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REVIEW ARTICLE

Genetics of fibrosing interstitial lung diseases

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ABSTRACT

Interstitial lung diseases (ILD) are a group of complex diseases characterized by inflammation and/or fibrosis of the lung interstitium. Idiopathic pulmonary fibrosis (IPF), the most common and aggressive form of ILD, has been at the central stage in genetic studies. To disentangle its genetic architecture and advance in developing precision medicine approaches for better care of patients, the studies have mostly relied on genome-wide association studies. Next-generation sequencing studies have also accelerated our understanding of IPF genetics, with approaches involving family studies and population-scale analyses. The emerging picture supports that IPF is governed by more than 30 genetic loci linked to telomere dysfunction, host defense, transforming growth factor-beta signaling, cell-cell adhesion, and mitotic spindle assembly, involving rare and common genetic variation, exerting non-additive effects in patient trajectories. In contrast, genetic research into non-IPF did not keep up the pace. However, a significant genetic overlap in terms of susceptibility and progression has been observed between IPF and other ILD subtypes. In this review, we summarize the main findings published in the literature and discuss their potential utility for diagnosis, risk stratification, and prognosis.

Keywords: Interstitial lung diseases. Genetics. Progression.

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INTRODUCTION

Interstitial lung diseases (ILDs) describe a heterogeneous group of lung disorders characterized by inflammation and/or fibrosis of the lung interstitium[1]. The most common symptom is dyspnea, although the onset and rate of progression vary depending on the specific type of ILD. The overall prevalence is estimated to be between 180 and 200 cases/100,000 individuals[2].

ILDs are defined based on a combination of histopathological, radiological, and clinical features. They comprise a wide range of entities which can be classified in autoimmune diseases ILDs, including the mixed connective tissue disease-associated ILD, hypersensitivity pneumonitis (HP), drug-induced ILD, postinfectious ILD, and idiopathic interstitial pneumonia (IIP), which includes idiopathic pulmonary fibrosis (IPF)[3]. While all ILDs can progress to fibrosis (a clinical behaviour referred to as progressive pulmonary fibrosis), IPF is the most aggressive form[4]. Moreover, it is the most common form of ILD, accounting for over 30% of ILD cases[2]. Both facts likely explain why it has become the most extensively studied model within the ILD spectrum.

IPF is characterized by progressive and irreversible lung fibrosis, which finally leads to the loss of lung function[5]. Its prognosis is generally poor, with considerable variability from patient to patient. However, the median survival is estimated to be between 3 and 5 years from the time of diagnosis[6]. In addition, treatment options are limited and only two antifibrotic drugs, pirfenidone and nintedanib, have been proven to slow the progression of the disease[7,8]. However, a phase III drug, nerandomilast, is also showing promising results in reducing the decline in forced vital capacity (FVC)[9].

Up to 20% of patients with IPF have a family history of ILD and are, therefore, termed as familial pulmonary fibrosis (FPF)[10]. In 25% of the FPF cases, a monogenic-like cause can be identified, and the disease often follows an autosomal dominant inheritance pattern. In contrast, monogenic variants can be identified in approximately 10% of sporadic IPF[11]. These findings support a significant genetic contribution to the pathogenesis of IPF, which may also be shared with other forms of ILD.

Despite the established role of genetics in the development of IPF, genetic testing remains limited and is only recommended in a subset of cases[10]. The diagnosis of IPF relies on the identification of a radiographic and/or histopathological pattern of usual interstitial pneumonia (UIP)[4]. Due to the lack of specific symptoms and the overlap with other ILDs, IPF is often diagnosed in advanced stages. A deeper understanding of the natural history of the disease and the identification of biomarkers of progression are essential to improve clinical management and develop effective therapies.

GENETICS OF ILDS

Over the past years, our understanding of the genetic contributors to ILD susceptibility has advanced significantly. Genome-wide association studies (GWAS) and next-generation

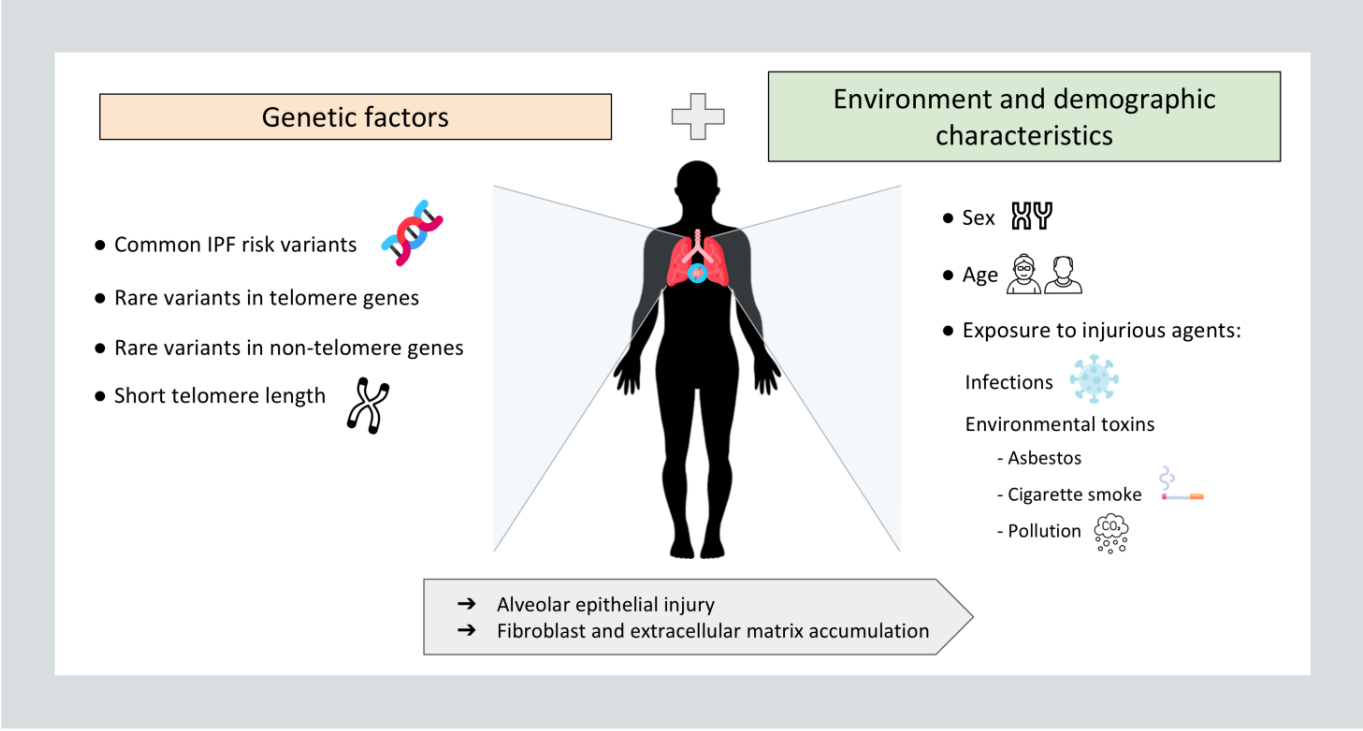

Figure 1. Genetic factors, environmental exposures, and demographic characteristics involved in idiopathic pulmonary fibrosis pathogenesis.

sequencing technologies, including whole-exome sequencing and whole-genome sequencing (WGS), have expanded the catalog of genetic variants associated with ILD[12]. In addition, reduced telomere length (TL) has emerged as a key factor in disease susceptibility. Since IPF represents the most prevalent form of ILD, much of our current knowledge of the genetic landscape of ILDs stems from discoveries in this prototypical subtype.

The available evidence supports that IPF develops in genetically susceptible individuals as a consequence of alveolar epithelial injury by environmental exposures that, together, cause excessive and progressive lung tissue scarring[1]. In this scenario, genetic risks would be necessary but not sufficient to cause IPF or govern disease progression. There is strong evidence supporting that aging is also central in contributing to risk, since patients usually show reduced TL compared to age-adjusted measures in the normal population. In fact, using Mendelian randomization analysis (which is based on Mendel's inheritance laws using genetic variation to address the causal effect of modifiable exposures on health), short TL has been shown to cause IPF[13]. While the pathogenesis is mechanistically complex in terms of the cellular and immune interactions involved[14], the consequence of the repeated exposures to the injurious agents (viral infections and environmental toxins such as asbestos, cigarette smoke, or particulate matter, among others) is an aberrant repair of the alveolar epithelium, promoting fibroblast and extracellular matrix accumulation on the lung foci (Fig. 1).

COMMON AND RARE VARIANTS AS BIOMARKERS OF IPF SUSCEPTIBILITY

In 2011, one study drastically changed our vision of IPF genetics. Using a genome-wide linkage scan in 82 affected families, Seibold et al.[15] identified for the first time the genetic effect of the rs35705950-T *MUC5B* promoter variant with a strong risk in IIP and IPF. Family-based studies such as this are designed for mapping disease genes in Mendelian disorders, and have failed to provide causal genes in most complex diseases in the past. However, identification of *MUC5B* with that approach was possible, in part, because of the large effect of the variant on IPF risk. The rs35705950-T allele was present in 34% and 38% of IIP and IPF cases, respectively, and only in 9% of controls, and the per allele odds ratio (OR) for IIP or IPF was strong (Table 1). *MUC5B* gene expression in the lung was higher in cases than in controls, and the MUC5B protein was present in type 2 alveolar epithelia and in epithelial cells lining honeycomb cysts[16]. Replication of the *MUC5B* risk effect in sporadic cases in an independent study further supported the discovery and the strong effect size in IPF risk[17]. Evidence from models of bleomycin-induced lung fibrosis in transgenic mice overproducing Muc5b and clinical observations in IPF patients suggest that mucociliary dysfunction in the airways might play a causative role[16].

Until then, most previous genetic studies in IPF had limited success in identifying firm IPF genes because they focused on candidate genes with suspected implications in disease mechanisms. In 2008, a seminal two-stage GWAS of IPF in a small sample of patients identified *TERT*, encoding a component of the telomerase (Fig. 2A)[18]. Since then, several other GWAS with ever-growing sample sizes have successfully identified more than 30 IPF genes, providing robust discoveries across patient cohorts (Table 1)[11,19]. These discoveries imply that telomere dysfunction, host defense, transforming growth factor beta (TGF-β) signaling, cell–cell adhesion, and mitotic spindle assembly are key biological pathways implicated in the polygenic inheritance of disease risk. However, despite disease affecting males more frequently than females, such differences do not seem to be influenced by genetic and sex interactions that could be identified by GWAS[20]. International collaboration has been a cornerstone of these genetic discoveries in IPF, which are necessary to overcome the analytical challenges due to the low disease prevalence. The last GWAS iteration constitutes a meta-analysis of seven genomic studies comprising 5,159 clinically diagnosed IPF cases and 27,459 controls of European ancestry. The study identified three novel risk genes (Table 1) and provided genetic support for the disease implication of a widely recognized alveolar epithelial damage biomarker, known as the Krebs Von Den Lungen-6 (KL-6), and of endothelial and vascular changes[21].

DNA sequencing-based studies in cohorts of sporadic IPF patients have also revealed that rare variants of less than 1% frequency in the population in some of the same genes mapped through GWAS (*TERT, RTEL1, PARN, SPDL1,* and *KIF15*) are also implicated in disease risk[22-25]. However, rarer (< 0.1% frequency) protein-truncating variants (i.e., variants affecting gene function) have a dramatic increase in effect sizes in IPF risk in the range

Table 1. Genetic IPF risk loci identified through genome-wide association studies

Gene/locus	SNP ID	Effect allele	Non-effect allele	OR	95%CI	Effect allele frequency	References
KIF15	rs2292181	C	G	1.52	1.36-1.70	5.2	19
TERC	rs9860874	A	C	1.29	1.22-1.37	27.6	19
FAM13A	rs2609259	A	C	1.30	1.22-1.39	22.4	19
TERT	rs7725218	G	A	1.41	1.33-1.50	67.1	19
DSP	rs2076295	G	T	1.49	1.41-1.57	46.7	19
MAD1L1	rs12537430	G	A	1.28	1.21-1.35	62.5	19
ZKSCAN1	rs2897075	T	C	1.30	1.23-1.37	38.2	19
DEPTOR	rs10808505	T	G	1.20	1.13-1.26	57.3	19
10q25.1	rs79684490	A	G	1.40	1.24-1.57	4.6	19
MUC5B	rs35705950	T	G	5.06	4.69-5.47	14.5	19
ATP11A	rs9577395	C	G	1.29	1.21-1.38	79.1	19
IVD	rs2304645	C	G	1.28	1.21-1.35	52.6	19
KNL1	rs12912339	A	G	1.30	1.21-1.39	15.9	19
AKAP13	rs11073517	T	C	1.19	1.13-1.26	32.7	19
NPRL3	rs74614704	A	G	1.49	1.33-1.67	5.6	19
17q21.31	rs2077551	G	A	1.42	1.32-1.53	80.7	19
DPP9	rs12610495	G	A	1.28	1.21-1.36	30.6	19
STMN3	rs112087793	C	T	1.34	1.21-1.48	91.5	19
RTEL1	rs41308092	A	G	1.75	1.45-2.10	2.1	19
DNAJB4/GIPC2	rs4130548	C	T	1.09	1.06-1.13	33.3	26
GPR157	rs7549256	A	C	0.91	0.88-0.94	64.16	26
RAPGEF2	rs76537958	T	A	1.29	1.18-1.42	2.92	26
FKBP5	rs9380529	G	A	1.08	1.05-1.12	51.72	26
RP11-286H14.4	rs34288126	A	G	1.13	1.09-1.19	12.7	26
PSKH1	rs539683219	T	TG	3.20	2.17-4.70	1.71	26
FUT6	rs708686	T	C	1.11	1.07-1.14	31.47	26
TRIM46	rs9426886	A	T	0.86	0.82-0.90	56.8	21
LSM3\ LINC01267	rs112271207	T	C	1.39	1.26-1.52	6.0	21
SNRPF	rs7957346	A	C	1.15	1.10-1.21	58.2	21

*Effect allele frequency as reported in the referenced study. SNP: single nucleotide variant; OR: odds ratio; CI: confidence interval, IPF: idiopathic pulmonary fibrosis.

of ORs between 2.87 and 62.6. Thus, their effect sizes are comparably larger than those of most common variants associated with the GWAS-discovered genes (Fig. 3). One exception is the *MUC5B* risk allele, which is associated with a strong (OR > 5) effect size

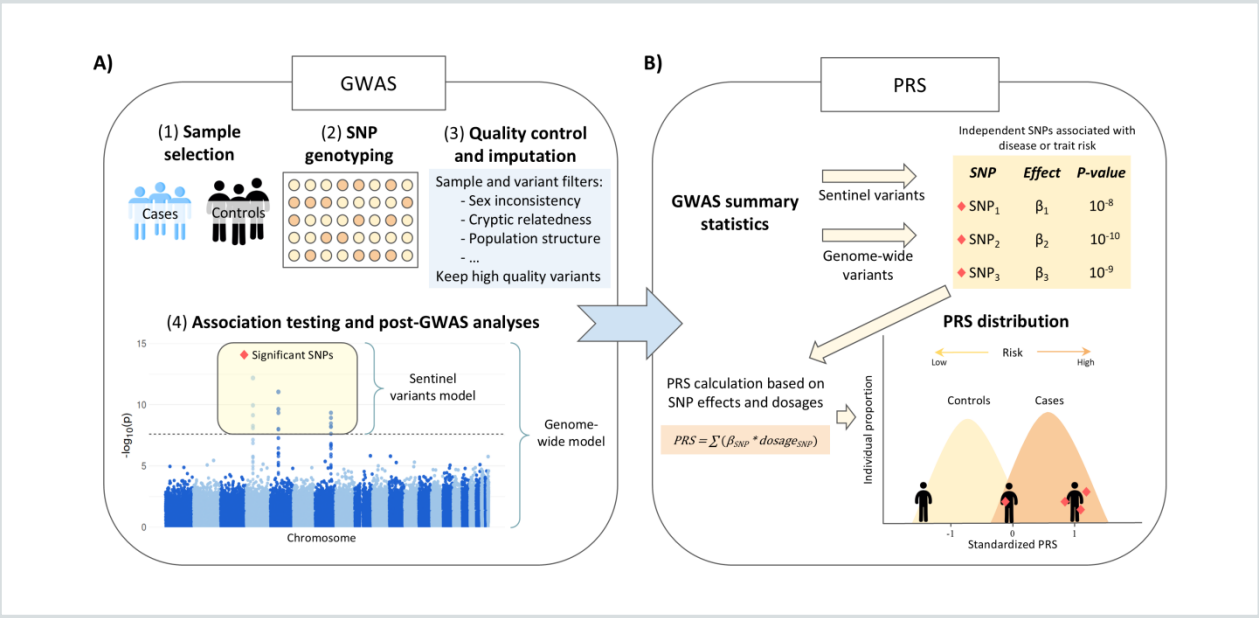

Figure 2. Schematic representation of the main stages involved in **A:** genome-wide association studies (GWAS); and **B:** polygenic risk score (PRS) modeling based on GWAS results, illustrating that PRS models can be derived either based on the most significant (sentinel) variants (single nucleotide variant) or based on genome-wide variation.

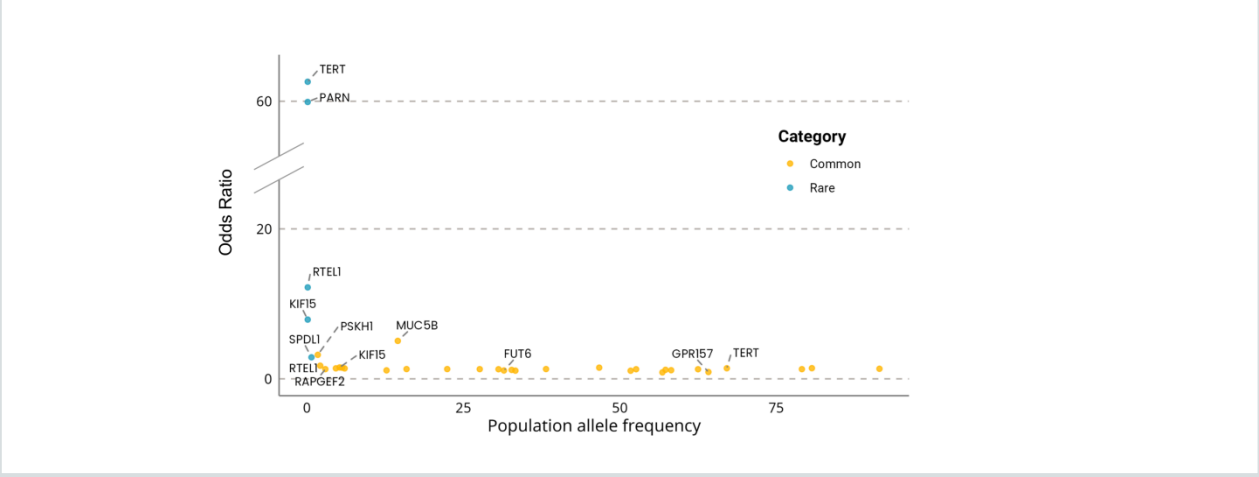

Figure 3. Effect sizes of common and rare genetic variants associated with the risk of idiopathic pulmonary fibrosis. The x-axis represents the effect allele frequency in the general population while the y-axis represents the effect size expressed as odds ratio estimates.

replicated across cohorts despite showing a frequency above 10% in European ancestry populations.

As for most complex diseases, a recognized gap of GWAS of IPF is that discoveries are mostly European-centric. To fill this gap, the first multi-ancestry GWAS was published in 2022 and aggregated genomic data from six genetic ancestries collected as part of 13 biobanks, comprising 8,492 IPF cases (identified from the International Classification Disease codes in the electronic health records) and nearly 1.36 million controls[26]. The risk allele in one (*PSKH1*) of the seven novel IPF genes discovered in that study (Table 1) was unique to South Asian ancestry populations. Risk alleles in three other novel IPF genes (*GPR157*, *RAPGEF2*, and *FUT6*) were also more frequent in non-Europeans compared to the European genetic ancestry populations. The novel IPF genes identified were involved in lung function, fibrinogenesis, and mucociliary clearance. Taken together, this evidence highlights the importance of leveraging diversity in genetic studies.

GENETIC FINDINGS IN NON-IPF ILDS

While significant advances have been made in the genetics of IPF, much less attention has been given to the understanding of the pathogenesis of non-IPF ILDs. Nonetheless, some genetic overlap between IPF and other ILD subtypes has been described, offering valuable insights into the mechanisms potentially involved across some of the ILD subtypes. The *MUC5B* polymorphism has shown association with HP[27] and rheumatoid arthritis-associated ILD (RA-ILD)[28]. In addition, it relates to interstitial lung abnormalities (ILA), which are assumed to represent early or mild forms of IPF[29,30]. In contrast, no association of the *MUC5B* promoter variant has been found with other forms of connective tissue disease-associated ILD, such as systemic sclerosis (SSc-ILD) or sarcoidosis[31-33], although they can also manifest pulmonary fibrosis[4]. Recent work suggests that *MUC5B* may be specifically related to unique radiological features, instead of the extension of fibrosis[34]. Accordingly, patients with RA-ILD frequently present the UIP pattern, in contrast with SSc-ILD which is mostly characterized by a non-specific interstitial pneumonia pattern[35]. A subset of patients with HP and RA-ILD also shows an increased burden of rare variants in *TERT*, *RTEL1*, and *PARN*, confirming that telomere dysfunction is a shared mechanism of susceptibility among IPF and these other ILDs[36]. However, more studies are needed to determine whether telomere biology genes are the primary cause of the disease or act instead as genetic modifiers of established causes of HP or RA.

GENETICS OF PF PROGRESSION

Progressive fibrosing disease refers to patients who, regardless of the specific ILD subtype, exhibit a worsening of symptoms, an increase in fibrosis is evident on a computed tomography scan, and declines in both FVC and gas exchange are significant. Although the underlying causes of this clinical behavior remain poorly understood, genetics is rapidly providing valuable insights into the mechanisms explaining this phenotype. Most of this work focuses on IPF, the prototypical progressive fibrosing ILD. However, emerging evidence

suggests a high degree of genetic overlap between IPF and other ILDs, supporting the idea that the key genomic biomarkers identified in IPF may also be relevant for non-IPF ILD subtypes.

TL

TL is one of the most consistent genomic biomarkers described in ILD. Therefore, short leukocyte TL has been identified as a predictor of disease progression and survival in IPF[37-39]. Patients with IPF who have shorter TL show worse survival and more rapid lung function decline, as measured by percent predicted FVC or diffusing capacity of the lungs for carbon monoxide (DL_{CO}). In addition, shorter TL is associated with an increased risk of acute exacerbations, a clinical event linked to poorer prognosis and higher mortality[40].

Although shorter TL has also been observed in other ILDs compared to unaffected individuals, its prognostic value in non-IPF ILD subtypes remains unclear. Newton et al. found that, although TL was longer in patients with interstitial pneumonia with autoimmune features (IPAF) compared to those with IPF, patients with TL below the 10th percentile experienced faster lung function decline and worse survival[39]. However, no association between TL and survival could be established in RA-ILD despite typically having a prognosis similar to IPF.

In contrast, some studies did not find a relationship between shorter TL and reduced survival in non-IPF ILD[38,40]. The lack of association in these studies may be due to small sample sizes, the inclusion of non-fibrotic ILDs, and the uncertainty of the threshold at which TL could be considered critical. Furthermore, since TL dynamics and their relationship with aging can vary significantly across populations, some studies emphasize the need to take ethnic differences into account. However, TL below the mean has been shown to be a strong predictor of poorer survival across all fibrotic ILD subtypes and diverse genetic ancestries[41].

Short TL has also been shown to interact with immunosuppressive therapies. For this reason, TL could also be considered a pharmacogenomic biomarker to identify patients at risk for adverse clinical outcomes when exposed to this medication. This correlation has been confirmed among IPF patients[42] and non-IPF ILD patients[43]. In addition, TL reduction is associated with increased complications after lung transplantation[44].

RARE DELETERIOUS VARIANTS

Common and rare variants in telomere-related genes are associated with short TL, although rare variants have larger effect sizes[45,46]. Consequently, rare protein-truncating variants are enriched among patients with short TL and poor survival. However, no study to date has demonstrated a complete overlap between the presence of rare variants and short TL, suggesting that the two should be considered as independent biomarkers.

The presence of rare deleterious variants in *TERT, RTEL1, NAF1*, and *PARN* leads to variable ILD subtypes[36,39]. Despite this phenotypic heterogeneity, one consistent feature

among carriers of variants in these and other telomere-related genes (*DKC1, TINF2, TERC, NHP2, NOP10, and ZCCHC8*) is a significantly increased risk of death or lung transplantation[36,39,46].

Survival studies in ILD patients have classically focused on telomere biology genes, given their high mutation burden in these populations and the known association between TL and disease progression. However, a recent study aggregating the effects of rare predicted protein-truncating variants (denoted as qualifying variants [QVs]) across both telomere and non-telomere genes related to adult pulmonary fibrosis (PF) has shown that non-telomere variants also contribute to survival outcomes[47]. These findings highlight the importance of non-telomere genetic factors in progression and reinforce the notion that TL and QV detection should be treated as independent and complementary predictors of clinical outcomes.

COMMON VARIANTS AND POLYGENIC RISK SCORES

Among common genetic variants, the common T allele of the promoter of *MUC5B* (rs35705950), which increases the risk for IPF[48], is also significantly associated with improved survival in IPF and other ILDs such as RA-ILD[49]. This paradoxical finding has been replicated in several independent studies[46-48,50,51], although some studies suggest that its association with IPF survival may be confounded by index event bias[52]. In contrast, the rs5743890 polymorphism near the *TOLLIP* gene has been associated with increased mortality in IPF, although this finding has not yet been replicated in independent cohorts[53]. A coding variant (L412F) in *TLR3*, a key mediator in the innate immune system responses during viral infections, was associated with worse survival and accelerated decline in FVC[54].

However, these association studies with IPF progression focused on candidate genes, providing no clues for the role of other genomic loci. To further understand the genetic determinants of disease progression, two GWAS have been conducted, focusing on IPF survival and longitudinal lung function decay. The first prioritized a variant in *PCSK6*, which was associated with differential survival and implicated this gene activity as a potential mediator of fibrosis progression[55]. The second identified a variant in the RNA antisense gene *PKN2* that was associated with a more rapid decline of the lung capacity of IPF patients[56]. This gene is a Rho and Rac effector protein with known roles in the fibrotic process through regulation of TGFβ signalling.

Given the minimal overlap between genetic variants associated with IPF susceptibility and those influencing disease progression, polygenic risk score (PRS) models (Fig. 2B) based solely on IPF susceptibility variants show significant association with survival only when the *MUC5B* locus is included. This indicates that *MUC5B* is the primary driver of differential survival. However, even when the *MUC5B* locus is excluded, individuals with higher PRS tend to have a reduced burden of QVs in genes known to cause monogenic forms of adult PF.

These findings suggest that, unlike what has been shown for many other complex diseases,

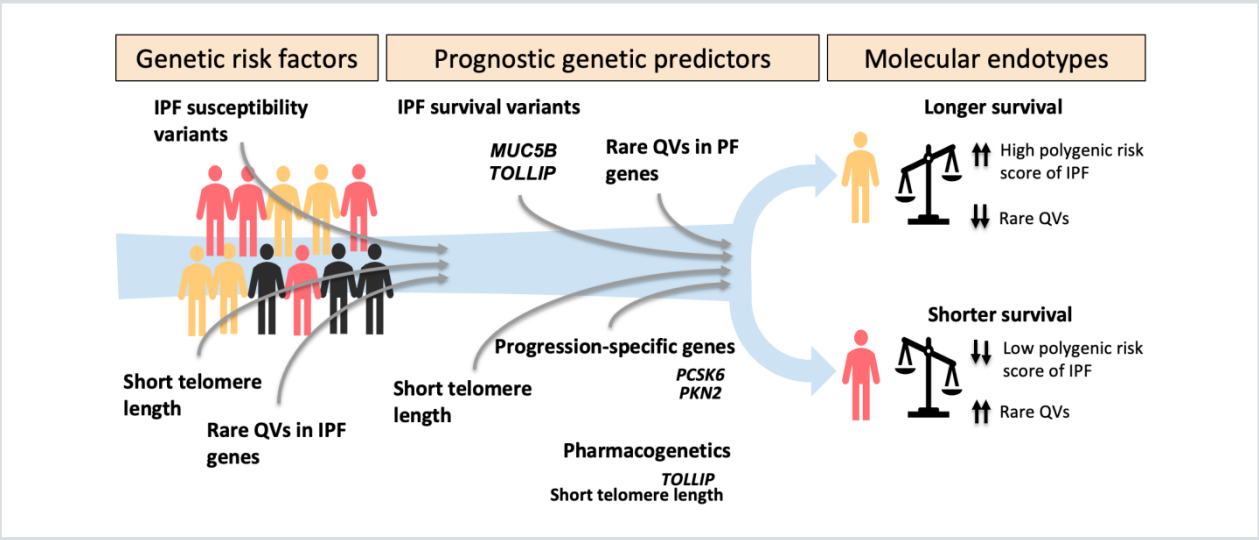

Figure 4. Simplified hypothetical modeling of the genetic architecture governing idiopathic pulmonary fibrosis susceptibility and prognosis and the distinct molecular endotypes resulting from the non-additive effects between rare variants and polygenic inheritance.

rare genetic variants in IPF may exert non-additive effects relative to common risk variants. Consequently, polygenic and monogenic forms of IPF may represent distinct disease subtypes with differential clinical trajectories (Fig. 4)[47].

NEW APPROACHES FOR IDENTIFYING GENETIC BIOMARKERS OF PROGRESSION

Despite GWAS having fruitfully identified genetic variants associated with IPF risk and progression, important challenges remain in terms of statistical power and biological interpretation of findings. This is because of the pervasive linkage disequilibrium patterns of the genome and the context-dependent regulation of the genomic elements, blurring our ability to precisely identify the disease genes. Among the novel approaches that aim to overcome some of these limitations is the transcriptome-wide association study (TWAS). Briefly, TWAS uses existing variant-to-gene expression data to impute gene expression levels on genotype information in the patients included in the GWAS and then tests the association of gene-level expression and the disease[57]. A recent study relied on TWAS to identify novel genes that could be associated with IPF survival, given the paucity of studies and the limited sample size involved in the studies at the time. Using TWAS and diverse complementary approaches, Hu et al.[58] identified two genes, *PTPN9* and *SNRPB2*, that were significant across whole-blood and lung tissues. *PTPN9* expression was also associated with a 12-month decline of predicted DL_{CO}. By its role in regulating VEGF receptor signaling, *PTPN9* connects IPF progression with vascular integrity.

KNOWLEDGE GAPS

Significant advances have been made in ILD genetics. With the results obtained over the

past decade of genomic studies, it is now clear that genetic risk factors play an important role in both the susceptibility and progression of ILDs. However, important gaps in knowledge remain across several areas of research, hindering the implementation of these findings into clinical practice and the development of precision medicine approaches.

With the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic causing COVID-19, shared genetic architecture between IPF and COVID-19 risk has also been observed. Large-scale GWAS have identified notable pleiotropy, demonstrated by a positive genome-wide correlation between IPF and severe COVID-19[26]. At least four of the shared genetic risk loci between IPF and COVID-19 (7q22.1, *MUC5B*, *ATP11A*, and *DPP9*) are likely due to the same causal variant. Interestingly, telomere dysfunction or mitotic spindle assembly are not shared mechanisms with COVID-19, as opposed to other non-IPF ILDs[59]. Subsequent studies have shown that PRS of IPF are associated with COVID-19 hospitalization, and the strength of this association is age and sex dependent[60]. In this scenario, individuals at higher risk of IPF could be at an increased risk of developing post-COVID-19 lung fibrosis. Taken together, these findings could also suggest that the genetic risk underlying IPF may not be sufficient on its own to cause disease. Instead, additional risk factors, such as viral infections, could be required to trigger the progression of the disease in some patients. In this context, further studies are also needed to understand the effect of rare pathogenic variants in PF genes in individuals with a high polygenic component of IPF.

A valuable approach to better understanding the natural history of ILDs is the study of family members of affected patients. First-degree relatives have a higher likelihood of developing ILD compared to the general population[61]. Studying these individuals could enable the identification and characterization of high-risk populations at early stages of PF pathogenesis, thereby helping to uncover risk factors that contribute to disease development. Radiological abnormalities, which may indicate subclinical forms of ILD, are present in 26% (95% confidence interval: 20-32%) of asymptomatic first-degree relatives[62]. In addition, the frequency of the *MUC5B* promoter risk allele is higher in these individuals compared to unaffected individuals, and short TL is also commonly observed. Longitudinal follow-up of these populations is necessary to determine whether they eventually develop symptomatic fibrotic ILD[29].

Another knowledge gap that should be further investigated is pharmacogenomics. Although only a few pharmacogenomic studies have been conducted in ILD patients, their findings are promising, while still requiring replication and functional validation. They suggest that genotypic information could be used to predict treatment responses in certain patients, paving the way toward more personalized therapeutic approaches. For instance, a significant interaction has been found between the T allele of rs3750920 within *TOLLIP* and N-Acetylcysteine (NAC) in patients with IPF. In the effectiveness of prednisone, azathioprine, and N-Acetylcysteine in patients with IPF (PANTHER-IPF) study, patients with the TT genotype, present in approximately 25% of the patients, showed a better response to NAC in comparison to

placebo, and this association was replicated in an independent cohort[63,64]. In addition, a more recent study in the EMPIRE registry, an improved response to nintedanib was found in G allele carriers of the *DSP* rs2076295 compared to those with the TT genotype, which would benefit from treatment with pirfenidone[65]. An important limitation of both studies is that they did not account for currently known biomarkers of disease progression, such as TL or the presence of monogenic variants in PF genes. As a result, both studies were conducted in heterogeneous cohorts that included patients with varying clinical trajectories. The efficiency and precision of future clinical trials evaluating responses to antifibrotic treatments will likely improve as stratification of patients based on these biomarkers becomes routine.

One of the major challenges in both pharmacogenomic and genetic studies of ILD is the limited sample size, particularly considering that IPF, the most common ILD subtype, is still classified as a rare disease, with a global prevalence ranging from 0.33 to 4.51 per 10,000 individuals[66]. Large population datasets such as the UK Biobank may provide valuable resources for increasing sample size. However, case identification in these resources may be less accurate than in clinically derived datasets. Misclassification of cases, therefore, reduces the expected statistical power to detect true genetic associations. For instance, in the UK Biobank, the available IPF code definitions do not replicate the strong effect size of the rs35705950 *MUC5B* risk allele obtained in clinically defined IPF cohorts[67].

In addition, the predictive performance of IPF PRS is substantially lower in biobank-derived cohorts than in clinically derived samples[68,69]. These findings highlight the importance of applying code-based exclusion criteria to avoid misclassification of IPF patients when using large population datasets for research purposes.

Advances in understanding the genetic basis of ILDs are gradually being translated into clinical practice. Two genetic testing approaches are currently available and provide complementary information for disease risk stratification: (1) gene sequencing to identify monogenic causes of disease, and (2) TL measurement to identify patients with severe TL shortening. The general workflow is summarized in Fig. 5. However, important barriers remain. Genetic testing is recommended for patients with a family history of ILD, patients with a suggestive telomere disorder (for instance, extrapulmonary manifestations), patients with early-onset disease (before the age of 50 years), and when another genetic syndrome associated with PF is suspected[11]. Nevertheless, emerging evidence indicates that relevant rare genetic variants are also present in a significant subset of patients who do not meet these criteria[46,47]. Furthermore, the lack of formal recommendations in the clinical practice guidelines for IPF issued by the American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society, and the Asociación Latinoamericana de Tórax contributes to heterogeneous implementation across countries. To promote equitable access and facilitate its integration into routine care, recent studies have proposed tiered strategies that aim to reduce the workload at the stage of interpreting the findings obtained by genetic tests[70]. Concurrently, new evidence suggests that WGS could be a

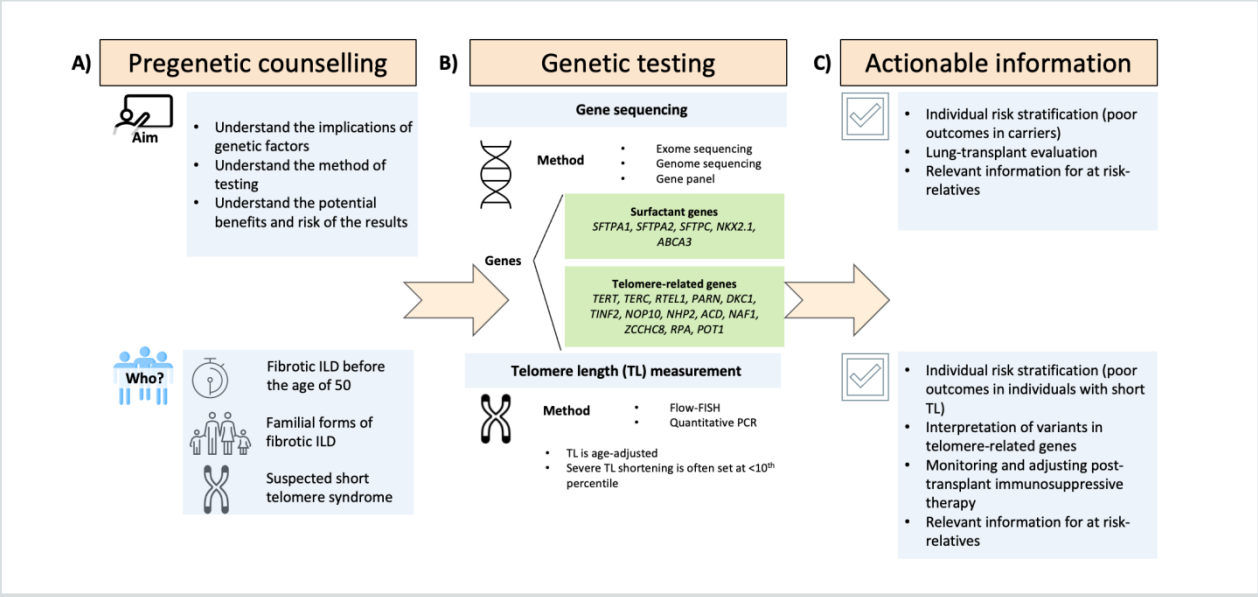

Figure 5. Workflow of genetic testing in the clinical setting. **A:** pre-genetic counselling should be offered to patients who meet clinical criteria for genetic testing. **B:** gene sequencing could be performed by different techniques to identify monogenic causes of fibrotic interstitial lung disease. Telomere length (TL) can be measured by several methods, with quantitative polymerase chain reaction and flow-fluorescence in situ hybridization being the most commonly used. Since TL decreases with age, measures are age-adjusted and reported as percentiles. C: genetic testing results provide clinically actionable information for both patients and their relatives.

valuable clinical tool, given its capacity to detect rare variants and estimate TL simultaneously[46]. In addition, WGS enables the identification of common variants, allowing the development of PRS for any trait, including IPF, which are emerging as promising tools for clinical practice[47].

CONCLUDING REMARKS

ILDs are a heterogeneous group of disorders that affect the lung interstitium. The most common and well-studied subtype so far is IPF, which is characterized by progressive and irreversible lung fibrosis. Although the etiology of ILDs is multifactorial, genetic factors have been shown to play a significant role in their predisposition for disease development, progression, and prognosis. Both rare and common genetic variants, along with TL, are known biomarkers associated with IPF progression. However, the primary mechanisms driving disease onset remain poorly understood. To fill this gap, genetic studies in at-risk populations, such as patients with post-acute COVID-19 lung abnormalities or ILAs, will be necessary. In addition, non-IPF ILDs remain largely unexplored, although it is suspected that genetic biomarkers identified in IPF might also be relevant in some of the other subtypes.

Advancing toward a precision medicine model in ILDs requires overcoming several significant barriers. Genetic testing is currently recommended only in a subset of cases, although evidence suggests that many

more affected patients might benefit from it in terms of disease progression. In addition, PRS are emerging as a powerful tool for risk stratification, but their application in clinical settings requires further validation. Finally, there is a lack of pharmacogenomic studies in ILD, and, consequently, treatment options are very limited. Stratifying patients based on genotypes in clinical trials may help identify effective therapies for specific genetic subgroups.

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CONFLICTS OF INTEREST

None of the authors have competing interests to disclose.

ETHICAL CONSIDERATIONS

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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