

# THE LANCET

## Respiratory Medicine

### **Supplementary appendix**

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# Supplementary material

## **Rare variants and survival of patients with idiopathic pulmonary fibrosis: analysis of a multicentre, observational cohort study with independent validation**

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# Supplementary methods

## Description of study cohorts

The Pulmonary Fibrosis Foundation Patient Registry (PFFPR) is a large multicentre based registry that collects baseline and longitudinal demographic and clinical information about well-characterized patients with interstitial lung diseases (ILD) in the United States since March 2016 to allow retrospective and prospective research<sup>1</sup>. In addition, the PFFPR major objective is to apply blood-based omics technologies (whole-genome sequencing [WGS], proteomic analysis, and transcriptional profiling) on blood samples from patients to study molecular markers of the onset or progression of diseases. Patients aged  $\geq 18$  years old who has ILD diagnosed and had not undergone lung transplantation were recruited from approximately 42 USA sites selected primarily from the familial pulmonary fibrosis (FPF) Care Center Network. They were followed for the progression of the disease through the lifetime of the PFFPR or the patient until the patient receives lung transplant. More details of the PFFPR including inclusion and exclusion criteria as well as collected clinical variables are described elsewhere<sup>1</sup>. The PFFPR cohort includes 1317 individuals with ILD for whom WGS data are available. For this study, we included the 917 PFFPR patients with a definitive IPF diagnosis. Family history was available for all of them although no genetic causes were previously assessed. After the quality control procedures, 888 of those patients remained in the study.

The PROFILE is a UK large, prospective, multicentre, longitudinal study conducted on patients with fibrotic ILD<sup>2,3</sup>. The cohort includes 541 patients with IPF or idiopathic non-specific interstitial pneumonia aged 18-85 recruited from tertiary specialist ILD and from local secondary care hospitals. Blood samples for genomic analysis were collected and they were followed for disease progression through 3 years. After quality control steps, the second stage of the study included 472 patients with a confirmed diagnosis of IPF.

Baseline characteristics of the PFFPR and the PROFILE cohorts are listed in **Supplementary Table 1**.

## Supplementary sequencing and bioinformatics analysis methods

In the PFFPR, library preparation and sequencing were performed by Psomagen (Rockville, MD). Genomic DNA libraries were prepared using the TruSeq DNA PCR Free kit (Illumina Inc.) and sequenced on an Illumina NovaSeq 6000 instrument (Illumina Inc.) with 150 bp paired-end reads at an average depth of 30X. At least 80% of the genome was covered by  $\geq 20$  reads, and  $\geq 90\%$  was covered by  $\geq 10$  reads. Whole genome sequencing (WGS) was processed using the Illumina DRAGEN Bio-IT Platform Germline Pipeline v3.10.4 (Illumina Inc.) using the Illumina DRAGEN Multigenome Graph hg38 as the reference genome. Only variants with a “PASS” filter were included in subsequent analyses.

To obtain estimates of telomere length (TL) from WGS BAM files (WGS-TL) we used TelSeq 0.0.2<sup>4</sup>. A hexamer repeat threshold of 12 was selected as described elsewhere<sup>5</sup>.

For the PROFILE cohort, WGS was performed at Human Longevity Inc. using the Illumina NovaSeq 6000 system with 150 pb paired-end reads. Coverage of at least 10X was achieved in over 98% of the Consensus Coding Sequence Release 22 (CCDS), with an average read depth of 42X across the CCDS as described previously<sup>6</sup>. Sequences were processed using the Illumina DRAGEN Bio-IT Platform Germline Pipeline v3.0.7, with the GRCh38 as the reference genome.

In both cohorts, several quality control (QC) analyses were performed: (i) detection of QC outliers, (ii) the kinship between patients, (iii) sample cross-contamination, and (iv) sex discordance. We used a combination of DRAGEN metrics, and assessments with PLINK v1.90b6.24<sup>2,3</sup>, SCE-VCF v0.1.2 (<https://github.com/HTGenomeAnalysisUnit/SCE-VCF>), Somalier v0.2.19<sup>2,3</sup>, and KING v2.3.2<sup>6</sup>.

Detection of QC outliers: Based on PLINK analysis, we detected abnormal heterozygosity rate and genotyping call rate to infer potential sample contaminations and/or a low DNA concentration. A heterozygosity rate value  $\pm 3$  standard deviations from the mean and/or genotype call rate  $< 0.95$  were considered as outliers.

Kinship between patients: We detected duplicates or monozygotic twins, and first-degree kinship relationships with three different tools: we considered two samples as duplicates or obtained from monozygotic twins if a PI\_HAT value was  $>0.9$  for PLINK, a Somalier relatedness value  $>0.9$ , and a KING kinship coefficient  $>0.354$ . We considered as first-degree relatives a PI\_HAT in the range of 0.4-0.6 for PLINK, a Somalier relatedness value in the range of 0.4-0.6, and a KING kinship coefficient in the range of 0.177-0.354. We found a complete consensus among these tools in the cohort. Second-degree relatives were not detected.

Sample cross-contamination: We used the “*estimated\_sample\_contamination*” parameter from DRAGEN metrics to exclude samples with evidence  $\geq 2\%$  of contamination. We also used SCE-VCF tool, which estimates contamination from VCF files using the CHARR method<sup>7</sup>, based on the recommended thresholds to consider a sample as contaminated (CHARR  $> 0.03$  and INCONSISTENT\_AB\_HET\_RATE  $> 0.15$ ). We found a complete consensus among these tools in the identification of potential sample contamination in the PFF-PR. For PROFILE, we only relied on SCE-VCF for the sample cross-contamination inference.

Sex discordance: Biological sex inference from genetic data was obtained with Somalier following recommendations. For that we compared the scaled mean depth on X and Y chromosomes for 365 and 17 genomic positions, respectively. Sex discordance, identified by comparing the genetically inferred sex with that recorded, was also used to exclude patients from the study. In the PFF-PR, a female was identified as a possible XO aneuploid due to the low number of heterozygous sites on the X chromosome and was excluded from the analysis.

### Identification of qualifying variants (QVs) in monogenic adult-onset PF genes

The identification of QVs was restricted to 13 PF genes classified as telomere related and non-telomere related (**Supplementary Table 2**). With the exception of *SPDL1*, and *KIF15*, this list includes genes with a known dominant inheritance pattern (presuming that QVs in these genes would have higher penetrance) and genes that are commonly found in familial IPF cohorts, although they also occur in sporadic cases<sup>7</sup>.

*KIF15* and *SPDL1* were incorporated to the list as recent large scale sequencing studies identified them as PF-related genes<sup>6,8,9</sup>. Both genes are critical for mitosis, pointing to a novel, non-telomeric mechanism underlying IPF. Rare deleterious variants in *KIF15* and three telomere genes (*TERT*, *PARN* and *RTEL1*) have been previously associated with IPF risk, early onset, and progression to early-age lung transplantation or death<sup>9</sup>. In *SPDL1*, a rare missense variant was confirmed as a new IPF risk allele, although carriers did not exhibit distinct clinical features<sup>6</sup>.

Variants in these genes were filtered based on read depth (DP)  $<10$ , mapping quality (MQ)  $<50$ , or the percentage of missing genotypes (FMISS)  $>0.05$  in the cohort. The remaining variants were annotated using the Variant Effect Predictor tool v109.3<sup>10</sup>. Variants with a global allele frequency (AF)  $>0.0005$  in gnomAD v2.1 were excluded from the study. For our analyses, we retained protein-truncating variants (including frameshift, stop-gained, start-loss, and splicing variants) and missense variants with a CADD  $>15$ .

For the non-coding RNA gene *TERC*, due to the difficulty in predicting functional effects in non-coding genes, variants were considered for the analysis if their global population AF was  $<0.0005$  and they were annotated by ClinVar as pathogenic (P), likely pathogenic (LP), or of uncertain significance (VUS).

### Principal components of genetic heterogeneity in the cohorts

Principal components (PC) were calculated after excluding single nucleotide polymorphisms (SNPs) with a minor allele frequency (MAF)  $<0.01$  from WGS data, using BCFtools (<https://samtools.github.io/bcftools/bcftools.html>). Genotyping QC was then performed using PLINK v.1.9. First, SNPs with a genotyping call rate (CR)  $<95\%$  or those deviating significantly from Hardy-Weinberg equilibrium (HWE) ( $p < 1.0 \times 10^{-6}$ ) were removed. After linkage disequilibrium pruning (indep-pairwise 100 5 0.01), the main PCs of genetic variation were calculated based on 110,951 independent SNPs in the PFFPR and 143,214 independent SNPs in PROFILE (**Supplementary Figure 1**).

### Estimation of polygenic risk scores (PRS)

We derived PRS-IPF from 19 previously published genome-wide significant IPF variants (**Supplementary Table 6**) using PRSice-2<sup>11</sup>. Briefly, PRS were calculated as the number of risk alleles carried by each individual, multiplied by the effect size of the variant as described in the GWAS study<sup>11</sup> summed across all variants included in the score:

$$PRS = \sum_{i=1}^n \beta_i G_i$$

where  $\beta_i$  is the OR (in the case of binary traits) from variant  $i$ ,  $G_i$  represents the number of risk alleles carried at the variant  $i$  and  $n$  represents the conditionally independent signals identified elsewhere. Raw polygenic scores were then standardized as z-scores using the following formula:

$$PRS_z = \frac{PRS - \text{Mean}(PRS)}{\text{standard deviations}(PRS)}$$

The same methodology was used to derive PRS for TL (PRS-TL) based on the 20 common variants that were previously found associated with leukocyte TL<sup>12</sup> (**Supplementary Table 7**). In this case, since TL is a quantitative trait,  $\beta_i$  is represented by beta coefficients in the PRS formula.

# Supplementary results

## Prevalence of QVs in the PFFPR

A total of 131 QVs were identified in monogenic adult-onset PF genes in 144 patients. Most patients (96.5%, 139 of 144) carried a single QV, while five patients (3.5% of the QV carriers) had two or more QVs, including combinations such as *NAF1/TERT*, *KIF15/RTEL1*, *TERT/SPDL1*, *TINF2/TERT/RTEL1*, and *RTEL1/RTEL1*. Consistent with previous studies, the prevalence of QVs was higher in patients with a familial history of disease (27.3%, 48 of 176) compared to those with sporadic disease (13.5%, 96 of 712) ( $p=3.08 \times 10^{-5}$ ). Most QVs were in telomere genes (75.6%, 99 of 131), while nearly a quarter were found in non-telomere genes (24.4%, 32 of 131). The highest number of QVs were identified in telomere-related genes including *RTEL1* (25.2%, 33 of 131), *TERT* (23.7%, 31 of 131), and *PARN* (12.2%, 16 of 131). These genes also had the highest proportion of P/LP variants (31.0%, 18 of 58, 31.0%, 18 of 58, and 20.7%, 12 of 58, respectively). In total, 42.7% (56 of 131) of QVs were previously annotated in ClinVar as VUS, LP, or P.

## Prevalence of QVs in PROFILE

Using the same classification of QVs as in PFFPR, the diagnostic yield of finding a QVs in PROFILE was 15.67 % (74 of 472) (95% CI=12.4-19.0%) (**Supplementary Table 4**). The genes with the highest burden of QVs were: *RTEL1* (20.5%, 15 of 73), *TERT* (15.1%, 11 of 73), and *PARN* (17.8%, 13 of 73) (**Supplementary Figure 2B-D**). The prevalence of QVs among carriers of the risk *MUC5B* genotype (rs35705950-T) was lower (14.97%, 44 of 294) than among those carrying the protective GG genotype (16.85%, 30 of 178), although the difference was not statistically significant ( $p=0.60$ ). We observed the same effect direction as in PFFPR when assessing the association between the lower PRS-IPF tertile and reduced survival (HR=1.49, 95% CI=0.14-1.95,  $p=3.1 \times 10^{-3}$ ).



# Supplementary Tables

**Supplementary Table 1. Baseline characteristics and outcomes of IPF patients from stage one and stage two cohorts.**

| Characteristics                        | PFFPR (n=888)*   | PROFILE (n=472) <sup>§</sup> |
|----------------------------------------|------------------|------------------------------|
| Age, yr, mean (SD)                     | 71.02 (7.8)      | 70.65 (7.9)                  |
| Male, n (%)                            | 676 (76.1)       | 366 (77.5)                   |
| Self-reported ethnicity, n (%)         |                  |                              |
| Unknown                                | 17               |                              |
| Asian                                  | 23               | -                            |
| Black                                  | 10               |                              |
| White                                  | 838              |                              |
| Ever smoker, n, (%)                    | 571 (64.3)       | 326 (69.1)                   |
| Familial history, n, (%)               | 176 (19.8)       | -                            |
| FVC% predicted, mean (SD)              | 67.74 (16.8)     | 78.97 (19.01)                |
| DLCO% predicted, mean (SD)             | 29.3 (4.8)       | 44.97 (14.98)                |
| Carriers of QVs                        | 144              | 74                           |
| Dead at 60 months, n, (%)              | 37 (25.7)        | 53 (71.6)                    |
| Transplant at 60 months, n (%)         | 22 (15.3)        | -                            |
| Non-carriers of QVs                    | 744              | 398                          |
| Dead, n, at 60 months (%)              | 163 (21.9)       | 239 (60.1)                   |
| Transplant at 60 months, n (%)         | 70 (9.4)         | -                            |
| Median survival in years (IQR)         | 4.86 (3.31-6.93) | 3.30 (1.74-5.71)             |
| <i>MUC5B</i> genotype with risk allele | 622 (70)         | 294 (62.3)                   |

PFFPR, The Pulmonary Fibrosis Foundation Patient Registry; SD, standard deviation; FVC, forced vital capacity; DLCO, diffusing capacity of the lungs for carbon monoxide; IQR=interquartile range; QVs, qualifying variant. \*Missing data: FVC predicted (n=41) and DLCO predicted (n=68); <sup>§</sup>Missing data: FVC predicted (n=12) and DLCO predicted (n=50).

**Supplementary Table 2. Regions of interest (ROIs) for  
qualifying variants annotations in hg38.**

| Chromosome | Gene           | Start       | End         |
|------------|----------------|-------------|-------------|
| 5          | <i>TERT</i>    | 1,253,047   | 1,295,168   |
| 3          | <i>TERC</i>    | 169,764,420 | 169,765,160 |
| 14         | <i>TINF2</i>   | 24,238,186  | 24,242,763  |
| X          | <i>DKC1</i>    | 154,762,642 | 154,777,789 |
| 20         | <i>RTEL1</i>   | 63,657,710  | 63,696,353  |
| 16         | <i>PARN</i>    | 14,435,600  | 14,632,828  |
| 4          | <i>NAF1</i>    | 163,109,973 | 163,166,990 |
| 12         | <i>ZCCHC8</i>  | 122,471,500 | 122,501,032 |
| 8          | <i>SFTPC</i>   | 22,156,813  | 22,164,579  |
| 10         | <i>SFTP A2</i> | 79,555,752  | 79,560,507  |
| 10         | <i>SFTP A1</i> | 79,610,839  | 79,615,555  |
| 5          | <i>SPDL1</i>   | 169,583,536 | 169,604,878 |
| 3          | <i>KIF15</i>   | 44,761,621  | 44,873,476  |

**Supplementary Table 3. Qualifying variants identified in the PFFPR.**

| Variant             | Gene          | HGVSc            | HGVSp               | Effect                                    | GnomADg AF | CADD  | Alpha Missense | Condel              | PrimateAI | REVEL | ClinVar                             | ACMG Class |
|---------------------|---------------|------------------|---------------------|-------------------------------------------|------------|-------|----------------|---------------------|-----------|-------|-------------------------------------|------------|
| 10_79557337_T_A     | <i>SFTPA2</i> | c.619A>T         | p.Asn207Tyr         | missense                                  | .          | 23    | 0.3054         | deleterious (0.998) | 0.47      | 0.16  | .                                   | VUS        |
| 10_79614091_G_A     | <i>SFTPA1</i> | c.725G>A         | p.Arg242Gln         | missense                                  | .          | 23.4  | 0.3594         | deleterious (1.000) | 0.54      | 0.348 | uncertain significance              | VUS        |
| 12_122473969_C_T    | <i>ZCCHC8</i> | c.938G>A         | p.Gly313Asp         | missense                                  | 0.000368   | 23.5  | .              | deleterious (1.000) | 0.64      | 0.115 | uncertain significance              | VUS        |
| 12_122481951_A_G    | <i>ZCCHC8</i> | c.155T>C         | p.Val52Ala          | missense                                  | .          | 24.6  | .              | deleterious (0.893) | 0.54      | 0.117 | .                                   | VUS        |
| 12_122483508_G_A    | <i>ZCCHC8</i> | c.557C>T         | p.Pro186Leu         | missense                                  | .          | 28    | 0.8556         | deleterious (0.999) | 0.73      | .     | pathogenic                          | P          |
| 12_122498861_G_A    | <i>ZCCHC8</i> | c.208C>T         | p.Leu70Phe          | missense                                  | .          | 25.8  | 0.3853         | deleterious (0.887) | 0.70      | .     | .                                   | VUS        |
| 12_122498866_T_C    | <i>ZCCHC8</i> | c.203A>G         | p.Gln68Arg          | missense                                  | .          | 20.4  | 0.0665         | Neutral (0.405)     | 0.51      | .     | .                                   | VUS        |
| 14_24240544_G_T     | <i>TINF2</i>  | c.936C>A         | p.Tyr312Ter         | stop gained                               | 5.92E-05   | 33    | .              | .                   | .         | .     | uncertain significance&not provided | LP         |
| 14_24240636_G_A     | <i>TINF2</i>  | c.844C>T         | p.Arg282Cys         | missense                                  | .          | 30    | 0.1866         | deleterious (0.976) | 0.51      | 0.878 | pathogenic                          | P          |
| 14_24241308_G_A     | <i>TINF2</i>  | c.403C>T         | p.Leu135Phe         | missense                                  | 0.0001192  | 23.8  | 0.2901         | deleterious (0.924) | 0.46      | 0.213 | uncertain significance              | LP         |
| 16_14447001_CCT_C   | <i>PARN</i>   | c.1566 1567del   | p.Glu524AspfsTer5   | frameshift                                | 5.26E-05   | 23.1  | .              | .                   | .         | .     | likely pathogenic&pathogenic        | P          |
| 16_14482829_T_C     | <i>PARN</i>   | c.1298-2A>G      | .                   | splice acceptor stop lost& NMD transcript | .          | 35    | .              | .                   | .         | .     | .                                   | LP         |
| 16_14531059_T_C     | <i>PARN</i>   | c.1377A>G        | p.Ter459TrpextTer19 | splice acceptor stop lost& NMD transcript | .          | 5.885 | .              | .                   | .         | .     | .                                   | VUS        |
| 16_14554139_C_T     | <i>PARN</i>   | c.1148G>A        | p.Arg383His         | missense                                  | 1.97E-05   | 31    | .              | deleterious (1.000) | 0.82      | 0.564 | uncertain significance              | LP         |
| 16_14554150_CAC_T_C | <i>PARN</i>   | c.1136-2 1136del | .                   | splice acceptor&coding sequence           | .          | .     | .              | .                   | .         | .     | .                                   | LP         |
| 16_14555675_G_C     | <i>PARN</i>   | c.1114C>G        | p.Leu372Val         | missense                                  | 9.87E-05   | 20.8  | .              | deleterious (0.567) | 0.70      | 0.086 | uncertain significance              | VUS        |
| 16_14555710_C_T     | <i>PARN</i>   | c.1080-1G>A      | .                   | splice acceptor                           | .          | 34    | .              | .                   | .         | .     | .                                   | LP         |
| 16_14582222_T_C     | <i>PARN</i>   | c.968A>G         | p.Tyr323Cys         | missense                                  | 0.0001051  | 28.9  | .              | deleterious (1.000) | 0.87      | 0.541 | uncertain significance              | LP         |
| 16_14582237_G_A     | <i>PARN</i>   | c.953C>T         | p.Ala318Val         | missense                                  | .          | 32    | .              | deleterious (1.000) | 0.84      | 0.789 | .                                   | LP         |

**Supplementary Table 3. Qualifying variants identified in the PFFPR.**

| Variant                                                                                                                   | Gene         | HGVSc                                  | HGVSp       | Effect                                                              | GnomADg AF | CADD  | Alpha Missense | Condel              | PrimateAI | REVEL | ClinVar                      | ACMG Class |
|---------------------------------------------------------------------------------------------------------------------------|--------------|----------------------------------------|-------------|---------------------------------------------------------------------|------------|-------|----------------|---------------------|-----------|-------|------------------------------|------------|
| 16_14582250_G_A                                                                                                           | <i>PARN</i>  | c.940C>T                               | p.Gln314Ter | stop gained                                                         | .          | 41    | .              | .                   | .         | .     | .                            | P          |
| 16_14584424_T_C                                                                                                           | <i>PARN</i>  | c.823-2A>G                             | .           | splice acceptor                                                     | .          | 34    | .              | .                   | .         | .     | likely pathogenic&pathogenic | P          |
| 16_14584781_T_C                                                                                                           | <i>PARN</i>  | c.790A>G                               | p.Thr264Ala | missense                                                            | .          | 27    | .              | deleterious (0.948) | 0.76      | 0.666 | .                            | VUS        |
| 16_14599924_T_TG<br>ACTCTAGAAATG<br>ATTCTA                                                                                | <i>PARN</i>  | c.636<br>637insTAGAAATC<br>ATTCTAGAGTC | p.Ile213Ter | stop gained&frameshift                                              | .          | .     | .              | .                   | .         | .     | .                            | P          |
| 16_14610732_C_A                                                                                                           | <i>PARN</i>  | c.283G>T                               | p.Ala95Ser  | missense                                                            | 0.0003614  | 22.3  | .              | deleterious (0.479) | 0.45      | 0.217 | uncertain significance       | VUS        |
| 16_14617596_G_A                                                                                                           | <i>PARN</i>  | c.199C>T                               | p.Arg67Ter  | stop gained                                                         | 1.32E-05   | 39    | .              | .                   | .         | .     | pathogenic                   | P          |
| 16_14629597_C_A                                                                                                           | <i>PARN</i>  | c.97G>T                                | p.Gly33Ter  | stop gained&splice region                                           | .          | 48    | .              | .                   | .         | .     | .                            | LP         |
| 20_63659405_G_A                                                                                                           | <i>RTEL1</i> | c.3G>A                                 | p.Met1?     | start lost                                                          | .          | 28.3  | .              | deleterious (0.984) | .         | .     | .                            | LP         |
| 20_63662544_A_G                                                                                                           | <i>RTEL1</i> | c.-274-2A>G                            | .           | splice acceptor                                                     | .          | 32    | .              | .                   | 0.56      | .     | .                            | P          |
| 20_63662590_A_G                                                                                                           | <i>RTEL1</i> | c.590A>G                               | p.His197Arg | missense                                                            | 6.57E-06   | 25.5  | .              | deleterious (0.541) | 0.49      | 0.702 | .                            | VUS        |
| 20_63667494_A_T                                                                                                           | <i>RTEL1</i> | c.790A>T                               | p.Asn264Tyr | missense                                                            | 4.60E-05   | 27.3  | .              | deleterious (0.500) | 0.55      | 0.297 | uncertain significance       | LP         |
| 20_63672560_G_A                                                                                                           | <i>RTEL1</i> | c.35G>A                                | p.Arg12His  | missense                                                            | .          | 26.1  | .              | deleterious (1.000) | 0.64      | 0.669 | uncertain significance       | LP         |
| 20_63674034_C_T                                                                                                           | <i>RTEL1</i> | c.191C>T                               | p.Thr64Ile  | missense                                                            | 0.0001448  | 20.9  | .              | deleterious (0.480) | 0.41      | 0.115 | uncertain significance       | LP         |
| 20_63678280_G_T                                                                                                           | <i>RTEL1</i> | c.302G>T                               | p.Arg101Leu | missense                                                            | .          | 17.73 | .              | deleterious (0.487) | 0.32      | 0.407 | uncertain significance       | VUS        |
| 20_63678292_C_A                                                                                                           | <i>RTEL1</i> | c.314C>A                               | p.Ala105Asp | missense                                                            | .          | 24.4  | .              | deleterious (0.774) | 0.50      | 0.68  | .                            | VUS        |
| 20_63685559_GGT<br>TCCCCAGCAGGG<br>CTGGGGGCCTTA<br>CAGTCCTATAAG<br>GTAGGGGCCACC<br>TCCAGGAGGCAG<br>GTGGAGGGCAGC<br>CCTT_G | <i>RTEL1</i> | c.567 597+47del                        | .           | splice donor&splice donor<br>5th base&coding<br>sequence&int<br>ron | .          | .     | .              | .                   | .         | .     | .                            | P          |

**Supplementary Table 3. Qualifying variants identified in the PFFPR.**

| Variant           | Gene         | HGVSc          | HGVSp              | Effect                 | GnomADg AF | CADD  | Alpha Missense | Condel              | PrimateAI | REVEL | ClinVar                           | ACMG Class |
|-------------------|--------------|----------------|--------------------|------------------------|------------|-------|----------------|---------------------|-----------|-------|-----------------------------------|------------|
| 20_63685825_C_T   | <i>RTEL1</i> | c.632C>T       | p.Thr211Met        | missense               | 0.0004336  | 16.46 | .              | deleterious (0.629) | 0.33      | 0.251 | uncertain significance            | VUS        |
| 20_63687740_C_T   | <i>RTEL1</i> | c.782C>T       | p.Pro261Leu        | missense               | 6.57E-06   | 27    | .              | deleterious (1.000) | 0.69      | 0.759 | uncertain significance&pathogenic | LP         |
| 20_63687765_G_T   | <i>RTEL1</i> | c.807G>T       | p.Met269Ile        | missense               | 6.57E-06   | 24.6  | .              | deleterious (0.534) | 0.62      | 0.74  | pathogenic&likely pathogenic      | P          |
| 20_63688016_G_A   | <i>RTEL1</i> | c.892G>A       | p.Asp298Asn        | missense               | .          | 25.1  | .              | deleterious (0.984) | 0.54      | 0.378 | .                                 | VUS        |
| 20_63688384_C_T   | <i>RTEL1</i> | c.1051C>T      | p.Arg351Trp        | missense&splice region | 6.58E-06   | 34    | .              | deleterious (0.976) | 0.47      | 0.691 | uncertain significance            | LP         |
| 20_63688572_T_A   | <i>RTEL1</i> | c.1098T>A      | p.Phe366Leu        | missense               | .          | 23    | .              | deleterious (0.914) | 0.69      | 0.711 | .                                 | LP         |
| 20_63689539_G_A   | <i>RTEL1</i> | c.1247G>A      | p.Arg416His        | missense               | 6.57E-06   | 29.9  | .              | deleterious (1.000) | 0.58      | 0.88  | .                                 | LP         |
| 20_63689566_A_A_C | <i>RTEL1</i> | c.1280dup      | p.Arg428ThrfsTer15 | frameshift             | .          | .     | .              | .                   | .         | .     | .                                 | P          |
| 20_63689807_A_T   | <i>RTEL1</i> | c.1414A>T      | p.Ile472Phe        | missense               | .          | 23.7  | .              | deleterious (0.999) | 0.59      | 0.856 | .                                 | LP         |
| 20_63690100_G_A   | <i>RTEL1</i> | c.1486G>A      | p.Asp496Asn        | missense               | 1.31E-05   | 22.7  | .              | deleterious (0.505) | 0.56      | 0.296 | uncertain significance            | LP         |
| 20_63690110_C_T   | <i>RTEL1</i> | c.1496C>T      | p.Ala499Val        | missense               | .          | 24.6  | .              | deleterious (0.725) | 0.48      | 0.626 | .                                 | VUS        |
| 20_63690206_G_A   | <i>RTEL1</i> | c.1592G>A      | p.Arg531Gln        | missense               | 5.26E-05   | 19.86 | .              | deleterious (0.513) | 0.37      | 0.055 | uncertain significance            | LP         |
| 20_63691777_G_C   | <i>RTEL1</i> | c.1923G>C      | p.Glu641Asp        | missense               | .          | 15.27 | .              | Neutral (0.432)     | 0.40      | 0.078 | .                                 | VUS        |
| 20_63692883_A_C   | <i>RTEL1</i> | c.2062A>C      | p.Asn688His        | missense               | 6.57E-06   | 17.53 | .              | deleterious (0.692) | 0.39      | 0.072 | uncertain significance            | VUS        |
| 20_63693145_TTC_T | <i>RTEL1</i> | c.2187 2188del | p.Phe729LeufsTer9  | frameshift             | .          | .     | .              | .                   | .         | .     | .                                 | LP         |
| 20_63693148_T_C   | <i>RTEL1</i> | c.2188T>C      | p.Tyr730His        | missense               | .          | 23.1  | .              | deleterious (0.889) | 0.53      | 0.188 | .                                 | VUS        |
| 20_63693161_G_A   | <i>RTEL1</i> | c.2201G>A      | p.Arg734Gln        | missense               | 1.32E-05   | 27.3  | .              | deleterious (0.924) | 0.45      | 0.293 | uncertain significance            | VUS        |
| 20_63693208_G_A   | <i>RTEL1</i> | c.2248G>A      | p.Gly750Arg        | missense               | 1.32E-05   | 25.1  | .              | deleterious (0.999) | 0.47      | 0.332 | .                                 | VUS        |
| 20_63693211_C_T   | <i>RTEL1</i> | c.2251C>T      | p.Arg751Ter        | stop gained            | 7.24E-05   | 39    | .              | .                   | .         | .     | pathogenic                        | P          |
| 20_63693220_G_C   | <i>RTEL1</i> | c.2260G>C      | p.Gly754Arg        | missense               | .          | 19.87 | .              | deleterious (0.940) | 0.29      | 0.104 | .                                 | VUS        |
| 20_63693223_T_A   | <i>RTEL1</i> | c.2263T>A      | p.Tyr755Asn        | missense               | .          | 17.05 | .              | deleterious (0.497) | 0.29      | 0.094 | .                                 | VUS        |

**Supplementary Table 3. Qualifying variants identified in the PFFPR.**

| Variant         | Gene         | HGVSc       | HGVSp        | Effect                     | GnomADg AF | CADD  | Alpha Missense | Condel              | PrimateAI | REVEL | ClinVar                                 | ACMG Class |
|-----------------|--------------|-------------|--------------|----------------------------|------------|-------|----------------|---------------------|-----------|-------|-----------------------------------------|------------|
| 20_63693226_C_T | <i>RTEL1</i> | c.2266C>T   | p.Arg756Trp  | missense                   | 9.21E-05   | 19.07 | .              | deleterious (0.675) | 0.21      | 0.086 | uncertain significance                  | VUS        |
| 20_63693247_C_T | <i>RTEL1</i> | c.2287C>T   | p.Arg763Ter  | stop gained                | 8.55E-05   | 36    | .              | .                   | .         | .     | pathogenic/likely pathogenic&pathogenic | P          |
| 20_63694956_G_A | <i>RTEL1</i> | c.2656G>A   | p.Asp886Asn  | missense                   | 6.57E-06   | 18.23 | .              | deleterious (0.486) | 0.35      | 0.305 | uncertain significance                  | VUS        |
| 3_169764646_G_A | <i>TERC</i>  | n.402C>T    | .            | non coding transcript exon | 1.31E-05   | 19.94 | .              | .                   | .         | .     | uncertain significance                  | VUS        |
| 3_169764856_G_A | <i>TERC</i>  | n.192C>T    | .            | non coding transcript exon | 1.97E-05   | 21.1  | .              | .                   | .         | .     | uncertain significance                  | VUS        |
| 3_169764862_G_A | <i>TERC</i>  | n.186C>T    | .            | non coding transcript exon | 3.28E-05   | 16.88 | .              | .                   | .         | .     | uncertain significance                  | VUS        |
| 3_169764930_G_A | <i>TERC</i>  | n.118C>T    | .            | non coding transcript exon | .          | 20.4  | .              | .                   | .         | .     | uncertain significance                  | VUS        |
| 3_44775328_A_G  | <i>KIF15</i> | c.137A>G    | p.Glu46Gly   | missense                   | .          | 25.4  | 0.0909         | deleterious (0.666) | 0.41      | 0.193 | .                                       | VUS        |
| 3_44786440_A_G  | <i>KIF15</i> | c.505A>G    | p.Ile169Val  | missense                   | 6.57E-06   | 22.8  | 0.0816         | deleterious (0.572) | 0.66      | 0.431 | .                                       | VUS        |
| 3_44786480_C_T  | <i>KIF15</i> | c.545C>T    | p.Ser182Leu  | missense                   | 0.0001907  | 25.7  | 0.1035         | deleterious (0.995) | 0.70      | 0.525 | .                                       | VUS        |
| 3_44800332_A_T  | <i>KIF15</i> | c.1117A>T   | p.Thr373Ser  | missense                   | 5.91E-05   | 22.9  | 0.1669         | deleterious (0.500) | 0.77      | 0.103 | .                                       | VUS        |
| 3_44801488_G_A  | <i>KIF15</i> | c.1261G>A   | p.Ala421Thr  | missense                   | 6.58E-06   | 26.1  | 0.4025         | deleterious (0.924) | 0.50      | 0.23  | .                                       | VUS        |
| 3_44802841_T_C  | <i>KIF15</i> | c.1537T>C   | p.Tyr513His  | missense                   | .          | 27    | 0.8168         | deleterious (0.998) | 0.83      | 0.342 | .                                       | LP         |
| 3_44810864_A_C  | <i>KIF15</i> | c.1990A>C   | p.Lys664Gln  | missense                   | .          | 25.3  | 0.1939         | deleterious (0.922) | 0.55      | 0.183 | .                                       | VUS        |
| 3_44815078_T_C  | <i>KIF15</i> | c.2549+2T>C | .            | splice donor               | .          | 33    | .              | .                   | .         | .     | .                                       | LP         |
| 3_44828239_A_G  | <i>KIF15</i> | c.2882A>G   | p.Glu961Gly  | missense                   | 0.0003678  | 25.3  | 0.0851         | deleterious (0.642) | 0.33      | 0.075 | .                                       | VUS        |
| 3_44838278_G_C  | <i>KIF15</i> | c.3175G>C   | p.Asp1059His | missense                   | 0.0003746  | 26.7  | 0.4345         | deleterious (0.745) | 0.60      | 0.1   | .                                       | VUS        |
| 3_44840427_G_T  | <i>KIF15</i> | c.3391G>T   | p.Val1131Leu | missense                   | .          | 21.9  | 0.2215         | neutral (0.449)     | 0.63      | 0.049 | .                                       | VUS        |

**Supplementary Table 3. Qualifying variants identified in the PFFPR.**

| Variant          | Gene         | HGVSc     | HGVSp              | Effect                 | GnomADg AF | CADD  | Alpha Missense | Condel              | PrimateAI | REVEL | ClinVar                                  | ACMG Class |
|------------------|--------------|-----------|--------------------|------------------------|------------|-------|----------------|---------------------|-----------|-------|------------------------------------------|------------|
| 3_44840456_G_C   | <i>KIF15</i> | c.3420G>C | p.Gln1140His       | missense&splice region | 1.32E-05   | 36    | 0.2366         | deleterious (0.968) | 0.42      | 0.138 | .                                        | VUS        |
| 3_44841128_C_G   | <i>KIF15</i> | c.3475C>G | p.Gln1159Glu       | missense               | 0.000138   | 22.1  | 0.0983         | deleterious (0.551) | 0.50      | 0.149 | .                                        | VUS        |
| 3_44851920_G_T   | <i>KIF15</i> | c.3940G>T | p.Glu1314Ter       | stop gained            | 0.000138   | 43    | .              | .                   | .         | .     | .                                        | LP         |
| 3_44852694_G_A   | <i>KIF15</i> | c.4126G>A | p.Glu1376Lys       | missense               | 5.93E-05   | 29.9  | 0.1411         | deleterious (0.881) | 0.61      | 0.174 | .                                        | VUS        |
| 4_163127016_G_GT | <i>NAF1</i>  | c.1132dup | p.Thr378AsnfsTer7  | frameshift             | 0.0002234  | 0.94  | .              | .                   | .         | .     | .                                        | LP         |
| 4_163129120_T_C  | <i>NAF1</i>  | c.1262A>G | p.Gln421Arg        | missense               | 1.32E-05   | 22.2  | 0.0842         | deleterious (0.517) | 0.37      | 0.025 | .                                        | VUS        |
| 4_163129217_T_C  | <i>NAF1</i>  | c.1165A>G | p.Arg389Gly        | missense               | .          | 17.2  | 0.0841         | deleterious (0.554) | 0.40      | 0.16  | .                                        | VUS        |
| 4_163133221_T_G  | <i>NAF1</i>  | c.966A>C  | p.Glu322Asp        | missense               | 0.0004073  | 24.2  | 0.3312         | deleterious (0.940) | 0.48      | 0.144 | .                                        | VUS        |
| 4_163140334_A_C  | <i>NAF1</i>  | c.767T>G  | p.Phe256Cys        | missense               | .          | 25.8  | 0.9299         | deleterious (1.000) | 0.72      | 0.674 | .                                        | VUS        |
| 4_163164384_C_T  | <i>NAF1</i>  | c.373G>A  | p.Asp125Asn        | missense               | 0.0002104  | 24.9  | 0.1694         | deleterious (0.530) | 0.84      | 0.145 | .                                        | VUS        |
| 5_1253777_G_T    | <i>TERT</i>  | c.3350C>A | p.Ala1117Asp       | missense               | .          | 18.97 | 0.1141         | deleterious (0.711) | 0.45      | 0.349 | uncertain significance                   | LP         |
| 5_1253804_G_A    | <i>TERT</i>  | c.3323C>T | p.Pro1108Leu       | missense               | 2.63E-05   | 20.7  | 0.1418         | deleterious (0.544) | 0.48      | 0.384 | uncertain significance&likely benign     | LP         |
| 5_1254406_C_T    | <i>TERT</i>  | c.3257G>A | p.Arg1086His       | missense               | 0.0001971  | 21    | 0.0838         | deleterious (0.816) | 0.26      | 0.248 | uncertain significance                   | LP         |
| 5_1254407_G_A    | <i>TERT</i>  | c.3256C>T | p.Arg1086Cys       | missense               | .          | 16.75 | 0.1256         | deleterious (0.837) | 0.29      | 0.365 | .                                        | VUS        |
| 5_1255344_G_A    | <i>TERT</i>  | c.3100C>T | p.Arg1034Cys       | missense               | .          | 20.4  | 0.1462         | deleterious (0.934) | 0.23      | 0.349 | uncertain significance                   | LP         |
| 5_1258638_AC_A   | <i>TERT</i>  | c.2991del | p.Cys998AlafsTer50 | frameshift             | .          | .     | .              | .                   | .         | .     | pathogenic                               | P          |
| 5_1260497_G_A    | <i>TERT</i>  | c.2947C>T | p.His983Tyr        | missense               | .          | 25.5  | 0.2451         | deleterious (0.957) | 0.45      | 0.439 | uncertain significance&likely pathogenic | LP         |
| 5_1260574_C_G    | <i>TERT</i>  | c.2870G>C | p.Ser957Thr        | missense               | .          | 25.1  | 0.2679         | deleterious (0.994) | 0.54      | 0.287 | .                                        | VUS        |
| 5_1264461_G_A    | <i>TERT</i>  | c.2786C>T | p.Pro929Leu        | missense               | .          | 22.6  | 0.2786         | deleterious (0.821) | 0.78      | 0.838 | .                                        | VUS        |
| 5_1264485_T_G    | <i>TERT</i>  | c.2762A>C | p.Gln921Pro        | missense               | .          | 24.4  | 0.1065         | deleterious (0.944) | 0.56      | 0.641 | .                                        | VUS        |
| 5_1268527_G_A    | <i>TERT</i>  | c.2575C>T | p.Arg859Trp        | missense               | .          | 25.4  | 0.1242         | deleterious (0.930) | 0.21      | 0.344 | uncertain significance                   | LP         |

**Supplementary Table 3. Qualifying variants identified in the PFFPR.**

| Variant                     | Gene  | HGVSc          | HGVSp              | Effect                          | GnomADg AF | CADD  | Alpha Missense | Condel              | PrimateAI | REVEL | ClinVar                            | ACMG Class |
|-----------------------------|-------|----------------|--------------------|---------------------------------|------------|-------|----------------|---------------------|-----------|-------|------------------------------------|------------|
| 5_1268573_G_C               | TERT  | c.2529C>G      | p.Ser843Arg        | missense                        | .          | 24    | 0.9856         | deleterious (0.997) | 0.48      | 0.758 | .                                  | LP         |
| 5_1268586_G_A               | TERT  | c.2516C>T      | p.Thr839Met        | missense                        | .          | 26.1  | 0.305          | deleterious (1.000) | 0.42      | 0.716 | uncertain significance             | VUS        |
| 5_1278686_GA_G              | TERT  | c.2240del      | p.Val747AlafsTer20 | frameshift                      | .          | .     | .              | .                   | .         | .     | pathogenic                         | P          |
| 5_1278692_GGCAT<br>ACCGAC G | TERT  | c.2225 2234del | p.Arg742ProfsTer22 | frameshift                      | .          | .     | .              | .                   | .         | .     | .                                  | LP         |
| 5_1278762_T_C               | TERT  | c.2131-2A>G    | .                  | splice acceptor&N MD transcript | .          | 24.7  | .              | .                   | 0.32      | .     | uncertain significance             | VUS        |
| 5_1279311_G_A               | TERT  | c.2110C>T      | p.Pro704Ser        | missense                        | 4.60E-05   | 16.1  | 0.1022         | deleterious (0.962) | 0.32      | 0.619 | uncertain significance&pat hogenic | P          |
| 5_1279328_C_T               | TERT  | c.2093G>A      | p.Arg698Gln        | missense                        | .          | 23.7  | 0.0997         | deleterious (0.843) | 0.46      | 0.406 | .                                  | VUS        |
| 5_1279340_A_T               | TERT  | c.2081T>A      | p.Val694Glu        | missense                        | 6.57E-06   | 17.01 | 0.7432         | deleterious (0.998) | 0.58      | 0.681 | uncertain significance             | LP         |
| 5_1279352_C_G               | TERT  | c.2069G>C      | p.Trp690Ser        | missense                        | .          | 25.1  | 0.96           | deleterious (0.995) | 0.66      | 0.89  | .                                  | LP         |
| 5_1279407_G_A               | TERT  | c.2014C>T      | p.Arg672Cys        | missense                        | 0.0002169  | 22.8  | 0.1047         | deleterious (0.897) | 0.40      | 0.44  | uncertain significance             | VUS        |
| 5_1279416_G_A               | TERT  | c.2005C>T      | p.Arg669Trp        | missense                        | 1.31E-05   | 22.8  | 0.2692         | deleterious (0.649) | 0.66      | 0.718 | uncertain significance             | VUS        |
| 5_1279464_G_A               | TERT  | c.1957C>T      | p.Arg653Cys        | missense                        | 2.63E-05   | 17.4  | 0.1146         | Neutral (0.456)     | 0.27      | 0.279 | uncertain significance             | VUS        |
| 5_1280313_G_A               | TERT  | c.1795C>T      | p.Arg599Trp        | missense                        | 6.57E-06   | 24.9  | 0.1544         | deleterious (0.993) | 0.38      | 0.454 | .                                  | VUS        |
| 5_1282594_C_T               | TERT  | c.1604G>A      | p.Arg535His        | missense                        | 6.57E-06   | 22.2  | 0.1095         | deleterious (0.762) | 0.37      | 0.418 | uncertain significance             | LP         |
| 5_1282609_G_A               | TERT  | c.1589C>T      | p.Pro530Leu        | missense                        | 1.32E-05   | 25    | 0.279          | deleterious (0.981) | 0.53      | 0.583 | uncertain significance             | VUS        |
| 5_1293588_C_T               | TERT  | c.1298G>A      | p.Gly433Asp        | missense                        | 7.88E-05   | 16.51 | 0.0718         | deleterious (0.882) | 0.56      | 0.289 | likely benign                      | VUS        |
| 5_1294470_A_C               | TERT  | c.416T>G       | p.Leu139Arg        | missense                        | .          | 24    | 0.1687         | deleterious (0.962) | 0.87      | 0.639 | uncertain significance             | LP         |
| 5_1294549_C_CG              | TERT  | c.336dup       | p.Glu113ArgfsTer79 | frameshift                      | 6.58E-06   | 16.1  | .              | .                   | .         | .     | pathogenic                         | P          |
| 5_1294619_G_C               | TERT  | c.267C>G       | p.Cys89Trp         | missense                        | .          | 22    | 0.7094         | deleterious (0.996) | 0.96      | 0.646 | .                                  | LP         |
| 5_1294913_G_A               | TERT  | c.77C>T        | p.Thr26Met         | missense                        | 6.58E-06   | 23.3  | 0.3319         | deleterious (0.807) | 0.93      | 0.301 | uncertain significance             | LP         |
| 5_169591225_G_A             | SPDL1 | c.336+1G>A     | .                  | splice donor                    | .          | 33    | .              | .                   | .         | .     | .                                  | LP         |



**Supplementary Table 3. Qualifying variants identified in the PFFPR.**

| Variant          | Gene         | HGVSc      | HGVSp       | Effect                                                  | GnomADg AF | CADD  | Alpha Missense | Condel              | PrimateAI | REVEL | ClinVar                                                    | ACMG Class |
|------------------|--------------|------------|-------------|---------------------------------------------------------|------------|-------|----------------|---------------------|-----------|-------|------------------------------------------------------------|------------|
| 5_169594287_C_T  | <i>SPDL1</i> | c.674C>T   | p.Ala225Val | missense                                                | 0.0001709  | 23    | 0.2653         | deleterious (0.999) | 0.54      | 0.233 | .                                                          | VUS        |
| 5_169594592_A_G  | <i>SPDL1</i> | c.802A>G   | p.Met268Val | missense                                                | 3.94E-05   | 22.8  | 0.123          | deleterious (0.984) | 0.49      | 0.213 | .                                                          | VUS        |
| 5_169594598_C_T  | <i>SPDL1</i> | c.808C>T   | p.Arg270Cys | missense                                                | .          | 23.5  | 0.2067         | deleterious (0.511) | 0.51      | 0.179 | .                                                          | VUS        |
| 5_169596559_A_G  | <i>SPDL1</i> | c.892-2A>G | .           | splice acceptor                                         | 0.0004009  | 35    | .              | .                   | .         | .     | likely benign                                              | VUS        |
| 5_169599138_A_G  | <i>SPDL1</i> | c.1303A>G  | p.Lys435Glu | missense                                                | 0.0002167  | 25.4  | 0.3092         | deleterious (0.811) | 0.59      | 0.153 | .                                                          | VUS        |
| 5_169599145_A_C  | <i>SPDL1</i> | c.1310A>C  | p.Lys437Thr | missense                                                | .          | 27.3  | 0.6537         | deleterious (0.930) | 0.72      | 0.312 | .                                                          | VUS        |
| 5_169601597_A_G  | <i>SPDL1</i> | c.1642A>G  | p.Arg548Gly | missense                                                | .          | 22.4  | 0.0901         | deleterious (0.567) | 0.30      | 0.129 | .                                                          | VUS        |
| 5_169604205_TA_T | <i>SPDL1</i> | c.*1del    | .           | frameshift&stop lost splice donor&non coding transcript | 1.31E-05   | 27.3  | .              | .                   | .         | .     | .                                                          | LP         |
| 8_22159082_G_T   | <i>SFTPC</i> | n.358+1G>T | .           | .                                                       | 3.94E-05   | 18.25 | .              | .                   | .         | .     | .                                                          | VUS        |
| 8_22161838_G_A   | <i>SFTPC</i> | c.10G>A    | p.Gly4Ser   | missense                                                | 3.29E-05   | 15.48 | 0.0978         | Neutral (0.107)     | 0.55      | 0.198 | uncertain significance                                     | VUS        |
| 8_22162605_G_A   | <i>SFTPC</i> | c.74G>A    | p.Gly25Asp  | missense                                                | .          | 21.3  | 0.2176         | deleterious (0.524) | 0.41      | 0.282 | .                                                          | VUS        |
| 8_22162681_T_G   | <i>SFTPC</i> | c.150T>G   | p.Ile50Met  | missense                                                | 5.26E-05   | 22.4  | 0.2106         | deleterious (0.967) | 0.64      | 0.658 | .                                                          | VUS        |
| 8_22163988_C_G   | <i>SFTPC</i> | c.541C>G   | p.Leu181Val | missense                                                | 0.0004007  | 23.9  | 0.1813         | Deleterious (0.998) | 0.53      | 0.65  | conflicting interpretations of pathogenicity&likely benign | VUS        |
| 8_22164440_C_A   | <i>SFTPC</i> | c.451C>A   | p.Pro151Thr | missense                                                | 0.0001314  | 17.12 | .              | .                   | .         | 0.047 | uncertain significance                                     | VUS        |
| X_154764944_C_T  | <i>DKCI</i>  | c.62C>T    | p.Ser21Leu  | missense                                                | 4.45E-05   | 19.32 | 0.0607         | Deleterious (0.490) | 0.41      | 0.242 | .                                                          | VUS        |

HGVSc, Human Genome Variation Society; VUS, variant of uncertain significance; P, pathogenic; LP, likely pathogenic

**Supplementary Table 4. Qualifying variants identified in PROFILE.**

| Variant           | Gene | HGVSp          | HGVSp              | Effect                   | GnomADg AF | CADD | Alpha Missense | Condel              | Primate AI | REVEL | ClinVar Sig                                             | ACMG Class |
|-------------------|------|----------------|--------------------|--------------------------|------------|------|----------------|---------------------|------------|-------|---------------------------------------------------------|------------|
| 5_1260499_C_T     | TERT | c.2945G>A      | p.Cys982Tyr        | missense                 | 4.01E-06   | 27.1 | 0.7986         | Deleterious (1.000) | 0.71       | 0.573 | uncertain significance                                  | VUS        |
| 5_1268521_C_T     | TERT | c.2581G>A      | p.Gly861Arg        | missense & splice region | .          | 24.9 | 0.8094         | Deleterious (0.861) | 0.44       | 0.801 | uncertain significance                                  | LP         |
| 5_1268577_C_T     | TERT | c.2525G>A      | p.Cys842Tyr        | missense                 | .          | 25   | 0.9447         | Deleterious (0.998) | 0.68       | 0.931 | uncertain significance                                  | LP         |
| 5_1271131_C_T     | TERT | c.2456G>A      | p.Arg819His        | missense                 | 8.06E-06   | 21.3 | 0.0834         | deleterious (0.955) | 0.29       | 0.312 | uncertain significance                                  | VUS        |
| 5_1271156_G_A     | TERT | c.2431C>T      | p.Arg811Cys        | missense                 | 0          | 23   | 0.1142         | deleterious (0.954) | 0.24       | 0.587 | uncertain significance & pathogenic & likely pathogenic | LP         |
| 5_1272184_C_G     | TERT | c.2382+1G>C    |                    | splice donor             | .          | 32   | .              | .                   | .          | .     | likely pathogenic                                       | LP         |
| 5_1279407_G_A     | TERT | c.2014C>T      | p.Arg672Cys        | missense                 | 5.19E-05   | 22.8 | 0.1047         | Deleterious (0.897) | 0.40       | 0.44  | uncertain significance                                  | VUS        |
| 5_1280244_G_A     | TERT | c.1864C>T      | p.Arg622Cys        | missense                 | .          | 27.3 | 0.6064         | Deleterious (0.988) | 0.58       | 0.9   | uncertain significance                                  | LP         |
| 5_1282573_G_A     | TERT | c.1625C>T      | p.Ala542Val        | missense                 | .          | 23.5 | 0.2754         | Deleterious (0.962) | 0.51       | 0.474 | uncertain significance                                  | VUS        |
| 5_1293522_T_A     | TERT | c.1364A>T      | p.His455Leu        | missense                 | 0          | 26.5 | 0.4173         | Deleterious (0.999) | 0.79       | 0.845 | uncertain significance                                  | LP         |
| 5_1294378_C_T     | TERT | c.508G>A       | p.Val170Met        | missense                 | 5.35E-06   | 25.3 | 0.6491         | Deleterious (0.913) | 0.89       | 0.686 | uncertain significance & pathogenic                     | LP         |
| 16_14447001_CCT_C | PARN | c.1566_1567del | p.Glu524AspfsTer5  | frameshift               | .          | 23.1 | .              | .                   | .          | .     | likely pathogenic & pathogenic                          | P          |
| 16_14482683_TG_T  | PARN | c.1441del      | p.Gln481SerfsTer23 | frameshift               | 4.02E-06   | .    | .              | .                   | .          | .     | pathogenic                                              | P          |
| 16_14482828_C_T   | PARN | c.1298-1G>A    |                    | splice acceptor          | 4.50E-06   | 35   | .              | .                   | .          | .     | .                                                       | LP         |
| 16_14554109_T_C   | PARN | c.1178A>G      | p.Lys393Arg        | missense                 | 8.05E-06   | 24.1 | .              | deleterious (0.816) | 0.76       | 0.172 | .                                                       | VUS        |
| 16_14554139_C_T   | PARN | c.1148G>A      | p.Arg383His        | missense                 | 4.04E-06   | 31   | .              | deleterious (1.000) | 0.82       | 0.564 | uncertain significance                                  | LP         |
| 16_14555652_A_G   | PARN | c.1135+2T>C    |                    | splice donor             | .          | 34   | .              | .                   | .          | .     | .                                                       | P          |
| 16_14593338_A_G   | PARN | c.698T>C       | p.Met233Thr        | missense                 | .          | 25.8 | .              | deleterious (0.974) | 0.78       | 0.277 | .                                                       | VUS        |
| 16_14617640_A_G   | PARN | c.155T>C       | p.Ile52Thr         | missense                 | 2.01E-05   | 27.2 | .              | deleterious (1.000) | 0.83       | 0.594 | .                                                       | LP         |

**Supplementary Table 4. Qualifying variants identified in PROFILE.**

| Variant          | Gene         | HGVSp               | HGVSp              | Effect                               | GnomADg AF | CADD  | Alpha Missense | Condel              | Primate AI | REVEL | ClinVar Sig                                                | ACMG Class |
|------------------|--------------|---------------------|--------------------|--------------------------------------|------------|-------|----------------|---------------------|------------|-------|------------------------------------------------------------|------------|
| 16_14617651_C_T  | <i>PARN</i>  | c.145-1G>A          |                    | splice acceptor                      | .          | 33    | .              | .                   | .          | .     | .                                                          | LP         |
| 16_14627163_G_C  | <i>PARN</i>  | c.87C>G             | p.Phe29Leu         | missense                             | .          | 26.3  | .              | deleterious (0.999) | 0.81       | 0.64  | .                                                          | LP         |
| 16_14628170_GC_G | <i>PARN</i>  | c.-7+1del           |                    | splice donor                         | .          | .     | .              | .                   | .          | .     | .                                                          | P          |
| 16_14628181_C_G  | <i>PARN</i>  | c.168G>C            | p.Lys56Asn         | missense                             | 2.43E-05   | 23.1  | 0.969          | deleterious (0.895) | 0.84       | 0.188 | uncertain significance                                     | VUS        |
| 16_14629675_C_T  | <i>PARN</i>  | c.-164-1G>A         |                    | splice acceptor                      | .          | 34    | .              | .                   | .          | .     | .                                                          | LP         |
| 8_22163546_GGT_G | <i>SFTPC</i> | c.435+12_435+13 del |                    | splice donor                         | 0.000588   | 24.5  | .              | .                   | .          | .     | .                                                          | LP         |
| 8_22163988_C_G   | <i>SFTPC</i> | c.541C>G            | p.Leu181Val        | missense                             | 0.000507   | 23.9  | 0.1813         | deleterious (0.998) | 0.53       | 0.65  | conflicting interpretations of pathogenicity&likely benign | VUS        |
| 8_22164440_C_A   | <i>SFTPC</i> | c.451C>A            | p.Pro151Thr        | missense                             | 7.59E-05   | 17.12 | .              | .                   | .          | 0.047 | uncertain significance                                     | VUS        |
| 3_44784844_G_A   | <i>KIF15</i> | c.362-1G>A          |                    | splice acceptor                      | 5.72E-05   | 35    | .              | .                   | .          | .     | .                                                          | LP         |
| 3_44797853_C_T   | <i>KIF15</i> | c.995C>T            | p.Ala332Val        | missense                             | 7.97E-06   | 27    | 0.8287         | deleterious (0.994) | 0.81       | 0.796 | .                                                          | LP         |
| 3_44801792_G_T   | <i>KIF15</i> | c.1327G>T           | p.Glu443Ter        | stop gained                          | 2.02E-05   | 38    | .              | .                   | .          | .     | .                                                          | LP         |
| 3_44801870_C_T   | <i>KIF15</i> | c.1405C>T           | p.Arg469Cys        | missense                             | 1.20E-05   | 29.6  | 0.13           | deleterious (0.978) | 0.60       | 0.576 | .                                                          | VUS        |
| 3_44830971_G_A   | <i>KIF15</i> | c.3124G>A           | p.Asp1042Asn       | missense                             | 1.59E-05   | 24.5  | 0.0846         | deleterious (0.736) | 0.45       | 0.159 | .                                                          | VUS        |
| 3_44841171_TG_T  | <i>KIF15</i> | c.3520del           | p.Glu1174AsnfsTer4 | frameshift                           | 3.98E-06   | .     | .              | .                   | .          | .     | .                                                          | LP         |
| 3_44851858_G_A   | <i>KIF15</i> | c.3878G>A           | p.Arg1293Gln       | missense                             | 1.59E-05   | 26.1  | 0.1084         | deleterious (1.000) | 0.42       | 0.257 | .                                                          | VUS        |
| 3_44851941_A_G   | <i>KIF15</i> | c.3961A>G           | p.Arg1321Gly       | missense                             | 7.99E-06   | 25.6  | 0.1275         | deleterious (0.520) | 0.36       | 0.103 | .                                                          | VUS        |
| 20_63661942_C_T  | <i>RTEL1</i> | c.394C>T            | p.Arg132Cys        | missense & splice region             | 3.98E-06   | 32    | .              | deleterious (0.574) | 0.43       | 0.645 | uncertain significance                                     | VUS        |
| 20_63665301_G_A  | <i>RTEL1</i> | n.235+1G>A          |                    | splice donor & non coding transcript | .          | 1.042 | .              | .                   | .          | .     | .                                                          | VUS        |
| 20_63679869_C_T  | <i>RTEL1</i> | c.389C>T            | p.Ala130Val        | missense                             | 2.01E-05   | 26.7  | .              | deleterious (0.917) | 0.49       | 0.591 | uncertain significance                                     | LP         |

**Supplementary Table 4. Qualifying variants identified in PROFILE.**

| Variant                                                                                                                   | Gene          | HGVSp             | HGVSp              | Effect                                                          | GnomADg AF | CADD  | Alpha Missense | Condel              | Primate AI | REVEL | ClinVar Sig                                | ACMG Class |
|---------------------------------------------------------------------------------------------------------------------------|---------------|-------------------|--------------------|-----------------------------------------------------------------|------------|-------|----------------|---------------------|------------|-------|--------------------------------------------|------------|
| 20_63679873_AG_A                                                                                                          | <i>RTEL1</i>  | c.394del          | p.Ala132ProfsTer99 | frameshift                                                      | .          | .     | .              | .                   | .          | .     | .                                          | LP         |
| 20_63680717_C_G                                                                                                           | <i>RTEL1</i>  | c.520C>G          | p.Gln174Glu        | missense & splice region                                        | 0.000595   | 24.4  | .              | deleterious (0.528) | 0.50       | 0.426 | uncertain significance                     | LP         |
| 20_63685567_AGC<br>AGGGCTGGGGGC<br>CTTACAGTCCTAT<br>AAGGTAGGGGCC<br>ACCTCCAGGAGG<br>CAGGTGGAGGGC<br>AGCCCTTGTTCC<br>CCG A | <i>RTEL1</i>  | c.597+3_597+80del |                    | splice donor & splice donor 5th base & coding sequence & intron | .          | .     | .              | .                   | .          | .     | .                                          | LP         |
| 20_63685593_A_G                                                                                                           | <i>RTEL1</i>  | c.593A>G          | p.Tyr198Cys        | missense                                                        | .          | 29    | .              | deleterious (0.998) | 0.63       | 0.808 | .                                          | LP         |
| 20_63685825_C_T                                                                                                           | <i>RTEL1</i>  | c.632C>T          | p.Thr211Met        | missense                                                        | 0.000454   | 16.46 | .              | deleterious (0.629) | 0.33       | 0.251 | uncertain significance                     | VUS        |
| 20_63689531_GA_G                                                                                                          | <i>RTEL1</i>  | c.1241del         | p.Asn414MetfsTer5  | frameshift                                                      | .          | .     | .              | .                   | .          | .     | .                                          | P          |
| 20_63689787_C_G                                                                                                           | <i>RTEL1</i>  | c.1394C>G         | p.Ser465Cys        | missense                                                        | 4.05E-06   | 26.8  | .              | deleterious (0.956) | 0.50       | 0.77  | uncertain significance                     | LP         |
| 20_63690206_G_A                                                                                                           | <i>RTEL1</i>  | c.1592G>A         | p.Arg531Gln        | missense                                                        | 0.000152   | 19.86 | .              | deleterious (0.513) | 0.37       | 0.055 | uncertain significance                     | LP         |
| 20_63693211_C_T                                                                                                           | <i>RTEL1</i>  | c.2251C>T         | p.Arg751Ter        | stop gained                                                     | 3.21E-05   | 39    | .              | .                   | .          | .     | pathogenic                                 | P          |
| 20_63693247_C_T                                                                                                           | <i>RTEL1</i>  | c.2287C>T         | p.Arg763Ter        | stop gained                                                     | 7.24E-05   | 36    | .              | .                   | .          | .     | pathogenic/ likely pathogenic & pathogenic | P          |
| 20_63694447_ACC<br>AGGGCAGGCCCC<br>ACCTGTCGC A                                                                            | <i>RTEL1</i>  | c.2405_2427del    | p.Gly802AlafsTer34 | frameshift                                                      | .          | .     | .              | .                   | .          | .     | .                                          | P          |
| 20_63694866_C_T                                                                                                           | <i>RTEL1</i>  | c.2566C>T         | p.Leu856Phe        | missense                                                        | 8.05E-06   | 15.6  | .              | neutral (0.163)     | 0.49       | 0.187 | .                                          | VUS        |
| 10_79557237_T_C                                                                                                           | <i>SFPA2</i>  | c.719A>G          | p.Tyr240Cys        | missense                                                        | .          | 22.5  | 0.3139         | deleterious (0.816) | 0.42       | 0.062 | .                                          | VUS        |
| 10_79560362_A_G                                                                                                           | <i>SFPA2</i>  | c.-54+2T>C        |                    | splice donor                                                    | .          | 23.9  | .              | .                   | .          | .     | .                                          | VUS        |
| 12_122474027_C_T                                                                                                          | <i>ZCCHC8</i> | c.880G>A          | p.Glu294Lys        | missense                                                        | .          | 22.9  | .              | deleterious (0.528) | 0.58       | 0.139 | .                                          | VUS        |
| 4_163128979_A_C                                                                                                           | <i>NAF1</i>   | c.1403T>G         | p.Leu468Arg        | missense                                                        | 5.49E-06   | 19.09 | 0.2804         | deleterious (0.636) | 0.57       | 0.13  | .                                          | VUS        |

**Supplementary Table 4. Qualifying variants identified in PROFILE.**

| Variant            | Gene         | HGVSp      | HGVSp       | Effect                        | GnomADg AF | CADD  | Alpha Missense | Condel              | Primate AI | REVEL | ClinVar Sig            | ACMG Class |
|--------------------|--------------|------------|-------------|-------------------------------|------------|-------|----------------|---------------------|------------|-------|------------------------|------------|
| 4_163129003_G_C    | <i>NAFI</i>  | c.1379C>G  | p.Pro460Arg | missense                      | 0.000129   | 19.87 | 0.158          | deleterious (0.989) | 0.68       | 0.059 | .                      | VUS        |
| 4_163133221_T_G    | <i>NAFI</i>  | c.966A>C   | p.Glu322Asp | missense                      | 0.00043    | 24.2  | 0.3312         | deleterious (0.940) | 0.48       | 0.144 | .                      | VUS        |
| 4_163133241_C_G    | <i>NAFI</i>  | c.946G>C   | p.Asp316His | missense                      | .          | 27.1  | 0.9948         | deleterious (1.000) | 0.79       | 0.86  | .                      | VUS        |
| 4_163164384_C_T    | <i>NAFI</i>  | c.373G>A   | p.Asp125Asn | missense                      | 0.000767   | 24.9  | 0.1694         | deleterious (0.530) | 0.84       | 0.145 | .                      | VUS        |
| 4_163164392_C_T    | <i>NAFI</i>  | c.366-1G>A |             | splice acceptor               | .          | 34    | .              | .                   | .          | .     | .                      | LP         |
| 4_163166459_G_A    | <i>NAFI</i>  | c.269C>T   | p.Pro90Leu  | missense                      | 4.81E-05   | 16.81 | 0.081          | deleterious (0.477) | 0.56       | 0.027 | .                      | VUS        |
| 5_169588441_C_T    | <i>SPDL1</i> | c.25C>T    | p.Leu9Phe   | missense                      | .          | 25.2  | 0.3016         | deleterious (1.000) | 0.47       | 0.286 | .                      | VUS        |
| 5_169588492_T_C    | <i>SPDL1</i> | c.74+2T>C  |             | splice donor & NMD transcript | 3.58E-05   | 27.3  | .              | .                   | 0.68       | .     | .                      | VUS        |
| 5_169588558_A_G    | <i>SPDL1</i> | c.142A>G   | p.Met48Val  | missense                      | 4.01E-06   | 23.2  | 0.162          | deleterious (0.536) | 0.53       | 0.091 | .                      | VUS        |
| 5_169591177_C_T    | <i>SPDL1</i> | c.289C>T   | p.Gln97Ter  | stop gained                   | .          | 35    | .              | .                   | .          | .     | .                      | LP         |
| 5_169591225_G_A    | <i>SPDL1</i> | c.336+1G>A |             | splice donor                  | 8.00E-06   | 33    | .              | .                   | .          | .     | .                      | VUS        |
| 5_169594221_G_T    | <i>SPDL1</i> | c.608G>T   | p.Arg203Leu | missense                      | 0.000442   | 24.7  | 0.1523         | deleterious (0.550) | 0.24       | 0.063 | .                      | VUS        |
| 5_169594287_C_T    | <i>SPDL1</i> | c.674C>T   | p.Ala225Val | missense                      | 0.0002     | 23    | 0.2653         | deleterious (0.999) | 0.54       | 0.233 | .                      | VUS        |
| 5_169596559_A_G    | <i>SPDL1</i> | c.892-2A>G |             | splice acceptor               | 0.000469   | 35    | .              | .                   | .          | .     | likely benign          | VUS        |
| 5_169599042_G_A    | <i>SPDL1</i> | c.1207G>A  | p.Ala403Thr | missense                      | .          | 21.1  | 0.1016         | deleterious (0.479) | 0.57       | 0.057 | .                      | VUS        |
| 3_169764827_G_A    | <i>TERC</i>  | n.221C>T   |             | non coding transcript exon    | .          | 15.5  | .              | .                   | .          | .     | uncertain significance | VUS        |
| 3_169764881_G_A    | <i>TERC</i>  | n.167C>T   |             | non coding transcript exon    | .          | 22.5  | .              | .                   | .          | .     | pathogenic             | VUS        |
| 3_169765024_T_A, C | <i>TERC</i>  | n.24A>T    |             | non coding transcript exon    | 1.30E-05   | 7.742 | .              | .                   | .          | .     | uncertain significance | LP         |

Supplementary Table 4. Qualifying variants identified in PROFILE.

| Variant         | Gene | HGVSp   | HGVSp | Effect                           | GnomADg<br>AF | CADD | Alpha<br>Missense | Condel | Primate<br>AI | REVEL | ClinVar Sig               | ACMG<br>Class |
|-----------------|------|---------|-------|----------------------------------|---------------|------|-------------------|--------|---------------|-------|---------------------------|---------------|
| 3_169765026_G_A | TERC | n.22C>T |       | non coding<br>transcript<br>exon | 2.17E-05      | 2    | .                 | .      | .             | .     | uncertain<br>significance | VUS           |

HGVS, Human Genome Variation Society; VUS, variant of uncertain significance; P, pathogenic; LP, likely pathogenic

**Supplementary Table 5. Alternative definitions for qualifying variants and the rare synonymous used for sensitivity analyses.**

|                                               | Ultra-rare<br>PTV | Ultra-rare<br>Ensemble#<br>(PTV +<br>Missense +<br>Indel) | Rare<br>PTV<br>only | Rare<br>Ensemble#<br>(PTV +<br>Missense +<br>Indel) | Semi-rare<br>PTV<br>only | Semi-rare<br>Ensemble#<br>(PTV +<br>Missense +<br>Indel) | Rare<br>synonymous <sup>^</sup> |
|-----------------------------------------------|-------------------|-----------------------------------------------------------|---------------------|-----------------------------------------------------|--------------------------|----------------------------------------------------------|---------------------------------|
| Missense AF*                                  | -                 | 0                                                         | -                   | 0.0005                                              | -                        | 0.01                                                     | -                               |
| PTV AF*                                       | 0                 | 0                                                         | 0.001               | 0.001                                               | 0.01                     | 0.01                                                     | -                               |
| Consensus in silico prediction for missense:& |                   |                                                           |                     |                                                     |                          |                                                          |                                 |
| Polyphen2                                     | -                 | Probably                                                  | -                   | Probably                                            | -                        | Probably                                                 | -                               |
| Humdiv                                        | -                 | >0.5                                                      | -                   | >0.5                                                | -                        | >0.5                                                     | -                               |
| REVEL                                         | -                 | >0.8                                                      | -                   | >0.8                                                | -                        | >0.8                                                     | -                               |
| PrimateAI                                     | -                 | >0.8                                                      | -                   | >0.8                                                | -                        | >0.8                                                     | -                               |
| Variants (n)                                  | 13                | 30                                                        | 28                  | 67                                                  | 29                       | 78                                                       | 38                              |

\*Below threshold for any population in gnomAD v2.1 exomes (AFR, AMR, ASJ, EAS, FIN, NFE, OTH, SAS) or gnomAD v3.2 genomes (AFR, AMR, ASJ, EAS, FIN, MID, NFE, OTH, SAS) or in The 1000 Genomes Project Phase 3 genomes (AFR, AMR, EAS, EUR, SAS).

&Consensus of three predictors (Polyphen2, REVEL, PrimateAI) for missense variants only if >2 out of 3, or 2 out of 2, or 1 out of 1 filters pass. Some predictors may have missing values.

<sup>^</sup>Allele frequency cutoff of 0.0005 in any population in gnomAD v2.1 exomes (AFR, AMR, ASJ, EAS, FIN, NFE, OTH, SAS) or gnomAD v3.2 genomes (AFR, AMR, ASJ, EAS, FIN, MID, NFE, OTH, SAS) or in The 1000 Genomes Project Phase 3 genomes (AFR, AMR, EAS, EUR, SAS), only synonymous variants.

<sup>#</sup>Ensemble models include non-coding *TERC* variants selected if passing missense AF level and involved in intramolecular base-pairing or previously described in pulmonary fibrosis or dyskeratosis congenita or hoyeraal hreidarsson.

PTV: Protein truncating variants.

**Supplementary Table 6. Common IPF risk variants and effects considered for PRS-IPF estimation.**

| Locus           | SNP ID      | Chr. | Position (hg38) | Effect | Non-effect | OR   | p-value                 |
|-----------------|-------------|------|-----------------|--------|------------|------|-------------------------|
| <i>KIF15</i>    | rs141979279 | 3    | 44,816,639      | C      | T          | 1.50 | 1.21x10 <sup>-10</sup>  |
| <i>TERC</i>     | rs10936601  | 3    | 169,810,661     | C      | T          | 0.79 | 2.10x10 <sup>-15</sup>  |
| <i>FAM13A</i>   | rs2013701   | 4    | 88,963,935      | G      | T          | 1.25 | 4.60x10 <sup>-16</sup>  |
| <i>TERT</i>     | rs7725218   | 5    | 1,282,299       | G      | A          | 1.41 | 4.90x10 <sup>-32</sup>  |
| <i>DSP</i>      | rs2076295   | 6    | 7,562,999       | G      | T          | 1.49 | 1.50x10 <sup>-48</sup>  |
| <i>MAD1L1</i>   | rs12699415  | 7    | 1,869,843       | A      | G          | 1.27 | 7.85x10 <sup>-18</sup>  |
| <i>ZKSCAN1</i>  | rs2897075   | 7    | 100,032,719     | T      | C          | 1.30 | 1.77x10 <sup>-21</sup>  |
| <i>DEPTOR</i>   | rs28513081  | 8    | 119,921,886     | A      | G          | 1.20 | 1.22x10 <sup>-9</sup>   |
| <i>10q25.1</i>  | rs79684490  | 10   | 109,470,103     | A      | G          | 1.40 | 3.52x10 <sup>-8</sup>   |
| <i>MUC5B</i>    | rs35705950  | 11   | 1,219,991       | T      | G          | 5.06 | 9.09x10 <sup>-418</sup> |
| <i>ATP11A</i>   | rs12585036  | 13   | 112,881,427     | C      | T          | 1.29 | 5.99x10 <sup>-14</sup>  |
| <i>IVD</i>      | rs59424629  | 15   | 40,428,343      | T      | G          | 1.27 | 4.98x10 <sup>-19</sup>  |
| <i>KNL1</i>     | rs12912339  | 15   | 40,639,510      | A      | G          | 1.30 | 7.41x10 <sup>-13</sup>  |
| <i>AKAP13</i>   | rs62023891  | 15   | 85,553,985      | A      | G          | 1.18 | 1.32x10 <sup>-8</sup>   |
| <i>NPRL3</i>    | rs74614704  | 16   | 112,241         | A      | G          | 1.49 | 2.57x10 <sup>-12</sup>  |
| <i>17q21.31</i> | rs3785884   | 17   | 45,980,229      | G      | A          | 1.40 | 2.53x10 <sup>-20</sup>  |
| <i>DPP9</i>     | rs35574495  | 19   | 4,686,976       | G      | T          | 0.80 | 1.08x10 <sup>-9</sup>   |
| <i>STMN3</i>    | rs112087793 | 20   | 63,652,817      | C      | T          | 1.34 | 1.09x10 <sup>-8</sup>   |
| <i>RTEL1</i>    | rs41308092  | 20   | 63,693,038      | A      | G          | 1.75 | 3.13x10 <sup>-9</sup>   |

SNP: single nucleotide polymorphism; Chr.: chromosome; OR: odds ratio; p-value: significance in the original study



**Supplementary Table 7. Common telomere length variants and effects considered for PRS-TL estimation.**

| Locus               | SNP ID     | Chr. | Position (hg38) | Effect | Non-effect | Beta   | p-value                |
|---------------------|------------|------|-----------------|--------|------------|--------|------------------------|
| <i>PARP1</i>        | rs3219104  | 1    | 226374920       | C      | A          | 0.042  | 9.60x10 <sup>-11</sup> |
| <i>TERC</i>         | rs10936600 | 3    | 169796797       | T      | A          | -0.086 | 7.18x10 <sup>-51</sup> |
| <i>NAF1</i>         | rs4691895  | 4    | 163127047       | C      | G          | 0.058  | 1.58x10 <sup>-21</sup> |
| <i>TERT</i>         | rs7705526  | 5    | 1285859         | A      | C          | 0.082  | 5.34x10 <sup>-45</sup> |
| <i>TERT</i>         | rs2853677  | 5    | 1287079         | A      | G          | -0.064 | 3.35x10 <sup>-31</sup> |
| <i>POT1</i>         | rs59294613 | 7    | 124914213       | A      | C          | -0.041 | 1.17x10 <sup>-13</sup> |
| <i>STN1</i>         | rs9419958  | 10   | 103916188       | C      | T          | -0.064 | 5.05x10 <sup>-19</sup> |
| <i>ATM</i>          | rs228595   | 11   | 108234866       | A      | G          | -0.029 | 1.43x10 <sup>-8</sup>  |
| <i>DCAF4</i>        | rs2302588  | 14   | 72938044        | C      | G          | 0.048  | 1.68x10 <sup>-8</sup>  |
| <i>MPHOSPH6</i>     | rs7194734  | 16   | 82166375        | T      | C          | -0.037 | 6.94x10 <sup>-10</sup> |
| <i>ZNF208</i>       | rs8105767  | 19   | 22032639        | G      | A          | 0.039  | 5.42x10 <sup>-13</sup> |
| <i>RTEL1/STMN3</i>  | rs75691080 | 20   | 63638397        | T      | C          | -0.067 | 5.99x10 <sup>-14</sup> |
| <i>RTEL1</i>        | rs34978822 | 20   | 63660246        | G      | C          | -0.140 | 7.26x10 <sup>-10</sup> |
| <i>RTEL1/ZBTB46</i> | rs73624724 | 20   | 63805045        | C      | T          | 0.051  | 6.33x10 <sup>-12</sup> |
| <i>SEN7</i>         | Rs551442   | 3    | 101346524       | T      | C          | -0.037 | 2.45x10 <sup>-8</sup>  |
| <i>MOB1B</i>        | rs13137667 | 4    | 70908630        | C      | T          | 0.077  | 2.43x10 <sup>-8</sup>  |
| <i>CARMIL1</i>      | rs34991172 | 6    | 25480100        | G      | T          | -0.061 | 6.19x10 <sup>-9</sup>  |
| <i>PRRC2A</i>       | rs2736176  | 6    | 31619784        | C      | G          | 0.035  | 3.53x10 <sup>-10</sup> |
| <i>TERF2</i>        | rs3785074  | 16   | 69373083        | G      | A          | 0.035  | 4.64x10 <sup>-10</sup> |
| <i>RFWD3</i>        | rs62053580 | 16   | 74646176        | G      | A          | -0.039 | 4.08x10 <sup>-8</sup>  |

SNP: single nucleotide polymorphism; Chr.: chromosome; Beta: effect; p-value: significance in the original study

**Supplementary Table 8. Schoenfeld residuals test for proportionality assumption of the Cox models.**

| Model | Variable                               | PFFPR   | PROFILE |
|-------|----------------------------------------|---------|---------|
|       |                                        | p-value | p-value |
| 1     | <b>All variants</b>                    | 0.371   | 0.663   |
|       | Age                                    | 0.348   | 0.361   |
|       | Sex                                    | 0.947   | 0.386   |
|       | PC1                                    | 0.433   | 0.085   |
|       | PC2                                    | 0.660   | 0.793   |
|       | <i>MUC5B</i>                           | 0.356   | 0.890   |
|       | Smoking                                | 0.051   | 0.423   |
|       | FVC pred                               | 0.646   | 0.011   |
|       | DLCO pred                              | 0.587   | 0.013   |
|       | Global                                 | 0.313   | 0.054   |
| 2     | <b>Pathogenic variants</b>             | 0.817   | 0.709   |
|       | Age                                    | 0.349   | 0.300   |
|       | Sex                                    | 0.990   | 0.388   |
|       | PC1                                    | 0.418   | 0.065   |
|       | PC2                                    | 0.629   | 0.820   |
|       | <i>MUC5B</i>                           | 0.338   | 0.815   |
|       | Smoking                                | 0.052   | 0.439   |
|       | FVC pred                               | 0.616   | 0.012   |
|       | DLCO pred                              | 0.559   | 0.023   |
|       | Global                                 | 0.344   | 0.059   |
| 3     | <b>Telomeric</b>                       | 0.195   | 0.768   |
|       | Age                                    | 0.350   | 0.328   |
|       | Sex                                    | 0.953   | 0.392   |
|       | PC1                                    | 0.427   | 0.079   |
|       | PC2                                    | 0.635   | 0.806   |
|       | <i>MUC5B</i>                           | 0.339   | 0.956   |
|       | Smoking                                | 0.049   | 0.411   |
|       | FVC pred                               | 0.645   | 0.012   |
|       | DLCO pred                              | 0.587   | 0.016   |
|       | Global                                 | 0.236   | 0.058   |
| 4     | <b>Pathogenic telomeric variants</b>   | 0.945   | 0.331   |
|       | Age                                    | 0.350   | 0.277   |
|       | Sex                                    | 0.987   | 0.429   |
|       | PC1                                    | 0.418   | 0.064   |
|       | PC2                                    | 0.628   | 0.790   |
|       | <i>MUC5B</i>                           | 0.337   | 0.885   |
|       | Smoking                                | 0.052   | 0.409   |
|       | FVC pred                               | 0.617   | 0.012   |
|       | DLCO pred                              | 0.559   | 0.021   |
|       | Global                                 | 0.354   | 0.038   |
| 5     | <b>Non-telomere variants</b>           | 0.646   | 0.973   |
|       | Age                                    | 0.340   | 0.331   |
|       | Sex                                    | 0.970   | 0.361   |
|       | PC1                                    | 0.438   | 0.079   |
|       | PC2                                    | 0.654   | 0.722   |
|       | <i>MUC5B</i>                           | 0.335   | 0.954   |
|       | Smoking                                | 0.051   | 0.355   |
|       | FVC pred                               | 0.624   | 0.011   |
|       | DLCO pred                              | 0.567   | 0.014   |
|       | Global                                 | 0.324   | 0.049   |
| 6     | <b>Surfactant variants</b>             | 0.554   | 0.986   |
|       | Age                                    | 0.341   | 0.343   |
|       | Sex                                    | 0.987   | 0.365   |
|       | PC1                                    | 0.439   | 0.081   |
|       | PC2                                    | 0.687   | 0.730   |
|       | <i>MUC5B</i>                           | 0.328   | 0.927   |
|       | Smoking                                | 0.049   | 0.370   |
|       | FVC pred                               | 0.606   | 0.010   |
|       | DLCO pred                              | 0.547   | 0.013   |
|       | Global                                 | 0.308   | 0.050   |
| 7     | <b><i>RTEL1/TERT/PARN</i> variants</b> | 0.351   | 0.989   |
|       | Age                                    | 0.345   | 0.290   |
|       | Sex                                    | 0.982   | 0.424   |
|       | PC1                                    | 0.415   | 0.074   |
|       | PC2                                    | 0.625   | 0.767   |
|       | <i>MUC5B</i>                           | 0.341   | 0.975   |
|       | Smoking                                | 0.047   | 0.438   |

|    |                          |       |       |
|----|--------------------------|-------|-------|
| 8  | FVC pred                 | 0.630 | 0.012 |
|    | DLCO pred                | 0.573 | 0.016 |
|    | Global                   | 0.249 | 0.057 |
|    | <b>RTEL1 variants</b>    | 0.280 | 0.466 |
|    | Age                      | 0.350 | 0.341 |
|    | Sex                      | 0.98  | 0.417 |
|    | PC1                      | 0.42  | 0.072 |
|    | PC2                      | 0.62  | 0.770 |
|    | <i>MUC5B</i>             | 0.33  | 0.984 |
|    | Smoking                  | 0.05  | 0.389 |
| 9  | FVC pred                 | 0.63  | 0.010 |
|    | DLCO pred                | 0.57  | 0.015 |
|    | Global                   | 0.250 | 0.040 |
|    | <b>TERT variants</b>     | 0.665 | 0.119 |
|    | Age                      | 0.342 | 0.309 |
|    | Sex                      | 0.975 | 0.463 |
|    | PC1                      | 0.430 | 0.073 |
|    | PC2                      | 0.632 | 0.701 |
|    | <i>MUC5B</i>             | 0.322 | 0.797 |
|    | Smoking                  | 0.049 | 0.358 |
| 10 | FVC pred                 | 0.625 | 0.009 |
|    | DLCO pred                | 0.568 | 0.012 |
|    | Global                   | 0.329 | 0.032 |
|    | <b>PARN variants</b>     | 0.870 | 0.497 |
|    | Age                      | 0.348 | 0.341 |
|    | Sex                      | 0.988 | 0.360 |
|    | PC1                      | 0.423 | 0.082 |
|    | PC2                      | 0.624 | 0.730 |
|    | <i>MUC5B</i>             | 0.338 | 0.925 |
|    | Smoking                  | 0.048 | 0.373 |
| 11 | FVC pred                 | 0.628 | 0.011 |
|    | DLCO pred                | 0.571 | 0.013 |
|    | Global                   | 0.338 | 0.046 |
|    | <b>SPDL1 variants</b>    | 0.670 | 0.753 |
|    | Age                      | 0.342 | 0.296 |
|    | Sex                      | 0.978 | 0.358 |
|    | PC1                      | 0.436 | 0.076 |
|    | PC2                      | 0.621 | 0.730 |
|    | <i>MUC5B</i>             | 0.327 | 0.954 |
|    | Smoking                  | 0.051 | 0.366 |
| 12 | FVC pred                 | 0.626 | 0.011 |
|    | DLCO pred                | 0.571 | 0.016 |
|    | Global                   | 0.330 | 0.048 |
|    | <b>KIF15 variants</b>    | 0.800 | 0.610 |
|    | Age                      | 0.340 | 0.348 |
|    | Sex                      | 0.970 | 0.359 |
|    | PC1                      | 0.430 | 0.085 |
|    | PC2                      | 0.630 | 0.774 |
|    | <i>MUC5B</i>             | 0.320 | 0.895 |
|    | Smoking                  | 0.050 | 0.405 |
| 13 | FVC pred                 | 0.630 | 0.011 |
|    | DLCO pred                | 0.570 | 0.015 |
|    | Global                   | 0.350 | 0.057 |
|    | <b>ClinVar variants</b>  | 0.797 | 0.059 |
|    | Age                      | 0.342 | 0.242 |
|    | Sex                      | 0.964 | 0.440 |
|    | PC1                      | 0.424 | 0.065 |
|    | PC2                      | 0.631 | 0.704 |
|    | <i>MUC5B</i>             | 0.335 | 0.791 |
|    | Smoking                  | 0.049 | 0.436 |
| 14 | FVC pred                 | 0.632 | 0.009 |
|    | DLCO pred                | 0.575 | 0.013 |
|    | Global                   | 0.344 | 0.021 |
|    | <b>PRS-IPF tertile 1</b> | 0.990 | 0.989 |
|    | Age                      | 0.340 | 0.341 |
|    | Sex                      | 0.980 | 0.358 |
|    | PC1                      | 0.430 | 0.081 |
|    | PC2                      | 0.630 | 0.733 |
|    | <i>MUC5B</i>             | 0.320 | 0.932 |
|    | Smoking                  | 0.050 | 0.369 |
| 15 | FVC pred                 | 0.630 | 0.011 |
|    | DLCO pred                | 0.570 | 0.013 |
|    | Global                   | 0.180 | 0.050 |
|    | <b>PRS-IPF tertile 2</b> | 0.590 | 0.899 |
|    | Age                      | 0.340 | 0.316 |
|    | Sex                      | 0.980 | 0.346 |

|           |                          |       |       |
|-----------|--------------------------|-------|-------|
|           | PC1                      | 0.430 | 0.075 |
|           | PC2                      | 0.630 | 0.728 |
|           | <i>MUC5B</i>             | 0.320 | 0.950 |
|           | Smoking                  | 0.050 | 0.391 |
|           | FVC pred                 | 0.630 | 0.011 |
|           | DLCO pred                | 0.570 | 0.012 |
|           | Global                   | 0.280 | 0.017 |
| <b>16</b> | <b>PRS-IPF tertile 3</b> | 0.570 | 0.824 |
|           | Age                      | 0.340 | 0.356 |
|           | Sex                      | 0.980 | 0.410 |
|           | PC1                      | 0.430 | 0.071 |
|           | PC2                      | 0.630 | 0.699 |
|           | <i>MUC5B</i>             | 0.320 | 0.918 |
|           | Smoking                  | 0.050 | 0.402 |
|           | FVC pred                 | 0.630 | 0.010 |
|           | DLCO pred                | 0.570 | 0.014 |
|           | Global                   | 0.350 | 0.037 |

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FVC, forced vital capacity; DLCO, predicted diffusing capacity of the lungs for monoxide; PC: principal component

**Supplementary Table 9. Genomic predictors of whole-genome sequencing telomere length (WGS-TL) in multivariate linear regression model stratified by groups of carriers with qualifying variants.**

|                 | All variants |                |                       | Telomere variants |                |                       | Non-telomere variants |               |         |
|-----------------|--------------|----------------|-----------------------|-------------------|----------------|-----------------------|-----------------------|---------------|---------|
|                 | Beta         | 95% CI         | p-value               | Beta              | 95% CI         | p-value               | Beta                  | 95% CI        | p-value |
| <b>Carrier</b>  | -0.243       | -0.377, -0.108 | 4.21x10 <sup>-4</sup> | -0.360            | -0.513, -0.206 | 4.86x10 <sup>-6</sup> | 0.099                 | -0.143, 0.340 | 0.423   |
| <b>Age</b>      | -0.002       | -0.009, 0.004  | 0.495                 | -0.003            | -0.009, 0.004  | 0.385                 | 0.000                 | -0.007, 0.006 | 0.930   |
| <b>Male sex</b> | -0.011       | -0.126, 0.104  | 0.495                 | -0.022            | -0.136, 0.093  | 0.713                 | 0.001                 | -0.114, 0.117 | 0.985   |
| <b>PC1</b>      | 1.21         | -0.255, 2.67   | 0.105                 | 1.16              | -0.292, 2.62   | 0.117                 | 1.09                  | -0.386, 2.56  | 0.148   |
| <b>PC2</b>      | -0.683       | -2.16, 0.793   | 0.364                 | -0.458            | -1.93, 1.02    | 0.542                 | -0.672                | -2.16, 0.821  | 0.377   |

PC: principal component; CI: confidence interval.

**Supplementary Table 10. Results of the random effects models with the age at diagnosis as the frailty term.**

|                             | <b>PFFPR</b>                              | <b>PROFILE</b>                            |
|-----------------------------|-------------------------------------------|-------------------------------------------|
|                             | <b>HR (95% CI), p-value</b>               | <b>HR (95% CI), p-value</b>               |
| <b>All variants</b>         | 1.61 (1.04-2.50), p=0.03                  | 1.37 (0.99-1.90), p=0.06                  |
| <b>Pathogenic</b>           | 1.77 (0.96-3.26), p=0.07                  | 1.97 (1.27-3.04), p=2.40x10 <sup>-3</sup> |
| <b>Telomeric</b>            | 1.54 (0.95-2.50), p=0.08                  | 1.65 (1.14-2.38), p=7.30x10 <sup>-3</sup> |
| <b>Pathogenic telomeric</b> | 1.90 (1.00-3.63), p=0.05                  | 2.01 (1.27-3.20), p=3.10x10 <sup>-3</sup> |
| <b>Non-telomere</b>         | 1.67 (0.70-4.02), p=0.25                  | 0.85 (0.45-1.57), p=0.60                  |
| <b>Surfactant</b>           | 2.09 (0.45-9.72), p=0.35                  | 1.04 (0.95-3.35), p=0.94                  |
| <b>ClinVar</b>              | 1.42 (0.75-2.70), p=0.28                  | 2.49 (1.63-3.83), p=2.80x10 <sup>-5</sup> |
| <b>TERT/PARN/RTTEL1</b>     | 1.47 (0.85-2.55), p=0.17                  | 1.76 (1.17-2.65), p=6.30x10 <sup>-3</sup> |
| <b>RTTEL1</b>               | 1.34 (0.61-2.96), p=0.47                  | 1.51 (0.82-2.81), p=0.19                  |
| <b>TERT</b>                 | 1.01 (0.40-2.55), p=0.98                  | 3.53 (1.83-6.79), p=1.60x10 <sup>-4</sup> |
| <b>PARN</b>                 | 2.82 (0.90-8.84), p=0.07                  | 1.07 (0.49-2.32), p=0.87                  |
| <b>SPDL1</b>                | 1.98 (0.38-10.25), p=0.41                 | 0.60 (0.24-1.49), p=0.27                  |
| <b>KIF15</b>                | 1.22 (0.33-4.47), p=0.77                  | 1.54 (0.49-4.87), p=0.46                  |
| <b>MUC5B</b>                | 0.44 (0.31-0.64), p=1.50x10 <sup>-5</sup> | 0.59 (0.45-0.76), p=6.20x10 <sup>-5</sup> |
| <b>PRS (Tertile 1)</b>      | 1.82 (1.28-2.60), p=9.50x10 <sup>-4</sup> | 1.50 (1.15-1.95), p=2.90x10 <sup>-3</sup> |
| <b>PRS (Tertile 2)</b>      | 0.74 (0.49-1.11), p=0.15                  | 1.16 (0.89-1.51), p=0.28                  |
| <b>PRS (Tertile 3)</b>      | 0.66 (0.42-1.05), p=0.08                  | 0.59 (0.45-0.78), p=1.90x10 <sup>-4</sup> |

HR: hazard ratio; CI: confidence interval

**Supplementary Table 11. Results of the random effects models with the predicted FVC as the frailty term.**

|                         | PFFPR                                     | PROFILE                                   |
|-------------------------|-------------------------------------------|-------------------------------------------|
|                         | HR (95% CI), p-value                      | HR (95% CI), p-value                      |
| All variants            | 1.53 (1.12-2.10), p=7.20x10 <sup>-3</sup> | 1.67 (1.01-2.78), p=0.04                  |
| Pathogenic              | 1.75 (1.13-2.70), p=0.01                  | 2.19 (1.17-4.11), p=0.01                  |
| Telomeric               | 1.50 (1.06-2.13), p=0.02                  | 2.00 (1.14-3.53), p=0.02                  |
| Pathogenic telomeric    | 1.80 (1.16-2.81), p=9.30x10 <sup>-3</sup> | 2.60 (1.32-5.10), p=5.20x10 <sup>-3</sup> |
| Non-telomere            | 1.41 (0.80-2.48), p=0.24                  | 0.90 (0.36-2.24), p=0.83                  |
| Surfactant              | 1.71 (0.62-4.73), p=0.29                  | 2.02 (0.32-12.88), p=0.45                 |
| ClinVar                 | 1.38 (0.89-2.13), p=0.15                  | 3.11 (1.63-5.95), p=6.10x10 <sup>-4</sup> |
| <i>TERT/PARN/RTTEL1</i> | 1.48 (1.00-2.18), p=0.05                  | 2.14 (1.16-3.96), p=0.02                  |
| <i>RTTEL1</i>           | 1.40 (0.80-2.46), p=0.24                  | 2.14 (0.78-5.90), p=0.14                  |
| <i>TERT</i>             | 1.09 (0.57-2.07), p=0.79                  | 4.48 (1.66-1204), p=3.00x10 <sup>-3</sup> |
| <i>PARN</i>             | 2.38 (1.17-4.87), p=0.017                 | 0.88 (0.31-2.47), p=0.81                  |
| <i>SPDL1</i>            | 1.30 (0.48-3.53), p=0.61                  | 0.58 (0.15-2.16), p=0.42                  |
| <i>KIF15</i>            | 1.27 (0.52-3.11), p=0.60                  | 0.98 (0.19-5.13), p=0.98                  |
| <i>MUC5B</i>            | 0.54 (0.42-0.70), p=2.20x10 <sup>-6</sup> | 0.52 (0.35-0.76), p=6.00x10 <sup>-4</sup> |
| PRS (Tertile 1)         | 1.61 (1.26-2.08), p=1.70x10 <sup>-4</sup> | 1.82 (1.23-2.71), p=3.00x10 <sup>-3</sup> |
| PRS (Tertile 2)         | 0.76 (0.58-0.99), p=0.04                  | 1.10 (0.75-1.60), p=0.61                  |
| PRS (Tertile 3)         | 0.79 (1.25-0.61), p=0.10                  | 0.50 (0.34-0.75), p=7.30x10 <sup>-4</sup> |

FVC, forced vital capacity; HR: hazard ratio; CI: confidence interval.

**Supplementary Table 12. Results of the random effects models with the predicted DLCO as the frailty term.**

|                        | PFFPR                                     | PROFILE                                    |
|------------------------|-------------------------------------------|--------------------------------------------|
|                        | HR (95% CI), p-value                      | HR (95% CI), p-value                       |
| All variants           | 1.53 (1.12-2.10), p=7.20x10 <sup>-3</sup> | 1.69 (1.06-2.72), p=0.03                   |
| Pathogenic             | 1.71 (1.10-2.65), p=0.02                  | 2.29 (1.20-4.35), p=0.01                   |
| Telomeric              | 1.49 (1.05-2.12), p=0.03                  | 1.94 (1.13-3.32), p=0.02                   |
| Pathogenic telomeric   | 1.77 (1.13-2.76), p=0.01                  | 2.33 (1.15-4.70), p=0.02                   |
| Non-telomeric          | 1.45 (0.83-2.57), p=0.19                  | 1.04 (0.43-2.53), p=0.91                   |
| Surfactant             | 1.83 (0.66-5.07), p=0.25                  | 0.78 (0.14-4.21), p=0.77                   |
| ClinVar                | 1.36 (0.88-2.10), p=0.15                  | 2.46 (1.37-4.41), p=2.30x10 <sup>-3</sup>  |
| <i>TERT/PARN/RTEL1</i> | 1.46 (0.99-2.16), p=0.06                  | 1.95 (1.06-3.55), p=0.03                   |
| <i>RTEL1</i>           | 1.40 (0.80-2.47), p=0.24                  | 2.61 (0.91-7.50), p=0.07                   |
| <i>TERT</i>            | 1.08 (0.57-2.06), p=0.81                  | 3.11 (1.23-7.89), p=0.02                   |
| <i>PARN</i>            | 2.25 (1.09-4.64), p=0.03                  | 0.79 (0.27-2.27), p=0.66                   |
| <i>SPDL1</i>           | 1.30 (0.48-3.51), p=0.61                  | 0.95 (0.26-3.58), p=0.95                   |
| <i>KIF15</i>           | 1.27 (0.52-3.10), p=0.60                  | 1.54 (0.34-7.01), p=0.58                   |
| <i>MUC5B</i>           | 0.54 (0.42-0.70), p=2.70x10 <sup>-6</sup> | 0.54 (0.37-0.79), p=1.30x10 <sup>-3</sup>  |
| PRS (Tertile 1)        | 1.61 (1.26-2.07), p=1.80x10 <sup>-4</sup> | 1.90 (1.27-2.87), p=1.90x10 <sup>-3</sup>  |
| PRS (Tertile 2)        | 0.76 (0.58-0.99), p=0.05                  | 1.18 (0.80-1.77), p=0.40                   |
| PRS (Tertile 3)        | 0.79 (0.60-1.04), p=0.09                  | 0.43 (0.29-0.655), p=7.20x10 <sup>-5</sup> |

DLCO, diffusing capacity of the lungs for carbon monoxide; HR: hazard ratio; CI: confidence interval.



**Supplementary Table 13. Weighted Cox regression analysis in patients carrying rare qualifying variants in PROFILE.**

|                        | PROFILE                                   |
|------------------------|-------------------------------------------|
|                        | HR (95% CI), p-value                      |
| All variants           | 1.39 (0.98-1.98), p=0.061                 |
| Pathogenic             | 2.03 (1.37-3.00), p=4.40x10 <sup>-4</sup> |
| Telomeric              | 1.69 (1.17-2.46), p=5.57x10 <sup>-3</sup> |
| Pathogenic telomeric   | 2.14 (1.38-3.33), p=6.63x10 <sup>-4</sup> |
| Non-telomere           | 0.83 (0.41-1.70), p=0.62                  |
| Surfactant             | 1.03 (0.23-4.63), p=0.96                  |
| ClinVar                | 2.36 (1.55-3.60), p=6.30x10 <sup>-5</sup> |
| <i>TERT/PARN/RTEL1</i> | 1.79 (1.19-2.68), p=4.99x10 <sup>-3</sup> |
| <i>RTEL1</i>           | 1.62 (0.80-3.26), p=0.17                  |
| <i>TERT</i>            | 3.28 (1.96-5.47), p=5.87x10 <sup>-6</sup> |
| <i>PARN</i>            | 1.11 (0.58-2.15), p=0.75                  |
| <i>SPDL1</i>           | 0.60 (0.22-1.65), p=0.32                  |
| <i>KIF15</i>           | 1.49 (0.75-2.96), p=0.26                  |
| <i>MUC5B</i>           | 0.58 (0.44-0.76), p=8.39x10 <sup>-5</sup> |
| PRS (Tertile 1)        | 1.54 (1.16-2.03), p=2.98x10 <sup>-3</sup> |
| PRS (Tertile 2)        | 1.17 (0.89-1.55), p=0.26                  |
| PRS (Tertile 3)        | 0.57 (0.42-0.76), p=1.77x10 <sup>-4</sup> |

HR: hazard ratio; CI: Confidence interval.

**Supplementary Table 14. Cox regression analysis at 24, 36, 48 and 60 months (m) from diagnosis in patients carrying rare qualifying variants in PROFILE.**

|                     | 24 m                |                       | 36 m                |                       | 48 m                |                       | 60 m                |                       |
|---------------------|---------------------|-----------------------|---------------------|-----------------------|---------------------|-----------------------|---------------------|-----------------------|
|                     | HR<br>(95%CI)       | p-value               | HR<br>(95%CI)       | p-value               | HR<br>(95%CI)       | p-value               | HR<br>(95%CI)       | p-value               |
| <b>All variants</b> | 1.52<br>(0.98-2.38) | 0.064                 | 1.40<br>(0.96-2.06) | 0.082                 | 1.40<br>(0.99-1.97) | 0.058                 | 1.37<br>(0.99-1.89) | 0.058                 |
| <b>Pathogenic</b>   | 2.30<br>(1.33-3.98) | 2.93x10 <sup>-3</sup> | 1.94<br>(1.17-3.20) | 9.76x10 <sup>-3</sup> | 1.99<br>(1.26-3.14) | 3.04x10 <sup>-3</sup> | 1.98<br>(1.28-3.05) | 2.13x10 <sup>-3</sup> |
| <b>Telomeric</b>    | 1.80<br>(1.09-2.97) | 0.023                 | 1.59<br>(1.04-2.45) | 0.034                 | 1.69<br>(1.15-2.48) | 7.05x10 <sup>-3</sup> | 1.66<br>(1.15-2.38) | 6.60x10 <sup>-3</sup> |
| <b>ClinVar</b>      | 2.36<br>(1.27-4.37) | 6.62x10 <sup>-3</sup> | 1.99<br>(1.18-3.37) | 0.02                  | 2.16<br>(1.36-3.44) | 1.10x10 <sup>-3</sup> | 2.50<br>(1.63-3.83) | 2.70x10 <sup>-5</sup> |

HR: hazard ratio; CI: Confidence interval.

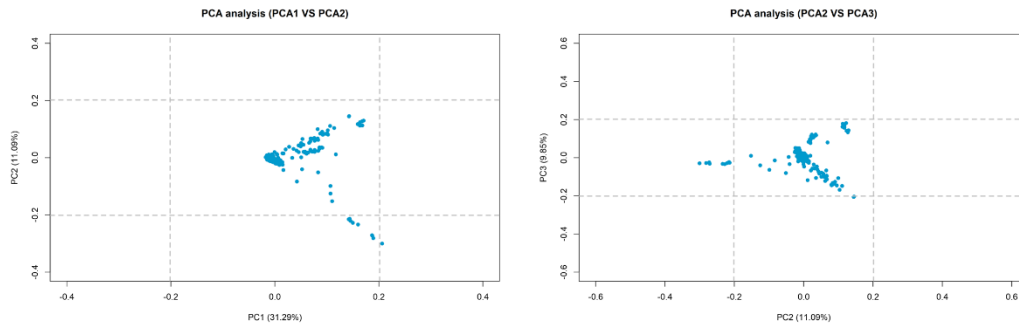
**Supplementary Table 15. Cox regression analysis at 60 months (m) from diagnosis in non-transplant patients carrying rare qualifying variants in PFFPR.**

|                      | 60 m                |         |
|----------------------|---------------------|---------|
|                      | HR<br>(95%CI)       | p-value |
| All variants (N=115) | 1.59<br>(1.08-2.35) | 0.020   |
| Pathogenic (N=47)    | 1.90<br>(1.11-3.26) | 0.020   |
| Telomeric (N=82)     | 1.55<br>(1.01-2.39) | 0.047   |
| ClinVar (N=47)       | 0.95<br>(0.50-1.81) | 0.871   |

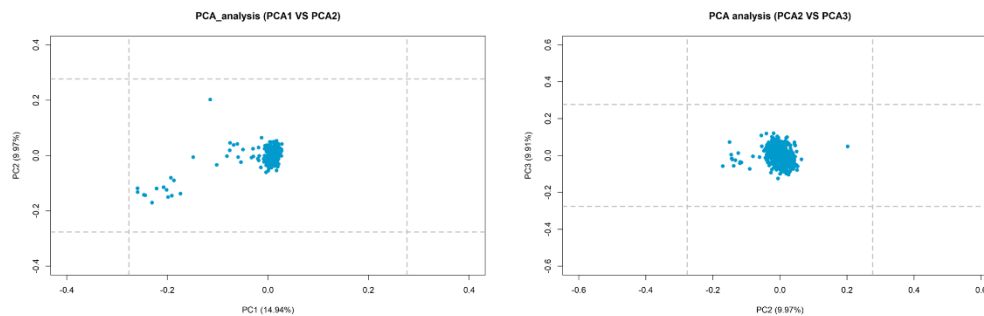
HR: hazard ratio; CI: Confidence interval.

# Supplementary Figures

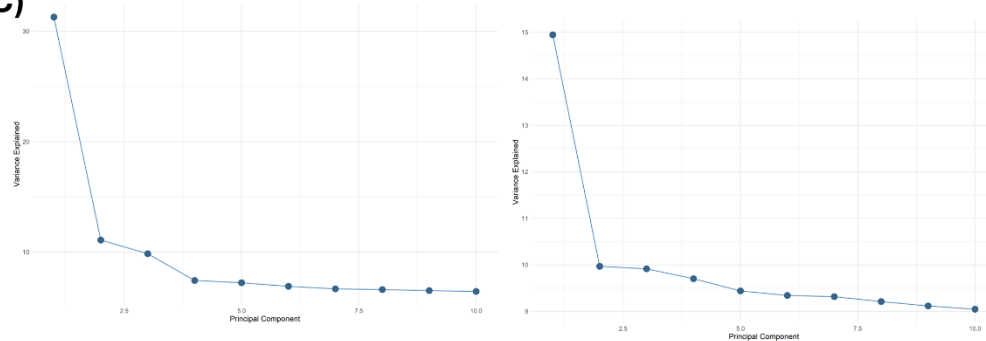
A)



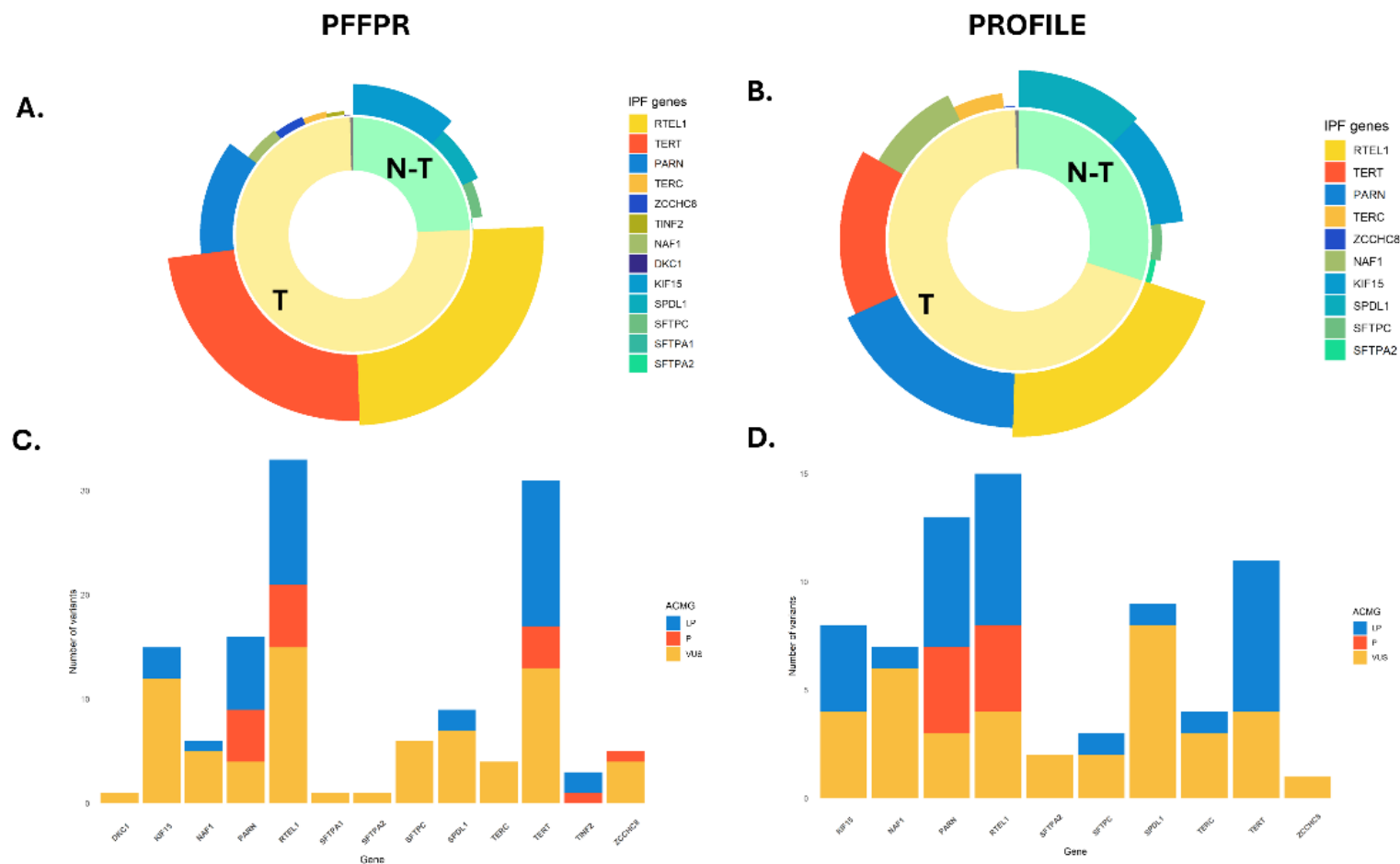
B)



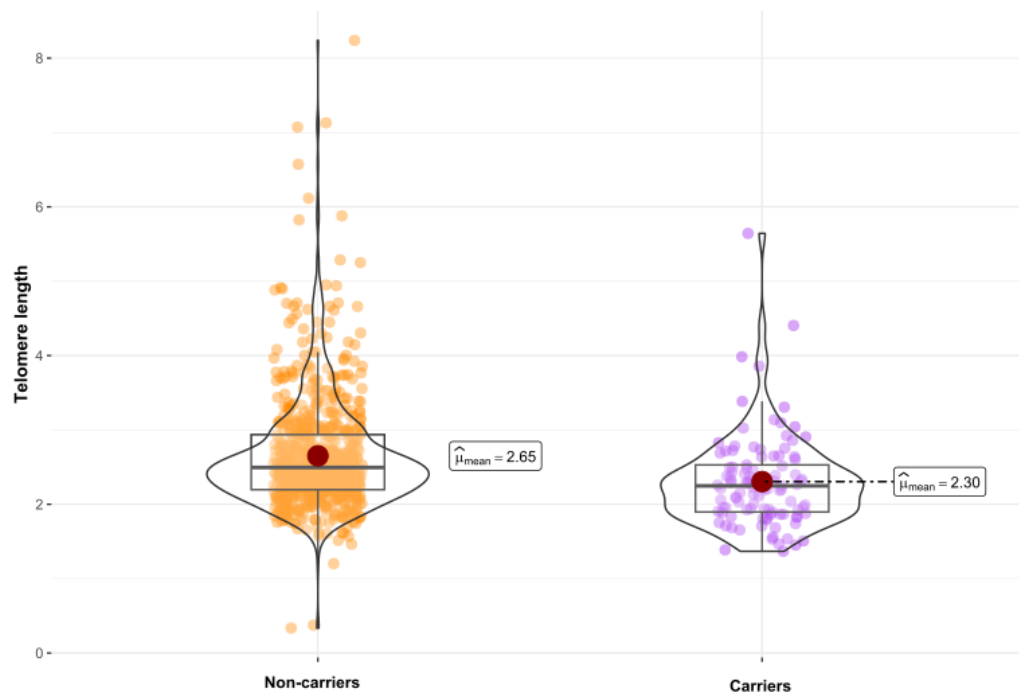
C)



**Supplementary Figure 1. Principal component analysis.** A) Plot of the first two (left) and the second and third (right) principal components of genetic variation of IPF patients in the PFFPR. B) Plot of the first two (left) and the second and third (right) principal components of genetic variation of IPF patient in PROFILE. C) Proportion of variance explained by each PC (PFFPR on the right, and PROFILE on the left).

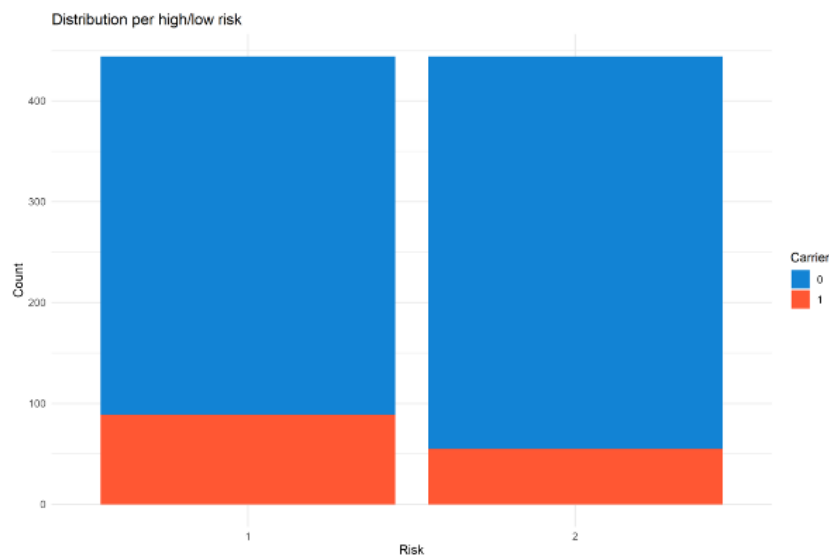


**Supplementary Figure 2. Distribution of qualifying variants (QV) in monogenic adult-onset pulmonary fibrosis (PF) genes in the PFFPR and PROFILE cohorts.** A) Total QVs in monogenic adult-onset PF genes in the PFFPR. B) Total QVs in monogenic adult-onset PF genes in the PROFILE cohort. C) Variants classified in P/LP/VUS per gene in the PFFPR. D) Variants classified in P/LP/VUS per gene in the PROFILE cohort. T: Telomere; N-T: Non-telomere.



**Supplementary Figure 3. Violin plots comparing telomere length estimated by whole-genome sequencing (WGS-TL) between carriers of qualifying variants in telomere genes and non-carriers.**

**A.**

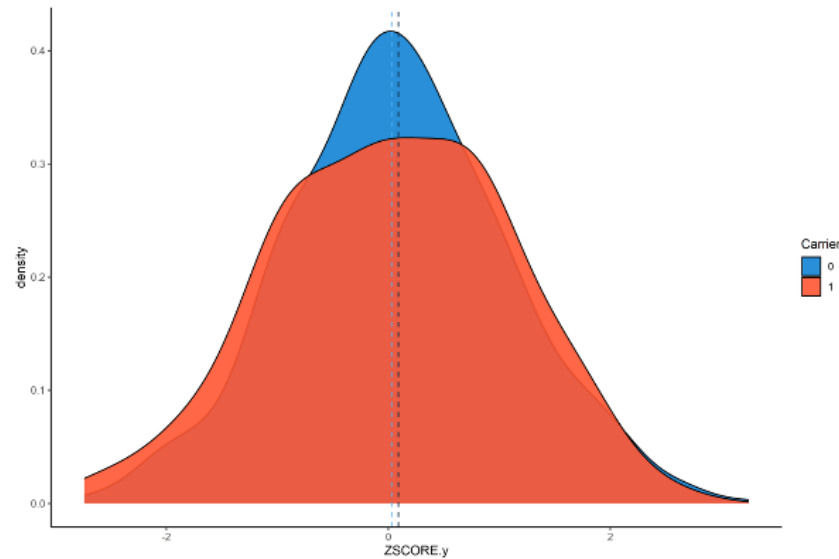


**B.**

|             | Low risk              | High risk |
|-------------|-----------------------|-----------|
| OR (95% CI) | 1.74 (1.20-2.53)      | reference |
| p-value     | $3.57 \times 10^{-3}$ | reference |

**Supplementary Figure 4. Association between prevalence of qualifying variants (QV) and PRS-IPF in the PFFPR.** A) Distribution of carriers (1) and non-carriers (0) in low and high PRS-IPF. B) Risk of carrying a QV in patients with low polygenic risk in comparison with individuals with high polygenic risk. The odds ratio (OR) and the 95% confidence interval (CI) were estimated using logistic regression adjusted by age of diagnosis, sex, and the two main principal components.

**A.**

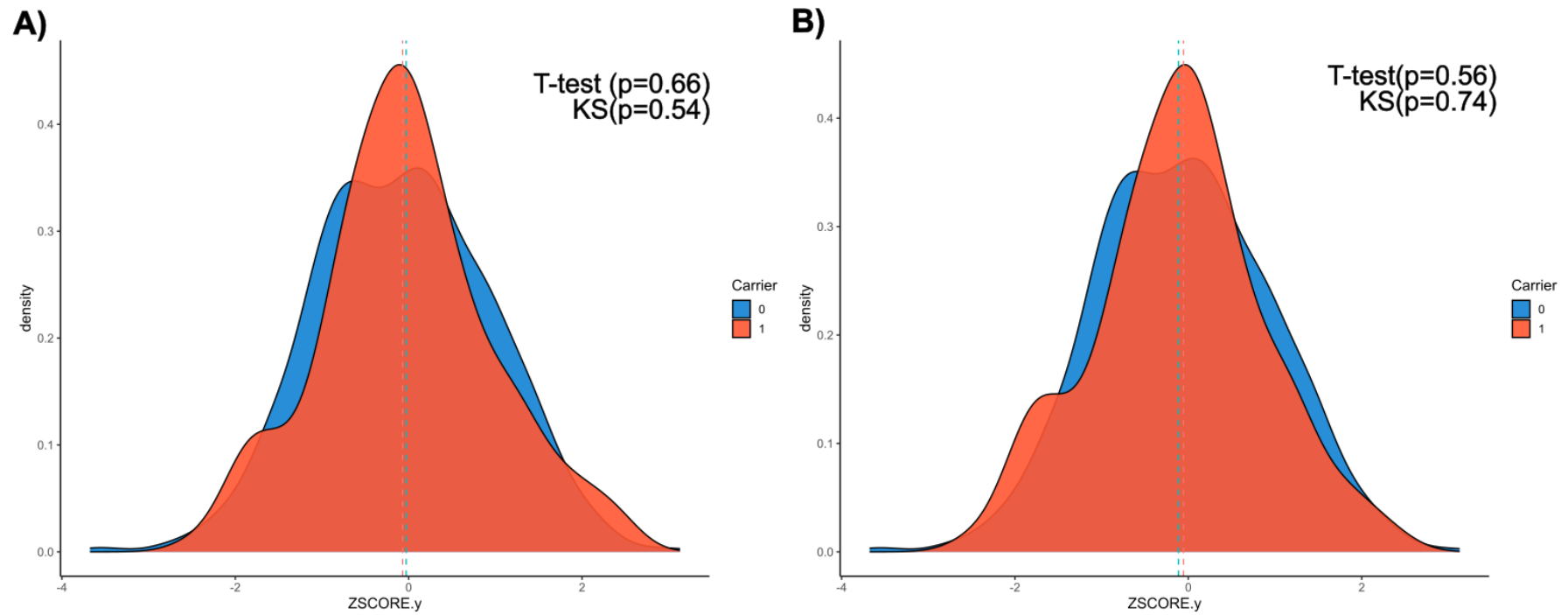


**B.**

|             | T1               | T2        | T3               |
|-------------|------------------|-----------|------------------|
| OR (95% CI) | 1.60 (1.01-2.54) | Reference | 1.46 (0.92-2.32) |
| p-value     | 0.05             | Reference | 0.11             |

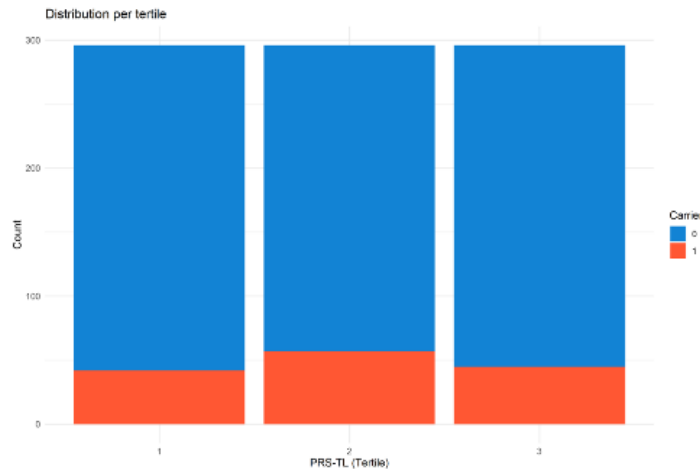
**Supplementary Figure 5. Association between prevalence of qualifying variants (QV) and PRS-IPF (after excluding the *MUC5B* locus) in the PFFPR.** A) Distribution of PRS-IPF in carriers (1) and non-carriers (0). Vertical dotted lines represent the mean value of the distribution. B) Risk of carrying a QV for patients with low polygenic risk (T1) and high polygenic risk (T3) compared to those in the middle tertile. The odds ratios (OR) and the 95% confidence intervals (CI) were estimated using logistic regression adjusted for age of diagnosis, sex, and the two main principal components.



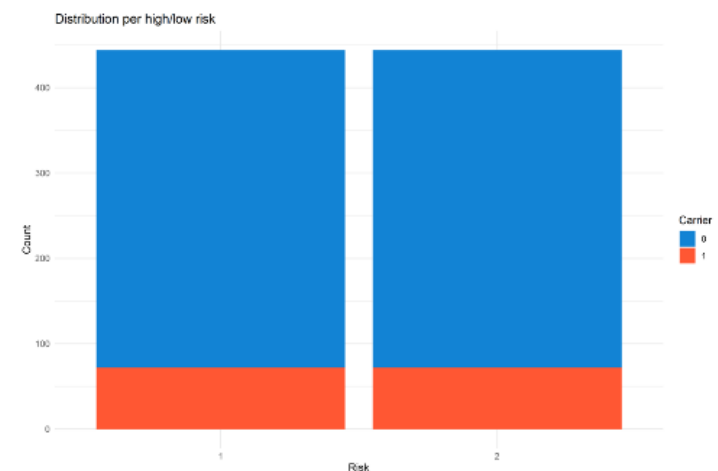


**Supplementary Figure 6. Association between the prevalence of qualifying variants (QV) and PRS-TL in the PFFPR.** Distribution of PRS-TL in carriers (1) and non-carriers (0). Vertical dotted lines represent the mean value of the distribution A) Carriers (1) and non-carriers (0) in telomere and non-telomere genes. B) Carriers (1) and non-carriers (0) in telomere genes. T-test: Student's t-test; KS: Kolmogorov-Smirnov test.

A)



C)



B)

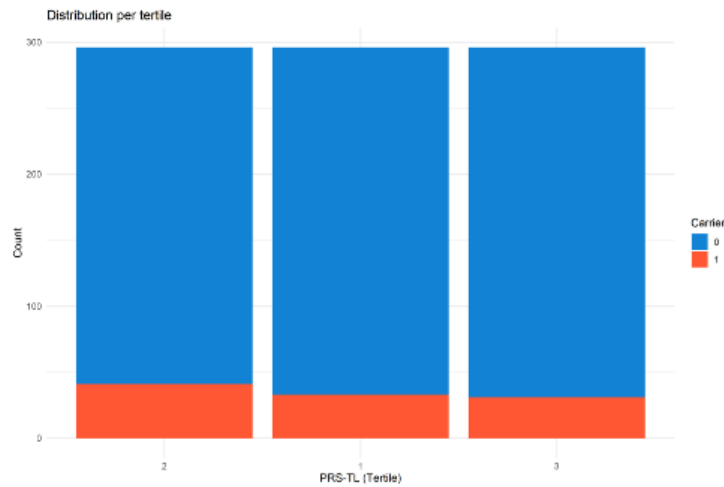
|             | T1               | T2        | T3               |
|-------------|------------------|-----------|------------------|
| OR (95% CI) | 0.71 (0.46-1.12) | Reference | 0.81 (0.53-1.26) |
| p-value     | 0.14             | Reference | 0.36             |

D)

|             | Low risk  | High risk        |
|-------------|-----------|------------------|
| OR (95% CI) | Reference | 1.01 (0.70-1.46) |
| p-value     | Reference | 0.95             |

**Supplementary Figure 7. Association between prevalence of qualifying variants (QV) in telomere and non-telomere genes and PRS-TL in the PFFPR.** A) Distribution of carriers (1) and non-carriers (0) in PRS-TL tertiles. B) Risk of carrying a QV for individuals with low polygenic risk (T1) and high polygenic risk (T3) compared to those in the middle tertile. C) Distribution of carriers (1) and non-carriers (0) in high and low PRS-TL. D) Risk of carrying a QV in patients with high polygenic risk in comparison with patients with low polygenic risk. The odds ratios (OR) and the 95% confidence intervals (CI) were estimated using logistic regression adjusted by age of diagnosis, sex, and the two main principal components.

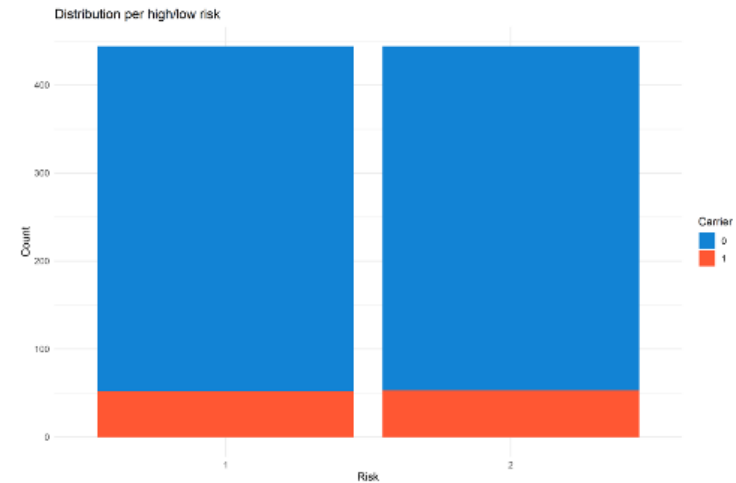
A)



B)

|             | T1               | T2        | T3               |
|-------------|------------------|-----------|------------------|
| OR (95% CI) | 0.81 (0.49-1.34) | Reference | 0.81 (0.49-1.35) |
| p-value     | 0.41             | Reference | 0.42             |

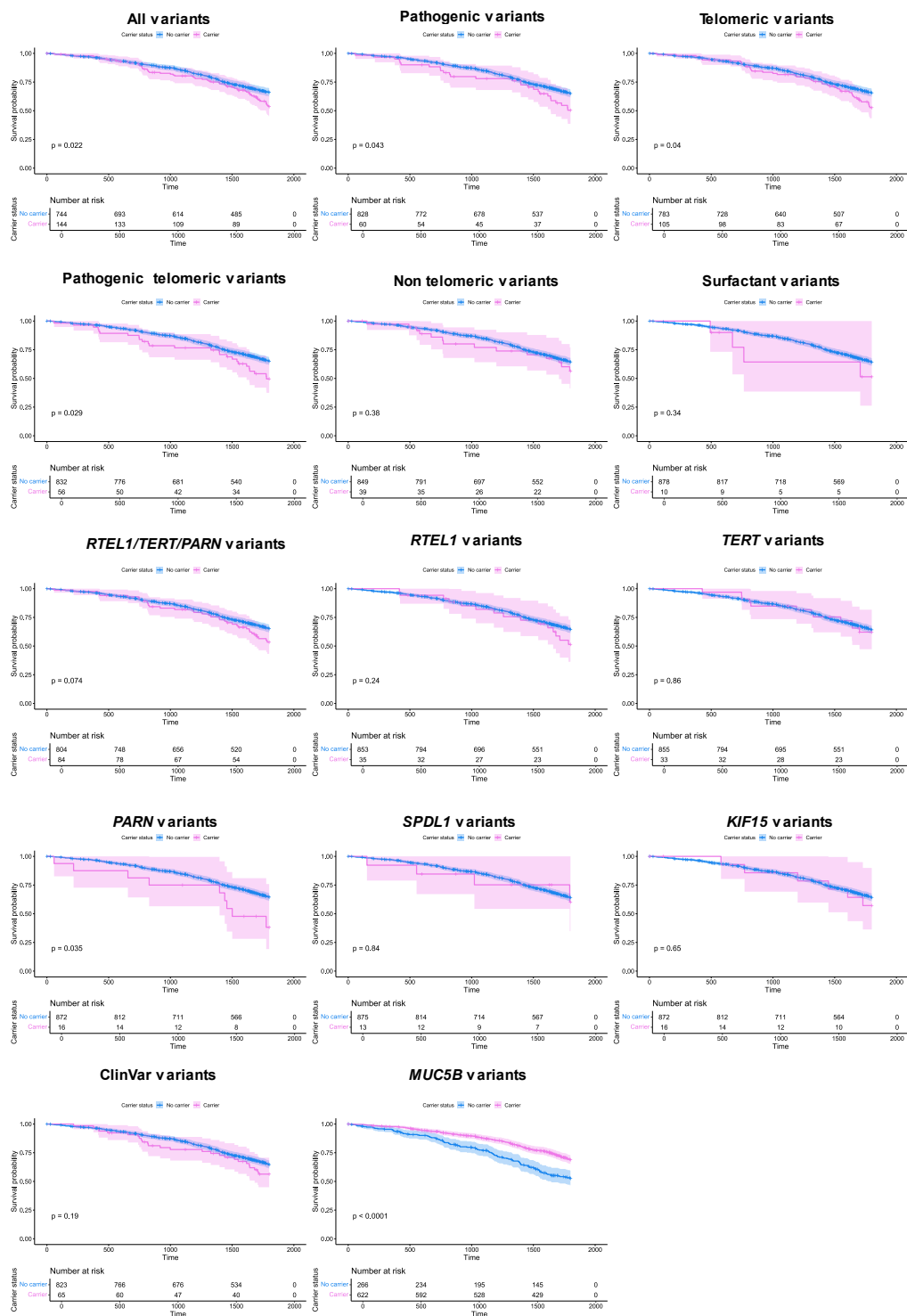
C)



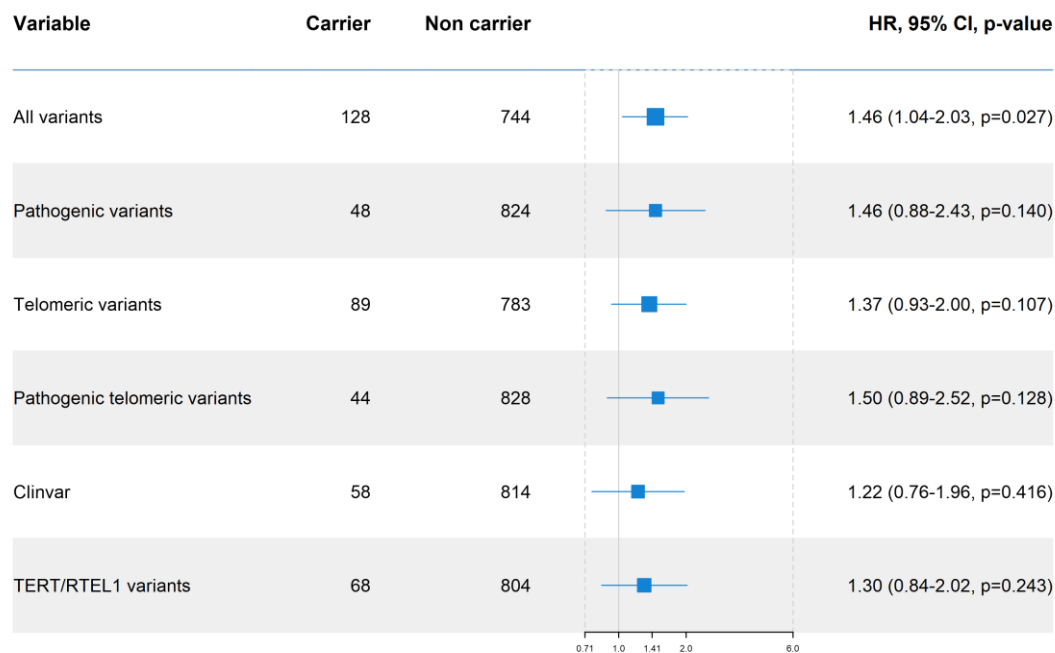
D)

|             | Low risk  | High risk        |
|-------------|-----------|------------------|
| OR (95% CI) | Reference | 1.04 (0.69-1.59) |
| p-value     | Reference | 0.83             |

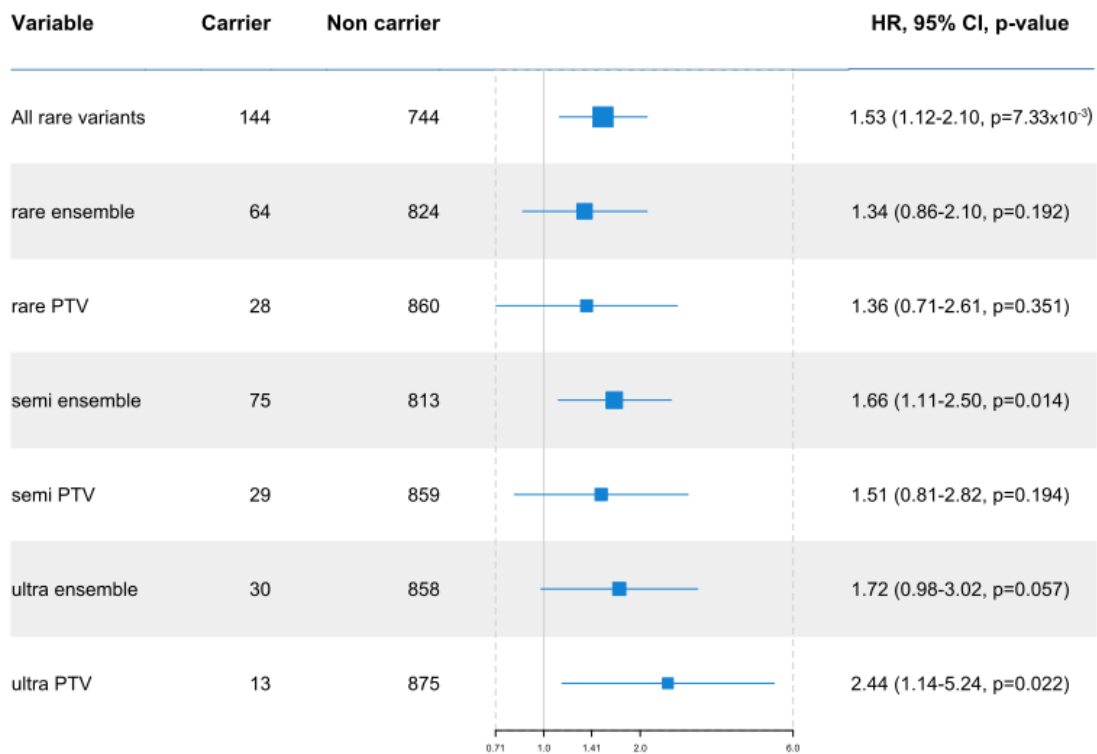
**Supplementary Figure 8. Association between prevalence of qualifying variants (QV) in telomere genes and PRS-TL in the PFFPR.** A) Distribution of carriers (1) and non-carriers (0) in PRS-TL tertiles. B) Risk of carrying a QV for individuals with low polygenic risk (T1) and high polygenic risk (T3) compared to those in the middle tertile. C) Distribution of carriers (1) and non-carriers (0) in high and low PRS-TL. D) Risk of carrying a QV in individuals with high polygenic risk in comparison with individuals with low polygenic risk. The odds ratios (OR) and the 95% confidence intervals (CI) were estimated using logistic regression adjusted by age of diagnosis, sex, and the two main principal components.



**Supplementary Figure 9. Kaplan-Meier survival analysis for qualifying variants (QV) (per gene and group of genes) and the *MUC5B* risk allele in the PFFPR. p-values for the log-rank test are shown.**

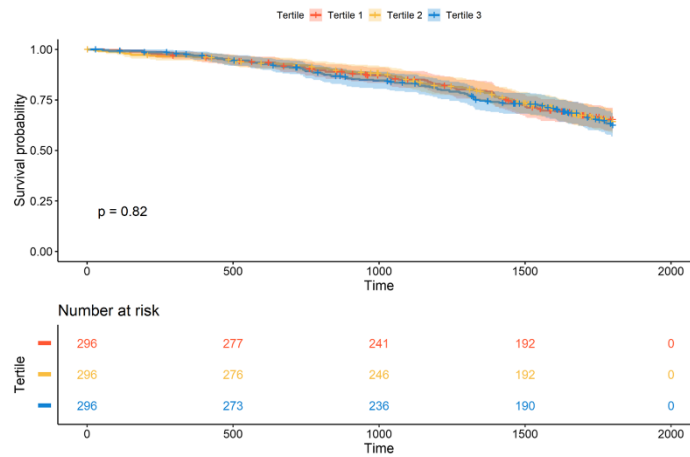


**Supplementary Figure 10. Qualifying variants (QV) effect on survival in the PFFPR (excluding carriers of QV within *PARN*).** All analysis were performed using Cox regression models adjusted for sex, age of diagnosis, the two main principal components, *MUC5B* risk allele, smoking history, forced vital capacity (FVC) % predicted, and diffusing capacity for carbon monoxide (DLCO) % predicted. The X-axis shows Hazard-ratios (HR); the grey solid line corresponds to the HR=1.0. The boxes correspond to adjusted HR and horizontal lines correspond to 95% confidence intervals (CI).

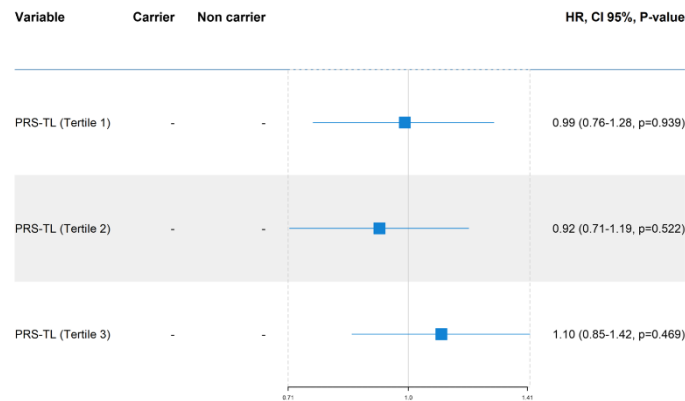


**Supplementary Figure 11. Alternative qualifying variants (QV) classifications and effects on survival in the PFFPR.** All analysis were performed using Cox regression models adjusted for sex, age of diagnosis, the two main principal components, *MUC5B* risk allele, smoking history, forced vital capacity (FVC) % predicted, and diffusing capacity for carbon monoxide (DLCO) % predicted. The X-axis shows Hazard-ratios (HR); the grey solid line corresponds to the HR=1.0. The boxes correspond to adjusted HR and horizontal lines correspond to 95% confidence intervals (CI).

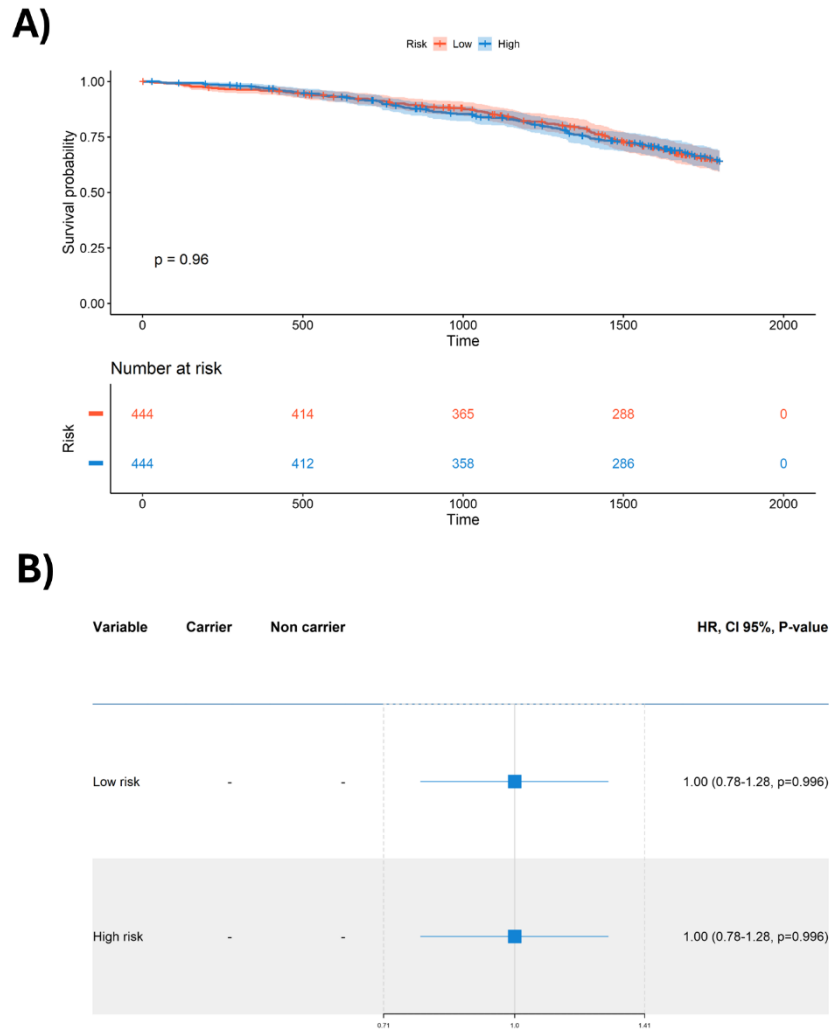
A)



B)

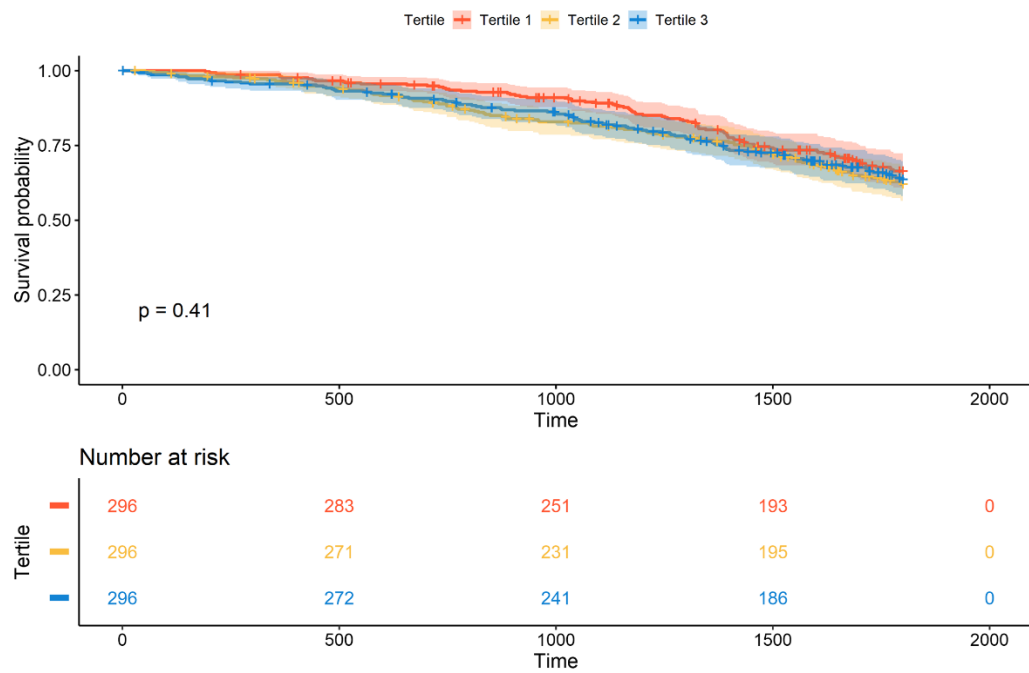


**Supplementary Figure 12. Association between PRS-TL tertiles and survival in the PFFPR.** A) Kaplan-Meier survival analysis for PRS-TL tertiles (p-value for the log-rank test is shown). B) PRS-TL effect on survival. The analysis was performed using Cox regression models adjusted for sex, age of diagnosis, the two main principal components, smoking history, forced vital capacity (FVC) % predicted, and diffusing capacity for carbon monoxide (DLCO) % predicted. The X-axis shows Hazard-ratios (HR); the grey solid line corresponds to the HR=1.0. The boxes correspond to adjusted HR and horizontal lines correspond to 95% confidence intervals (CI).

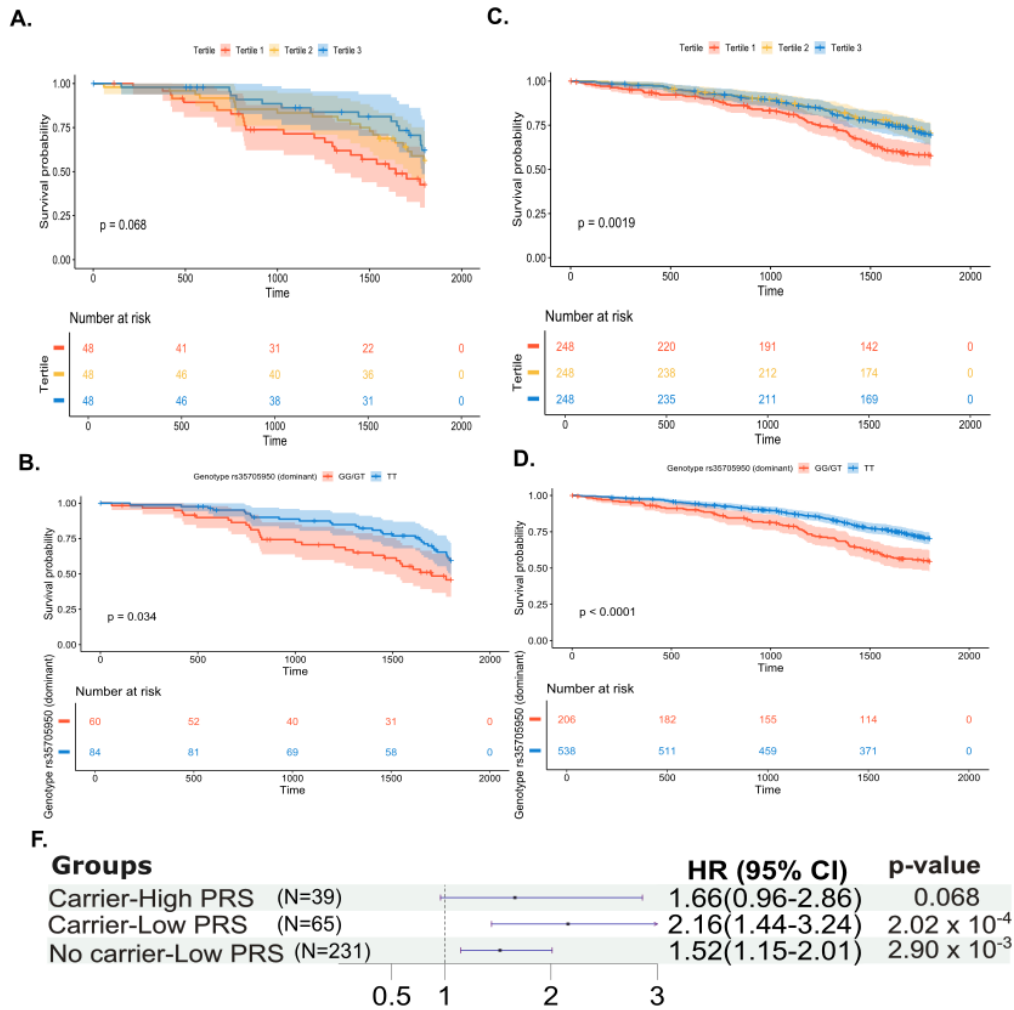


**Supplementary Figure 13. Association between high and low PRS-TL and survival in the PFFPR.** A) Kaplan-Meier survival analysis for high/low risk PRS-TL (p-value for the log-rank test is shown). B) PRS-TL effect on survival. The analysis was performed using Cox regression models adjusted for sex, age of diagnosis, the two main principal components, smoking history, forced vital capacity (FVC) % predicted, and diffusing capacity for carbon monoxide (DLCO) % predicted. The X-axis shows Hazard-ratios (HR); the grey solid line corresponds to the HR=1.0. The boxes correspond to adjusted HR and horizontal lines correspond to 95% confidence intervals (CI).

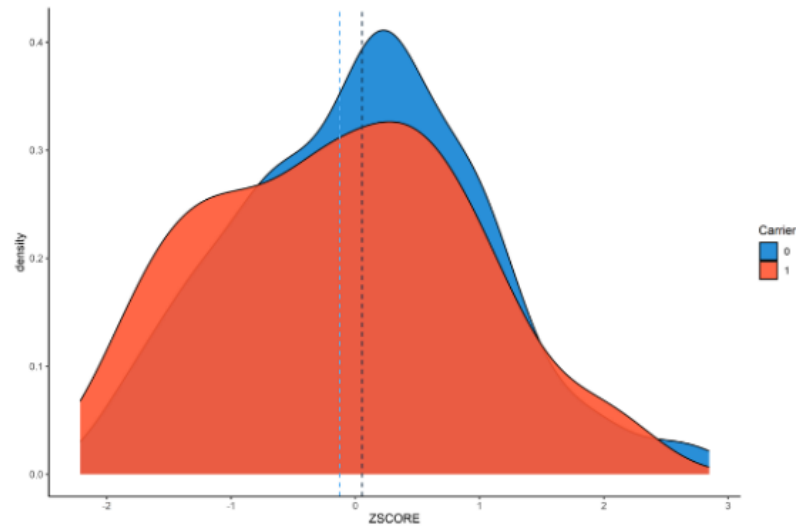
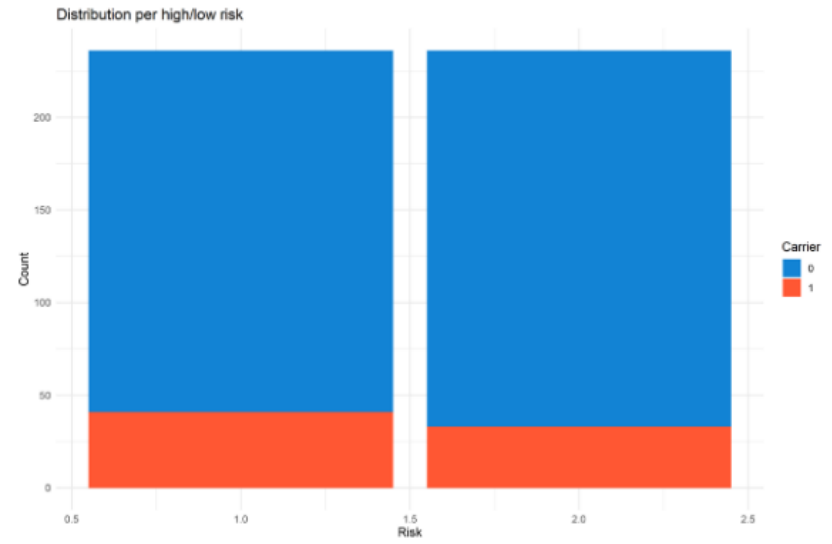




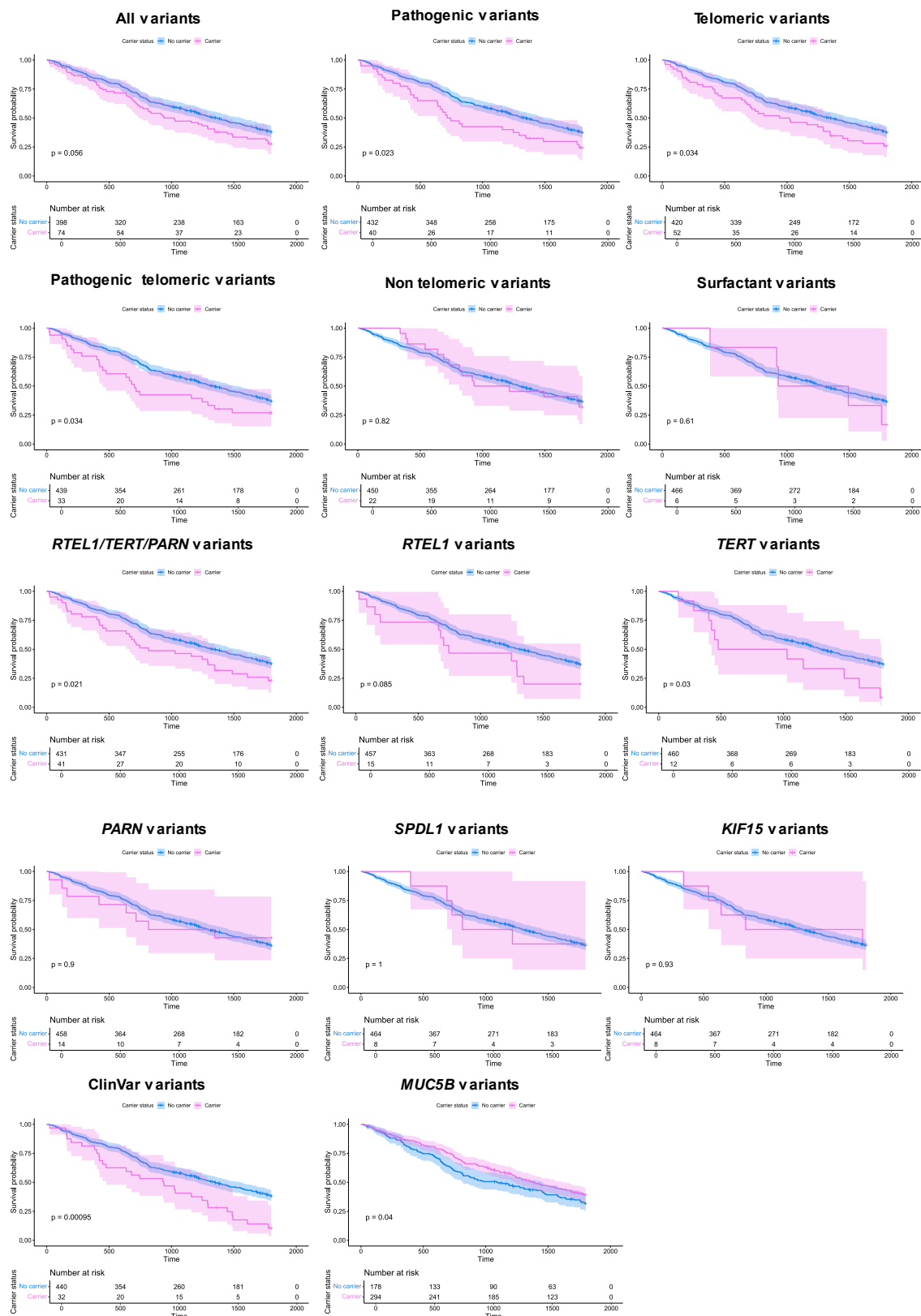
**Supplementary Figure 14. Association of PRS-IPF (after excluding the *MUC5B* locus) and survival in the PFFPR. Kaplan-Meier analysis showing p-values for the log-rank test.**



**Supplementary Figure 15. Associations between PRS-IPF and *MUC5B* rs35705950 genotypes with survival among carriers and non-carriers of qualifying variants (QV) in the PFFPR.** A) Association between PRS-IPF and survival in carriers. B) Association between PRS-IPF and survival in non-carriers. C) Association between *MUC5B* rs35705950 genotypes and survival in carriers. D) Association between *MUC5B* rs35705950 genotypes and survival in non-carriers. Kaplan-Meier analysis, showing p-values for the log-rank test. E) Cox regression analysis for subgroups of patients combining information of PRS-IPF and carrier status of QVs. The reference group was defined as non-carriers with high polygenic risk (N=257).

**A.****B.**

**Supplementary Figure 16. Association between prevalence of qualifying variants (QV) and PRS-IPF in PROFILE.** A) Distribution of PRS-IPF in carriers (1) and non-carriers (0). Vertical dotted lines represent the mean value of the distribution. B) Distribution of carriers (1) and non-carriers (0) in high and low PRS-IPF.



**Supplementary Figure 17. Kaplan-Meier survival analysis for qualifying variants (QV) (per gene and group PF genes) and the *MUC5B* risk allele in PROFILE. p-values for the log-rank test are shown.**

### Supplementary references

1. Wang, B. R. *et al.* The Pulmonary Fibrosis Foundation Patient Registry. Rationale, Design, and Methods. *Ann Am Thorac Soc* **17**, 1620–1628 (2020).
2. Maher, T. M. PROFILEing idiopathic pulmonary fibrosis: rethinking biomarker discovery. *European Respiratory Review* **22**, 148–152 (2013).
3. Maher, T. M. *et al.* An epithelial biomarker signature for idiopathic pulmonary fibrosis: an analysis from the multicentre PROFILE cohort study. *The Lancet Respiratory Medicine* **5**, 946–955 (2017).
4. Ding, Z. *et al.* Estimating telomere length from whole genome sequence data. *Nucleic acids research* **42**, e75–e75 (2014).
5. Lee, M. *et al.* Comparative analysis of whole genome sequencing-based telomere length measurement techniques. *Methods* **114**, 4–15 (2017).
6. Dhindsa, R. S. *et al.* Identification of a missense variant in SPDL1 associated with idiopathic pulmonary fibrosis. *Commun Biol* **4**, 1–8 (2021).
7. Zhang, D. *et al.* Utility of whole genome sequencing in assessing risk and clinically relevant outcomes for pulmonary fibrosis. *European Respiratory Journal* **60**, (2022).
8. Zhang, D. *et al.* Rare and Common Variants in KIF15 Contribute to Genetic Risk of Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med* **206**, 56–69 (2022).
9. Hollmén, M. *et al.* KIF15 missense variant is associated with the early onset of idiopathic pulmonary fibrosis. *Respir Res* **24**, 240 (2023).
10. Harrison, P. W. *et al.* Ensembl 2024. *Nucleic Acids Research* **52**, D891–D899 (2024).
11. Allen, R. J. *et al.* wide association study across five cohorts identifies five novel loci associated with idiopathic pulmonary fibrosis. 1–5 (2022) doi:10.1136/thoraxjnl-2021-218577.
12. Li, C. *et al.* Genome-wide Association Analysis in Humans Links Nucleotide Metabolism to Leukocyte Telomere Length. *Am J Hum Genet* **106**, 389–404 (2020).