Supplemental figures for

Identification of a missense variant in *SPDL1* associated with idiopathic pulmonary fibrosis

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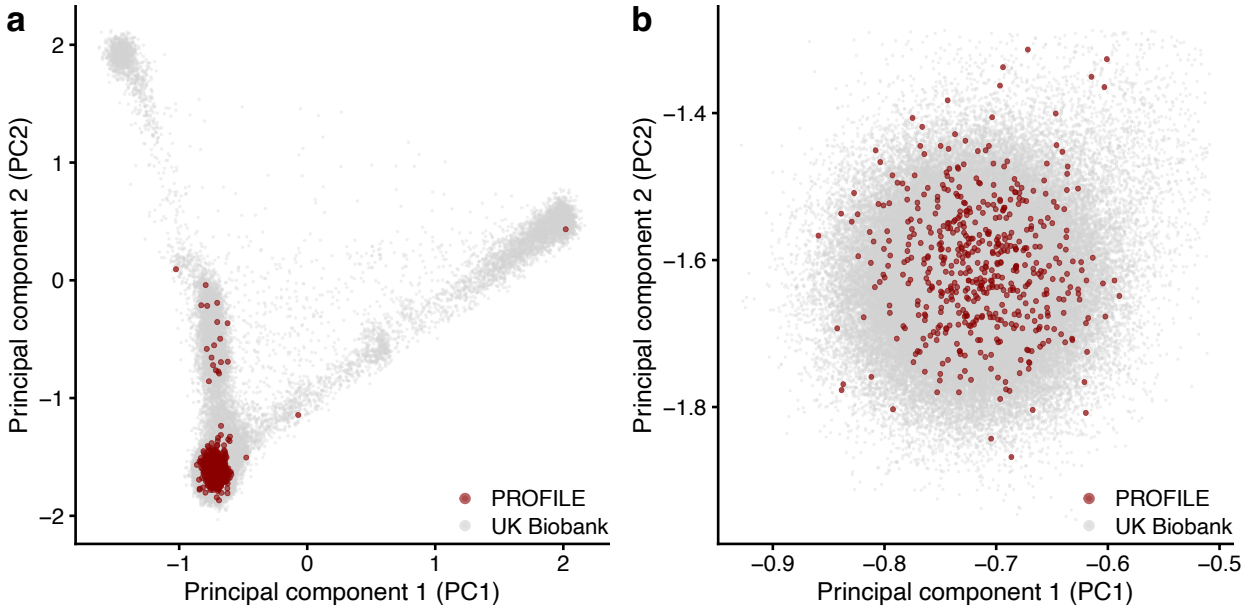
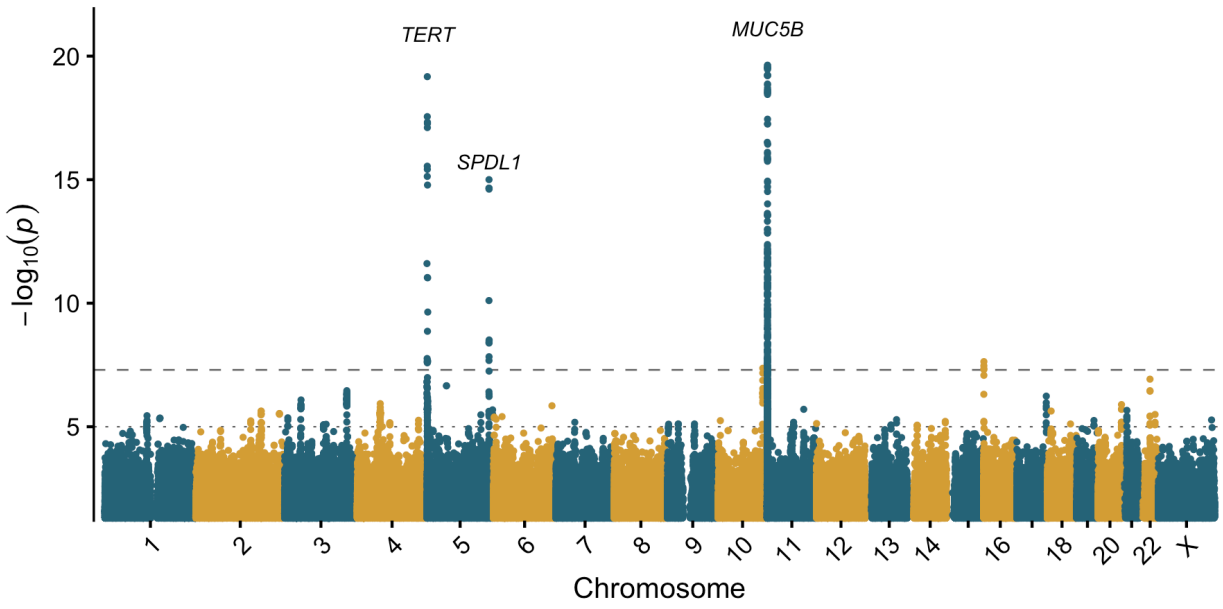
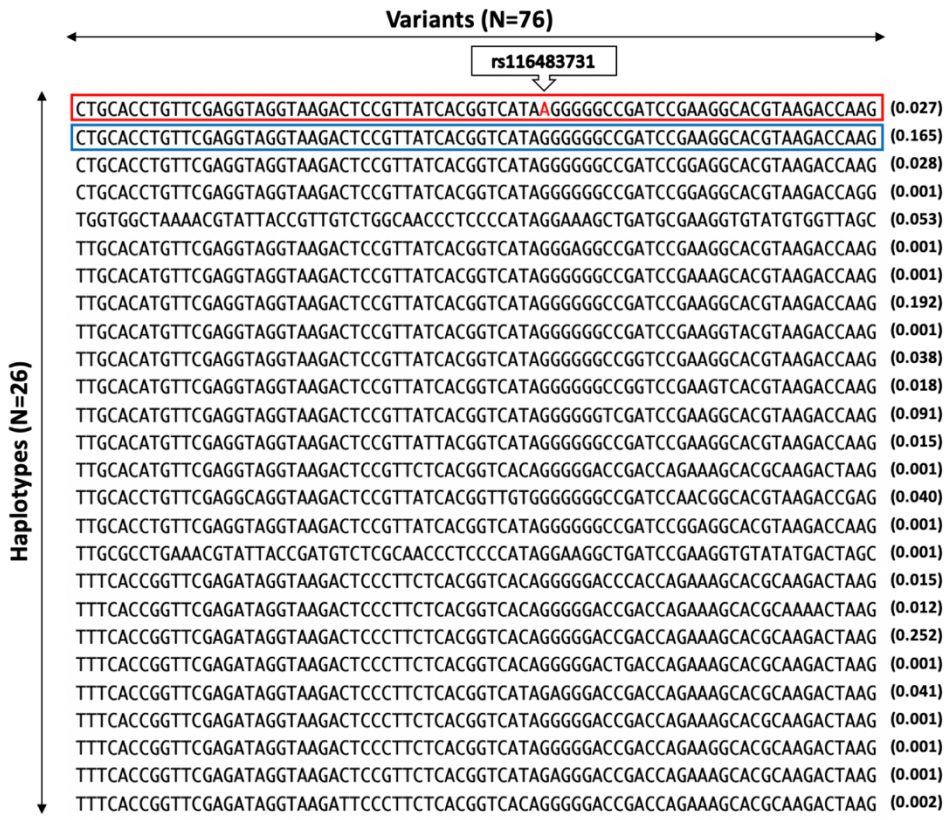


Supplementary Figure 1. Principal component plot of ancestry axes. (a) Principal components (PCs) 1 and 2 for 133,056 samples contained in the UK Biobank and 530 samples from the PROFILE cohort. **(b)** Samples retained after filtering for individuals with Peddy-based probability of being European was greater than 0.98 and the sample was within the quadrant boundary defined by: [PC1: -0.9280 to -0.5092] and [PC2: -1.953 to -1.288].

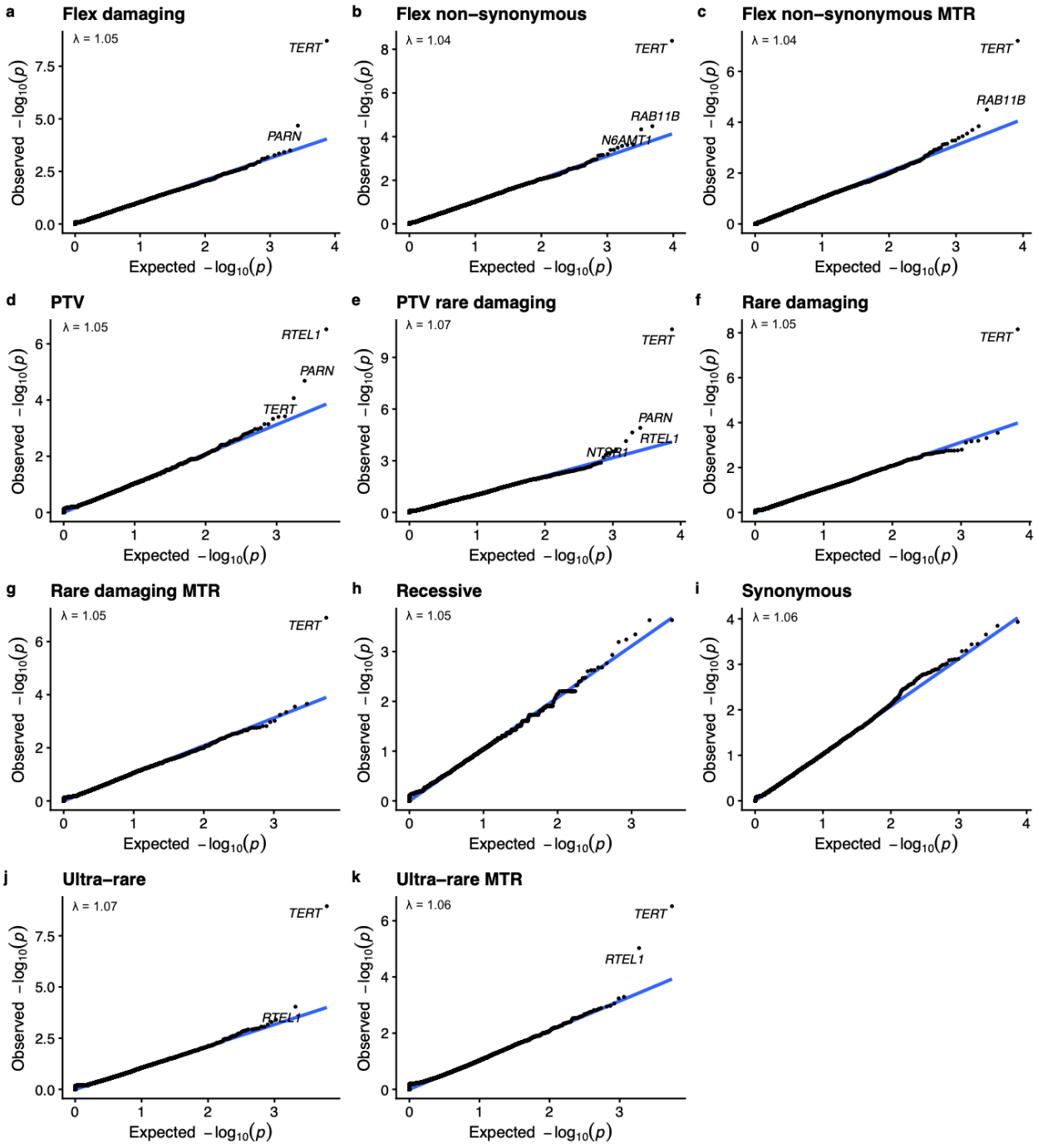


Supplementary Figure 2. Association of single-nucleotide variants with IPF in the FinnGen cohort. Manhattan plot depicting *p*-values of the 16,380,412 tested for association with IPF status in the FinnGen cohort (release 5). The y-axis has been capped at 25.

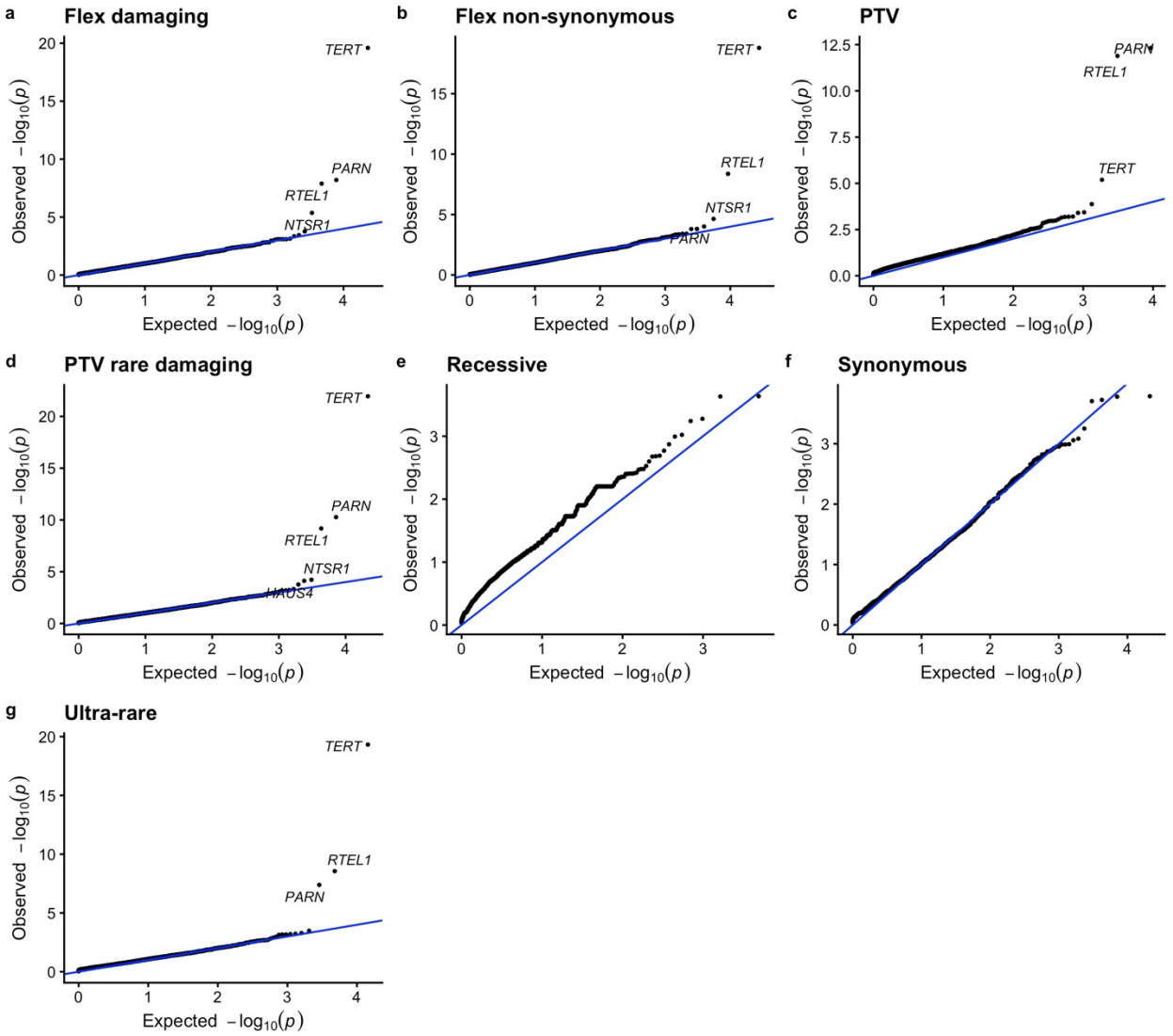


Supplementary Figure 3. Haplotype analysis. Depiction of the 26 distinct haplotypes that were identified for 76 variants within a 10 kilobase window of the *SPDL1* index variant rs116483731 in the PROFILE cohort. The risk allele 'A' for rs116483731 was present on only one of the 26 haplotypes (red box), while the remaining haplotypes all harboured the ancestral "G" allele at this position. The blue box represents the corresponding ancestral haplotype, which was present in 16.5% of the cohort. The numbers in parentheses adjacent to each haplotype represents the observed frequency in the cohort.

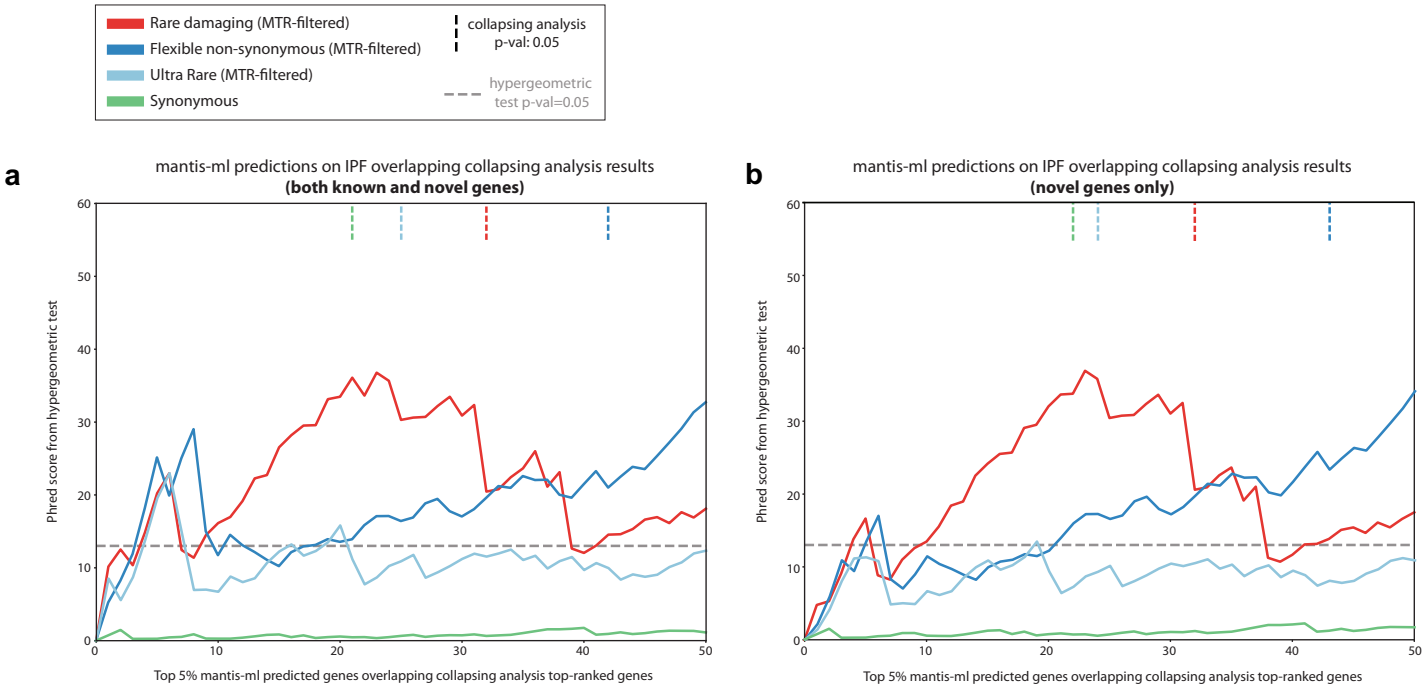
We further confirmed the finding of a shared common haplotype for the rs116483731 variant using an independent population-based dataset of 25,000 individuals sampled from the UK Biobank and found >99% of the rs116483731 risk alleles had an identical ancestral haplotype structure to the *SPDL1* risk haplotype observed among Imperial IPF cases.



Supplementary Figure 4. **Gene-level collapsing results. (a-k)** Quantile-quantile plots for each gene-level collapsing model. Each model included 18,665 protein-coding genes. No novel genes achieved study-wide significance (adjusted $\alpha < .05 / [18{,}665 \times 10] = 2.7 \times 10^{-7}$). Linear regression lines are indicated in blue.



Supplementary Figure 5. **Combined analysis for gene-level collapsing results. (a-g)** Quantile-quantile plots for each gene-level collapsing model, in which we combined data from the present study with a previous IPF collapsing study[1]. Each model included 18,665 protein-coding genes. No novel genes achieved significance. Linear regression lines are indicated in blue.



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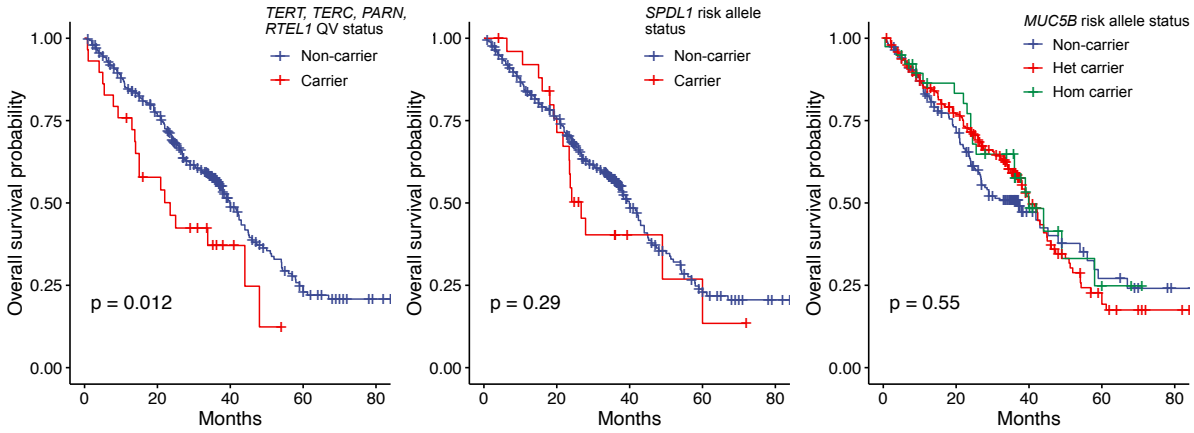
	Min. p-value (up to last significant gene)		p-value at last significant gene from collapsing	
QV model	All genes	Novel genes only	All genes	Novel genes only
Rare damaging	**0.00021**	**0.000203**	**0.00899**	**0.00873**
Flex non-synonymous	**0.00124**	**0.00267**	**0.00792**	**0.00468**
Ultra-rare damaging	**0.00504**	**0.0454**	0.0814	0.118
Synonymous	0.715	0.713	0.902	0.856

Supplementary Figure 6. Cross-validation of *mantis-ml* predictions with cohort-level rare-variant association studies. (a) Hypergeometric test enrichment of IPF-specific *mantis-ml* predictions against three collapsing models: "rare damaging MTR," "flexible non-synonymous MTR," and "ultra-rare damaging MTR." The synonymous collapsing model is included as a negative control. The horizontal dashed grey line corresponds to the significance threshold of $p = 0.05$ for the hypergeometric tests, with signals above this line indicating a significant enrichment. The vertical dashed lines indicate the p-value of the top-ranked gene from each collapsing model achieving a p-value < 0.05. **(b)** Same analysis as (a), except that known IPF genes were removed. **(c)** Hypergeometric test *p*-values.



Supplementary Figure 7. Kaplan-Meier survival curves of PROFILE cases stratified by genetic risk factor. (a) Comparison of 31 cases with qualifying rare variants (QVs) in *TERT*, *TERC, PARN,* and *RTEL1* versus 476 non-carriers. **(b)** Comparison of 26 cases carrying the *SPDL*1 risk allele versus 481 non-carriers. **(c)** Comparison of *MUC5B* risk allele carriers (269 heterozygous carriers, 40 homozygous carriers) versus the remainder of the PROFILE cohort (198 noncarriers). Log-rank p-values are indicated on each plot.

Exclusion Criteria	UK Biobank Field
ICD10 Chapter X Diseases of the respiratory system (root node ID 10)	41270
ICD10 Chapter XVIII Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (root node 18; Respiratory Block R05-R06, R08-R09)	41270
ICD9 Chapter VIII Diseases of the respiratory system (460-519)	41271
ICD10 Chapter X Diseases of the respiratory system (root node ID 10)	40001
keywords – “pulmon,” “respire,” “asthma,” “airways,” “bronchi,” “interstitial lung,” “pneumonia,” “asbestosis,” “pneumothorax,” “lung abscess,” “emphysema,” “empyema,” “pleural plaques,” “pleural effusion,” “alveolitis”	40010
Self-declared respiratory (root node ID 1072)	20002
Online follow-up > Work environment > Medical information > Doctor Diagnosed	22127 - 22141

Supplementary Table 1: Exclusion criteria used for screening UK Biobank controls.

Inclusion Criteria	PROFILE	UK Biobank IPF	UK Biobank Controls
Initial Cohort	541 (100%)	272 (100%)	302,081
Restrict controls to non-respiratory disease (Table S2)	541 (100%)	272 (100%)	219,704 (72.7%)
Contamination FREEMIX < 4% based on VerifyBamID	540 (99.8%)	270 (99.3%)	219,627 (72.7%)
Gender concordance between reported and genetic gender	534 (98.7%)	270 (99.3%)	219,627 (72.7%)
≥95% of CCDS r22 bases covered with ≥10-fold coverage	534 (98.7%)	270 (99.3%)	219,622 (72.7%)
Probability of European ancestry ≥ 0.98 based on PEDDY	512 (94.6%)	251 (92.3%)	206,938 (68.5%)
Within 4 standard deviations (SD) of PC 1-4 for probability of European ancestry mean	511 94.5%	251 (92.3%)	206,415 (68.2%)
Cryptic Relatedness Pruning (up to 3rd degree based on KING)	507 (93.7%)	245 (90.1%)	200,203 (66.3%)
Within ±4SD of Novel CCDS SNV mean	507 (93.7%)	245 (90.1%)	199,963 (66.2%)
Sex match controls (Male 75%)	507 (93.7%)	245 (90.1%)	119,055 (39.4%)
Final Test Cohort	**507 (**93.7%)	**245** (90.1%)	**119,055** (39.4%)

Supplementary Table 2: Sample-level quality control filtering and case-control harmonization.

	UK 612 cases, 3,666 controls						Colorado 1,515 cases, 4,683 controls				Chicago 541 cases, 542 controls				Meta	
	Ref allele	**Effect allele**	**MAF**	**Rsq**	**OR [95% CI]**	**p**	**MAF**	**Rsq**	**OR [95% CI]**	**p**	**MAF**	**Rsq**	**OR [95% CI]**	**p**	**OR [95% CI]**	**p**
rs116483731	G	A	0.8%	0.84	1.38 [0.70, 2.74]	0.354	0.9%	0.81	3.95 [2.49, 6.28]	6.01×10^{-9}	1.2%	0.83	1.19 [0.55, 2.61]	0.656	2.40 [1.70, 3.40]	7.55×10^{-7}

Supplementary Table 3: *P*-values for the *SPDL1* risk variant (rs116483731) from the latest GWAS meta-analysis of IPF risk alleles, which included some overlapping samples from the PROFILE study[2]. Allen et al. required $p < 0.05$ in all 3 contributing studies to be tested in the replication cohort. Though the *SPDL1* risk allele was not formally assessed by Allen et al., it achieved a similar effect size. The *SPDL1* risk variant likely achieved significance in the Colorado cohort due to the larger sample size compared to the UK and Chicago cohorts.

Collapsing model	GnomAD MAF	Internal MAF	Variant type	REVEL[3] cutoff	MTR cutoff
Synonymous (negative control)	≤ 0.005%	≤ 0.05%	Synonymous	-	-
PTV (Protein Truncating Variant)	≤ 0.1% (popmax)	≤ 0.1%	PTV	-	-
Ultra-rare damaging	<0.0004%	≤ 0.025%	PTV, missense, inframe indels	≥ 0.25	-
Ultra-rare damaging MTR	<0.0004%	≤ 0.025%	PTV, missense, inframe indels	≥ 0.25	MTR ≤ 25th percentile or Intragenic MTR ≤ 50th %ile
Rare damaging	≤ 0.005%	≤ 0.05%	missense	≥ 0.25	-
Rare damaging MTR	≤ 0.005%	≤ 0.05%	missense	≥ 0.25	MTR ≤ 25th percentile or Intragenic MTR ≤ 50th %ile
Flexible damaging	≤ 0.05% (global) ≤ 0.1% (popmax)	≤ 0.1%	PTV, missense, inframe indels	≥ 0.25	-
Flexible non-synonymous	≤ 0.05% (global) ≤ 0.1% (popmax)	≤ 0.1%	PTV, missense, inframe indels	-	-
Flexible non-synonymous MTR	≤ 0.05% (global) ≤ 0.1% (popmax)	≤ 0.1%	PTV, missense, inframe indels	-	MTR ≤ 25th percentile or Intragenic MTR ≤ 50th %ile
PTV or rare damaging missense	PTV ≤ 0.1% missense ≤ 0.005% (global) missense ≤ 0.05% (popmax)	PTV ≤ 0.1% missense ≤ 0.05%	PTV, missense, inframe indels	≥ 0.25	-
Recessive non-synonymous	≤ 0.5% (popmax)	≤ 0.5%	PTV, missense, inframe indels	-	-

Supplementary Table 4. Collapsing models. MTR = missense tolerance ratio[4]. REVEL and MTR cutoffs only apply to missense variants.

Field	**All**	**MUC5B** (rs35705950)	**p-value** (vs. others)	**SPDL1** (p.Arg20Gln)	**p-value** (vs. others)	**TERT, TERC, RTEL1, PARN** (rare variant)	**p-value** (vs. others)
Sample size	507	309	N/A	26	N/A	31	N/A
Male gender	387	232	0.454	17	0.233	17	0.007
Survival months* (median)	21.1	22.5	0.046	22.55	0.569	14	0.067
Sample age (median)	71	71	0.127	69.5	0.379	**66**	**0.0008**
Height (median)	171	171	0.212	171	0.348	169.5	0.103
Weight (median)	82.6	82.6	0.159	79.25	0.287	82.6	0.968
FVC pp (median)	76.86	76.79	0.16	77.94	0.49	76.82	0.35
DLCO pp (median)	47.9	47.68	0.088	46.52	0.981	47.9	0.958
TelSeq (median)	0.77	0.77	0.180	0.77	0.947	**0.68**	**0.002**
Family history	42	26	1	4	0.259	3	0.734

Supplementary Table 5. Clinical characteristics of PROFILE cohort. P-values for gender were generated via Fisher's exact test. P-values for values with reported medians were calculated using the Mann-Whitney U test. Bonferroni corrected *p*-values ≤ 0.003 are bolded. *Survival months were only considered for the 238 samples with reported mortality data (deceased).

Covariate	***MUC5B*** **(rs35705950)**	***SPDL1*** **(p.Arg20gln)**	***TERT, TERC, RTEL1, PARN*** **(rare variant)**
Age Odds Ratio (p-value)	1 (0.03)	0.98 (0.4)	0.94 (0.002)
Gender Odds Ratio (p-value)	0.84 (0.4)	0.58 (0.2)	0.32 (0.004)
TelSeq-inferred telomere length (kb) Odds Ratio (p-value)	0.86 (0.2)	0.62 (0.6)	0.03 (0.004)

Supplementary Table 6. TelSeq logistic regression analysis. Odds ratios with *p*-values in parentheses**.**

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