S64 USE OF PATHOLOGICAL PHENOTYPE TO DETERMINE OPTIMAL MANAGEMENT FOR MODERATE TO SEVERE PRESCHOOL WHEEZE

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Introduction Persistent episodes of wheezing are common in preschool children, however we have few effective therapies. We hypothesised that objective biomarker based management of preschool wheeze would be superior to current clinical guidelines.

Methods A single-centre randomised, controlled trial in children aged 1–5 years with moderate to severe recurrent wheeze, requiring at least 2 admissions ± short courses of oral steroids in the last 12 months, with at least one in the last 6 months. Children were recruited from September-April over a 3 year period. Clinical (episodic viral wheeze [EVW], or multiple trigger wheeze [MTW][1]) and pathological phenotypes based on blood eosinophilia ≥3%, or bacterial infection in sputum or cough swab were determined at recruitment. Children were randomised to pathological phenotype based management (beclomethasone 400 mcg/day if blood eosinophils ≥3%, or targeted antibiotics if positive culture on sputum/cough swab) or clinician directed care (control arm) for 4 months. Primary outcome was number of unscheduled healthcare visits (UHCVs). Daily symptoms were reported via a text message system. Patients treated with inhaled corticosteroids (ICS) had adherence assessed using an electronic monitoring device.

Results 60 children were randomised, 30 in each group. Baseline blood eosinophils were similar in the two groups (5.18% control, 5.15% intervention). 6 children had positive sputum cultures. 38/60 had EVW and 22/60 had MTW. Prevalence of clinical phenotypes was similar in both groups (control-EVW 18/30, MTW 12/30; intervention- EVW 20/30, MTW 10/30). In both groups 20/30 (67%) were prescribed ICS, with median adherence 67% (range 0–91%). There was no significant difference in the rate of UHCVs or symptoms between the two groups (p=0.46).

Conclusions Phenotype based management of children with moderate to severe preschool wheeze did not result in a significant reduction in UHCVs compared to clinical guideline based management. However, 56% of children in the control group with EVW were prescribed ICS by their clinician even though this is not recommended in clinical guidelines and 80% of those with EVW in the pathological phenotype had blood eosinophilia, suggesting little relationship between clinical phenotype and objective biomarkers to guide ICS prescription.

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S65 CAPILLARY CARBON DIOXIDE AS A MEASURE OF DISEASE SEVERITY IN ACUTE BRONCHIOLITIS

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Carbon dioxide (CO_2) using capillary blood gas (CBG) analysis is commonly used children with acute bronchiolitis. Evidence to support its use is limited.

A retrospective observational study was conducted over two bronchiolitis seasons (2014 -2016) of infants admitted to a tertiary teaching hospital using patient electronic medical records. Using logistical regression models (STATA/IC 12.1) the association between CBG pCO_2 and markers of disease severity (length of stay (LOS) and high dependency admission (HDU)) was examined.

332 children were assessed with 526 CBG performed in 158 infants (mean age 0.31 years, 54% male, 27% premature, 77% RSV positive). The initial CBG pCO_2 was a mean 5.9kPa (SD1.1) and a maximum mean of 6.4kPa (SD1.5). Median LOS was 3 days (range 0–35). A CBG pCO_2 >7.0kPa during the admission (in 23% infants (36/158)) was significantly associated with younger age (OR 0.005 (95%CI 0.0007, 0.03); p<0.0001), the use of supplemental oxygen (OR 1.9 (95%CI 1.1, 3.3); p=0.033) (adjusted for age) and inspired fraction of oxygen (FiO_2) (slope coefficient 2.01 (95%CI 1.08, 2.94), p<0.0001) (adjusted for age). In 62% (98/158) a CBG was performed in ED and a pCO_2 >7kPa (N=26/98) in ED was significantly associated with LOS (IRR 1.4 (95%CI 1.1,1.8); p=0.008) and HDU admission (OR 3.5 (95%CI 1.7,7.8); p=0.001).

CBG pCO_2 >7 kPa identifies children in ED with more severe disease with longer length of stay and risk of admission to HDU. Our results suggest that CBG pCO_2 may be a possible marker of severity in future intervention trials for bronchiolitis.

ILD and rare respiratory diseases: cracking the code

S66 DELIVERING THE 100,000 GENOMES PROJECT TO ESTABLISH THE FUNCTIONAL ROLE OF DNA SEQUENCE VARIANTS IN RESPIRATORY RARE DISEASES

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Background and aims Between July 2016 and September 2018, NHS Genomic Medicine Centres (GMCs) recruited families with specified rare diseases to the 100,000 Genomes Project for whole genome sequencing (WGS), and linkage to phenotypic information from NHS Health Records.

Methods Genomics England protocols were followed for disease nominations, data model generation based on human phenotype ontology (HPO) terms,[1] and development/review of PanelApp gene panels.[2] Genomics England performed all WGS, data alignments, and initial variant tiering. This incorporated appropriate familial segregation patterns for variants in genes known to cause the patient's disease (Tier 1: clear loss of function variants, Tier[2]: other variants), and

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.

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S67 EVIDENCE THAT TELOMERE LENGTH IS CAUSAL FOR IDIOPATHIC PULMONARY FIBROSIS BUT NOT CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A UK BIOBANK MENDELIAN RANDOMISATION STUDY

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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 ± 0.60 vs 1.15 ± 0.6, p=0.0001 for IPF[1] and 0.68 ± 0.25 vs. 0.88 ± 0.52 (smoking controls), p = 0.003 for COPD.[2]

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.

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S68 UNDERSTANDING THE PATHOLOGICAL ROLE OF A GENETIC ABNORMALITY IN DOCK3 IN FAMILIAL PULMONARY FIBROSIS

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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