Methods A total of 16 GWAS-established single nucleotide polymorphisms (SNPs) associated with IPF that meet genome-wide significance (p<5×10⁻⁸) in published studies were identified for evaluation. The Phenoscaner and IEU Open GWAS databases were queried via the phenoscaner and ieneucvarez packages, respectively, in R (R Version 4.0.5). To maximise data retrieval, no p-value threshold filter was applied in initial SNP-trait association data collection. Subsequent statistical analysis and data plotting was performed in R to characterise significant phenotypic associations (p<5×10⁻⁸).

Results Statistically significant (p<5×10⁻⁸) phenotype associations were identified for 13/16 IPF risk loci (table 1). Associated phenotypes included lung function measures (FEV1/FVC, FVC), overall health, blood cell traits (eosinophil percentage of granulocytes, red blood cell (erythrocyte) count, neutrophil count) and multiple types of cancer (ovarian, prostate, breast, and lung). SNP-trait associations with blood cell traits and cancers observed for three SNPs (TERT prostate, breast, and lung). SNP-trait associations with blood neutrophil count) and multiple types of cancer (ovarian, FVC, FVC), overall health, blood cell traits (eosinophil percentage of granulocytes, red blood cell (erythrocyte) count, neutrophil count) and multiple types of cancer (ovarian, prostate, breast, and lung). SNP-trait associations with blood cell traits and cancers observed for three SNPs (TERT prostate, breast, and lung). SNP-trait associations with blood neutrophil count and multiple types of cancer (ovarian, prostate, breast, and lung). SNP-trait associations with blood cell traits and cancers observed for three SNPs (TERT prostate, breast, and lung). SNP-trait associations with blood neutrophil count and multiple types of cancer (ovarian, prostate, breast, and lung). SNP-trait associations with blood cell traits and cancers observed for three SNPs (TERT prostate, breast, and lung).

Conclusions Virtual PheWAS identified phenotypes associated with IPF risk loci that include blood cell traits and multiple cancers. Combining PheWAS results across multiple datasets is necessary to detect established phenotypes, demonstrating the importance of complementary sources in detecting novel pleiotropy. Open virtual analysis tools offer an efficient exploratory approach which can identify SNP-phenotype associations that warrant focused investigation through large scale PheWAS with disease-agnostic data.

REFERENCE

GENOME-WIDE ASSOCIATION STUDY OF SURVIVAL TIMES AFTER DIAGNOSIS OF IDIOPATHIC PULMONARY FIBROSIS

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Introduction Idiopathic pulmonary fibrosis (IPF) is a devastating lung disease where the lungs become progressively scarred. The median survival time after diagnosis is three years, albeit disease progression varies greatly between individuals. Recently, large genome-wide association studies (GWAS) have shown there are a number of DNA regions associated with disease risk, however these variants are generally not associated with disease progression.

Aim To identify genetic variants associated with disease progression.

Methods We performed a two-stage GWAS of transplant-free survival times after diagnosis of IPF. In stage 1, genome-wide analyses were performed in three separate studies using a Cox proportional hazards models adjusting for age, sex, study centre and genetic principal components and the results were meta-analysed across the studies. In stage 2, variants with p<5×10⁻⁵ in the stage 1 meta-analysis and p<0.05 in each separate study with consistent direction of effects were tested for their association with IPF survival in independent samples. Variants were deemed associated with IPF survival if they were genome-wide significant in a meta-analysis of stages 1 and 2 (p<5×10⁻⁸). Immunohistochemistry and transcriptomics were performed to follow-up genes implicated by the genome-wide analysis.

Results A total of 1,481 IPF cases and 9 million genetic variants were included in the stage 1 analysis, and 397 individuals in stage 2. One variant, rs35647788 in an intron of PCSK6, was genome-wide significant in the stage 1 and 2 meta-analysis, and showed nominal significance (p<0.05) in each study with consistent direction of effects across all studies. Gene-prioritisation analyses identified PCSK6, of which rs35647788 lies in an intron of, as the most likely gene of interest. Immunohistochemistry showed that PCSK6 was highly expressed in lung tissue samples from IPF cases compared to controls, specifically in the lung epithelium. In IPF cases, higher levels of circulating PCSK6 were associated with poorer survival times and increased PCSK6 gene expression was associated with a greater annual decline in lung capacity. There was little overlap between the genetic determinants of disease risk and survival times.

Conclusions This is the first GWAS of IPF survival which has identified novel important biological processes involved in the progression of IPF.

IRON DEFICIENCY: COMPLICATIONS, COMPENSATIONS AND TREATMENTS BY HEREDITARY HAEMORRHAGIC TELANGECTASIA MOLECULAR GENOTYPE

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Introduction and objectives Patients with pulmonary arteriovenous malformations (PAVMs) require normal iron levels in order to compensate appropriately for hypoxaemia. Low serum iron has also been shown to be associated with ischaemic stroke and venous thromboembolism risk in the population. Those with hereditary haemorrhagic telangiectasia (HHT) are at risk of developing iron deficiency if the iron lost during nosebleeds and/or gastrointestinal haemorrhage is not adequately replaced. The aims of this study were to examine associations between the HHT molecular genotype and iron deficiency indices.

Methods A database containing repeated measurements from 426 genotyped HHT and PAVM patients was retrospectively analysed to compare iron deficiency rates, complications,