What's in a genotype? Unpicking genetic links in complex disease

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GENOME-WIDE SEX-BY-SNP INTERACTION ANALYSIS OF SUSCEPTIBILITY TO IDIOPATHIC PULMONARY FIBROSIS

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10.1136/thorax-2021-BTSabstracts.69

Idiopathic pulmonary fibrosis (IPF) is a complex and heterogeneous fibrotic lung disease with median survival of 3 years. The disease has a genetic component, with genome-wide association studies (GWAS) identifying 15 genetic loci that influence IPF risk. The rs35705950 SNP (single nucleotide polymorphism), in the promoter region of the *MUC5B* gene, is the largest common genetic risk factor of IPF (OR=4.84 [95%CI: 4.37, 5.36], minor allele (T) frequency in cases=29.1%). IPF is more prevalent in males than females but the reasons behind this are not understood. We hypothesised that the genetic determinants of IPF might help to identify biological mechanisms that drive differences in IPF susceptibility and presentation between males and females. To address this, we performed a genome-wide sex-by-SNP interaction analysis of IPF susceptibility.

A genome-wide sex-by-SNP interaction meta-analysis was performed that included four independent IPF case-control data sets comprising a discovery of 3,432 cases (2,421 males & 1,011 females) and 18,559 controls (12,096 males & 6,463 females) of European descent. We sought replication in an independent dataset comprising 664 cases (488 males &

176 females) and 1,874 controls (507 males & 1,367 females).

We defined suggestive statistical significance as independent variants with $P < 5 \times 10^{-5}$, and consistent direction of effect with $P < 0.05$ in at least 3 of the 4 studies. Eight independent variants meeting these criteria were identified in the meta-analysis. Five variants had $P < 0.05$ for IPF risk in both males and females when analysed separately; all five were observed to have an opposite direction of effect on males compared to females. None of the eight significant variants were associated ($P < 0.05$) with IPF susceptibility when males and females were combined, and none reached our replication significance threshold in the independent dataset.

Our findings suggest that there may be differences in genetic determinants of IPF risk between males and females, but larger studies are needed to confirm the reported variants. Understanding the mechanisms behind these could provide further insight into different biological pathways that underlie pulmonary fibrosis.

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APPLICATION OF OPEN VIRTUAL PHEWAS TOOLS FOR EXPLORATORY ANALYSES OF RISK ALLELES IN IDIOPATHIC PULMONARY FIBROSIS

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10.1136/thorax-2021-BTSabstracts.70

Introduction and Objectives Publicly available databases are becoming increasingly valuable resources for exploratory analyses of multi-omics data. This virtual PheWAS method demonstrates the application of open databases of GWAS summary data in identifying genetic disease-associated phenotypes, which can support further investigation into disease pathways and novel treatment targets.

We aimed to assess the application of open virtual PheWAS tools to identify significant phenotypic associations with established genomic risk loci in idiopathic pulmonary fibrosis (IPF).

Abstract S64 Table 1 Grouped phenotypic associations with IPF risk loci

Gene/locus - SNP	GWAS p-value	Phenotypic associations ($p < 5 \times 10^{-8}$)				
		Blood cell traits	Lung function	Cancer	IPF	General health and physical measurements
<i>KIF15</i> - rs78238620	4.05x10 ⁻¹⁴	No	No	No	No	No
<i>MAD1L1</i> - rs12699415	9.38x10 ⁻²⁰	No	No	No	No	Yes**
<i>DEPTOR</i> - rs28513081	1.93x10 ⁻¹¹	No	No	No	No	Yes**
<i>RTEL1</i> - rs41308092	2.24x10 ⁻¹⁰	No	No	No	No	No
<i>HECTD2</i> - rs537322302	3.43x10 ⁻⁸	No	No	No	No	No
<i>TERC</i> - rs12696304	7.09x10 ⁻¹³	Yes**	No	No	Yes	Yes*
<i>FAM13A</i> - rs2013701	3.30x10 ⁻¹³	Yes*	Yes**	No	No	No
<i>TERT</i> - rs7725218	1.54x10 ⁻²⁰	Yes**	No	Yes**	No	Yes*
<i>DSP</i> - rs2076295	2.79x10 ⁻³⁰	No	Yes*	No	Yes	No
<i>MUC5B</i> - rs35705950	1.18x10 ⁻²⁰³	No	No	No	Yes	No
<i>ATP11A</i> - rs9577395	1.34x10 ⁻¹⁰	Yes**	No	No	No	No
<i>IVD</i> - rs59424629	7.30x10 ⁻¹⁶	Yes*	Yes*	No	No	Yes*
<i>AKAP13</i> - rs62023891	1.27x10 ⁻¹⁰	Yes*	No	No	No	Yes*
<i>MAPT</i> - rs2077551	2.83x10 ⁻¹⁶	Yes**	Yes**	Yes	No	Yes**
<i>DPP9</i> - rs12610495	2.92x10 ⁻¹²	No	No	No	Yes	No
7q22.1 - rs2897075	3.10x10 ⁻¹⁴	Yes*	Yes*	No	No	Yes*

Key	
Phenoscaner
IEU OpenGWAS
Replicated in both databases

Table 1: Grouped phenotypic associations with IPF risk loci.