Giacomelli,[4] S Bombardieri,[5] C Montecucco,[6] R Abbate,[3] G Valentini,[7] M Matucci-Cerinic[2] *[1]Department of Anatomy, Histology and Forensic Medicine, University of Florence, Florence, Italy; [2]Department of Biomedicine, Division of Rheumatology, AOUC, and Excellence Centre for Research, Transfer and High Education, University of Florence, Florence, Italy; [3]Department of Medical and Surgical Critical Care, Thrombosis Centre, University of Florence, Florence, Italy; [4]Department of Internal Medicine and Public Health, Division of Rheumatology, University of L'Aquila, L'Aquila, Italy; [5]Division of Rheumatology, University of Pisa, Pisa, Italy; [6]IRCCS Policlinico San Matteo, University of Pavia, Italy; [7]Division of Rheumatology, II University of Naples, Naples, Italy*

10.1136/ard.2010.129619u

Background Systemic sclerosis (SSc) is a life-threatening autoimmune disease characterised by autoimmunity, widespread microvascular involvement and progressive fibrosis of the skin and internal organs. Recent evidence indicates that matrix metalloproteinase-12 (MMP-12) plays a critical role in pathological lung tissue remodelling and in transforming growth factor β-induced and bleomycin-induced pulmonary fibrosis. The authors have previously shown that different cell types (ie, fibroblasts and microvascular endothelial cells) isolated from the skin of patients with diffuse cutaneous SSc (dcSSc) constitutively overexpress and secrete MMP-12. Of note is the observation that MMP-12 overproduction by SSc cells was shown to be a permanent alteration over multiple generations in vitro. The human MMP-12 gene on chromosome 11q22.3 contains a common A-to-G functional single nucleotide polymorphism (SNP) in the promoter region (MMP-12 rs2276109) which modulates transcriptional activity in an allele-specific manner. The A allele has a greater affinity to the transcription factor AP-1, resulting in increased promoter activity and enhanced MMP-12 expression.

Objective To investigate the possible involvement of MMP-12 rs2276109 SNP in influencing both SSc susceptibility and clinical phenotype.

Methods The MMP-12 rs2276109 functional SNP was genotyped by PCR-RFLP assay in 500 subjects of Italian Caucasian origin: 250 SSc patients (146 with limited cutaneous SSc (lcSSc) and 104 with dcSSc) and 250 healthy individuals. Patients were assessed for anti-centromere and anti-topoisomerase I antibodies, interstitial lung disease (ILD) and isolated pulmonary arterial hypertension (PAH).

Results A significant difference in MMP-12 rs2276109 genotype distribution between SSc patients and healthy individuals ($p<0.0001$) and between lcSSc and dcSSc ($p=0.003$) was observed. The A allele frequency was significantly higher in SSc patients than in controls ($p<0.0001$), as well as in dcSSc than in lcSSc ($p=0.003$). The homozygosity for the A allele significantly influenced the predisposition to SSc (OR 2.76, 95% CI 1.84 to 4.13, $p<0.0001$). In particular, the MMP-12 rs2276109 AA genotype increased the susceptibility to dcSSc sixfold in comparison with that observed in lcSSc (OR 6.16, 95% CI 3.06 to 12.41, $p<0.0001$; OR 1.86, 95% CI 1.19 to 2.92, $p=0.006$, respectively). Furthermore, the MMP-12 rs2276109 A allele frequency was significantly higher in anti-topoisomerase I antibody-positive SSc ($p=0.0004$), anti-centromere antibody-negative SSc ($p=0.003$) and SSc-ILD ($p=0.03$). No association between MMP-12 rs2276109 polymorphism and SSc-related PAH was found.

Conclusions The MMP-12 rs2276109 SNP is associated with susceptibility to SSc, in particular to the dcSSc subset, and with the presence of anti-topoisomerase I antibodies and ILD. Our results suggest that this SNP might be a powerful indicator of severe skin and lung involvement in SSc.