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Title: Telomere (TL) shortening is associated with disease severity in scleroderma (SSC) associated interstitial lung disease (ILD)

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Body: Attrition of TL is associated with the development and progression of pulmonary fibrosis. TL length has been shown to be reduced in individuals with SSC vs healthy controls. ILD develops in over 25% of individuals with SSC. We hypothesized that TL shortening is an important mechanism driving the pathogenesis of SSC-ILD. Methods: Whole blood was collected from SSC-ILD patients(n=132). SSC-ILD was defined as extensive or limited disease (Goh et al, AJRCCM 2008;177). DNA, isolated using a Promega extraction kit, was analysed using quantitative real time PCR. TL length was calculated using the method described by O'Callaghan and Fenech (Biol Proced. 2011; 31). Results: Mean±SEM TL length in SSC cohort was 65.1±4.7 kb/diploid genome. In limited disease (n=100, 74 female, age 53.2±1.1 yrs) mean TL length was 77.0 ± 5.5 kb/diploid genome (see figure 1). In extensive disease (n=32, 18 females, age 46.5±3.5 yrs), the mean TL length was 24.8±3.5 kb/diploid genome($p<0.0001$). TL length correlated with extent of fibrosis on CT ($p<0.001$). TL typically shorten with age. In our cohort TL length increased with age($p=0.02$) perhaps reflecting a trend towards more extensive disease in younger subjects. Conclusion: TL length is significantly associated with disease extent in SSC-ILD. Our observation suggests an important role for premature cellular senescence in the pathogenesis of SSC-ILD. HA is an ERS-Fellow.