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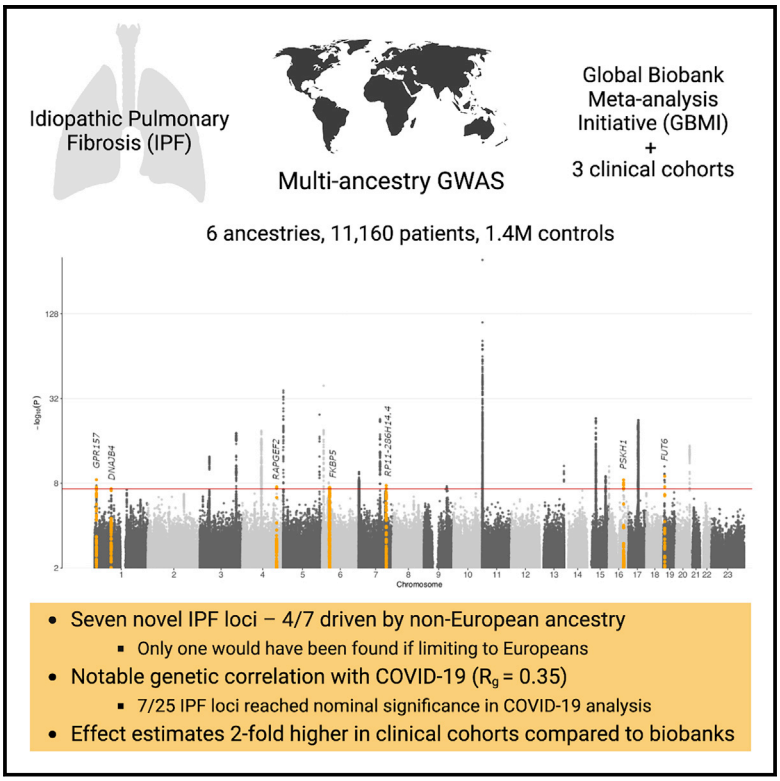
Leveraging global multi-ancestry meta-analysis in the study of idiopathic pulmonary fibrosis genetics

Graphical abstract



Highlights

- IPF meta-analysis across 6 ancestries with 11,160 cases and 1.4 M controls
- Seven novel IPF loci—only one found if restricted to individuals of European ancestry
- Genetic overlap with severe COVID-19: $R_g \sim 0.35$, p = 0.001
- Two-fold higher effect size estimates in clinical cohorts compared with biobanks

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In brief

Partanen et al. present a multi-ancestry IPF meta-analysis with 11,160 cases and 1.4 M controls. They identify seven novel genome-wide significant loci, only one of which would have been identified if the analysis had been limited to Europeans. They also report notable pleiotropy across IPF susceptibility and severe COVID-19 infection.

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Leveraging global multi-ancestry meta-analysis in the study of idiopathic pulmonary fibrosis genetics

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SUMMARY

The research of rare and devastating orphan diseases, such as idiopathic pulmonary fibrosis (IPF) has been limited by the rarity of the disease itself. The prognosis is poor—the prevalence of IPF is only approximately four times the incidence, limiting the recruitment of patients to trials and studies of the underlying biology. Global biobanking efforts can dramatically alter the future of IPF research. We describe a large-scale meta-analysis of IPF, with 8,492 patients and 1,355,819 population controls from 13 biobanks around the globe. Finally, we combine this meta-analysis with the largest available meta-analysis of IPF, reaching 11,160 patients and 1,364,410 population controls. We identify seven novel genome-wide significant loci, only one of which would have been identified if the analysis had been limited to European ancestry individuals. We observe notable pleiotropy across IPF susceptibility and severe COVID-19 infection and note an unexplained sex-heterogeneity effect at the strongest IPF locus *MUC5B*.

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrotic disease of the lungs. It has no known etiology and pathogenesis, poor prognosis, and limited treatment options. The prevailing model of IPF pathogenesis suggests recurrent epithelial injury followed by aberrant repair and dysregulated interstitial matrix deposition with cell senescence playing an important role in promoting lung fibrosis.[1]

As IPF has, by definition, no identifiable cause, genome-wide approaches are especially attractive as they may provide insight into underlying causes, pathogenesis, and might potentially reveal novel therapeutic avenues. Genome-wide association studies (GWAS) of IPF have thus far reported at least 23 associated loci[2–11] highlighting genes involved in telomere maintenance,[12] cell adhesion, airway clearance, and innate immunity. These studies have mainly been restricted to common variants in individuals of European descent, and have identified few associations to functional variants. The most recent and largest meta-analysis concluded that IPF is highly polygenic with a significant number of associated variants remaining to be identified.[2] In addition, considerable genetic overlap between IPF and severe coronavirus disease 2019 (COVID-19) has been reported.[13–16]

To further explore the genetics of IPF susceptibility, we performed the first multi-ancestry study on the genetics of IPF in six populations, altogether comprising a 4-fold increase in the number of patients compared with the largest IPF study to date, via meta-analysis of the Global Biobank Meta-Analysis Initiative (GBMI) with the most recent published IPF study.[2] This allowed assessment of heterogeneity of effects over different ancestries, sex, and IPF diagnosis ascertainment between biobank and clinical cohort studies. With the increase in power, we were able to study population specific and rare variant effects. A notable fraction of the proposed loci have previously been associated with lung function. Fine-mapping in the Finnish population, making use of reduced allelic heterogeneity of a population isolate, identified a putative functional causal variant in the previously reported *KIF15* locus. We also describe significant pleiotropy between IPF and COVID-19, beyond what is known to date. Finally, we suggest possible sex-based heterogeneity at *MUC5B*, the strongest genetic risk factor for IPF.

RESULTS

Multi-ancestry meta-analysis reveals seven novel IPF loci

The GBMI IPF meta-analysis consisted of 8,492 cases and 1,355,819 controls representing 6 ancestries (Table 1). Out of 66.6 M variants included in analysis, 21.0 M were not present in the non-Finnish European (NFE) ancestry studies. While IPF prevalence and recruitment strategies varied greatly across contributing biobanks, the overall prevalence was 0.62% (Table S1). The GBMI IPF meta-analysis discovered 16 genome-wide significant loci, highlighting 2 potentially novel loci (Figure 1).

We then meta-analyzed the GBMI data with the largest IPF meta-analysis[2] to date, later referred to as the Allen et al. study, including 10.8 M variants and increasing the number of cases and controls to 11,160 and 1,364,410, respectively. Altogether the joint meta-analysis identified 25 independent IPF-associated loci (Figure 1; Data S1; Table S2). We report genome-wide significant results at 14/23 previously reported loci, with a further 7/23 showing consistent direction of effects at varying levels of significance (Table S3). The linkage disequilibrium (LD) score regression intercept[17] for the joint meta-analysis was not inflated (1.011) indicating independence of included studies. Quantile-quantile plots for meta-analyses are available in Figure S1.

Table 1. Ancestries in the GBMI IPF meta-analysis

Ancestry	Biobanks	N IPF patients	N controls	Frac cases (%)
NFE	BioVU, CCPM, ESTBB, HUNT, MGB, MGI, UCLA, UKBB	5,229	750,630	0.69
FIN	FinnGen	1,514	306,063	0.49
EAS	BBJ, CKB, UCLA	1,210	254,409	0.47
AMR	BioMe, UCLA	319	14,452	2.16
AFR	BioMe, UCLA	169	8,368	1.98
SAS	GNH	51	21,897	0.23
6*	13*	8,492*	1,355,819*	0.62*

AFR, African/African American; AMR, Latino/admixed American; EAS, East Asian; FIN, Finnish; NFE, non-Finnish European; SAS, South Asian. Biobanks: BioME, BioVU, Colorado Center for Personalized Medicine Biobank (CCPM), Michigan Genome Initiative (MGI), UCLA Precision Health Biobank (UCLA), and Mass General Brigham (MGB) in America, BioBank Japan (BBJ) and China Kadoorie Biobank (CKB) in East Asia, and Genes & Health (GNH), Estonian Biobank (ESTBB), FinnGen project, Trøndelag Health Study (HUNT), and UK Biobank (UKBB) in Europe. Frac cases, fraction of cases in total sample. *Refers to values for GBMI as a whole.

Beyond confirming nearly all of the previous signals, we identified seven potentially novel loci (Table 2; Figure 1). One locus was driven by rs539683219 at 16q22.1, an intronic *PSKH1* variant only found in the East Asian (EAS) population. Highlighting the importance of multi-ancestry analysis, four out of the seven novel loci were mostly driven by non-European ancestry, when assessed by highest minor allele frequency at population level within the meta-analysis. Minor allele frequency enrichment within the meta-analysis compared with NFEs was over 1.5-fold for these four index variants. Moreover, if only the European populations (including NFE and Finnish) were analyzed, only one of the seven loci reached genome-wide significance (Table S4).

Further replication of the novel loci was attempted in two individual European ancestry cohorts (case count 792 and 664), where six loci were polymorphic and imputed at high quality (minimum imputation $R^2 = 0.98$). Three of the six potentially novel findings replicated (at p value < 0.01 and with consistent direction of effects, Table S5).

Multiple novel variants associated with lung function and different organ manifestations

The Open Targets[18] resource was used to assess previous findings for the proposed novel loci (Table S6).

Three of the seven novel loci have previously been implicated with lung function parameters forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC). First, at 6p21.31, the

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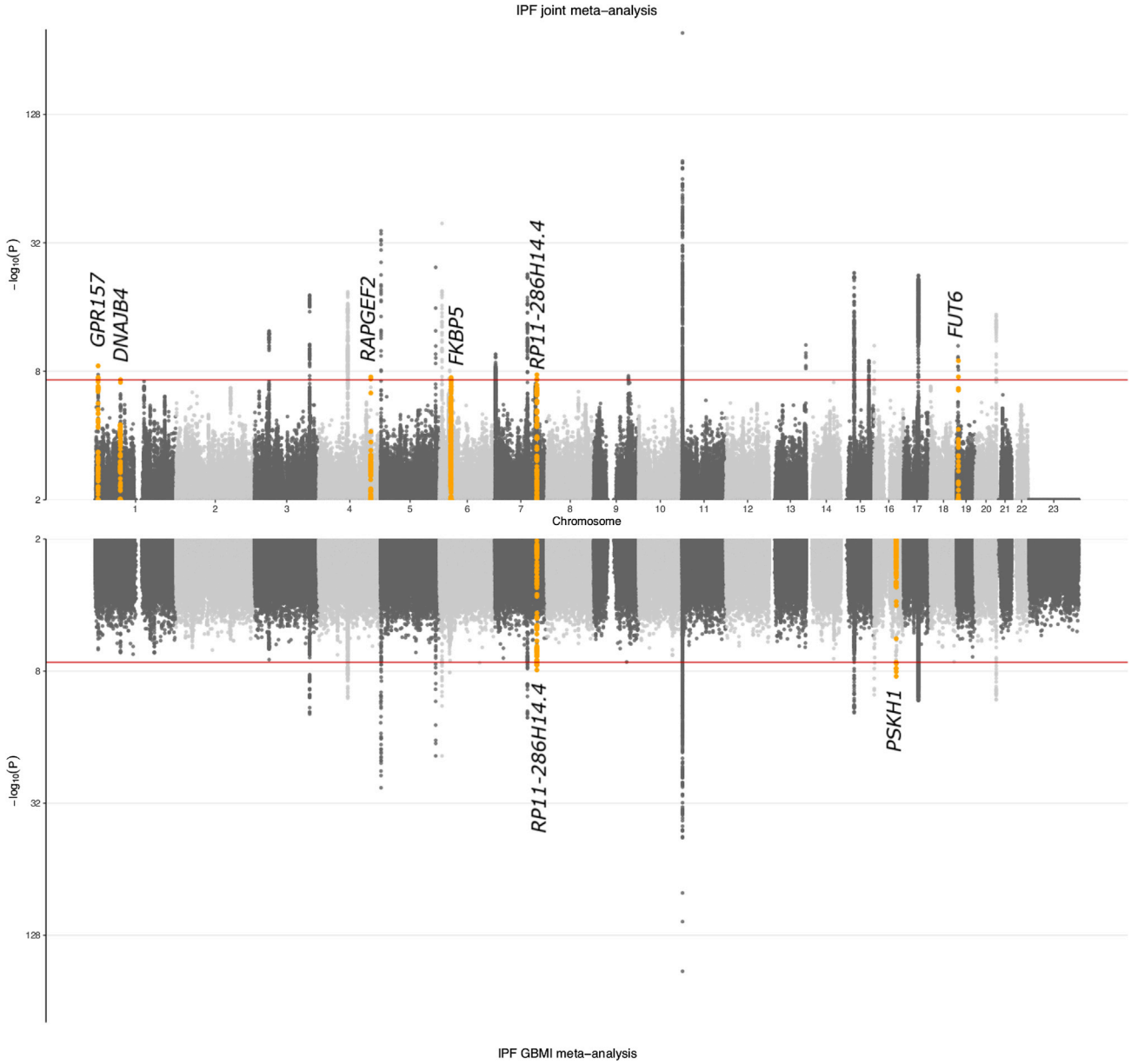

Figure 1. Genome-wide association results for IPF

Results from the joint meta-analysis are plotted in the top panel of the Miami plot and results from the GBMI meta-analysis in the bottom panel. Novel associations are highlighted in orange and annotated with the closest gene (index variant and variants in LD at $r^2 > 0.05$ are highlighted, except for the *PSKH1* signal for which variants within a 1 Mb window are highlighted due to missing LD information). Variants with p values ≤ 0.01 are plotted.

index variant rs9380529 in *FKBP5* was in the 95% credible set of a FVC signal.[19] The index variant for FVC (rs28435135, LD, $r^2 = 0.28$) had a negative beta coefficient, i.e., decreasing vital capacity, consistent with higher risk of IPF suggested in the present study. In addition, rs9380529 was in LD ($r^2 = 0.64$) with the lead variant (and included in the 95% credible set) for trunk and leg fat percentages in the UKB Neale v.2 analysis (http://www.nealelab.is/uk-biobank/). *FKBP5* encodes a FK506-binding protein that has been shown to modulate the mTOR signaling pathway[20] central in lung fibrinogenesis.[21]

Second, *GPR157* at 1p36.22 has been associated with FEV1/FVC ratio,[22] as the index variant rs7549256 from the current analysis was in LD ($r^2 = 0.55$) with the reported index variant (no data on credible set or effect available). rs7549256 was also in LD ($r^2 = 0.64$) with the index variant for insulin-like growth factor 1 levels.[23]

Third, no previous associations were found for the intergenic rs76537958 at 4q32.1, whereas variants in *RAPGEF2* (LD with rs76537958: $r^2 < 0.1$) have been associated with FVC in the UKB Neale v.2 analysis, as well as childhood and lifetime

Table 2. Novel associations from the GBMI and joint IPF meta-analyses

Variant	Rsid	Index variant gene	Most severe consequence	AF alt (%)	Max MAF pop	MAF enrichment vs NFE	OR [95% CI]	p value
1_9107187_C_A	rs7549256	*GPR157*	intron	64.16	EAS	1.5	0.91 [0.88–0.94]	3.29E−09
1_77998184_T_C	rs4130548	*DNAJB4*, *GIPC2*	intron	33.30	NFE	1	1.09 [1.06–1.13]	4.91E−08
4_159892716_A_T	rs76537958	*RAPGEF2*	intergenic	2.92	AFR	2.5	1.29 [1.18–1.42]	2.94E−08
6_35707919_A_G	rs9380529	*FKBP5*	intron	51.72	NFE	1	1.08 [1.05–1.12]	3.33E−08
7_129095384_G_A	rs34288126	*RP11-286H14.4*	noncoding transcript exon	12.70	FIN	1.1	1.13 [1.09–1.19]	1.50E−08
16_67895674_TG_T	rs539683219	*PSKH1*	intron	1.71	EAS	Inf	3.20 [2.17–4.70]	3.52E−09
19_5840608_C_T	rs708686	*FUT6*	upstream gene	31.47	AMR	1.6	1.11 [1.07–1.14]	1.08E−09

Sample size weighted mean imputation info score ≥0.80 for all variants, index variant gene and most severe consequence information from variant effect predictor (VEP), variant = chrom_pos_ref_alt (GRCh38); AF alt = within the meta-analysis sample size weighted GRCh38 alternate allele frequency; max MAF population = population with highest minor allele frequency (MAF), MAF enrichment is calculated as highest MAF divided by MAF in NFE. Effects are given for the alt allele. AFR, African/African American; AMR, Latino/admixed American; EAS, East Asian; FIN, Finnish; NFE, non-Finnish European; SAS, South Asian. Inf, polymorphic in only one population. p value threshold for genome-wide significance pval < 5E−8.

pneumonia.[24] In addition, *RAPGEF2* has been reported as a shared risk factor for both IPF and chronic obstructive pulmonary disease (COPD) in a network analysis.[25]

Regarding the four additional loci, rs4130548 at 1p31.1, has been implicated especially in body mass index, and was the index variant of the association signal.[26] At 19p13.3, rs708686 upstream of *FUT6* has been previously associated with carbohydrate antigen 19.9,[27] blood protein levels (FUT3),[28] and gallstones,[28,29] among others. *FUT6* affects fucosylation of mucins, including MUC5B, which may affect mucociliary clearance via changes in mucus viscoelasticity and pathogen binding.[30] No previously reported associations were found for the non-coding transcript exon variant rs34288126 at 7q32.1, or the EAS-specific intronic rs539683219 in *PSKH1* at 16q22.1. However, rs116906005, which is 190 kB downstream of the index variant in the *PSKH1* locus (LD with rs539683219: r^2 = 0.67 in EAS), has been previously associated with interstitial lung disease (ILD) in BioBank Japan.[31]

In contrast to other pulmonary diseases attributed to tobacco smoke exposure, such as COPD and lung cancer, no genome-wide significant association signal was seen in the *CHRNA3/5* locus (OR[95% CI] = 1.05[1.02–1.08], p = 0.0034 for rs16969968), a known nicotine dependence locus.[32]

Expression levels and profiles across tissues and cell types for the genes at the novel loci, obtained from GTEx[33,34] and IPF RNA sequencing studies,[35–37] are displayed[38] in Table S6, Figure S2, and Data S2. In summary, genes at five of the seven loci were expressed in the lung tissue (median TPM > 1, Table S6). Furthermore, genes at two loci (*GIPC2* and *FKBP5*) have been reported to be differentially expressed in IPF lung compared with controls[36] and, in addition to these, two more (*GPR157* and *RAPGEF2*) in end-stage IPF[37] (Table S6). Expression of the genes at the novel loci varied in level and tissue or cell-type specificity (Figure S2; Data S2). Of the genes differentially expressed in IPF, *FKBP5*, the gene with the highest expression level in lung, was expressed across different lung tissue cell types with highest expression levels among immune cells and fibroblasts, whereas *GIPC2* was almost exclusively expressed in ciliated and endothelial/lymphatic cells.

Fine-mapping in the Finnish population suggests missense variant in *KIF15* to be causal

To identify potential causal alleles within the identified loci, we performed fine-mapping of all identified loci in FinnGen, resulting in eight independent loci with suggested causal alleles (Table 3). None of the novel loci were successfully fine-mapped (i.e., had good quality credible sets with minimum LD between variants $r^2 \geq 0.25$).

Fine-mapping suggested deleterious coding causal variants at three loci. In addition to the previously reported coding variants in *TERT* and *SPDL1*,[4,6] fine-mapping identified a coding variant in *KIF15* (predicted missense, rs138043992, AF = 0.29%, OR[95% CI] = 1.71[1.39–2.10], posterior inclusion probability (PIP) = 0.24, ENSP00000324020.4:p.Arg501Leu), enriched 2.6-fold in the Finnish population compared with non-Finnish non-Estonian Europeans (NFEEs) (gnomAD v2.1.1), and predicted as probably damaging by Polyphen and deleterious by SIFT.[39,40]

When a known locus near *KANSL1/MAPT* was assessed, the signal was fine-mapped to *CRHR1* (intronic rs1568002709, AF = 11.7%, OR[95% CI] = 0.62[0.53–0.73], PIP = 0.003). There was, however, little resolution in the locus due to its exceptional LD structure[41] (Data S1).

Fine-mapping further suggested two independent signals at 11p15.5; the well-established *MUC5B* and an independent signal downstream of *MOB2*. Causality of the *MOB2* downstream variant (rs546531844, AF = 0.29%, 17 times enriched in Finns compared with NFEEs gnomAD v.2.1.1) was corroborated by two different fine-mapping methods. The "Sum of Single Effects" (SuSie) model[42] suggested two 95% credible sets at the 11p15.5 locus. One of the credible sets included the *MUC5B* upstream gene variant rs35705950 (PIP = 1) and the other included two variants: a *MOB2* downstream gene variant rs546531844 (PIP = 0.92) and a *MUC6* missense variant rs148815783 (PIP = 0.072). Another fine-mapping method, FINEMAP,[43,44] suggested four 95% credible sets (p = 0.55) at the locus. Three of the four credible sets consisted of one variant. Both the *MUC5B* upstream gene variant rs35705950 and the *MOB2* downstream gene variant rs546531844

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Table 3. Fine-mapped good quality (minimum LD between variants $r^2 \geq 0.25$) credible sets in FinnGen

Locus	N variants in credible set	Credible set min LD (r^2)	Highest PIP variant	rsid	Gene for most severe consequence	Most severe consequence	PIP
3q26.2	35	0.91	3_169759718_A_G	rs12638862	*ACTRT3*	downstream gene	0.080
3p21.31	22	0.48	3_44801967_G_T	rs138043992	*KIF15*	missense	0.243
5p15.33	1	1.00	5_1272247_G_A	rs770066110	*TERT*	stop gained	1.000
5p15.33	1	1.00	5_1279370_T_C	rs776981958	*TERT*	missense	0.997
5q35.1	2	0.82	5_169588475_G_A	rs116483731	*SPDL1*	missense	0.875
11p15.5	1	1.00	11_1219991_G_T	rs35705950	*MUC5B*	upstream gene	1.000
11p15.5	2	0.34	11_1468491_G_A	rs546531844	*MOB2*	downstream gene	0.919
16p13.3	5	0.78	16_276685_G_A	rs184954013	*ARHGDIG*	intron	0.618
17q21.31	2,180	0.95	17_45753401_45753524del	rs1568002709	*CRHR1*	intron	0.003
20q13.33	17	0.51	20_63582806_G_A	rs73315845	*GMEB2*	downstream gene	0.077

Highest PIP variant = chrom_pos_ref_alt (GRCh38); PIP, posterior inclusion probability.

constructed their own one-variant credible sets (PIP = 1 and PIP = 0.96, respectively).

After conditioning the REGENIE GWAS on the *MUC5B* variant rs35705950 the *MOB2* downstream gene variant rs546531844 association was no longer genome-wide significant and the effect size estimate was notably decreased (original beta = 1.35, original p = 1.33E–37, conditioned beta = 0.53, conditioned p = 1.41E−7). Imputation accuracy of the *MOB2* variant was not optimal (INFO = 0.85) and LD between the *MOB2* downstream variant and the *MUC5B* lead variant was low but not inexistent (r^2 = 0.072, D' = 0.766). Thus, the signal at *MOB2* remains to be confirmed.

Pleiotropy of effects across COVID-19 severity

As considerable genetic overlap between IPF and severe COVID-19 caused by SARS-CoV-2 infection has been reported,[13–16,45] we assessed the shared genetic background of IPF and severe COVID-19 using the largest sample sizes available for both traits: the joint IPF meta-analysis reported here and the most recent COVID-19 Host Genetics Initiative results (data release 6[46]). We discovered that, in addition to the four loci (*MUC5B*, *DPP9*, *KANSL1/CRHR1*, and *ZKSCAN1*)[13–16] previously associated with both IPF and COVID-19 hospitalization at a genome-wide level, three other genome-wide significant loci in the IPF meta-analysis passed the FDR-adjusted p value threshold of 0.05 in the COVID-19 scan (total 7/25, 28%; Figure 2; Table 4). As previously reported, the effect of *MUC5B* was reversed: the strong, established risk allele in IPF is clearly protective for severe COVID-19 (OR = 0.89, p = 1.2E−8). The *ATP11A* locus also demonstrated opposite effects for the two traits, while for the rest of the loci the direction of effects was shared. While genome-wide associations for both IPF and COVID-19 hospitalization have been reported separately in the 17q21.31 locus, we noted a shared signal at the locus with very high LD between the index variants (r^2 = 0.97).

Secondly, 6 of the 17 loci from the COVID-19 hospitalization scan passed the FDR-adjusted p value threshold of 0.05 in the IPF meta-analysis (35%, Table S7), suggesting further shared etiology at *CCHCR1*, *SLC22A31*, and *TAC4*.

Formal colocalization analysis was not possible as COVID-19 results have not been fine-mapped. Genetic correlation between the traits, determined by LDSC,[47] restricting to European samples for COVID-19 hospitalization and NFE samples for IPF, was 0.35 (95% CI 0.14–0.56, p = 0.001), somewhat higher compared with a previous estimate[14] and with less uncertainty.

Pleiotropy of the IPF signals beyond COVID-19 hospitalization was explored by colocalization analysis in FinnGen, pointing to shared signals between IPF and osteoporosis, cancers, and hypothyroidism (Table S8). At 16p13.3 an intronic *ARHGDIG* variant (rs184954013, AF in Finns = 2.5%, AF in NFE = 0.29%) colocalized with the osteoporotic fracture signal (causal posterior agreement [CLPA] = 0.74) and also with any form of osteoporosis (CLPA = 0.58). As we have reported prior to this study,[4] multiple malignancy-related colocalization signals were also detected (Table S8).

Sex-stratified analysis in biobanks suggests heterogenic effects at strongest IPF signal

Sex-stratified meta-analysis in the GBMI across six biobanks with results for both sexes identified a 1.6-fold larger effect for the strongest IPF-associated variant rs35705950 in the *MUC5B* locus in males (OR[95% CI] = 3.22[2.92–3.55], p = 1.0E−121) compared with females (OR[95% CI] = 2.04[1.82–2.29], p = 2.9E−34), Cochran's Q p value for heterogeneity = 3.4E−9. To investigate whether the difference in effects was due to confounding by case ascertainment differences across contributing biobanks, we assessed the effect of rs35705950 in each contributing biobank in males and females, noting a weaker effect in females across biobanks (Figure S3; Table S9). The result was, however, not replicated in four clinical cohorts in sex-stratified analysis or sex interaction analysis ($OR[95\% CI]_{males}$ = 4.81[4.37–5.30], $OR[95\% CI]_{females}$ = 4.75[4.13–5.45] [Tables S10 and S11], and results in subsets of the FinnGen study [Table S12]). The lifetime incidence of IPF in the longitudinal FinnGen register follow-up stratified by sex and carrying a *MUC5B* risk allele is illustrated in Figure S4. *MUC5B* carrier status did not have an effect on the number of IPF deaths or lung transplants among IPF cases in FinnGen (Table S13).

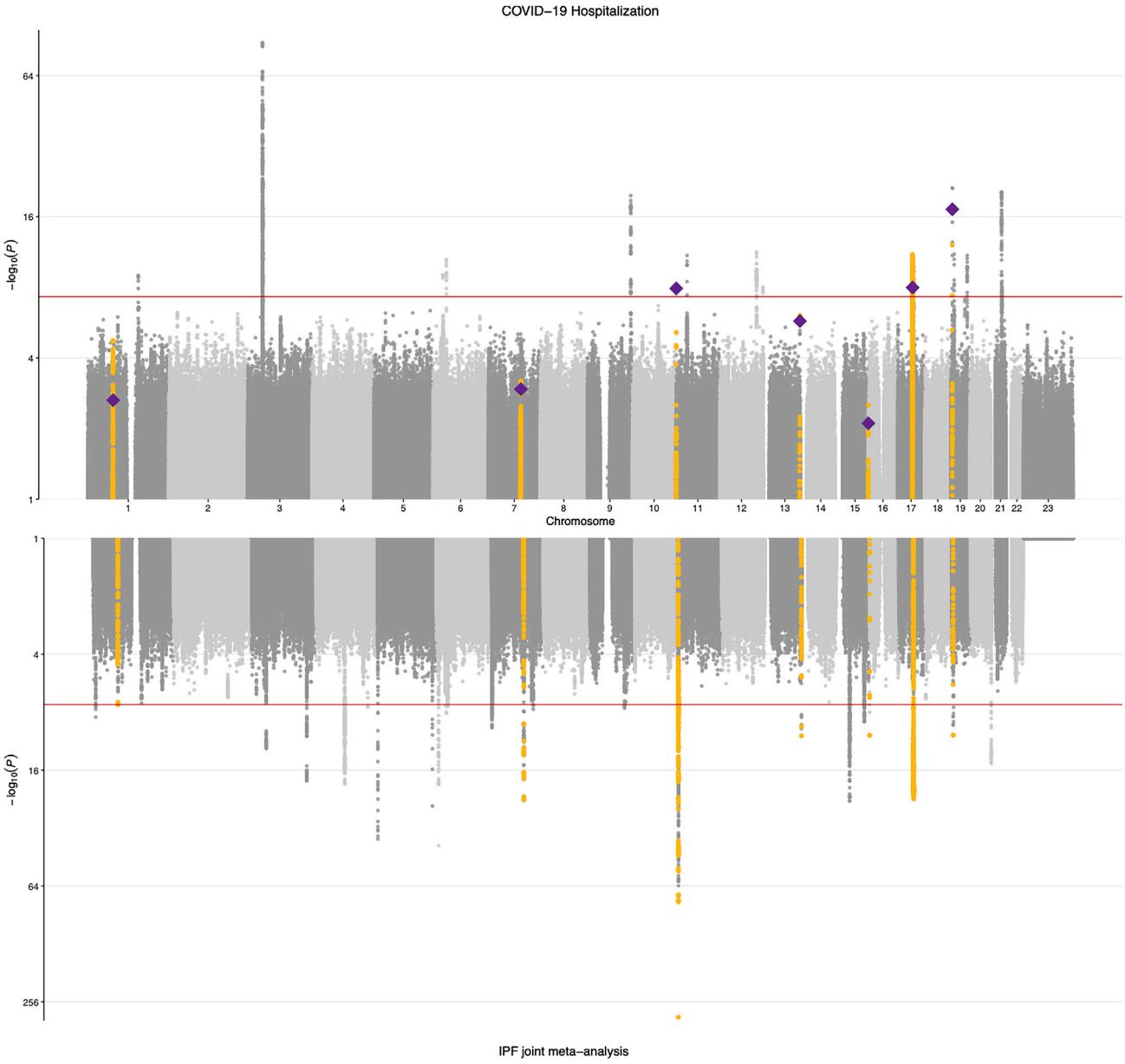

Figure 2. IPF meta-analysis and COVID-19 hospitalization results

COVID-19 hospitalization results are shown in the top panel and IPF joint meta-analysis results in the bottom panel. Genome-wide significant IPF signals that reached FDR-adjusted p value < 0.05 in COVID-19 hospitalization scan are highlighted in yellow. Index variants in the IPF scan are plotted as diamonds in the COVID-19 results. Variants with p values $\leq$ 0.1 are plotted.

The male-only meta-analysis identified two additional loci: 19q13.32 with index variant rs71338787 in *EML2* and Xq28 with index variant rs5945238 in *MPP1* (Table S14).

Heterogeneity assessment points to large effect of sample ascertainment

We observed heterogeneous effects across biobanks and ancestry at nearly half of the IPF genome-wide significant loci (11/25, 44%, FDR-adjusted Cochran's Q p value < 0.05, mean heterogeneity index I^2 = 0.62; Data S3; Table S2). Therefore, we explored whether there was a systematic difference between the effects observed in the latest IPF meta-analysis, involving carefully curated clinically defined IPF, and biobank defined IPF, generally obtained from ICD codes in electronic health records (EHR). Sample recruitment periods and time periods covered by the EHRs are available in Table S15. Limiting to samples of NFE descent and genome-wide significant loci in the meta-analysis, the effect size estimates were 2.1 times larger in the clinical cohort compared with the meta-analyzed biobank studies (Figure 3).

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Table 4. COVID-19 pleiotropy

Variant	rsid	Index variant gene	Most severe consequence	OR [95% CI] IPF	OR [95% CI] COVID-19	p value IPF	p value COVID-19
1_77998184_T_C	rs4130548	*DNAJB4*, *GIPC2*	intron	1.09 [1.06–1.13]	1.04 [1.01–1.06]	4.91E−08	2.28E−03
7_100020983_G_A	rs6963345	*ZKSCAN1*	intron	1.16 [1.13–1.20]	1.04 [1.02–1.06]	1.27E−23	1.14E−03
11_1219991_G_T	rs35705950	*MUC5B*	upstream gene	2.76 [2.62–2.90]	0.89 [0.86–0.93]	<1E−300	1.22E−08
13_112881427_C_T	rs12585036	*ATP11A*	noncoding transcript exon	0.89 [0.86–0.92]	1.07 [1.04–1.09]	2.35E−11	1.80E−06
16_276685_G_A	rs184954013	*ARHGDIG*	intron	1.87 [1.55–2.25]	1.43 [1.1–1.86]	1.30E−13	7.83E−03
17_46126154_C_T	rs113120855	*KANSL1*	intron	0.80 [0.77–0.84]	0.92 [0.89–0.95]	8.92E−23	1.04E−08
19_4717660_A_G	rs12610495	*DPP9*	missense	1.12 [1.08–1.15]	1.11 [1.09–1.14]	2.95E−11	6.09E−18

Results for genome-wide significant index variants in joint IPF meta-analysis with FDR-adjusted p value < 0.05 in COVID-19 hospitalization scan (n = 7/25, 28%). Variant = chr_pos_ref_alt (GRCh38), effects are given for the alt allele.

Per each biobank, the median beta ratio ($\beta_{GBMI}/\beta_{Allen}$) varied from −0.04 to 0.62 (Figure S5).

To further study the effect of case ascertainment on effect size estimates, we divided the FinnGen study into three subsets based on diagnosis and original study cohort: a clinical IPF cohort (FinnishIPF,[48] n cases = 205), other IPF patients (n = 1,366), and non-IPF ILD patients (n = 1,624) and compared effect size estimates from these cohorts with those of the latest IPF meta-analysis. Again, effect size estimates were 0.9, 1.4, and 2.5 times larger in the latest IPF meta-analysis compared with the Finnish IPF, other IPF, and non-IPF ILD cohorts (Figure S6), providing further evidence that effect sizes in highly ascertained IPF patients are substantially higher compared with patients identified from biobanks. We further explored the effect of defining IPF cases based on the slightly more inclusive PheCode definition used by most biobanks compared with a more rigorous definition (International Classification of Diseases [ICD]-10 code J84.1) in FinnGen and noted that effect size estimates were somewhat attenuated in the PheCode-based IPF cases (0.87-fold, 95% CI 0.83–0.91; Figure S7).

The large effect of case ascertainment on effect size estimates was corroborated by meta-regression results, where case ascertainment explained most of the observed heterogeneity (mean R^2 = 55.8%), while ancestry, by comparison, explained very little (mean R^2 = 6.2%). After adjusting for ancestry, all 11 loci with heterogeneous effects expressed evidence of remaining heterogeneity. To study the effect of case ascertainment, we compared the effect estimates of two clinical cohorts, the latest IPF meta-analysis and the FinnishIPF subcohort of FinnGen, to the estimates of the 13 GBMI biobanks (excluding the clinical subcohort from FinnGen). Having divided FinnGen into 2 subcohorts, 10 of the 25 loci expressed evidence of heterogeneity. However, after accounting for case ascertainment status (whether the studies were based on clinical cohorts or not), only 4 of these 10 loci expressed evidence of remaining heterogeneity.

DISCUSSION

We conducted the first multi-ancestry meta-analysis of IPF increasing the number of cases over 4-fold compared with the latest IPF meta-analysis. Incorporating 11,160 patients from 6 ancestries allowed us to identify 7 novel loci associated with IPF susceptibility. Three of the identified loci, *GPR157*, *FKBP5*, and *RAPGEF2* have been previously associated with lung function measurements. Furthermore, *FKBP5* affects the mTOR signaling pathway,[20] central in lung fibrinogenesis,[21] and another novel locus, *FUT6*, affects mucin fucosylation potentially influencing mucociliary clearance.[30] Genes at two of the novel loci (*GIPC2*, *FKBP5*) have been reported to be differentially expressed in IPF lung compared with controls.[36]

Highlighting the importance of multi-ancestry analysis, one of the novel loci (*PSKH1*) was only polymorphic in the EAS population and three additional index variants were enriched within the meta-analysis at least 1.5-fold in a non-European population compared with NFEs. Moreover, only one of the loci would have reached genome-wide significance had the analysis been restricted to European populations. The power boost of the multi-ancestry meta-analysis comes from an increase in both sample size and sample diversity, allowing identification of loci whose index variants are more frequent in other ancestries than European. In addition to boosting power, increasing the ancestral diversity of IPF genetic association studies allows analyzing a broader set of genetic variation, as nearly a third of the variants in GBMI were not present in the GBMI NFE studies. It also enables cross-validating new findings across biobanks and increases representation of understudied populations.

Fine-mapping in the Finnish population, enriched for deleterious low-frequency coding variants,[49] suggested a predicted missense variant causal at the *KIF15* locus. In future studies, after further increases in samples sourced from diverse ancestries, fine-mapping in multiple populations should be undertaken. Cross-ancestry fine-mapping, however, still has notable challenges to be resolved.[50]

COVID-19 severity and IPF share a notable proportion of their genetic background, as genetic correlation was estimated to be substantial ($R_g \sim 0.35$), higher than previous estimates.[14] Of the 25 IPF index variants, seven reached the FDR-adjusted nominal p value in the COVID-19 hospitalization scan (out of which three were genome-wide significant: *CRHR1*, in addition to the previously reported *MUC5B* and *DPP9*). Effects at these loci were mostly in the same direction for the two traits, but variants in *MUC5B* and *ATP11A* showed opposite directions of effects. The strongest IPF risk locus *MUC5B* confers protection from

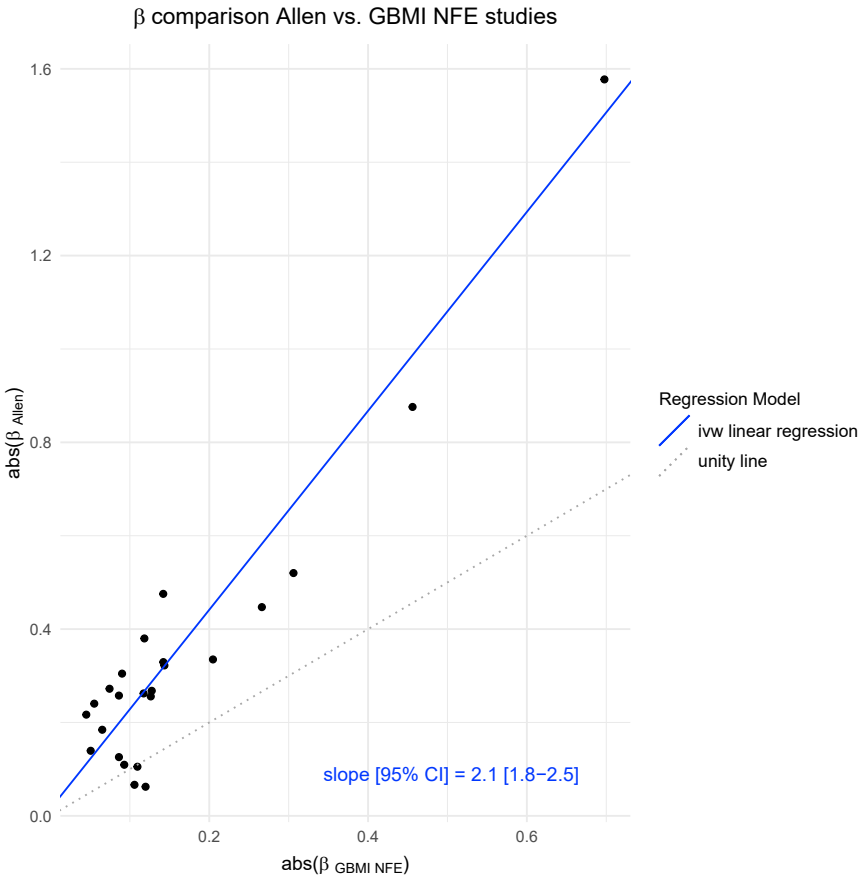

Figure 3. Effect size estimate comparison latest IPF meta-analysis versus GBMI

Scatter plot of absolute value of latest IPF meta-analysis beta against absolute value of meta-analyzed GBMI NFE beta with inverse variance weighted linear regression line (weights from Allen et al. study) and accompanying slope estimate. The analysis was performed within the non-Finnish European ancestry and variants included were genome-wide significant in the joint IPF meta-analysis.

severe COVID-19 and has been associated with survival in IPF patients.[51] Histologically, acute exacerbations of IPF present with diffuse alveolar damage, which is also present in severe COVID-19.[52]

Interestingly, we observed a sex-stratified effect in GBMI at *MUC5B*, the strongest common genetic risk factor for IPF, where the effect was 1.6 times larger in males compared with females. This result should, however, be considered with caution as it was not replicated in four clinical cohorts and may arise from confounding factors, such as ascertainment and age distribution differences in the sexes. These confounders should be investigated in future studies before the observed difference is inferred to represent a biological difference between the sexes. Yet, patient gender bias has been suggested to cause overdiagnosis of IPF in males and underdiagnosis in females,[53] which would attenuate effect estimates in males and increase them in females. With relevance to misexpression of MUC5B in IPF, rs35705950 has been suggested to introduce a *de novo* binding site for HOXA9,[54] a transcription factor differentially expressed by sex in whole blood[55] and transcriptionally regulated by sex hormones.[56,57] Also, FOXA2, a transcription factor binding 32 bp downstream of rs35705950 in the enhancer region 3 kB upstream of *MUC5B*, has a strong effect on MUC5B expression[54] and has been shown essential for sexual dimorphism in liver cancer.[58]

The meta-analysis with contributing biobanks featuring a wide variety of sampling strategies enabled studying between study heterogeneity, which revealed that case ascertainment has a large effect on IPF effect size estimates. Nearly a half of the genome-wide significant IPF loci expressed evidence of heterogeneity, which was mainly due to differences in case ascertainment—whether the patients were recruited from a hospital's pulmonary clinic or identified from health registries. Effect size estimates were more than 2-fold for clinical IPF cohorts compared with patients recruited from biobanks, in part due to the marginally more inclusive PheCode-based case definition used in the biobanks. For GWAS, however, the substantially larger number of patients available from biobanks benefits discovery even given the attenuated effect size estimates.

We present the first multi-ancestry meta-analysis of IPF to date with an over 4-fold increase in cases compared with the latest IPF meta-analysis. We discover multiple novel loci, the vast majority of which are driven by non-European populations and many of which have been linked to lung traits. We confirm and further describe the notable overlap of genetic determinants of IPF and severe COVID-19, calling for functional research. We describe a possible sex-dependent effect at the strongest IPF risk factor, the *MUC5B* locus, and demonstrate a 2-fold difference in effect size estimates derived from clinical cohorts as opposed to biobanks. To conclude, leveraging global multi-ancestry analysis further elucidates the genetic background of IPF by both revealing novel loci and providing increased resolution into previously identified ones.

Limitations of the study

Limitations of the study include between study heterogeneity, pointing to differing ascertainment between studies. However, this has limited impact on our novel findings, as only one of the novel loci showed evidence of heterogeneity (*DNAJB4/GIPC2*). Second, and with relevance to the former, the PheCode-based IPF case definition including other interstitial idiopathic

pneumonias increased the risk of misclassification in biobanks and contributed to the observed heterogeneity. In addition, as recruitment of participants spanned over two decades, changes in diagnostic practices for IPF may introduce chronological bias. Third, even though samples representing four non-European ancestries were included, the sample was still dominated by participants of European ancestry. Furthermore, fine-mapping was successful for only a minority of the loci. Finally, the novel findings of this study require future functional studies to elucidate their possible biological effects.

CONSORTIA

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STAR★METHODS

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AUTHOR CONTRIBUTIONS

Study design, J.J.P., P.H., W.Z., M.J.D., and J.T.K.; data collection/contribution, W.Z., J.M.O., N.J.C., J.B.H., D.A.S., T.E.F., C.F., I.N., B.L.Y., R.G.J., L.V.W., International IPF Genetics Consortium, GBMI, R.K., and M.M.; data analysis, J.J.P., P.H., W.Z., A.A.L., R.J.A., A.D.S., O.C.L., B.G.-G., and

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DECLARATION OF INTERESTS

A.S. and B.L.Y. are full-time employees of Genentech with stock and stock options in Roche. D.A.S. is the founder and chief scientific officer of Eleven P15, a company focused on the early diagnosis and treatment of IPF. T.E.F. is a consultant to Eleven P15. R.G.J. has received research funding from Astra Zeneca, Biogen, Galecto, GlaxoSmithKline, RedX, and Pliant; consulting fees from Bristol Myers Squibb, Daewoong, Veracyte, Resolution Therapeutics, RedX, and Pliant; payment for lectures, presentations, speakers bureaus, manuscript writing or educational events from Chiesi, Roche, PatientMPower, and AstraZeneca; payment for Participation on a Data Safety Monitoring Board or Advisory Board from Boehringer Ingelheim, Galapagos, and Vicore, had a Leadership or fiduciary role in other board, society, committee or advocacy group (unpaid) in NuMedii and Action for Pulmonary Fibrosis; and is a trustee for Action for Pulmonary Fibrosis. L.V.W. has received research funding from GSK and Orion Pharma and consultancy for Galapagos. M.J.D. is a founder of Maze Therapeutics. J.T.K. and M.J.D. are members of the Pfizer Finland FinnGen Advisory Board.

INCLUSION AND DIVERSITY

We worked to ensure ethnic or other types of diversity in the recruitment of human subjects. The author list of this paper includes contributors from the location where the research was conducted who participated in the data collection, design, analysis, and/or interpretation of the work.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
Global Biobank Meta-Analysis Initiative (GBMI) genome-wide meta-analysis results	GBMI	https://www.globalbiobankmeta.org/resources
Allen et al. genome-wide meta-analysis results	Allen et al. (2020)	https://github.com/genomicsITER/PFgenetics
Software and algorithms		
UCSC liftOver		https://genome.ucsc.edu/cgi-bin/hgLiftOver
REGENIE	Mbatchou J. et al. (2021)	https://doi.org/10.1038/s41588-021-00870-7
LD score regression	Bulik-Sullivan B. K. et al. (2015)	https://github.com/bulik/ldsc/
PLINK 2.0	Chang et al. (2015)	https://www.cog-genomics.org/plink/2.0/
R statistical programming		https://www.r-project.org/
Other		
GBMI custom scripts used for quality control, meta-analysis and summary		https://github.com/globalbiobankmeta
FinnGen fine-mapping pipeline		https://github.com/FINNGEN/finemapping-pipeline
Project code	This paper	https://doi.org/10.5281/zenodo.6993906

RESOURCE AVAILABILITY

Lead contact

Further information and requests should be directed to and will be fulfilled by the lead contact, Jukka Koskela (jukka.koskela@helsinki.fi).

Materials availability

This study did not generate new materials.

Data and code availability

Full joint meta-analysis summary statistics and GBMI meta-analysis results are available for downloading at https://www.globalbiobankmeta.org/resources and can be browsed at the PheWeb Browser http://results.globalbiobankmeta.org. Custom scripts used for quality control, meta-analysis and summary of the GBMI results are available at https://github.com/globalbiobankmeta. FinnGen fine-mapping pipeline scripts are available at https://github.com/FINNGEN/finemapping-pipeline. Original code generated within this project has been deposited at Zenodo and is publicly available at https://doi.org/10.5281/zenodo.6993906. Any additional information is available from the lead contact upon request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

13 biobanks in Europe, Asia, and USA encompassing 6 ancestries contributed to the Global Biobank Meta-Analysis Initiative (GBMI) IPF meta-analysis, totaling 8,492 cases and 1,355,819 controls (Table 1, Table S1). Sample ancestry was determined by individual biobanks and successful determination was ensured by comparing projected principal components, calculated by each biobank for their samples based on marker loadings standardized for all GBMI biobanks, to the 1000 Genomes Project and the Human Genome Diversity Project (HGDP). Sample recruitment strategies differed between the biobanks (Table S1). The three clinical IPF cohorts of the latest IPF meta-analysis (Chicago, Colorado and UK), totaling 2,668 cases and 8,591 controls, all of European ancestry, are described elsewhere.[2] The two cohorts used for replication (UUS and Genentech) were also used for replication in the latest IPF meta-analysis and are described elsewhere.[2] There was sample overlap of 3,366 controls between the GBMI meta-analysis (UKBB) and the three clinical IPF cohorts (UK cohort) of the latest IPF meta-analysis, but there was no IPF case overlap. All analyses were limited to adults (age $\geq$18).

METHOD DETAILS

Phenotype definition and quality control

The GBMI phenotypic and genotypic quality control are described elsewhere.[59] Analysis was performed in most biobanks for PheCode 502, constructed from health data available from each biobank (Table S16, phenotype definitions used in each biobank are in Table S15). IPF cases for the PheCode 502 were determined using the following International Classification of Diseases (ICD)-codes: ICD-9: 515, 515.0, ICD-10: J84.1, J84.10, J84.17, J84.8, J84.89. In the latest IPF meta-analysis, case definition was based on American Thoracic Society and European Respiratory Society guidelines, and quality control steps are described elsewhere.[2]

Meta-analysis

For GBMI, GWASs stratified by ancestry and sex were conducted in each biobank after standard sample-level and variant-level quality control. Thereafter, inverse-variance weighted fixed-effect meta-analyses were performed for all biobanks across all ancestries, all biobanks by each ancestry, and all biobanks by sex, detailed description elsewhere.[59] Meta-analysis of the GBMI meta-analysis and the latest IPF meta-analysis, referred to as the joint meta-analysis, was likewise performed using the inverse-variance weighted fixed effects model in R (version 4.1). Prior to meta-analysis, the summary statistics of the latest IPF meta-analysis were lifted over from GRCh37 to GRCh38 using UCSC liftOver (https://genome.ucsc.edu/cgi-bin/hgLiftOver). Liftover results were verified by comparing the results to LiftOver results from Picard: of the 10,790,934 variants lifted over by UCSC liftOver 10,777,976 (99.9%) overlapped with LiftOver results from Picard, indicating high concordance in the results of the two methods.

All variants are reported based on the human genome reference sequence GRCh38. Only variants that were genome-wide significant in the joint meta-analysis were considered in downstream analyses. Genome-wide significant loci were determined by taking a 1 Mb region around each genome-wide significant variant and merging overlapping regions. The HLA region on chromosome 6 (GRCh38 chr6:28,510,120-33,480,577) was considered as one locus. Loci which did not include a previously reported IPF associated variant irrespective of the variant's p value in the meta-analysis were considered novel.

Fine-mapping

Fine-mapping was performed for the IPF GWAS in FinnGen release 7 using the "Sum of Single Effects" (SuSie) model[42,60] and FINEMAP[43,44] for corroborative analyses. Fine-mapping regions were defined by taking a 3 Mb window around each index variant in the joint IPF meta-analysis and merging overlapping regions. 95% credible sets (encompassing at least 95% of the probability of including the causal variant) were analyzed and the probability of variant causality was evaluated using the posterior inclusion probability (PIP). Conditional analysis in FinnGen was performed using REGENIE[61] with dosages of the variant conditioned on as covariates alongside other covariates (age, sex, ten first principal components, and batch). Individual causal signals were explored in FinnGen using logistic regression with Firth correction implemented in the "logistf" R package.[62]

Phenome-wide lookup

To assess the shared effects of potentially novel loci, we considered associations with phenotypes in the Open Targets Genetics (OTG) obtained from the GWAS catalog. Linkage disequilibrium (LD) between variants was assessed using the LD pair tool[63] (https://ldlink.nci.nih.gov/), restricting to the 1000 Genomes Project non-Finnish European sub-populations for variants polymorphic in non-Finnish Europeans and source population otherwise.

LD score regression intercept and genetic correlation

The LD score regression v.1.0.1 intercept[17] was used to quantify the contribution of confounding biases to the IPF meta-analysis results. As this method depends on matching the LD structure of the analysis sample to a reference panel, the analysis was restricted to the NFE samples. LD score regression[47] was also used to estimate the genetic correlation between IPF and COVID-19 hospitalization using samples of NFE and European ancestry for IPF and COVID-19, respectively. Pre-calculated LD scores from the 1000 Genomes European reference population were obtained online (https://data.broadinstitute.org/alkesgroup/LDSCORE/) and the analysis was conducted using the standard program settings for variant filtering (removal of non-HapMap3 SNPs, minor allele frequency of <1%, or allele mismatch with reference).

Colocalization

Colocalization analysis was performed in FinnGen release 7. Colocalization analysis was based on assessing agreement of the fine-mapped credible sets across two traits. Agreement was measured by causal posterior agreement (CLPA), calculated as the sum of minimum PIP between the two traits per variant in overlapping credible sets.

Sex-stratified and sex interaction analyses

We performed sex-stratified analysis in six biobanks in the GBMI. In FinnGen sex-stratified analyses were conducted in release 5 with 378 and 110524 female, and 650 and 86462 male IPF cases and controls, respectively. In addition, we performed sex-stratified and sex interaction analyses in four clinical cohorts (Colorado, UK, UUS, and Genentech) using the PLINK 2.0 software[64] (https://www.cog-genomics.org/plink/2.0/). The analyses were not performed in the Chicago study for rs35705950 as the imputation quality

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(imputation R^2) was less than 0.5. In the sex-stratified analysis the effect of the *MUC5B* variant rs35705950 on IPF case status was tested in males and females separately using logistic regression adjusting for the ten first principal components. The rs35705950-by-sex interaction analysis was performed using the following logistic regression model:

$$\text{logit}(P(\text{Phenotype}_i)) = \beta_0 + \beta_1 \text{rs35705950}_i + \beta_2 \text{Sex}_i + \beta_3 \text{rs35705950}_i{}^{*}\text{Sex}_i + \beta_4 \text{PC}_{1i} + \ldots + \beta_{14} \text{PC}_{10i} + \varepsilon_i$$

where

Phenotype$_i$ is IPF status for individual *i*, *rs35705950* is the dosage for rs35705950 (additive effect), *Sex* is binary coded, *rs35705950*Sex* is the interaction term and PC_1 to PC_{10} are the first ten standardised principal components.

The results from the four clinical cohorts were meta-analyzed using inverse-variance weighted fixed effect meta-analysis, implemented using the R package "metagen" (https://www.rdocumentation.org/packages/meta/versions/4.9-6/topics/metagen).

Heterogeneity evaluation

Heterogeneity of effect sizes across studies and between sexes was evaluated at each variant using Cochran's Q p value and heterogeneity index. To study the contribution of different sample recruitment strategies on heterogeneity, effect size estimates of selected studies for genome-wide significant IPF loci were compared and an inverse-variance weighted linear regression line was fitted. To evaluate the extent to which sample recruitment and ancestry contributed to heterogeneity, we used meta-regression[65] using the "meta" R package.[66]

QUANTIFICATION AND STATISTICAL ANALYSIS

Sample sizes and sample age and sex characteristics are available in Tables 1 and S1. All meta-analyses were performed using the inverse-variance weighted fixed effects model in R. The p value threshold for genome-wide significance was $P < 5E\text{-}8$. The p value for heterogeneity was calculated based on Cochran's heterogeneity statistic.