**Families At-Risk for Interstitial Lung Disease Study**

**NCT number:** NCT03641742

**Document Date:** 9/1/2023

**Published Manuscript reporting Results**: McGroder et al Chest 2023 (PMID 36649755)

**Study Protocol and Statistical Analysis:**

*Participants*

The institutional review board at Columbia University Irving Medical Center approved this study (AAAR1916). Written informed consent was obtained from all participants. We enrolled asymptomatic first-degree relatives, hereafter referred to as at-risk participants (ARPs), of patients clinically diagnosed with any number of fibrotic lung diseases, including IPF, CHP, CTD-ILD, pleuroparenchymal fibroelastosis (PPFE) and unclassifiable fibrotic ILD. At-risk participants were at least 35 years old and were excluded if they had underlying lung disease, a history of chronic heart failure, liver or kidney disease, a history of drug use during the last year, or if they were pregnant. Each ARP was interviewed by research personnel and detailed family pedigrees were created. If the affected individual's pedigree contained at least two family members with pulmonary fibrosis, they were deemed a familial case. Sporadic cases included those with no known family history of a fibrotic ILD. Affected probands with Interstitial Lung Disease, that is, those who were related to the ARPs, were enrolled if alive and available to participate in the study.

*Testing*

Each ARP underwent a high-resolution computed tomography (HRCT) scan of the chest at full inspiration using a single GE 64 VCT machine. The presence of a preclinical ILA, defined as non-dependent ground-glass abnormalities, reticulations, non-emphysematous cysts, traction bronchiectasis or honeycombing affecting > 5% of any lung zone[1], was determined by consensus of two thoracic radiologists. Focal findings or patterns taking up less than 5% of a

lung zone were deemed “indeterminate” for ILA and disregarded. If architectural distortion with bilateral fibrosis was present, the radiologists categorized the HRCT pattern per the American Thoracic Society criteria (usual interstitial pneumonia (UIP) pattern, probable UIP pattern, indeterminate for UIP, or suggestive of alternate diagnosis)[2].

We obtained a quantitative assessment of lung attenuation using the Pulmonary Analysis Software Suite[3,4]. High attenuation areas (HAA) were defined as percentage of the lung with attenuation between -600 and -250 HU as previously described[5].

Spirometry was performed in accordance with American Thoracic Society/European Respiratory Society guidelines. ARPs completed a 6-minute walk tests and the cough visual analog score.

We obtained genomic DNA from blood leukocytes using the Gentra Puregene Blood kit (Qiagen, Valencia CA). Blood leukocyte telomere length (LTL) was measured using a quantitative PCR assay[6]. Age-adjusted LTL percentiles were calculated after comparison with normal controls. Genotyping for the *MUC5B* (rs35705950) risk allele was obtained by Sanger sequencing and the minor allele frequency was calculated.

*Statistical Analysis*

We compared clinical characteristics of ARPs with and without ILA/ILD using chi-squared tests, Fisher’s exact tests, and Wilcoxon rank sum tests, where appropriate. We used generalized linear models to account for family clustering. Within these models, we included the variable of interest in addition to a random intercept for household number to account for the hierarchical nature of the data.

**References**


1. Hatabu H, Hunninghake GM, Richeldi L, et al. Interstitial lung abnormalities detected incidentally on CT: a Position Paper from the Fleischner Society. The lancet Respiratory medicine 2020;8(7):726-737. DOI: 10.1016/S2213-2600(20)30168-5.
2. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2022;205(9):e18-e47. DOI: 10.1164/rccm.202202-0399ST.
3. Guo J, Reinhardt JM, Kitaoka H, Zhang L, Sonka M, McLennan G, Hoffman EA. Integrated system for CT-based assessment of parenchymal lung disease. Proceedings IEEE International Symposium on Biomedical Imaging 2002:871-874. DOI: 10.1109/ISBI.2002.1029398.
4. Hu S, Hoffman EA, Reinhardt JM. Automatic lung segmentation for accurate quantitation of volumetric X-ray CT images. IEEE Trans Med Imaging 2001;20(6):490-8. DOI: 10.1109/42.929615.
5. Hoffman EA, Jiang R, Baumhauer H, et al. Reproducibility and validity of lung density measures from cardiac CT Scans--The Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study. Acad Radiol 2009;16(6):689-99. DOI: 10.1016/j.acra.2008.12.024.
6. Stuart BD, Lee JS, Kozlitina J, et al. Effect of telomere length on survival in patients with idiopathic pulmonary fibrosis: an observational cohort study with independent validation. The lancet Respiratory medicine 2014;2(7):557-65. DOI: 10.1016/S2213-2600(14)70124-9.