4.10 Determining Diagnostic Yield of Genomic Testing from Pulmonary Fibrosis ascertained in Ireland

Jisha Jasmin [1 2], Wan Lin Ng [3 4], Anja Schweikert [4], Laura Durcan [3], Donough Howard [3], Gianpiero L. Cavalleri [1 2], Katherine A. Benson [1 2], Killian Hurley [2 3 4]

[1] Royal College of Surgeons in Ireland, Dublin, Ireland

[2] Science Foundation Ireland Centre for Research Training in Genomics Data Science, Ireland

[3] Beaumont Hospital, Dublin, Ireland

[4] Royal College of Surgeons in Ireland, Education and Research Centre, Beaumont Hospital, Dublin, Ireland

Background: Idiopathic pulmonary fibrosis (IPF) is a fatal, progressive, irreversible lung disease. When IPF occurs in more than one first-degree relative it is termed familial pulmonary fibrosis (FPF). Patients with connective tissue disease (CTD) can develop inflammation and scarring in their alveolar cells, which may progress to pulmonary fibrosis. We compared the diagnostic yield of genomic testing when applied to IPF, FPF and CTD and catalogued the genetic landscape of pulmonary fibrosis mutations in Ireland.

Methods: We recruited and consented 112 patients to the study via the Respiratory and Rheumatology clinics at Beaumont Hospital, Dublin. To date, we have analysed whole-exome sequencing (WES) data of 26 patients with IPF, 23 patients with FPF and 63 with CTD related ILD. WES was obtained from blood-derived DNA and processed using a GATK-V4.2 bioinformatics pipeline. A diagnostic assessment of the pathogenicity of each variant was conducted according to the American College of Medical Genetics and Genomics (ACMG) guidelines.

Results: We identified a pathogenic *RTEL1* variant [NM_001283009: c.2920C>T] in a family with FPF and a variant of unknown significance in *RTEL1* [NM_001283009:c.1189C>G:p.Q397E] in another family with FPF. No pathogenic/likely pathogenic variants were identified in the IPF and CTD datasets, although we did identify variants of unknown significance in *RTEL1*, *SFTPA1*, *NAF1* and *ZCCHC8*.

Conclusion: These results indicate a diagnostic yield for FPF of 5.26% in the Irish population, although the sample size analysed to date is small. A lack of pathogenic variants in the IPF or CTD groups is consistent with the literature.

Keywords: pulmonary fibrosis, pathogenic, variants.

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