

clear loss of function or de novo variants in other genes (Tier 3). The Respiratory GeCIP (Clinical Interpretation Partnership) was established to analyse full WGS/phenotypic datasets.

**Results** Six respiratory diseases were nominated and passed through 100K pipelines: primary ciliary dyskinesia (PCD), familial pulmonary fibrosis (FPF), aggressive non-CF bronchiectasis, pulmonary arteriovenous malformations (PAVMs), hereditary haemorrhagic telangiectasia (HHT) and familial pneumothorax. National and international networks were established for each, including a focus on patient/public engagement. Patient results were returned to UK GMCs from August 2017. Recruited participants with recessive and dominant diseases each had 0–2 Tier 1 variants, 0–2 Tier 2 variants and up to 536 Tier 3 variants. Genomic diagnoses have been fed back to 57 respiratory families for 15 different genes in PCD, FPF, non-CF bronchiectasis, and PAVMs/HHT, already modifying PanelApp, with validations in two potentially new ciliopathy genes in progress. Full WGS results have been released quarterly to the Research Data Embassy at steadily increasing numbers. HPO term capture identifies further patients; for example, there are data on 269 families recruited with bronchiectasis plus another 27 with relevant HPO terms. Respiratory GeCIP Data Embassy access and Projects were secured through 2018–2019. New analytic resources available through the Data Embassy (particularly LabKey and IVA 2.0) enable >90 Domain members to identify annotated variants through indexed systems. Custom scripts are being used to access variant information from the whole genome.

**Conclusions** The Respiratory GeCIP has established a collaborative resource for the advancement of NHS Respiratory Genomics.

## REFERENCES

1. <http://human-phenotype-ontology.github.io/>
2. <https://bioinfo.extge.co.uk/crowdsourcing/PanelApp>

S67

## EVIDENCE THAT TELOMERE LENGTH IS CAUSAL FOR IDIOPATHIC PULMONARY FIBROSIS BUT NOT CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A UK BIOBANK MENDELIAN RANDOMISATION STUDY

<sup>1</sup>A Duckworth, <sup>2</sup>MA Gibbons, <sup>1</sup>AR Wood, <sup>1</sup>K Lunnon, <sup>1</sup>MA Lindsay, <sup>1</sup>J Tyrrell, <sup>1</sup>CJ Scotton. <sup>1</sup>University of Exeter, Exeter, UK; <sup>2</sup>Royal Devon and Exeter NHS Foundation Trust, Exeter, UK

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**Introduction and objectives** Idiopathic Pulmonary Fibrosis (IPF) is a fatal lung disease that accounts for 1% of UK deaths. Causal genes have been found accounting for about 30% of familial cases of pulmonary fibrosis and the majority relate to telomere maintenance. However, no evidence of causality in the idiopathic form of the disease has yet been found.

Prematurely shortened leukocyte telomere length (LTL) has been associated with IPF and also Chronic Obstructive Pulmonary Disease (COPD), a disease with a similar demographic and symptomatology. Studies have shown age adjusted LTL values of  $0.85 \pm 0.60$  vs  $1.15 \pm 0.6$ ,  $p=0.0001$  for IPF<sup>1</sup> and  $0.68 \pm 0.25$  vs.  $0.88 \pm 0.52$  (smoking controls),  $p = 0.003$  for COPD.<sup>2</sup>

We sought to investigate causality in IPF using Mendelian randomisation (MR) with UK Biobank data. To our

knowledge, this is the first genetic study of this IPF cohort and the first application of MR to investigate causality in IPF. We hypothesised that prematurely shortened telomeres are causal in IPF but not in COPD.

**Methods** We performed one- and two-sample MR in the UK Biobank data. This study had 1,133 IPF cases (defined by ICD10 code J84.1), 11,413 COPD cases and 378,575 controls, all of European ancestry. Seven variants previously associated with telomere length were used in the MR analysis. Pleiotropy was explored using MR approaches including MR-Egger and Median MR.

**Results** A genetically instrumented one unit LTL shorter telomere length was associated with higher odds of IPF (OR 4.19 [95%CI: 2.33–7.55],  $P=0.0031$ ). Similar results were found in males and females separately. Despite being an age-related lung disease with similar symptoms, there was no evidence that telomere length caused COPD.

**Conclusions** Prematurely shortened telomeres have a likely causal effect in IPF. This enables a greater focus on telomere-related diagnostics, treatments and the search for a cure. Safe telomere activation therapy is being explored in the cardiology field, amongst others, using transient delivery of telomerase and there are also accessible therapies that show improved telomere length. Such approaches warrant investigation in IPF.

## REFERENCES

1. Dai, J., et al, *Respirology*, 2015.
2. Rode, L., et al, *Thorax*, 2013.

S68

## UNDERSTANDING THE PATHOLOGICAL ROLE OF A GENETIC ABNORMALITY IN DOCK3 IN FAMILIAL PULMONARY FIBROSIS

<sup>1</sup>R Kaur, <sup>1</sup>I Stewart, <sup>1</sup>RG Jenkins, <sup>1</sup>A John, <sup>2</sup>D Brown, <sup>3</sup>L Wain. <sup>1</sup>Respiratory Research Unit NIHR Biomedical Research Centre, University of Nottingham, Nottingham, UK; <sup>2</sup>Genomic England, London, UK; <sup>3</sup>Department of Health Sciences, University of Leicester and National Institute for Health Research, Leicester Respiratory Biomedical Research Centre, Glenfield Hospital, Leicester, UK

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Idiopathic Pulmonary Fibrosis (IPF) is an uncommon but serious progressive fibrotic lung disease characterised by deteriorating symptoms, respiratory failure and death, often within 5 years from diagnosis. Up to 10% of patients with IPF have a family history of this disease, known as Familial Pulmonary Fibrosis (FPF). Prior genetic studies have identified rare variants in genes relating to telomere and epithelial function and are responsible for about 20% of FPF cases. To identify the missing heritability we recruited FPF patients to the 100k Genome Project and analysed data from the Whole Genome Sequencing from 169 cases (140 probands and 29 family members) and 8127 controls. Our filtering strategy identified rare deleterious variation (tier 1 and tier 2) in over 20% of the patients. Novel variants in over 20 genes, not previously associated with pulmonary fibrosis, were found to be present at much greater frequency in FPF patients compared with controls, including two missense exonic DOCK3 variants.

DOCK3 is a member of the DOCK-B subfamily of guanine nucleotide exchange factors (GEFs) which function as activators of small G proteins. DOCK3 specifically activates the small G protein *Rac* and can promote reorganisation of the