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Authors
Wolters, Paul J
Blackwell, Timothy S
Eickelberg, Oliver
et al.

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Time for a change: is idiopathic pulmonary fibrosis still idiopathic and only fibrotic?

Paul J Wolters, MD [Prof],
Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of California, San Francisco, CA, USA

Timothy S Blackwell, MD [Prof],
Department of Medicine, Vanderbilt University, Nashville, TN, USA

Oliver Eickelberg, MD [Prof],
Division of Pulmonary Sciences and Critical Care Medicine, Department of Medicine, University of Colorado Denver, Aurora, CO, USA

James E Loyd, MD [Prof],
Department of Medicine, Vanderbilt University, Nashville, TN, USA

Naftali Kaminski, MD [Prof],
Section of Pulmonary, Critical Care, and Sleep Medicine, Yale University School of Medicine, New Haven, CT, USA

Gisli Jenkins, MD [Prof],
Division of Respiratory Medicine, University of Nottingham, Nottingham University Hospitals, Nottingham, UK

Toby M Maher, MD [Prof],
Fibrosis Research Group, National Heart and Lung Institute, Imperial College London, London, UK

Maria Molina-Molina, MD [Prof],
Department of Pneumology, Unit of Interstitial Lung Diseases, University Hospital of Bellvitge Institute for Biomedical Research (IDIBELL), Barcelona, Spain

Paul W Noble, MD [Prof],
Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Ganesh Raghu, MD [Prof],
Center for Interstitial Lung Disease, University of Washington, Seattle, WA, USA

Luca Richeldi, MD [Prof],

Correspondence to: Prof Paul J Wolters, Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of California, San Francisco, CA 94143, USA, paul.wolters@ucsf.edu.

Contributors

PJW and DAS did the literature searches and wrote the first draft of the paper. All authors contributed to and revised drafts and approved the final version.

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Division of Pulmonary Medicine, A Gemelli University Hospital, Catholic University of the Sacred Heart, Rome, Italy

Marvin I Schwarz, MD [Prof],
Division of Pulmonary Sciences and Critical Care Medicine, Department of Medicine, University of Colorado Denver, Aurora, CO, USA

Moises Selman, MD [Prof],
Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico City, Mexico

Wim A Wuyts, MD [Prof], and
Department of Pulmonary Medicine, Unit for Interstitial Lung diseases. University Hospitals Leuven, Leuven, Belgium

David A Schwartz, MD [Prof]
Division of Pulmonary Sciences and Critical Care Medicine, Department of Medicine, University of Colorado Denver, Aurora, CO, USA

Abstract

Idiopathic pulmonary fibrosis (IPF) is a progressive, irreversible, and typically fatal lung disease characterised by subpleural fibrosis, subepithelial fibroblast foci, and microscopic honeycombing. Although understanding of the pathogenic mechanisms continues to evolve, evidence indicates that distal airway and alveolar epithelial cells are central drivers of the disease. In this Viewpoint, we review the history of naming and classifications used to define the disease now referred to as IPF, in the context of understanding the clinical presentation, causes, and pathogenesis of the disease. We aim to generate discussion on whether, given the substantial progress made in understanding the clinical, genetic, cellular, and molecular mechanisms involved in the development of IPF, a change of name should be considered. To initiate this discussion, we offer new suggestions to update the name of this disease and new approaches to classify all forms of pulmonary fibrosis.

Disease characteristics

Idiopathic pulmonary fibrosis (IPF) is a progressive, irreversible, and usually fatal lung disease, for which the average life expectancy is 3–5 years after diagnosis. The histopathological hallmarks of the disease are subpleural fibrosis, subepithelial fibroblast foci, and microscopic honeycombing. Affected areas are adjacent to histopathologically normal regions, in a pattern termed usual interstitial pneumonia.[1–4] Although understanding of the pathogenic mechanisms continues to evolve, strong evidence indicates that aberrantly activated lung epithelial cells secrete mediators, leading to fibroblast proliferation and differentiation to highly active myofibroblasts, which deposit excessive amounts of extracellular matrix and irreversibly destroy the lung architecture.[5]

Origin of term idiopathic pulmonary fibrosis

IPF has had multiple names. First recognition of the disease is attributed to D J Corrigan in 1838, who called it cirrhosis of the lung. The clinical and pathological features described

were typical of what has since been recognised as a distinct fibrotic lung disease in adults. Corrigan's descriptor prevailed until 1893, when, in the text *Principles and Practice of Medicine*, William Osler renamed it chronic interstitial pneumonia but kept cirrhosis of the lung as a subtitle.

In 1948, Robbins[6] first used the term IPF to describe patients with interstitial opacities on chest radiographs that were suggestive of pulmonary fibrosis but had no identifiable cause. At that time, associations between pulmonary fibrosis and postinfection fibrosis, pneumoconiosis, radiation therapy, and autoimmune diseases, such as rheumatoid arthritis or systemic sclerosis, had been recognised. IPF was found to occur in families, which inferred a genetic component.[7] However, the term IPF was used infrequently until a 1976 review article by Crystal and colleagues[8] popularised the term. Acquisition of surgical lung biopsy samples, led to the recognition of dissimilar histopathological patterns of pulmonary fibrosis that were separated into subtypes, such as usual interstitial pneumonia, desquamative interstitial pneumonia, and giant-cell interstitial pneumonia, by Liebow[3] and by others, with different causes implied for the specific subtypes. The causes of some subtypes are now known: giant-cell interstitial pneumonia is caused by exposure to hard-metal dust and desquamative interstitial pneumonia is strongly associated with smoking. Nevertheless, in most patients specific causes could not be identified and, therefore, IPF included several histopathological subtypes of interstitial lung disease, such as usual interstitial pneumonia and non-specific interstitial pneumonia.[9] At the same time, other terms were used to describe these diseases, including idiopathic interstitial pneumonia and cryptogenic fibrosing alveolitis. With the introduction of high-resolution CT, radiological patterns could be identified that corresponded to the pathological features of usual interstitial pneumonia.[10] Clinicians began to apply the name IPF more selectively to patients with a pattern of lung fibrosis indicative of usual interstitial pneumonia on high-resolution CT, relevant lung pathology, or both, without a known cause.

Two advances led to further phenotyping of IPF. First, clinicians and pathologists with expertise in interstitial lung disease recognised that pathological subtypes of IPF were clinically distinct.[11] A consensus statement was published that defined specific clinical and histopathological features of IPF. Evidence that accumulated over the next decade led to guidelines that further refined the definition of IPF and established precise criteria for the radiological and histopathological features of usual interstitial pneumonia.[12] The term IPF was reserved for patients with usual interstitial pneumonia patterns of lung disease in the absence of known secondary causes, such as autoimmune diseases or defined environmental exposures. Second, combined input of clinicians, radiologists, and pathologists was recognised as being the most accurate way to diagnose the disease.[13] The diagnostic criteria might be viewed as restrictive because they led to a substantial proportion of patients being judged to have unclassifiable fibrosis,[14] but they have been useful in defining a population of patients with a fairly uniform clinical and pathological pattern of lung disease.

Risk factors for idiopathic pulmonary fibrosis

Over the past decade, IPF has been revealed to be a complex, heterogeneous disorder associated with rare and common sequence variants in several genes (*MUC5B*, *TERT*,

TERC, *RTEL1*, *PARN*, *DKC1*, *TINF2*, *SFTPC*, *SFTPA2*, and *ABCA3*)[15–25] and in at least 11 loci[26,27] associated with multiple emerging epigenetic[28–32] and transcriptional[31,33–36] profiles. The *MUC5B* promoter variant rs35705950 has been validated as a risk variant for IPF in 11 independent studies.[26,37–46] This variant is the strongest known risk factor (odds ratio [OR] for carriers of the T (minor) allele 4·51, 95% CI 3·91–5·21),[26] accounting for at least 30% of the overall risk of developing IPF,[26,38–46] and might be useful to identify individuals early in the disease course.[47,48] Family history of more than one case of IPF in the previous one or two generations and in biological siblings is an independent risk factor for this disease.[49] Familial and sporadic IPF share many genetic risk factors,[16,20,22–24,26,38–43,45,46] which suggests that family members of people with sporadic IPF could also represent an at-risk population.

Various exposures, such as microaspiration,[50,51] metal and wood dust,[52–54] viruses,[55–57] and drugs, have been associated with the development of IPF, but the most important environmental risk factor is smoking cigarettes (of note, some of the cited studies were completed before the current classification criteria were established). Ever having smoked cigarettes remains an important risk factor for the development of sporadic IPF even many years after smoking cessation.[58] Cigarette smoking is also a strong risk factor for the development of familial interstitial pneumonia (OR 3·6, 95% CI 1·3–9·8),[49] which suggests that cigarette smoking contributes substantially to familial cases of IPF.

Primary role of lung epithelia in disease pathogenesis

An approach to understanding IPF pathogenesis is to consider it as a three-stage process: predisposition, activation, and progression (figure).[4] With this approach, ageing, smoking, environmental exposures (eg, accumulation of environmental chitin[59]), and genetic background are predisposing risk factors.[60,61] Epidemio logical studies confirm IPF as a disease of ageing, with interstitial lung abnormalities becoming increasingly prevalent with advancing age.[47] IPF is unusual in individuals younger than 50 years, but prevalence nearly doubles with every decade of life thereafter.[61] These intrinsic and extrinsic risk factors only increase an individual's probability of developing IPF. That is, many individuals might have one or more risk factors but never develop the disease.

During the activation phase, accumulated environmental exposures in a genetically predisposed individual lead to pathological alterations to the lung epithelium.[5,62] One durable alteration is the critical shortening of telomeres in alveolar type II cells,[63,64] which can lead to molecular changes within lung epithelial cells sufficient to promote lung remodelling and fibrosis.[65] Other epithelial alter ations are activation of senescence pro gramming,[66–68] accumulation of dysfunctional mitochondria,[69] and activation of the unfolded protein response.[70] The abnormal epithelium expresses numerous mediators that might lead to mesenchymal-cell activation and lung remodelling. Activation may be direct or indirect via immune cells, such as macrophages or lymphocytes,[71] although the exact roles of immune cells in IPF remain unclear. Candidate mediators include transforming growth factor (TGF) β, its activating integrin αvβ6, platelet-derived growth factor β, and Wnts, which activate mesenchymal cells when expression is increased.[4,5] Conversely, dysfunctional epithelium might reduce the expression of some mediators, such as

prostaglandin E2, that under normal circumstances suppress mesenchymal cell expansion.[72,73] Additionally, alveolar type II cells are thought to act as stem cells in adult lungs, and can form so-called alveolar organoids in vitro.[74] Alveolar type II cells isolated from the lung tissue of individuals with IPF at the time of transplantation have impaired ability to form organoids, which suggests that alveolar stem-cell failure contributes to IPF pathogenesis.[75,76] Thus, lung remodelling in IPF arises from alterations in epithelial-cell growth and repair and epithelial–mesenchymal crosstalk.

In the progression phase, the normal alveolar structure of the lung is lost and replaced by remodelled fibrotic tissue characterised by bronchiolised cystic airspaces, which might include continuous proliferation of bronchiolar epithelium to honeycomb cysts. During this phase, the pathological matrix might contribute to remodelling via mechanisms independent of epithelial-cell dysfunction. Examples include increased stiffness and stretch-induced activation of TGFβ by the remodelled lung.[77–79] Remodelling of lung tissue in patients with IPF alters expression of multiple matrix molecules,[80] many of which can activate profibrotic-signalling pathways in the mesenchymal cells that engage them.[78] These IPF fibroblasts, which are potentially metabolically aberrant,[81] can acquire destructive properties, such as the ability to invade matrix, which could contribute to chronic remodelling.[82]

This overview of the pathogenesis of IPF does not include all candidate cellular or molecular mediators, but biological findings can be incorporated in the organisational concepts of predisposition, activation, and progression as more is learned about their specific roles in the disease process. Our proposed organisational framework (figure) also identifies two potential feed-forward loops of disease activity that might explain the relentless progression of IPF. The first is senescence of alveolar type II cells. Because these cells act as the functional stem cells of the lung, when one becomes senescent, adjacent non-senescent alveolar type II cells must compensate, which leads to increased frequency of replication, accelerated telomere attrition, and a predisposition to senescence. A second feed-forward loop is triggered by matrix deposition, which stiffens lung tissue,[80] and can lead to the conversion of fibroblasts to myofibroblasts[79] and increased epithelial-cell activation, collagen and matrix deposition, and lung remodelling.

Overall, when the pathogenesis of IPF is considered as a continuum of predisposition, activation, and progression, distal bronchiolar and alveolar epithelial lung cells are shown to be the pathologically abnormal cells in IPF lungs, and fibrosis to be the consequence of epithelial-cell dysfunction. Therefore, IPF is a disease of lung epithelial cells that manifests as fibrosis rather than being an intrinsically fibrotic disease.

The case to rebrand idiopathic pulmonary fibrosis

With growing understanding of the causes and pathogenesis of IPF, the term idiopathic no longer seems to describe this progressive lung disease accurately. Furthermore, the term fibrosis limits consideration of the clinical and pathological attributes of this complex interstitial lung condition and does not highlight the primary role of lung epithelia in its pathogenesis. Because the name of a disease can affect a patient’s (or caregiver’s) under

standing of their disease and expectations for its behaviour and management,[83] we propose renaming IPF.

There is precedent for changing the name of diseases. For example, eponymous diseases named to honour the individual who first described them have been renamed when scientific understanding of the disease no longer reflects the first description. Diseases named initially as idiopathic, which implies a distinct, primary entity for which the cause is unknown, have been changed when causes are recognised. For instance, idiopathic thrombocytopenia purpura was renamed as immune-mediated thrombocytopenia to reflect the disease mechanism.[84] The term idiopathic might falsely convey that there is little or no understanding for the cause or pathogenesis. For IPF, however, although uncertainties remain, genetic, environmental, cellular, and molecular mechanisms are now well recognised as being involved in its development.

The term fibrotic implicates only matrix accumulation, yet, although fibrosis is a major contributor to the disease process in IPF, it is only one component and is the consequence of dysfunctional epithelia. Moreover, IPF is a biologically and temporally heterogeneous process within and across patients. The most frequently identified pathological abnormalities in lung remodelling are subpleural fibrosis, subepithelial foci of fibroblasts and myofibroblasts, metaplastic and hyperplastic changes of epithelial cells lining the alveoli, re-epithelialised air spaces (microscopic honeycombing), lymphoid aggregates, and increased numbers and subtypes of haemopoietic cells, including macrophages, dendritic cells, and mast cells.[4,65,85,86] Although none of these features occurs alone, transcriptional studies suggest that they can be grouped into at least two major categories: IPF that predominantly expresses genes associated with the respiratory bronchiolar epithelium (cilia and mucins) and is more likely to have histological honeycomb cysts in the lungs, and IPF that primarily expresses matrix-related genes.[35] Moreover, the lung epithelia in IPF represent a broad biological phenotype in which markers of conducting airway cells and type I and type II alveolar epithelial cells are co-expressed.[87]

Use of the term fibrosis also implies that only the extracellular matrix components of the remodelled lung represent IPF and neglects the other elements. It further implies that the non-fibrotic changes must either directly contribute to development of or be a consequence of fibrosis. Bronchoalveolar epithelial cells, however, seem to be the most important dysfunctional cells in IPF, and in many cases the temporal components of cell–cell interactions are unknown. For example, although microscopic honeycombing and fibrosis are characteristic features of IPF, no specific interactions between these pathological processes have been described. Without this knowledge, it is equally conceivable that microscopic honeycombing evolves from mechanisms independent of the fibrotic process. It is time to recognise specific elements of remodelling in the IPF lung and to define whether they arise from separate pathological drivers or relate specifically to matrix deposition and fibrosis. Independently considering other elements of lung remodelling does not challenge the importance of fibrosis in IPF. Rather, it enhances understanding of the relationships between fibrosis and these elements.

Use of the name IPF potentially limits understanding of therapeutic advances. Use of the term antifibrotic therapy to describe pirfenidone and nintedanib is somewhat premature. Although these medications slow the loss of forced vital capacity (FVC) in patients with IPF,[88,89] there is no evidence that they slow fibrosis (ie, extracellular matrix deposition and scar formation). Thus, describing them as antifibrotic potentially discourages investigation of their possible effects on elements of the activation phase or non-fibrotic elements of lung tissue remodelling that might explain the preservation of FVC. Embracing the pathogenic heterogeneity of IPF could lead to the development of drugs specifically effective against fibrotic or non-fibrotic elements in remodelled IPF lung tissue. Identifying differences in the contri butions of these elements between patients might lead to implementation of precision medicine approaches in IPF.

Suggestions for moving forwards

In view of the latest understanding of the clinical, aetiological, genetic, and molecular features of IPF, we propose that it is time to reconsider whether the name accurately represents the underlying disease. We suggest several approaches that could be used to rename IPF. These suggestions are intended to start discussions that will need input from the wider IPF community to develop further.

One approach would be to simply rename IPF consistent with its pathogenesis, for instance epithelial-driven pulmonary fibrosis, primary pulmonary fibrosis, or progressive age-dependent pulmonary fibrosis. Another approach would be to reclassify pulmonary fibrosis by clinical and aetiological criteria, using a format similar to that for pulmonary hypertension (table 1). We suggest separating the subtypes of pulmonary fibrosis into four groups. Group 1 could be pulmonary fibrosis driven by epithelial cell dysfunction, representing the disease currently known as IPF. Group 2 could be pulmonary fibrosis driven by inflammatory-cell dysfunction, representing diseases such as pulmonary fibrosis associated with connective-tissue diseases or hypersensitivity pneumonitis. Group 3 could include pulmonary fibrosis due to occupational exposures or medications, such as asbestosis or nitrofurantoin. Hypersensitivity pneumonitis could also be positioned in group 3 if a definite exposure is identified. Group 4 could include pulmonary fibrosis due to smoking-related diseases, such as desquamative interstitial pneumonitis. Each group could be further separated to distinguish between patients with known and no known genetic causes. Patients could be reclassified if causes are identified or they are found to share genetic risk with another category, such as IPF, which has been described for a subset of patients with rheumatoid arthritis or hypersensitivity pneumonitis.[90,91]

An alternative reclassification could use a personalised medicine approach to distribute pulmonary fibrosis into two classes. Class 1 could include cases of pulmonary fibrosis of unknown cause and class 2 those with a known cellular or molecular cause (table 2). These two classes would have clinical subcategories, such as autoimmune diseases and known environmental exposures, with further separation of patients by known cellular or molecular causes. Categories to consider include pulmonary fibrosis driven by epithelial-cell dysfunction, telomere dysfunction, or known gene mutations (eg, surfactant protein C). This

approach would enable dynamic categorisation of pulmonary fibrosis that could be adapted with advances in cellular and molecular understanding of disease pathogenesis.

To reach a consensus for renaming IPF or reclassifying all forms of pulmonary fibrosis, we propose that a committee of stakeholders that includes experienced clinicians and scientists, as well as patients and their advocates, assembles to review the literature with the objective of answering the following questions: whether IPF is idiopathic; whether definable subgroups exist; and whether the term fibrosis mischaracterises a disease that primarily involves abnormal lung epithelia. If the consensus to these questions is yes, the committee should be charged with deriving a new name or classification of pulmonary fibrosis that is less confining than IPF and is sufficiently broad to incorporate advances in the clinical, aetiological, and molecular understanding of the disease.

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Key messages

- Idiopathic pulmonary fibrosis (IPF) is a disease primarily of epithelial-cell dysfunction, the consequence of which is fibrosis
- The IPF lung contains elements of remodelling that might occur independently of fibrosis
- Two unique feed-forward loops might explain the relentless progression of IPF
- The name IPF no longer accurately represents understanding of the disease pathogenesis
- It is time to consider renaming IPF in a way that reflects the disease process

Search strategy and selection criteria

We searched PubMed with the search terms “lung”, “fibrosis”, “idiopathic pulmonary fibrosis”, “pathogenesis”, “interstitial”, “genetic”, “epithelium”, “cryptogenic fibrosing alveolitis”, “fibroblast”, “senescence”, “stem cell”, “telomere”, “macrophage”, “lymphocyte”, and “inflammation” for articles published from 1898 onwards. We searched the references of retrieved articles for further articles, and additional citations were suggested during peer review. We selected articles for citation if they reviewed or presented human data relating to pulmonary fibrosis or established the importance of specific pathological mechanisms.

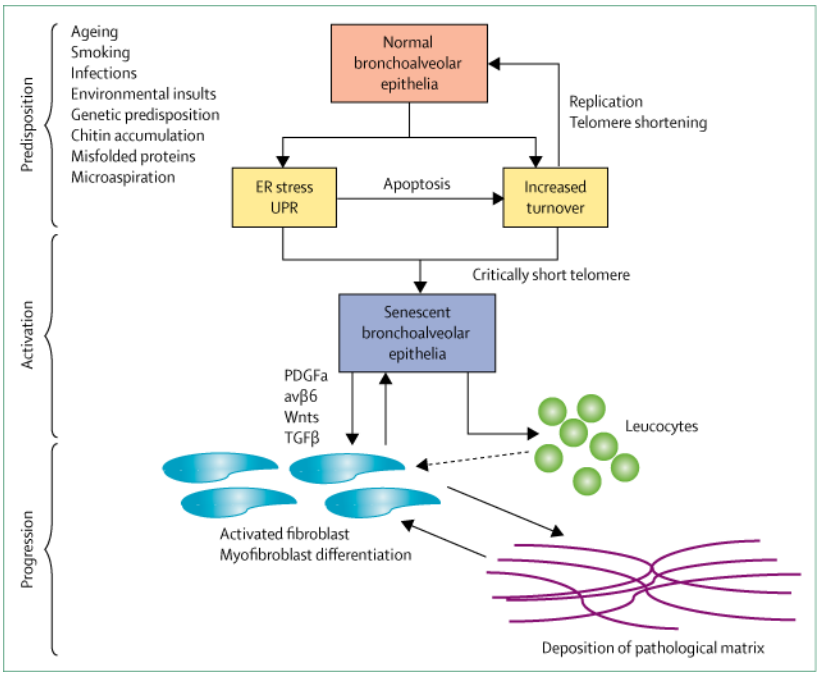

Figure. Three-stage description of the pathogenesis of idiopathic pulmonary fibrosis

In the predisposition stage, recurrent environmental insults lead, in genetically predisposed individuals, to increased turnover of alveolar type II cells, ER-stress-mediated activation of UPR, apoptosis, and progressive telomere attrition. In the activation stage, accumulation of a lifetime insults leads to pathological alterations of the lung epithelium, such as senescence reprogramming, and release of profibrotic mediators (eg, TGFβ, Wnts, and PDGFβ) by the alveolar epithelium. These mediators, either directly or indirectly via leucocytes, activate fibroblasts to deposit pathological matrix. In the progression stage, the pathological matrix promotes additional differentiation of fibroblasts to myofibroblasts, which deposit more matrix and further activate fibroblasts in a feed-forward loop of lung remodelling. ER=endoplasmic reticulum. UPR=unfolded protein response. PDGF=platelet-derived growth factor. TGF=transforming growth factor.

Table 1

Proposed groups for subtypes of pulmonary fibrosis

	Disorders in classification
Group 1: pulmonary fibrosis driven by epithelial cell dysfunction	IPF
Group 2: pulmonary fibrosis driven by inflammatory cell dysfunction	RA-ILD, scleroderma, MCTD, Sjogren's syndrome, hypersensitivity pneumonitis, sarcoidosis, NSIP
Group 3: occupational or drug induced pulmonary fibrosis	Asbestosis, silicosis, medications
Group 4: pulmonary fibrosis due to smoking	RBILD, DIP, LCH

RA-ILD=rheumatoid-arthritis-associated interstitial lung disease. IPF=idiopathic pulmonary fibrosis. MCTD=mixed connective-tissue disease. NSIP=non-specific interstitial pneumonitis. RBILD=respiratory bronchiolitis with interstitial lung disease. DIP=desquamative interstitial pneumonia. LCH=Langerhan's cell histiocytosis.

Table 2

Proposed reclassification of pulmonary fibrosis

	Considerations for classification
Class 1: no evidence of molecular markers	Autoimmune disease Known environmental exposures No autoimmune disease or environmental exposure
Class 2: genetic, transcriptomic, or proteomic explanation for pulmonary fibrosis *	Autoimmune disease Known environmental exposures No autoimmune disease or environmental exposure

* For example, carriers of *MUC5B* minor allele or mutations in *TERT*, *TERC*, *RTEL1*, *SFTPC*, and other genes.