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Review Article

Familial Idiopathic Pulmonary Fibrosis (FIPF): A Comprehensive Review

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ABSTRACT Familial Idiopathic Pulmonary Fibrosis (FIPF) is a subset of idiopathic pulmonary fibrosis (IPF) characterized by familial clustering, affecting multiple relatives across generations. While most IPF cases are sporadic, FIPF accounts for approximately 5–20% of cases and is linked to genetic mutations that predispose individuals to the disease. This review provides a comprehensive overview of FIPF, focusing on its genetic basis, clinical manifestations, diagnostic approaches, and therapeutic strategies. It also highlights recent research findings and future directions in the field.

Keywords: Familial idiopathic pulmonary fibrosis (FIPF), idiopathic pulmonary fibrosis (IPF), genetic, surfactant-related gene mutations, telomere-related gene mutations.

INTRODUCTION

Idiopathic Pulmonary Fibrosis (IPF) is a chronic, progressive fibrotic lung disease marked by excessive extracellular matrix deposition and irreversible lung scarring [1,2]. While most IPF cases are sporadic, 10–20% exhibit familial clustering, termed Familial Idiopathic Pulmonary Fibrosis (FIPF) [3, 4]. FIPF is defined by the presence of two or more affected individuals within a single family, often showing an autosomal dominant inheritance pattern with variable penetrance [5]. First described in 1907 and formally defined in 2000, FIPF was later recognized by the ATS/ERS/JRS/ALAT in 2010 as a familial form of IPF [6,7]. The disease's etiology involves genetic predisposition, environmental factors (e.g., smoking, occupational exposures, viral infections), and mutations in genes related to surfactant proteins (e.g., *SFTPA1*, *SFTPB*) and telomerase (e.g., *TERT*, *TERC*) [7, 8]. These mutations impair lung epithelial cell function and repair mechanisms, leading to progressive fibrosis [9].

METHODS

A systematic literature search was performed in databases including PubMed, Web of Science, Embase, and Cochrane Library, and selected relevant studies. We evaluated the included studies, extracted and synthesized data to summarize the current update about Familial Idiopathic Pulmonary Fibrosis. We excluded non-peer-reviewed articles from the preprint databases. Inclusion criteria: the topic of the study must be related to FIPF.

1. Epidemiological Challenges in Familial IPF:

Epidemiological studies on FIPF face multiple challenges. The rarity of the disease makes large-scale research difficult, and identifying familial cases often depends on self-reported family history, which may be incomplete or inaccurate [9, 10]. Additionally, variations in diagnostic criteria and limited access to genetic testing further complicate the estimation of prevalence and incidence rates [11, 12].

1.1 Prevalence of Familial IPF

Familial IPF is defined as the occurrence of idiopathic pulmonary fibrosis (IPF) in two or more members of the same family. Research estimates suggest that FIPF accounts for 10–20% of all IPF cases [13–16]. However, the exact prevalence varies across studies due to differences in diagnostic criteria, genetic testing availability, and cohort selection. Furthermore, studies conducted in different geographic regions have reported varying prevalence rates, suggesting that both genetic and environmental factors may influence disease occurrence [17].

1.2 Demographics and Risk Factors

The demographic characteristics of familial IPF are broadly similar to those of sporadic IPF [18]. The disease is more common in older adults, with a peak incidence between the ages of 40 and 50 years [19]. Both men and women are affected, but a slight male predominance is observed, similar to sporadic IPF [20, 21]. Key risk factors

for FIPF include a positive family history of interstitial lung disease and specific genetic mutations, which are thought to contribute to disease susceptibility and progression [22, 23].

2. Genetic Basis of FIPF

2.1 Genetic Factors

Genetic predisposition plays a crucial role in the pathogenesis of FIPF [33,34]. Among the most well-established genetic contributors are mutations in genes responsible for telomere maintenance, such as *TERT* (telomerase reverse transcriptase) and *TERC* (telomerase RNA component). These genes are essential for maintaining chromosomal stability and cellular longevity by preserving telomere length. Mutations in these genes lead to telomere shortening, a hallmark feature in many FIPF patients, which contributes to alveolar epithelial cell senescence, apoptosis, and impaired tissue regeneration [24, 34, 35, 36].

Additionally, rare mutations in genes encoding surfactant proteins particularly *SFTPC* (surfactant protein C) and *SFTPA2* (surfactant protein A2) have also been implicated in FIPF. These mutations can result in the accumulation of misfolded proteins within alveolar type II epithelial cells, triggering endoplasmic reticulum (ER) stress, unfolded protein responses, and ultimately, cellular injury and fibrosis. The pathological consequences of these mutations underscore the role of epithelial dysfunction in fibrotic remodeling of lung tissue [25, 37].

Variants in genes associated with host defense and cell stress responses, such as *MUC5B*, have been linked to an increased risk of both sporadic and familial idiopathic pulmonary fibrosis (IPF) [37,38]. The *MUC5B* promoter variant (rs35705950) is a single-nucleotide polymorphism (a G-to-T change) that elevates the expression of the *MUC5B* protein in the lungs. This increased production of *MUC5B* disrupts immune signaling pathways, including heightened IL-3 activity, and activates cellular stress responses, which may collectively "prime" lung tissue for future injury and fibrosis. Over time, these effects contribute to the development of IPF, making the *MUC5B* variant the strongest known genetic risk factor for the disease. Interestingly, while this variant predisposes individuals to fibrosis, it may also have a protective role by enhancing mucociliary clearance and strengthening host defense mechanisms, highlighting its complex and dual impact on lung health. This duality underscores the intricate balance between beneficial and detrimental effects of genetic variants in disease pathogenesis [26, 38, 39,40].

2.2 Environmental and Epigenetic Contributions

In addition to genetic factors, environmental exposures and epigenetic modifications are thought to contribute to the development and progression of familial IPF. However, the incomplete penetrance of these mutations suggests the involvement of additional factors. Environmental triggers, such as occupational exposure to metal or wood dust, air pollution (including PM2.5, ozone, and nitrogen oxides), and smoking, interact with genetic risks to amplify disease susceptibility. These exposures contribute to oxidative stress, impaired mucociliary clearance, and epithelial injury, further exacerbating the condition. Epigenetic mechanisms, including DNA methylation and histone modifications, also play a critical role by modulating gene expression in response to environmental insults. For instance, promoter variants in *MUC5B* and *DSP* are linked to differential methylation patterns, which can alter epithelial barrier function and mucin production. Additionally, accelerated biological aging, as measured by epigenetic clocks, has been observed in both familial IPF patients and asymptomatic carriers, independent of telomere length, suggesting senescence as a potential mediator of fibrosis [29-31]. These epigenetic changes may serve as a molecular bridge, integrating cumulative environmental damage with genetic risk to drive disease progression in susceptible families. Together, these interconnected pathways highlight the multifaceted nature of FIPF pathogenesis, Figure (1).

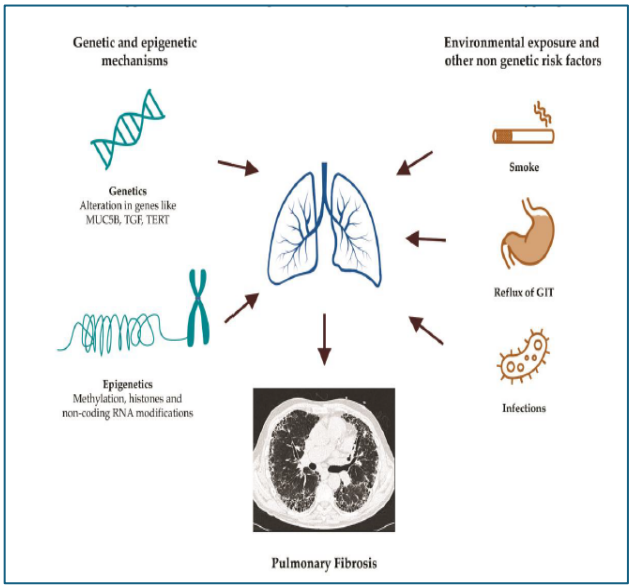

Figure 1: The image outlines the factors contributing to pulmonary fibrosis, categorized into genetic and epigenetic mechanisms and environmental/non-genetic risk factors. Adapted from Tirelli, Claudio et al., [4].

2.3 Genetic and Ethnic Heterogeneity in Familial Idiopathic Pulmonary Fibrosis

FIPF exhibits significant genetic and ethnic variability, influencing its prevalence, progression, and clinical outcomes. Studies have identified several genetic mutations associated with familial IPF, though their

prevalence varies across ethnic groups. For instance, telomere-related mutations are more commonly observed in Caucasian populations, whereas other genetic factors may play a more prominent role in non-European ancestries. Additionally, ethnic disparities in disease susceptibility and severity have been reported, with some studies suggesting a higher risk or earlier onset in certain populations, possibly due to genetic, environmental, or socioeconomic factors [10,11,15,35].

2.4 The Heritability Gap

FIPF demonstrates a notable heritability gap, meaning that while there is clear evidence of inherited risk, current genetic testing and research explain only a portion of this familial clustering. Although about 5-20% of IPF patients have a family history of interstitial lung disease, known rare pathogenic variants in genes related to telomere maintenance or surfactant production account for only a small fraction of familial cases. Common genetic variants, such as those in the MUC5B promoter, contribute to overall risk but still leave much of the heritability unexplained. This gap is likely due to a combination of factors, including the involvement of many genes with small effects, incomplete penetrance of known variants, the influence of non-coding or regulatory regions of the genome, and possible gene-environment interactions. Additionally, some at-risk family members may not yet show symptoms due to the age-dependent nature of IPF, making it harder to trace inheritance patterns. Epigenetic factors and limitations in current genetic testing technologies may also play a role in this heritability gap. Bridging this gap will require more comprehensive genetic studies, including whole-genome sequencing, better characterization of non-coding variants, and long-term follow-up of families with a history of IPF [8, 9, 10, 14, 31,37].

2.5 Genetic Variants Associated with FIPF, Figure 2, [33].

- Telomerase Complex Mutations (*TERT*, *TERC*): Present in 15–20% of familial cases, leading to telomere shortening and fibrosis [24, 34, 35, 36].
- Surfactant Protein Mutations (*SFTPC*, *SFTPA2*): Associated with early-onset disease [25, 37].
- Other Contributors (*PARN*, *RTEL1*, *MUC5B*): Involved in telomere maintenance and mucus production [26, 38, 39,40].

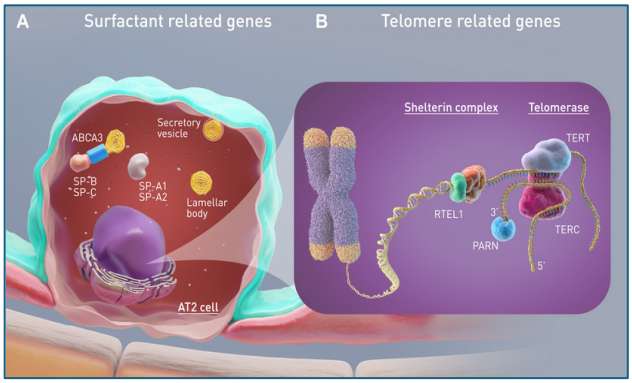

Figure 2: The image illustrates genetic components involved in lung surfactant production and telomere maintenance, which are critical for normal lung function and cellular aging and development of FIPF. Adapted from Hurley, Killian et al., [33].

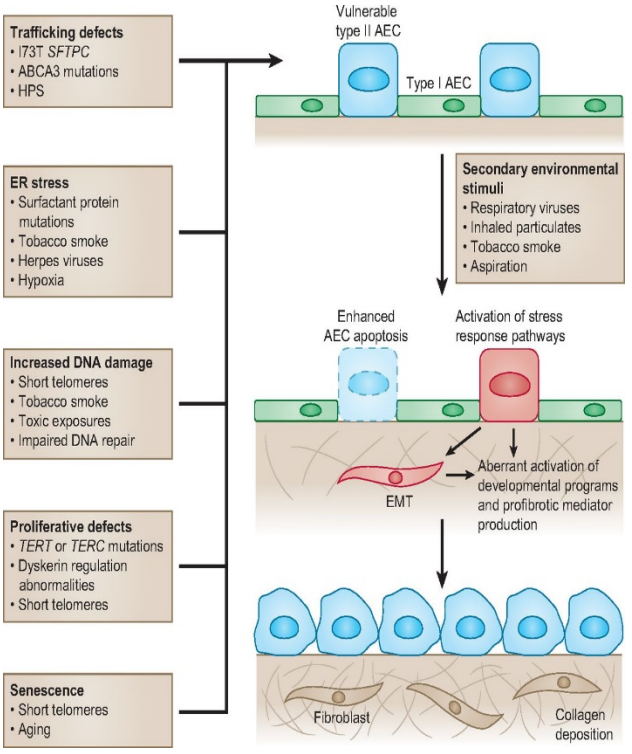

Figure 3: The image illustrates the pathogenesis of pulmonary fibrosis, highlighting various factors and cellular processes that contribute to FIPF. Adapted from Kropski, Jonathan A et al., [41].

3. Pathogenesis

FIPF pathogenesis involves a complex interplay of genetic predisposition and environmental triggers. Key mechanisms include:

- Telomere Dysfunction**:** Accelerated cellular senescence in alveolar epithelial cells impairs regeneration and promotes fibrosis [24,34].
- Surfactant Dysfunction: Mutations in *SFTPC* and *SFTPA1/A2* cause ER stress and epithelial injury [25,37].
- Dysregulated *MUC5B* Expression: Overexpression increases fibrosis risk [26, 38].
- Aberrant Wound Healing: Repetitive alveolar injuries lead to fibroblast activation and excessive extracellular matrix deposition [43].
- Environmental Triggers: Smoking, pollution, and viral infections exacerbate disease progression in genetically predisposed individuals, Figure 3, [21].

4. Clinical Manifestations

Clinically, FIPF presents similarly to sporadic IPF, with common symptoms including chronic dry cough, exertional dyspnea, and bibasilar inspiratory crackles. Over time, patients may develop clubbing of the fingers, hypoxemia, and worsening pulmonary function, often reflected in a restrictive pattern on spirometry with reduced diffusion capacity for carbon monoxide (DLCO). However, FIPF may have an earlier onset and more aggressive course in some families [2, 9, 13]

4.1 Clinical Implications of Surfactant-Related Gene Variants

Surfactant-related gene variants, such as mutations in *SFTPB*, *SFTPC*, *ABCA3*, and *NKX2-1*, can lead to significant pulmonary disorders, particularly neonatal respiratory distress syndrome (NRDS), interstitial lung diseases (ILDs), and chronic lung conditions [37,41].

- SFTPB & SFTPC mutations: Cause surfactant protein deficiencies, leading to severe neonatal respiratory failure or progressive ILD in older children and adults.
- ABCA3 mutations: Affect surfactant metabolism, resulting in surfactant dysfunction disorders with variable severity.
- NKX2-1 mutations: Associated with lung, thyroid, and neurological disorders (brain-lung-thyroid syndrome).

These genetic abnormalities impact surfactant production, metabolism, and function, often necessitating lung transplantation in severe cases. Genetic screening and personalized treatment approaches, including experimental surfactant replacement and targeted therapies, are crucial for management.

4.2 Clinical Implications of Telomere-Related Gene Variants

Telomere-related gene variants impact telomere maintenance, influencing aging, cancer risk, and various telomere biology disorders (TBDs). Mutations in genes like *TERT*, *TERC*, *DKC1*, and *RTEL1* can lead to conditions such as dyskeratosis congenita, pulmonary fibrosis, and bone marrow failure syndromes [25]. These variants contribute to genomic instability, increasing susceptibility to cancers like leukemia and melanoma. Conversely, telomerase activation in cancer cells promotes uncontrolled proliferation. Clinically, telomere length assessment and genetic testing aid in disease diagnosis, prognosis, and personalized treatment strategies, such as stem cell transplantation for TBDs or telomerase-targeted therapies in oncology, [37].

4.3 Clinical Features and Disease Course

The clinical presentation of familial IPF is largely indistinguishable from that of sporadic IPF. Patients typically present with progressive exertional dyspnea, a dry cough, and bilateral pulmonary crackles on auscultation. Radiological findings on high-resolution computed tomography (HRCT) commonly show a usual interstitial pneumonia (UIP) pattern. Familial IPF may have a slightly earlier age of onset compared to sporadic cases, although this observation has not been consistently reported. The disease course in familial IPF is variable, with some individuals experiencing rapid progression and others having a more indolent disease trajectory. Familial Idiopathic Pulmonary Fibrosis (FIPF) is distinguished from sporadic Idiopathic Pulmonary Fibrosis (IPF) by its earlier age of onset and its occurrence within related families [6,7,13,14,15]. Table 1.

Table 1: Clinical Features for Familial Pulmonary Fibrosis.

Category	Clinical Features
Family History	- History of pulmonary fibrosis in one or more family members
	- Age of pulmonary fibrosis onset within family
	- Younger age of onset with each generation affected (genetic anticipation)
	- Lung cancer and pulmonary fibrosis co-segregation within kindred
Extrapulmonary Manifestations	- Bone marrow failure (e.g., aplastic anemia, myelodysplastic syndrome)
	- Macrocytosis with or without anemia
	- Cryptogenic cirrhosis or portal hypertension
	- Premature graying of the hair by the third or fourth decade of life
Age of Onset	- Pediatric onset (age <18 years)

5. Diagnostic Approaches

5.1 High-Resolution Computed Tomography (HRCT)

HRCT is the imaging modality of choice for diagnosing IPF. Typical findings include subpleural reticulation,

honeycombing, and traction bronchiectasis. In FIPF, HRCT findings are indistinguishable from those of sporadic IPF, but the presence of a family history of IPF should raise suspicion for FIPF [42-44].

5.2 Lung Biopsy

In cases where HRCT findings are atypical, surgical lung biopsy may be required to confirm the diagnosis. Histopathological features of FIPF include usual interstitial pneumonia (UIP) pattern, characterized by temporal heterogeneity, fibroblastic foci, and honeycombing [46, 47].

5.3 Clinical Genetic Testing Considerations

- Genetic Counseling: Families with multiple members affected by familial idiopathic pulmonary fibrosis (FIP) often worry about the risk to other relatives. FIP appears to follow an autosomal dominant pattern with reduced penetrance, which complicates the estimation of precise risk figures for family members, especially when no known mutation has been identified. While the exact penetrance of FIP is unknown, the risk to the offspring of FIP patients may be as high as 50%, although reduced penetrance suggests a lower risk. Second- and third-degree relatives are presumed to have a lower risk compared to immediate family members, but still higher than that of the general population. Notably, unaffected relatives with one or two copies of the MUC5B SNP may have a 6.8 to 20.8-fold increased risk of developing pulmonary fibrosis [16, 22].
- Genetic Variants: Common genetic variants, such as a polymorphism in the *mucin 5B (MUC5B)* promoter, have been associated with an increased risk of both familial and sporadic forms of IPF. Testing for these variants could serve as a useful screening approach for IPF [34, 35].
- Biomarkers: Research has identified various biomarkers in blood and bronchoalveolar lavage (BAL) fluid that could aid in the diagnosis of IPF. These include cytokines, chemokines, surfactant protein D, Krebs von den Lunge-6 antigen (KL-6), defensins, and matrix metalloproteinases (MMP) 1 and 7. By integrating genetic testing with clinical and biomarker assessments, a more accurate diagnosis and risk assessment for familial IPF can be achieved [34-39].
- The psychological impact is more closely linked to receiving evidence of actual disease rather than simply learning about genetic risk factors. Abnormal genetic test results (e.g., short telomeres or PF-related variants) do not significantly increase regret or negative feelings when compared to abnormal clinical findings. Living with a known genetic predisposition to pulmonary fibrosis can create ongoing uncertainty and anxiety, as the disease may present with varying severity and age of onset within families [40].

5.4 The Impact of AI and Digital Pathology on Diagnosing Familial Idiopathic Pulmonary Fibrosis

Advances in artificial intelligence (AI) and digital pathology hold significant promise for improving the diagnosis and subclassification of Familial IPF. Machine learning algorithms can analyze high-resolution histopathological images to identify subtle patterns that may distinguish familial cases from sporadic IPF or other interstitial lung diseases. Deep learning models, trained on large datasets of digitized lung biopsies, could uncover novel biomarkers or morphological signatures associated with genetic mutations (e.g., in *SFTPC*, *TERT*, or *MUC5B*). Additionally, AI-powered tools may integrate radiological, genomic, and clinical data to enhance diagnostic accuracy and predict disease progression. By enabling precise, automated analysis, these technologies could facilitate earlier detection, personalized risk assessment, and targeted therapeutic strategies for FIPF [42,43].

Table (2): Diagnostic Criteria.

Diagnostic Criteria of FIPF
Presence of two or more affected first-degree relatives.
HRCT showing UIP pattern.
Exclusion of other ILD causes.
Genetic testing for telomere-related and surfactant-associated mutations.

6. Therapeutic Strategies

The management of FIPF is similar to that of sporadic IPF, with a focus on slowing disease progression and improving quality of life. However, the recognition of genetic mutations in FIPF has opened new avenues for targeted therapies [33, 48, 52].

6.1 Antifibrotic Agents

While antifibrotic drugs such as pirfenidone and nintedanib have shown efficacy in slowing disease progression in sporadic IPF, their effectiveness in familial IPF remains limited. These drugs primarily target pathways involved in fibrosis, such as TGF-β and tyrosine kinase signaling, but familial IPF often involves genetic mutations (e.g., in *TERT*, *SFTPC*, or *MUC5B*) that drive fibrogenesis through distinct mechanisms, potentially reducing therapeutic responsiveness. Additionally, antifibrotics do not reverse existing fibrosis and only modestly delay decline in lung function, leaving a significant unmet need for more targeted therapies [53-60]. Research into novel treatments for familial IPF is ongoing, with several investigational drugs in clinical trials. For example, inhibitors of LOXL2 (lysyl oxidase-like 2), such as simtuzumab, have been explored, though earlier trials showed limited efficacy. Other approaches include

targeting senescence-associated pathways with drugs like danazol (in trials for telomere-related pulmonary fibrosis) or modulating mucin production in *MUC5B* variant carriers. Additionally, gene therapy and precision medicine strategies are being investigated to address specific genetic defects underlying familial IPF. Despite these efforts, challenges remain in developing therapies that can halt or reverse fibrosis in genetically predisposed individuals, highlighting the need for further research into the molecular mechanisms driving familial IPF and more personalized treatment approaches [53-60].

6.2 Lung Transplantation

Lung transplantation is a viable option for FIPF patients with advanced disease. However, the presence of telomere-related mutations may impact post-transplant outcomes, as these patients are at increased risk of complications such as bone marrow failure and infections. Careful evaluation and management of extrapulmonary manifestations are essential in FIPF patients undergoing lung transplantation [60-64].

6.3 Emerging Therapies

The identification of genetic mutations in FIPF has spurred interest in developing targeted therapies. For example, telomerase activation strategies are being explored as a potential treatment for FIPF patients with telomere-related mutations. Additionally, therapies aimed at reducing endoplasmic reticulum stress and alveolar epithelial cell injury are under investigation for FIPF patients with surfactant protein-related mutations. Moreover, precision medicine strategies, including targeted therapies and gene editing, hold potential for improving treatment outcomes. As research progresses, integrating genetic insights with clinical management could enhance patient care and disease-modifying strategies in FPF, [11, 31, 33].

7. Prognosis

FIPF has a variable disease course, with a mean survival of 3–5 years post-diagnosis. Telomere mutations (e.g., *TERT*, *TERC*) are associated with more aggressive disease [62, 63].

8. Future Directions

The future of familial idiopathic pulmonary fibrosis (IPF) research holds promising avenues for understanding and managing this complex disease. One key area of focus is telomere biology, where further research is needed to elucidate the underlying mechanisms driving telomere dysfunction in familial IPF and explore potential therapeutic interventions to mitigate its effects. Additionally, the development of targeted therapies tailored to specific genetic mutations could revolutionize treatment, offering personalized approaches that improve patient outcomes [46-51].

Another critical direction involves enhancing genetic counseling practices by refining guidelines and better understanding the psychological impact of genetic testing on patients and families. This will ensure that individuals at risk receive comprehensive support and informed decision-making tools. Finally, investigating gene-environment interactions will be essential to unravel how genetic predispositions and environmental exposures collectively contribute to disease progression. By addressing these key areas, researchers can pave the way for more effective prevention, diagnosis, and treatment strategies for familial IPF [65-70].

CONCLUSION

FIPF is a genetically predisposed form of IPF with earlier onset and familial clustering. Mutations in telomere maintenance and surfactant protein genes play a central role in its pathogenesis. Early diagnosis, genetic counseling, and antifibrotic therapy are crucial for managing FIPF. Lung transplantation remains the only curative option, highlighting the need for continued research into disease-modifying therapies. Future studies should focus on large, multicenter collaborations to improve outcomes for affected families.

INFORMED CONSENT STATEMENT

No consent for this review.

ETHICAL APPROVAL

Not applicable.

DATA AVAILABILITY STATEMENT

Literature review.

SUPPLEMENTARY MATERIALS

Figures 1, 2, 3 and Table 1,2.

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CONFLICTS OF INTEREST

The author declares no conflicts of interest.

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