Genetics of idiopathic pulmonary fibrosis

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Summary

Idiopathic pulmonary fibrosis (IPF) is a chronic and invariably lethal lung disorder, of unknown origin and for which there is no cure. Whilst uncertainty remains about the leading cause/s, the disease is believed to occur in genetically susceptible hosts as a consequence of an aberrant wound-healing response following repetitive alveolar microinjury, resulting in scarring of the lung parenchyma and irreversible loss of function. The heterogeneous radiological and histopathologic appearances coupled with its variable disease behaviour and rate of progression suggest that in IPF a multitude of genetic and nongenetic factors interacting with each other are at play. Such factors however are largely unknown. Familial clustering of cases and the occurrence of pulmonary fibrosis in the context of rare genetic disorders (e.g. Hermansky-Pudlak syndrome and dyskeratosis congenita) indicate that genetic predisposition contributes significantly to the pathogenesis of IPF. Genome-wide association and linkage studies have recently identified several rare and common genetic variants that confer susceptibility to both familial and sporadic IPF. These discoveries have the potential to increase our understanding of disease pathogenesis and facilitate the development of targeted more effective therapies.

KEY WORDS: genetics, idiopathic pulmonary fibrosis, polymorphisms, interstitial lung disease.

Introduction

Idiopathic pulmonary fibrosis (IPF), the most common and severe of the idiopathic interstitial pneumonias (IIPs), is a chronic, progressive and almost invariably lethal lung disease of unknown origin, with a 5-year survival of approximately 20% (1). The disease, which primarily affects older adults (typically current or former smoking males of over 60 years of age), is believed to occur in genetically susceptible individuals as a consequence of an aberrant wound-healing response following repetitive alveolar microinjury, leading to scarring of the lung parenchyma and irreversible loss of function (1). Clinically, IPF is characterized by progressively worsening dyspnea, dry cough and restrictive lung physiology with impaired gas exchange (2, 3). The precise global incidence and prevalence of the disease remain unclear, with incidence estimates ranging from 1.2 to 9.6 per 100,000 person-years (4). In the US, between 150,000 and 200,000 people are believed to be affected, and as many as 40,000 people die from IPF each year. Similar figures have been reported in Europe (5, 6).

The clinical course of patients with IPF is highly variable and unpredictable. Indeed, while in most cases the inexorable decline in lung function occurs over a period of years, 10-15% of individuals experience a much faster disease course progressing from initial symptoms to respiratory failure and death over a period of months. The third pattern of disease progression is one of relatively slow decline punctuated by episodes of acute worsening (acute exacerbations), which prove fatal in the majority of cases (7). The heterogeneity in radiological and histopathological appearances, and rate of progression observed in individuals with IPF suggests that the disease results from a complex interaction between a multitude of co-activated pathogenic pathways (8). This multiple-pathway model is also likely to account for the suboptimal efficacy of therapies targeting single molecules/pathways in IPF. There are no therapies known to prolong life of patients with IPF, apart from lung transplantation, although two compounds have proven effective in slowing down the inexorable progression of the disease.

Evidence for a role of genetic factors in IPF

Despite uncertainty about its leading cause/s, a number of potential risk factors have been suggested, including older age, cigarette smoking, environmental/occupational exposures, microbial agents and mi-

The existence of a genetic predisposition to pulmonary fibrosis and the occurrence of pulmonary fibrosis in the context of rare genetic disorders emphasize the role of genetic factors in IPF.

croaspiration of gastroesophageal reflux (GER). Yet, IPF is likely to result from a complex interaction between environment and genetic factors, most of which remain unknown (9). Several lines of evidence suggest the existence of a genetic predisposition to pulmonary fibrosis, including different susceptibility to pulmonary fibrosis among mice challenge with the same amount of bleomycin, and the occurrence of pulmonary fibrosis in the context of rare genetic disorders, such as Hermansky-Pudlak syndrome (HPS) and dyskeratosis congenita (DC).

HPS is an autosomal recessive disorder caused by defects in intracellular protein trafficking (10). Eight human HPS-related genes have been identified (i.e mutations in *AP3B1* gene), each of which can lead to a diverse clinical HPS phenotype (10). Most commonly, patients with HPS present with oculo-cutaneous albinism and prolonged bleeding, increased predisposition to infection and pulmonary fibrosis (10). DC, a rare genetic disease secondary to altered telomere biology, is complicated by pulmonary fibrosis in as many as 20% of cases (11). DC is associated with mutations within dyskerin (dyskeratosis congenita 1, *DKC1*), a gene involved in telomere biology and maintenance (12-14). Patients with DC exhibit a classical triad of abnormal reticular skin pigmentation, leukoplakia, and nail dystrophy (13, 15). In childhood, bone marrow failure is the most frequent complication, while pulmonary fibrosis is a frequent cause of death in adults (15).

Familial pulmonary fibrosis

Most forms of IPF are sporadic. However, contrary to the initial belief, familial forms appear to be relatively common, accounting for about 10% of cases (3). Moreover, current evidence suggests that sporadic and familial cases of IPF may reflect a continuum of genetic risk rather than existing as distinct forms (3). The term familial interstitial pneumonia (FIP) refers to the occurrence of disease in two or more members of the same family (3). The criteria used to diagnose IPF are the same in familial and sporadic cases. Indeed, familial and sporadic forms of IPF are clinically and histologically indistinguishable, although younger age at diagnosis and different patterns of gene expression appear to distinguish between the two. In addition, recent family-based studies have identified rare genetic variants, which are shared by both familial and sporadic IPF (3). The occurrence of IPF in twins raised apart along with geographical clustering of cases reinforce the role of genetic factors in the development of the disease (16, 17).

Sporadic and familial cases of IPF may reflect a continuum of genetic risk rather than distinct forms of pulmonary fibrosis.

Specific genetic variants

Genome-wide association studies (GWAS) and linkage studies have identified common genetic variants that appear to contribute to the development of IPF (3, 10, 18) (Table 1).

- *Surfactant protein C (SFTPC)* and *A2 (SFTPA2)* genes. The first genetic variants associated with pulmonary fibrosis were identified after 2000 (19). Nogee et al. reported on an infant girl of 6 weeks of age who was diagnosed with nonspecific interstitial pneumonitis. Her mother had been diagnosed with desquamative interstitial pneumonitis (DIP) at 1 year of age. In both the patient and the mother, the *SFTPC* mutation was identified on only one allele, indicating an autosomal dominant pattern of inheritance. The baby was treated successfully with corticosteroids and supplemental oxygen, and the respiratory symptoms improved. Since the initial description by Nogee, several mutations in *SFPTC* and *SFTPA2* have been associated with familial pulmonary fibrosis (20-22).
- *Mucin 5B gene (MUC5B)*. In 2011, Seibold et al. (23) published the most important article on genetics of IPF to date. By applying a genome-wide linkage analysis followed by sequencing, they were able to identify a single nucleotide polymorphism (SNP) (rs35705950) located in the promoter region of *MUC5B* on 11p15.5, which was strongly associated both with sporadic IPF and with FIP. Individuals carrying the mutant allele (T) either in heterozygous (GT) or homozygous form had an odds ratio of 6.8 and 20.8 respectively for FIP, and 9.0 and 21.8 respectively for IPF. The frequency of the T allele was 34% in familial cases, 38% in sporadic IPF cases, and 9% in control subjects (23).
- Altered *MUC5B* expression is associated with chronic airway disease and these findings suggest a role in the pathogenesis of pulmonary fibrosis (23, 24). Additionally, the same Authors reported on the intriguing tightly connection between *MUC5B* gene variants and honeycomb cysts, one of the pathologic hallmarks of IPF (25).
  The association between *MUC5B* and IPF has been validated in several independent cohorts (26-31), so that the *MUC5B* promoter polymorphism remains the strongest and most replicated genetic risk factor for pulmonary fibrosis to date. Interestingly, a study by Hunninghake et al. (32) has shown that the odds for radiographic interstitial lung abnormalities (ILA) were 2.8 times greater for each copy of the rs35705950 minor allele. The term ILA refers to the presence on chest CT scans of subtle abnormalities such as subpleural reticular changes, honeycombing, traction bronchiectasis, ground glass, and centrilobular nodules (33). This study for the first time suggests a link between the polymorphism of *MUC5B* and ILA, suggesting that *MUC5B* genotype may potential be useful for early detection of fibrosis in asymptomatic individuals. *MUC5B* promoter polymorphism

is specific for IPF and FIP, as it does not appear to be associated with pulmonary fibrosis secondary to other conditions, such systemic sclerosis, asbestosis, sarcoidosis among others (34). More recently, Peljto et al. showed that *MUC5B* rs35705950 T, previously reported to be strongly associated with the development of sporadic IPF and FIP, confers improved survival in IPF (35).

- *Human telomerase reverse transcriptase (hTERT)* or *human telomerase RNA (hTR)*. Telomeres consist of repetitive DNA sequences of TTAGGG at the ends of linear chromosomes, which protect the chromosome ends that progressively shorten with each cell division (12). Telomerase is a specialized DNA polymerase responsible for telomere elongation onto chromosome ends. Telomerase has two different components that carry out the function of telomere repeat addition: the core telomerase protein *TERT*, which contains the telomerase reverse transcriptase domain, and an essential RNA component, *TR* (also known as *TERC*), which complexes with *TERT* and provides the template for telomere elongation (36).

Mutations and FIP/sporadic IPF

Reduced telomerase function leads to accelerated telomere shortening, which, under normal circumstances, occurs with aging. Short telomeres also induce a DNA damage response leading to cell death or permanent cell cycle arrest. As such, telomere shortening has been involved in a number of degenerative age-related diseases. Accelerated telomere shortening may lead to a number of clinical features, referred to as "premature aging syndrome" (36). Pulmonary fibrosis, similar to bone marrow failure (i.e., bone marrow dysplasia, aplasia or myelodysplastic syndromes) and liver fibrosis/cryptogenic cirrhosis may result from loss of regenerative capacity, and is among the more severe clinical consequences of telomere shortening (37, 38). Accordingly, compared to age-matched controls, IPF patients display higher frequencies of fibrotic disease outside the lung. Abnormalities of telomere biology and maintenance are believed to represent the "missing" link between ageing and IPF. Several reports have described that mutations within either of the essential components of the telomerase complex, the human telomerase reverse transcriptase (*hTERT*), or the human telomerase RNA (*hTR*), are associated with familial IPF (15). Germline mutations in *hTERT* and *hTR* are present in 8-15% of pulmonary fibrosis families (15, 39). Mutations in *hTERT* and *hTR* determine loss of function and decreased telomere activity (35) leading to haploinsufficiency (15). Interestingly, a small minority (approximately 1-3%) of sporadic cases also carry these same mutations, suggesting the existence of shared pathogenetic mechanisms (13, 19, 39-41). Some studies have tested the hypothesis that short telomeres contribute to disease risk also in sporadic IPF by examining telomere length in peripheral blood leukocytes and alveolar cells (39). Alder et al. evaluated patients with sporadic IPF, patients with IPF and known telomerase mutations and healthy lungs. Telomere length was assessed by using quantitative FISH analysis. IPF patients irrespective of carriage of telomerase gene-associated mutations have indistinctly shorter telomeres than controls (39). Moreover, individuals affected by FIP are clinically indistinguishable from patients with sporadic disease although familial cases have a younger age at presentation and may present some differences in radiological pattern (42, 43).

Pulmonary fibrosis, similar to bone marrow failure and liver fibrosis/cryptogenic cirrhosis may result from loss of regenerative capacity, and is among the more severe clinical consequences of telomere shortening.

In the case of patients with TERT mutations, complications of lung transplantation, such as renal failure, may be more common.

Mutations within *hTERT* and *hTR* are also found in 1-3% of sporadic IPF patients (42). *RTEL1*, which encodes a key regulator of telomere elongation, *PARN*, which encodes an exoribonuclease in mRNA pathway, and *TINF* are also involved in telomere biology and maintenance, and mutations in these genes have been associated with both sporadic and familiar pulmonary fibrosis (11, 44-46). Cogan et al. have recently shown that rare variants in *RTEL1* and *PARN* are associated with familial disease (45). Patients with these variants seem to have significant shortening of telomeres in peripheral blood mononuclear cells, though the mechanism by which loss of *PARN* affects telomere length is unknown.

Lung transplantation is the only treatment that is able to prolong survival in IPF, although in a minority of highly selected patients (2). In the case of patients with *TERT* mutations, complications of lung transplantation, such as renal failure, may be more common in IPF patients with telomerase mutations and/or shortened telomere syndrome (47). Moreover, patients with telomerase mutations experience increased rates of bone marrow suppression and medication-related complications (47), which may reflect their underlying diminished bone marrow reserves. Specific recommendations for appropriate guidance regarding hematologic risk assessment before transplantation and management of the post-transplantation immunosuppressive regimen are needed.

While about 1/3 of patients with familiar and sporadic IPF carry rare variants in telomerase associated genes, short telomere length is a more common finding in these patients, indicating that additional factors (e.g., smoking or infection), beyond genetics, significantly contribute to telomere shortening (48). Further studies are necessary to establish which telomere length thresholds are clinically relevant for the disease

Table 1 - Summary of the main genetic associations with sporadic and familial idiopathic pulmonary fibrosis.

Familial pulmonary fibrosis			Sporadic pulmonary fibrosis		
Gene	**Variant**	**Reference**	**Gene**	**Variant**	**Reference**
SFTPC	Several loss-of-function mutations	19,20,21	*SFTPC*	Several loss-of-function mutations	19,20,21
SFTPA2	G231V and F198S loss-of-function mutations	22	*IL1RN*	rs408392 rs419598 rs2637988	26
MUC5B	rs35705950	23-35	*TOLLIP*	rs5743890 rs5743894 rs111521887	28
TERT	Leu55Gln Thr1110Met	15,40	*TERT*	Leu55Gln Thr1110Met	15,40
TERC	rs6793295	15,40	*TERC*	98 G > A 37 A > G	15,40
DKC1	Several loss-of-function mutations	12-14	*CDKN1A*	rs2395655 rs733590	18
RTEL1	Several loss-of-function mutations	45	*TINF2*	Several loss-of-function mutations	44
PARN	Several loss-of-function mutations	45,46	*ELMOD2* *IL8*	Unknown rs4073 rs2227307	11 18
			TLR3	rs3775291	11

progression, treatment response and may be useful as potential IPF biomarker for new therapies.

Sporadic IPF

Polymorphisms of several genes have been associated with increased risk of sporadic IPF. Genetics appears to influence also disease progression. Despite this evidence, none of these findings has been validated in further studies. Table 1 summarizes the main genetic associations with sporadic IPF.

Genetic variants and survival implications

Genetic variants may also be associated with survival. Noth et al. found that variants within Toll interacting protein (*TOLLIP*) and signal peptide peptidase like 2C (*SPPL2C*) influence risk of developing IPF (28). Specifically, carriers of the minor allele (G) of rs5743890 had both decreased risk of IPF and increased mortality (26), a finding difficult to explain. Similarly, Peljto et al. observed that carriers of the *MUC5B* rs35705950 risk allele had a survival advantage (35). A functional SNP in Toll-like receptor 3 (*TLR3*) has also been associated with accelerated disease progression and with increased mortality in patients with IPF (49). The mechanism for these observed differences in mortality remains unknown, but could be related to underlying differences in disease pathogenesis or in the clinical response to commonly prescribed therapies.

Conclusions

Genome-wide association studies and linkage studies have identified a number of genetic associations with familial and sporadic IPF. Of these, the association with *MUC5B* is the strongest and the most replicated. Yet, approximately half of IPF patients lack a clear genetic signature. As such, with very few exceptions, genetic testing is not recommended in the routine evaluation of patients with either familial or sporadic IPF. The identification of a genetic signature however has the potential to provide us with crucial information regarding prediction of disease behaviour and, owing to the availability of two effective IPF-specific antifibrotic therapies, response to treatment.

The identification of a genetic signature in patients with IPF has the potential to identify compounds that may be effective in selected groups of patients.

In clinical trials of IPF, a major obstacle is the heterogeneity of the patient population enrolled, wherein the rate of disease progression is not uniform. In this scenario, genotype-guided enrolment has the potential to identify compounds that are effective in selected groups of patients. Much work remains to be done; however, advances in genetics of IPF have the potential to revolutionize our approach to this devastating disease in the near future.

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