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| **The genetic landscape of familial interstitial lung disease (ILD) is similar to sporadic idiopathic pulmonary fibrosis (IPF)** |
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| **Introduction/Aim:** The identification of rare and common genetic variation in ILD, including IPF, is of increasing clinical significance. Sporadic and familial disease are thought to represent different ends of the spectrum regarding the relative contribution of common and rare genetic variants. This study aimed to explore genetic variation in a familial ILD (fILD) cohort.  **Methods:** Genome sequencing data for 84 affected and 12 unaffected relatives from 55 Australian families with fILD were interrogated to identify rare variants in 37 known IPF genes. Variants that a) segregated with disease, b) had a minor allele frequency <0.01 in the general population, and c) were predicted to be deleterious using *in silico* tools, were curated using international guidelines for identifying disease-causing variants. A polygenic risk score (PRS) was generated using 16 common IPF variants and applied to study populations. PRS in 84 familial cases was compared to population controls (n=404), and Australian IPF Registry participants (TaqMan genotyping or direct sequencing), including individuals with family history (R-FH, n=42), and sporadic cases (n=284). A one-way ANOVA with a Tukey HSD test was performed.  **Results:** Four families (7.3%) harboured a disease-causing variant, and a further seven families (12.7%) carried a potentially disease-causing variant. This included five *TERT* variants, five in *RTEL1* and one in *SFTPA2*.  No significant differences between PRS were seen in patient groups: familial: 0.59±1.01 (SD); R-FH: 0.56±1.14; sporadic: 0.41±1.13. However, the PRS for all patient groups were significantly higher than population controls (-0.69±0.94; p<1x10-5). From the 11 families with (potentially) disease-causing variants, 12/16 (75%) of the affected individuals had a PRS below the familial median, despite nine carrying the *MUC5B* risk variant, the biggest contributor to the PRS.  **Conclusion:** The genetic underpinnings of sporadic and familial disease may be more similar than previously thought. Ongoing work will determine the functional impact of identified potentially disease-causing variants.        **Grant Support:** |

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