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Genetic Susceptibility and Interstitial Lung Diseases

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Abstract

Purpose of Review—Recent genetic findings have identified new targets of investigation in the field of interstitial lung diseases and have the potential to change clinical care.

Recent Findings—These findings implicate abnormalities in (1) host defense, (2) cell-cell adhesion, and (3) aging and senescence in the pathophysiology of pulmonary fibrosis. At least one common genetic variant strongly associated with pulmonary fibrosis appears to have prognostic implications for patients.

Summary—The inherited risk for pulmonary fibrosis is substantial, and recent data suggests that genetic risk for familial and sporadic forms of the disease are similar. Further characterization of the genetic risk will influence clinical practice in terms of categorization, diagnosis, and screening of individuals for this disease.

Keywords

IPF; pulmonary fibrosis; MUC5B; telomere; desmosome

Introduction

Despite decades of research, the etiology of fibrosing idiopathic interstitial pneumonias (IIPs), also known as fibrosing interstitial lung diseases (ILDs), has remained elusive. In the past few years, genetic studies of IIPs have led to new insights into disease susceptibility and identified new targets for further investigation.

Idiopathic Pulmonary Fibrosis (IPF) is the most common of the fibrosing IIPs. IPF is characterized by scarring of the lung parenchyma, leading to characteristic peripheral and basilar-predominant reticular opacities, volume loss with traction bronchiectasis, and honeycombing on high-resolution computed tomography and the pattern of Usual Interstitial

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Pneumonia (UIP) on histopathology [1]. The prognosis is poor, with no effective therapies and a median survival time from diagnosis of three years [2].

The etiology of IPF remains unknown, though it has long been known that specific environmental exposures are associated with disease [3-6]. Numerous studies have indicated that there is a genetic basis for pulmonary fibrosis – twin studies and familial aggregation of cases provided the first signs that inherited factors played a role in disease development [7-10]. For instance, abnormalities in surfactant proteins in particular are strongly implicated in familial pulmonary fibrosis [11-13]. In addition, pleiotropic genetic disorders such as dyskeratosis congenita [14] and Hermansky-Pudlak syndrome [15] are associated with pulmonary fibrosis. However, these mutations account for a small proportion of the population risk of disease making further research into genetic predisposition necessary.

Recent population studies have pointed to numerous additional specific genetic variants that confer significant risk to development of IPF and other fibrosing IIPs [16-18*]. Notably, pre-clinical evidence of interstitial lung abnormalities appears in asymptomatic patients carrying these genetic variants [19**]. This finding could have implications for the clinical care of those found to have genotypes conferring disease risk, particularly in light of the recent finding that genotype may help predict prognosis [20**]. As the body of evidence illustrating the genetic predisposition to development of fibrosing lung disease grows, the distinction between “familial” and “idiopathic” forms of the disease is becoming less clear —indeed, recent findings indicate that both sporadic and familial presentations of IPF have similar genetic risk factors [17**, 21].

In this review, we summarize current knowledge about genetic risk for the development of ILDs with a focus on the most recent findings in the field. Genes implicated in the development of ILDs can be categorized into three main categories, which will create a framework for the discussion: (1) genes implicated in host defense; (2) genes involved in aging and senescence; (3) and genes involved in cell-cell adhesion. We conclude by addressing the implications of recent findings—specifically, that there may be no genetic difference between sporadic and familial cases of IPF.

1. Host Defense

Alterations in an individual's host defense mechanisms have been the target of previous research examining genetic predisposition to disease. Genetic variation in cytokine genes has been implicated in fibrosis in prior studies [22-24]. More recently, genome-wide association studies have further expanded investigators' focus from the alveolar epithelia and the fibroblast to the role of host defense in pathogenesis of disease.

Mucins—In 2011, Seibold and colleagues determined through genome-wide linkage analysis and subsequent fine-mapping/sequencing that a single nucleotide polymorphism (SNP) rs35705950 on the p-terminus of chromosome 11 is strongly associated with IPF and with Familial Interstitial Pneumonia (FIP), as defined by the presence of two or more cases of definite or probable idiopathic interstitial pneumonia within three generations of a family [16]. This SNP resides in the promoter region of the *MUC5B* gene, which codes for an airway mucin that is highly conserved across primate species. Analysis of other loci in the

region showed that rs35705950 remained the most significant SNP. The odds ratios for disease among those who are heterozygous (GT) and homozygous (TT) for the minor allele at this site were 6.8 and 20.8 for FIP and 9.0 and 21.8, respectively, for IPF [16], indicating a strong influence of the SNP on disease development. Not only was IPF diagnosis associated with greater than 14-fold increase in expression of *MUC5B* in lung tissue regardless of genotype, but presence of the minor allele (T) at rs35705950 was associated with a 37.4-fold increase in gene expression among unaffected individuals [16]. In the healthy human lung, MUC5B is found in the cytoplasm of secretory columnar cells in the bronchi as well as in bronchioles. In the setting of IPF, MUC5B appears in these locations as well as the characteristic honeycomb cysts [25*].

The association of this *MUC5B* promoter variant with pulmonary fibrosis has been confirmed in multiple cohorts [17**, 18] [26-28*], and remains the most robust genetic finding association with IPF to date (Table 1). Intriguingly, the rs35705950 variant has also been shown in the general population to be associated with subclinical interstitial lung abnormalities, which may be precursor lesions to clinically evident pulmonary fibrosis [19]. The odds of having definite fibrosis on a CT scan were 6.3 times higher for each copy of the *MUC5B* variant [19]. Though this polymorphism is strongly associated with both subclinical interstitial lung abnormalities and with pulmonary fibrosis, it is also associated with improved survival in IPF patients, as shown by a retrospective analysis of two independent cohorts, suggesting that genotype may be a marker of prognosis [20**]. A remarkable aspect of the *MUC5B* variant finding is its high frequency, being found in approximately 20% of the European Centre d'Etude du Polymorphisme Humain (CEPH, individuals with Northern and Western European ancestry) population and 19% of the Framingham Heart Study population [19]. Yet the apparent effect size of this common variant is significant [16]. The frequency of the variant in the CEPH population and the relative infrequency of IPF in the general population suggest a significant role for gene by gene or gene by environment interactions in the development of disease. In addition, the *MUC5B* variant confers specific genetic risk for IPF, as studies of ILD secondary to sarcoidosis and scleroderma have failed to show an association [27-29*], though other groups have previously found *MUC5B* variants associated with diffuse panbronchiolitis in Asian populations [30].

Despite the strength and reproducibility of these findings, the mechanism by which the *MUC5B* variant leads to pulmonary fibrosis remains unknown. Recent, findings in murine models indicate that Muc5b is critical in airway response to pathogens [31**]. These findings suggest that dysregulation of *MUC5B* could impair host defense or contribute to poor clearance of inhaled particles and toxins via disordered mucociliary clearance. Alternatively, excess MUC5B may impair the alveolar repair response, leading to disordered signaling between alveolar epithelia and other matrix producing cells.

Inflammatory mediators—Toll like receptors (TLRs) are transmembrane receptors that recognize structurally conserved molecules derived from microbes. Another recent GWAS confirmed the *MUC5B* SNP association and identified three SNPs in Toll interacting protein (TOLLIP) significantly associated with pulmonary fibrosis [18]. These variants, all associated with differential expression of the gene, implicate the innate immune response in IPF pathogenesis. Intriguingly, one *TOLLIP* variant (rs5743890) was associated with

mortality, providing another example of genotype affecting prognosis [18]. In a smaller study, a specific variant in Toll-like receptor 3 (*TLR3*) leading to a functional amino acid substitution (L412F) was found to be associated with decreased TLR3 activity in primary fibroblasts from IPF patients. This nonsynonymous mutation was also associated with early mortality and accelerated lung function decline in those carrying the variant [32]. In the case of asbestos-related lung disease, functional polymorphisms (rs35829419) in the *NLRP3* gene, whose product is thought to play a role in inflammation and apoptosis, have also been linked to risk of pulmonary fibrosis [33*].

2. Aging & Senescence

The ability of the alveolar epithelium to respond to stress and injury has also long been a hypothesized etiology of pulmonary fibrosis, especially since so many presumably injurious exposures (e.g., asbestos, cigarette smoking) have been associated with the disease. Prior studies have indicated that the abnormalities in the ability of epithelial cells to divide and replace epithelia could be central to the pathophysiology of disease [34-36*], and correspondingly genetic variants in cell cycle genes have been associated with IPF and disease progression [37].

Telomeres are repetitive nucleotide sequences at the ends of chromosomes that protect genes from being damaged through the normal DNA replication process, and so are critical to maintaining genomic stability and regulating a cell's replicative capacity [38*]. Once telomeres shorten past a threshold, they activate a DNA damage response leading to cell death or cell-cycle arrest. Telomerase maintains telomere length by adding nucleotide repeats to the ends of chromosomes during the replication process and is composed of a reverse transcriptase component (TERT) and an RNA component, which serves as a template for elongation (TERC). Not only is telomerase activity ubiquitous in cancerous cells, it is also found in cells undergoing injury and repair, including fibrogenesis [39].

Sequence variants in genes regulating telomere length have been associated with numerous age-related diseases, including pulmonary fibrosis [38*]. Familial pulmonary fibrosis has been linked to shortened telomeres [40], and more specifically to specifically *TERT* and *TERC* mutations [40-42] some of which are inherited in an autosomal dominant fashion and show evidence of genetic anticipation [40] [12]. Interestingly, IPF patients have shortened telomeres even without the presence of known telomerase mutations [43, 44], suggesting that there may be factors other than previously described mutations that affect telomere length and, by extension, risk of disease.

Subsequent studies have found similar associations of *TERT* mutations with sporadic IPF [45-47]. *TERT* mutations have been found in 10-15% of FIP families, but in the majority of FIP patients, the responsible genetic abnormality has not been found [48, 49*]. However, recently an X-linked mutation in a third telomerase-associated gene, dyskerin (*DKC1*), has been described in a family with FIP [49*]. DKC1 binds to TERC and stabilizes the telomerase complex; as such, this newly described mutation led to decreased telomerase activity in affected individuals [49*]. The genetic risk for pulmonary fibrosis conferred by variants in *TERT* and *TERC* was confirmed by a large GWAS of individuals with fibrotic IIPs that found common variants in the *TERC* and *TERT* loci, 3q26 and 5p15, respectively

[17**]. Telomerase activity was further implicated in this GWAS by the finding that a common variant in *OBFC1*, a gene implicated in variation of leukocyte telomere length [50-52], was also associated with fibrotic IIP [17**].

There is mounting evidence that specific variants in genes affecting telomerase activity or telomere length confer risk of pulmonary fibrosis, but the mechanism(s) by which these genetic changes lead to fibrosis remains unclear. Better understanding of the gene's role in the pathophysiology of fibrosis has the potential to direct us to therapeutic targets.

3. Cell-Cell Adhesion

A third category of genes recently identified as targets for future investigation are those involved in cell-cell adhesion. Specifically, variants in desmoplakin (*DSP*) and dipeptidyl peptidase 9 (*DPP9)* are associated with fibrotic IIP [17**]. In addition, *DSP* expression in lung tissue varied with the number of copies of the most statistically significant common variant, rs2076295 [17**], and *DSP* and *DPP9* have been shown in various organs (heart, skin, kidney) to be critical in epithelial integrity [53-55].

DSP is an important component of the desmosome, a transmembrane structure particularly abundant in cells undergoing constant stretch (heart, skin, airway). As such, DSP may be particularly important in the regions of the lung that experience constant mechanical stress, such as the peripheral and basilar segments, those that are preferentially affected in IPF patients [56]. Intriguingly, other investigations have illustrated that *DSP* acts as a tumor suppressor by suppressing the WNT/β -caten in pathway [57], a pathway that itself has been implicated in the pathogenesis of IPF [58-60]. Further investigations into desmosomes in IPF may suggest a conduit by which environmental exposures could induce intracellular signaling changes, since the intracellular DSP interacts closely with cytoskeleton. Non-small cell lung cancer and other cancers illustrate that the desmosome is not merely an adhesion structure, but instead is a dynamic part of the epithelial cell and can alter phenotype via intracelleular signaling [61].

Implications of recent findings

Recent genetic findings in the field of fibrotic lung disease have broadened the scope of inquiry into the pathogenesis of disease, prompting numerous questions requiring further investigation. In the case of the promoter polymorphism in *MUC5B*, the variant rs35705950 is not only associated with an increased risk of IPF, but also with a 2.8-fold increased risk of having interstitial lung abnormalities and a 6.3-fold increased risk of having definite radiographic evidence of pulmonary fibrosis [19**]. Yet, those IPF patients with the rs35705950 allele also had improved survival when compared to those without it [20**]. These findings have significant clinical implications, specifically in the use of clinical genetic testing and prospective screening for patients deemed at increased risk of disease. A more complete understanding of the genetic risk of IPF will allow early detection and more accurate prognostication for patients whose clinical course has been considered unpredictable.

Genes and the Environment

The frequency with which many of the variants strongly associated with pulmonary fibrosis (e.g., rs35705950, rs2076295) are found in the general population suggests that though these genetic variants confer risk for the development of fibrotic lung disease, there are likely environmental factors contributing to risk of disease development. As illustrated by the 2013 Framingham population study, 19% of the population carries the rs35705950 variant, but the incidence of IPF within that population itself is far less than 1% [19**].

Epidemiologists have long observed a link between environmental exposures and the development of both familial and sporadic pulmonary fibrosis, specifically: cigarettes smoke, farming, livestock exposure, wood dust, metal dust, and stone/sand [62-64]. Other occupational exposures such as asbestos, drug exposures such as bleomycin [65, 66], and therapeutic exposures such as radiation [67, 68] have been linked to various forms of pulmonary disease, including fibrosis [69]. Future investigation into the role of gene by environment interactions will be critical to understanding the role that genetic variation plays in disease pathogenesis.

Familial vs. Idiopathic Pulmonary Fibrosis

The framework under which clinicians and investigators have understood genetic risk and pulmonary fibrosis to date makes a clear distinction between “familial” forms of the disease (familial IIP) and “idiopathic” fibrosing lung diseases (sporadic IIP). Data from the Fingerlin 2013 study illustrates that odds ratios for development of pulmonary fibrosis for each of the significant genetic variants reported in the manuscript are equivalent in familial and sporadic forms of disease (Figure 1). While we have previously written of familial and sporadic disease as distinct entities, based on such data, from the perspective of genetic risk of developing pulmonary fibrosis, they appear equivalent.

Conclusion

Many fibrotic IIP patients are diagnosed late in the course of their disease, limiting therapeutic options. Screening family members of affected individuals may prove a means of detecting and treating early-stage disease. As we understand better gene by environment interaction in the pathogenesis of fibrosis, we can target patients earlier in their disease course. Furthermore, given initial findings suggesting differential prognosis based on genotype and the overall genetic heterogeneity of fibrotic lung diseases, genetic variants may prove instrumental in redefining IIP subtypes. Finally, deeper understanding of genetic risk of disease points us to new investigational and therapeutic targets.

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Key Points

- Recently, genetic studies of IIPs have led to new insights into the susceptibility of individuals for IIPs.

- This progress provides investigators new targets to understand the pathophysiology of disease, specifically in the areas of (1) host defense, (2) cell-cell adhesion, and (3) aging and senescence.

- Genetic risk for development of pulmonary fibrosis appears to be similar in familial as well as sporadic forms of the disease.

- Further characterization of the genetic risk of developing pulmonary fibrosis will lead to novel approaches to prevent or delay the onset of this devastating disease.

- Better understanding of the genetic risk of developing pulmonary fibrosis also points investigators to new potential therapeutic targets.

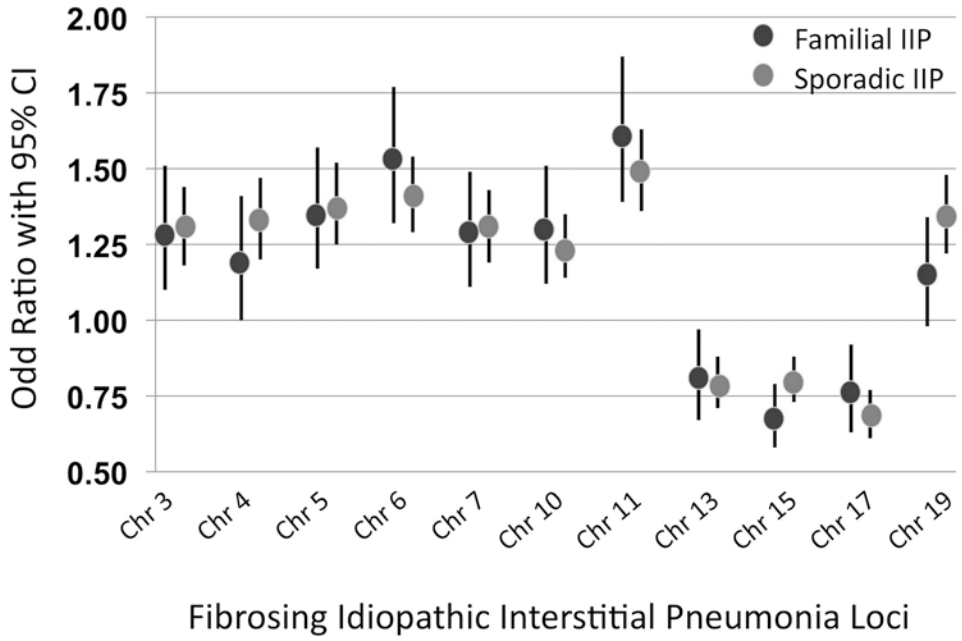

Figure 1. The Genetic Basis of Familial and Sporadic Idiopathic Interstitial Pneumonia is Similar

Data from Fingerlin et al. *Nature Genetics* 2013 depicted above illustrates that the genetic loci significantly associated with fibrotic IIP conferred the same increased risk of disease in both familial IIP and sporadic IIP cases [17**]. These data suggest that from the perspective of genetic risk, these diseases appear equivalent.

Table 1

Summary of studies supporting association of rs35705950 minor allele with IPF

This table summarizes the published literature confirming the association between the rs35705950 minor allele and IPF that was originally described in 2011 by Seibold and colleagues [16].

Location	IPF (% SNP)	Controls (% SNP)	Odds Ratio (GT vs GG)	Odds Ratio (TT vs GG)	p-value	Reference
USA	367 (60.8%)	802 (20.7%)	5.7 (4.3-7.5)	9.6 (4.7-19.4)	8.9×10^{-41}	Zhang et al. *NEJM* 2011 [26]
UK	110 (67.0%)	416 (19.6%)	6.6 (4.1-10.7)	11.8 (4.3-33.7)	2.0×10^{-17}	Stock et al. *Thorax* 2013 [27*]
France	142 (65.5%)	1383 (20.2%)	6.4 (4.5-9.0)	19.1 (9.0-36.1)	9.0×10^{-29}	Borie et al. *PLoS One* 2013 [28*]
USA	2492 (63.1%)	1890 (19.6%)	4.5 (3.9-5.2) - overall		7.2×10^{-95}	Fingerlin et al. *Nat Genetics* 2013 [17**]
USA	324 (57.2%)	702 (21.3%)	2.4 (2.1-2.8) - overall		2.4×10^{-50}	Noth et al. *Lancet Resp* 2013 [18*]