

00469 **Genetic Screening for Identifying Human Genes Regulating Fibrosis in Systemic Sclerosis**

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Aims: To discover novel genes/pathways involved in elevated collagen synthesis in systemic sclerosis

Methodology: We conducted a pioneering forward-genetics approach using genome-wide ribonucleic acid interference-(RNAi) –screening. We performed RNAi-screening in dermal fibroblasts from three patients with early diffuse cutaneous systemic sclerosis (onset from the first non-Raynaud's manifestation of less than 3 years). Dermal fibroblasts were immortalized using ectopic expression of human telomerase. The assay used a collagen promoter driver reporter system for identifying genes regulating collagen transcription.

Result: The genetic screen identified 187 genes whose silencing altered the activation of collagen promoter activity. This included 82% and 18% positive and negative regulators, respectively. A system-level view of genes and signaling pathways regulating collagen synthesis was generated using bioinformatics analysis.

Conclusion: We anticipate that this catalogue of collagen expression regulating genes will help to unravel the dysregulated genetic regulatory modules of fibrosis and may aid in the diagnostics of different clinical subsets of SSc.