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GENETICS IN PULMONARY FIBROSIS – FAMILIAL CASES PROVIDE CLUES TO THE PATHOGENESIS OF IPF

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Abstract

Idiopathic pulmonary fibrosis (IPF) is the most common form of the idiopathic interstitial pneumonias (IIP) and remains a disease with a poor prognosis. Familial interstitial pneumonia (FIP) occurs when two or more individuals from a given family have an IIP. FIP cases have been linked to mutations in surfactant protein C (*SFTPC*), surfactant protein A2 (*SFTPA2*), telomerase reverse transcriptase (*TERT*), and telomerase RNA component (*TERC*). Together, mutations in these four genes likely explain only 15-20% of FIP cases, and are even less frequent in sporadic IPF. However, dysfunctional aspects of the pathways that are involved with these genes are present in sporadic forms of IPF even in the absence of mutations, suggesting common underlying disease mechanisms. By serving as a resource for identifying the current and future genetic links to disease, FIP families hold great promise in defining IPF pathogenesis, potentially suggesting targets for the development of future therapies.

Keywords

familial interstitial pneumonia; idiopathic pulmonary fibrosis; lung; surfactant protein; telomerase

Idiopathic Pulmonary Fibrosis and Familial Interstitial Pneumonia

Idiopathic pulmonary fibrosis (IPF) is the most common form of the idiopathic interstitial pneumonias (IIP) and is characterized by progressive dyspnea, interstitial infiltrates on radiologic imaging, and restriction on pulmonary function testing.^{1,2} A disease with a dire prognosis, the outcome in most patients with IPF is gradual progression with respiratory failure in 3-5 years.² Unfortunately, short of lung transplantation, no clearly effective therapy exists. Perhaps, one of the main reasons for the continued lack of an effective therapy is that the cause of IPF and many aspects of its pathogenesis remain unknown.

Over the past decade, one aspect that has held great promise in helping the medical community to better define the pathogenesis of IPF is the recognition that genetic factors

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DISCLOSURES

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may play a role in this disease. It has long been recognized that several defined genetic disorders, including dyskeratosis congenita, Hermansky-Pudlak syndrome, and familial hypocalciuric hypercalcemia can present with pulmonary fibrosis as one manifestation of disease. However, more convincing evidence for a genetic link to IPF comes from the fact that clustering of individuals with pulmonary fibrosis can be found in families, most of which appear to have an autosomal dominant inheritance pattern (as demonstrated in an example pedigree in Figure 1), suggesting that a single dysfunctional gene may be responsible for disease in an individual family.^{3;4}

Familial interstitial pneumonia (FIP) is identified when two or more individuals in a family have pulmonary fibrosis that appears consistent with an IIP.^{4;5} The exact percentage that FIP represents of the overall cases of IIP is not entirely known, with multiple studies suggesting a wide range. Reports from studies in the United Kingdom and Finland suggested that 0.05-2.2% and 3.3-3.7% of their IPF cases, respectively, had a familial basis.^{6;7} In contrast, analysis of two other cohorts suggests this percentage may be higher. Among patients who went to lung transplant at Vanderbilt prior to 2003, 19/47, or approximately 19%, of patients with IPF had a family history of interstitial lung disease (ILD).³ A recent study by van Moorsel and colleagues revealed that approximately 10% of the IIP individuals followed in a single ILD clinic in The Netherlands in fact had FIP.⁸

In most instances, the family history is the only identifying feature that differentiates the diagnoses of IPF and FIP in an individual patient. In fact, one of the most common ways in which IPF is identified is when an individual is diagnosed with IPF by a physician and then relates that he or she had a relative who had the same diagnosis. Two prominent studies, one by Marshall and colleagues in the United Kingdom⁶ and one by Lee and colleagues at the Mayo Clinic in Rochester, Minnesota⁹ revealed that clinical findings were similar between individuals with FIP and IPF, including symptoms, physical exam, pulmonary function testing, radiologic imaging, pathology, and survival, except that subjects with FIP tended to present at a younger age.

In 2005, Steele and colleagues published a report on the largest cohort of FIP families assembled to date that represented the collaboration among investigators at Duke University, Vanderbilt University, and National Jewish Hospital/University of Colorado.⁴ From this analysis of 111 FIP families, it was recognized that older age, male sex, and history of cigarette smoking were important risk factors for the development of disease in these families. The finding that cigarette smoking was a risk factor suggests that environmental factors may accentuate genetic risk and that gene-environment interactions may be important in IPF disease pathogenesis. Another important finding from this study was that there was pathologic heterogeneity within many individual families. Usual interstitial pneumonia (UIP) is the pathologic correlate to the clinical diagnosis of IPF. Interestingly, only 54.9% of the families had a uniform diagnosis of IPF/UIP, while the remaining 45.1% had radiographic or pathologic findings suggestive of another IIP within at least one affected family member.

Genetic Approaches in FIP

To date, large scale linkage attempts across multiple families have had limited success in identifying genetic links to disease in FIP. This is likely due to the fact that different genes may be involved across different families. Furthermore, most FIP families are not highly genetically informative for linkage because in many instances only a few individuals are recognized in a given family or DNA is available on only one or two individuals with disease. To date, successful identification of genetic causes of FIP has come from utilization of the candidate gene approach or from linkage studies in a few rarely encountered highly

genetically informative families. To date, genetic mutations have been reported in four well described genes: surfactant protein C (*SFTPC*)¹⁰⁻¹², surfactant protein A2 (*SFTPA2*)¹³, telomerase RNA component (*TERC*),^{14;15} and telomerase reverse transcriptase (*TERT*).^{14;15} A fifth gene, *ELMOD2*, whose role remains largely undefined, has been associated with FIP by a linkage study in a report from Finland.¹⁶

Surfactant Protein C Mutations

Multiple reports have clearly implicated *SFTPC* mutations in several cases of FIP. In 2001, Nogee and colleagues described a carboxy terminal mutation in *SFTPC* that resulted in the deletion of exon 4 (*SFTPC* ^{Δ exon4}) of the pro-surfactant protein C (pro-SPC) in an infant with non-specific interstitial pneumonia (NSIP) and a mother with desquamative interstitial pneumonia (DIP).¹⁰ Subsequently, multiple other *SFTPC* mutations have been described in association with pediatric ILD.^{17;18} Soon after the initial report by Nogee and colleagues, our group at Vanderbilt selected *SFTPC* as a candidate gene to analyze in one of our highly genetically informative families.¹¹ This family spanned five generations, with 6 adults with biopsy proven UIP, 5 adults with IPF on clinical grounds in the absence of lung biopsy, and 3 children with biopsy proven cellular NSIP. Here, a mutation in the carboxy-terminal region results in a substitution of glutamine for leucine at the highly conserved amino acid 188 position (L188Q) in the pro-SPC pro-protein. Immunohistochemistry for pro-SPC on lung tissue from affected family members suggested a pattern of abnormal SPC distribution within type II alveolar epithelial cells (AECs), while transfection studies where the mutant L188Q SPC protein was expressed in mouse lung epithelial cells revealed a collection of numerous vesicles within the cytoplasm. Together, these analyses suggested that the L188Q mutation led to aberrant processing of SPC within the type II AEC. Since this initial report, multiple other cases of adult FIP have been linked to mutations in *SFTPC* including a recent report from van Moersel in which approximately 25% of their FIP cases were explained by *SFTPC* mutations,⁸ a percentage considerably higher than we have seen in our cohort or that others have reported.

Transcription of *SFTPC* and translation of its mRNA results in an 197 amino acid precursor pro-SPC protein. Pro-SPC is then processed at multiple steps through the secretory pathway to the final functional 35 amino acid protein that is secreted into the alveolar space.¹⁹ With carboxy-terminal mutations in *SFTPC* such as the Δ exon4 and L188Q mutations described above, a pro-SPC product is produced that cannot be processed and folded correctly in the endoplasmic reticulum (ER), leading to protein accumulation and ER stress, with activation of a cascade of events known as the unfolded protein response (UPR).²⁰⁻²² The UPR is a collection of pathways designed to protect the cell during periods in which proteins accumulate in the ER. The UPR includes pathways to attenuate protein translation, upregulate factors designed to protect the cell including metabolism and redox proteins, enhance the production of protein folding chaperones, and increase the production of degradation factors. While designed to protect the cell, severe or long-standing UPR activation can lead to AEC death through caspase pathway activation.²³ *In vitro* evaluations of carboxy-terminal mutations in *SFTPC*, including the Δ exon4 and L188Q mutations described above, indicate that these mutations lead to ER stress, UPR activation, and AEC apoptosis.²⁰⁻²²

When analyzed in a cohort of individuals with sporadic cases of UIP (89 individuals) and NSIP (46 individuals), we observed that only one individual in this cohort of 135 had a mutation in *SFTPC*, illustrating that *SFTPC* mutations are rarely observed in IPF.²⁴ Nevertheless, reports from two groups suggest that ER stress and UPR activation are prominent features of sporadic IPF, raising our suspicion that *SFTPC* mutation mediated lung fibrosis may serve as a paradigm for understanding IPF in general. In 2008, we

evaluated lung biopsies from individuals from the L188Q family and noted that UPR pathway markers were heavily expressed in the alveolar epithelium lining areas of fibrosis, while normal lung had only minimal expression in normal lung biopsy samples of the UPR marker BiP (heavy chain immunoglobulin protein) and no expression of the UPR markers XBP-1 (X-box binding protein 1) and EDEM (ER degradation enhancing α -mannosidase-like protein).²² We then analyzed lung biopsies from individuals with non-*SFTPC* mutation associated FIP and sporadic IPF and noted a similar staining pattern, suggesting that ER stress and UPR pathways are prominent in IPF in general. Shortly after our report, Korfei and colleagues reported similar findings of ER stress and UPR activation in the alveolar epithelium in additional cases of sporadic IPF, also noting increased AEC apoptosis in the same cells demonstrating ER stress.²⁵ Taken together, these two studies demonstrate that AEC ER stress and UPR activation may be key components in the pathogenesis of IPF.

Surfactant Protein A2 Mutations

After identifying *SFTPC* mutations in FIP, investigators speculated that mutations in the other surfactant proteins (A,B,D) might be found as well. In 2009, Wang and colleagues reported the identification of two families in which mutations in *SFTPA2* were the basis of FIP.¹³ Surfactant protein A has two isoforms encoded by adjacent genes (*SFTPA1*, *SFTPA2*). In their study, Wang and colleagues performed whole genome linkage on a family with 15 family members who either had FIP, bronchoalveolar cell carcinoma (BAC), or undefined lung disease and linked to an area near *SFTPA1* and *SFTPA2*. Genetic sequencing of both isoforms then led to the identification of a substitution of valine for a highly conserved glycine at codon 231 (G231V) in *SFTPA2*. Sequencing of *SFTPA1* and *SFTPA2* in an additional 58 FIP kindreds led to the discovery of a second *SFTPA2* mutation in one additional family. *In vitro* studies of these two mutations suggested retention of the mutant SPA forms in the ER, raising speculation that ER stress pathways may be involved as well.¹³

Telomerase Mutations

In addition to *SFTPC* and *SFTPA2* mutations, recent reports have linked mutations in genes for the two key components of the telomerase complex, *TERC* and *TERT*. Telomeres are the tandem repeats of TTAGGG that are found at the ends of chromosomes and serve to protect the ends of chromosomes during DNA replication and cell division. The telomerase complex is required to maintain telomere length during cell division. Several different proteins are involved in the complex, but the two key components involved in telomere lengthening are the telomerase reverse transcriptase component TERT and the RNA template component TERC. In the presence of telomerase dysfunction, telomere shortening occurs with successive cell divisions.²⁶

Dyskeratosis congenita (DKC) is a rare hereditary disorder initially described based on a triad of mucocutaneous manifestations which include abnormal skin pigmentation, nail dystrophy, and oral leukoplakia.²⁷ DKC, in its X-linked form, was first linked to mutations in dyskerin, also a component of the telomerase complex.²⁸ Subsequently, autosomal dominant forms have been linked to mutations in either *TERC*²⁹ or *TERT*.³⁰ Interestingly, pulmonary fibrosis is common in patients with DKC, with 20% of patients developing pulmonary fibrosis. In fact, respiratory failure, is the second most common cause of death behind bone marrow failure.³¹ Based on this information, Armanios and colleagues at Johns Hopkins University in Baltimore in collaboration with our group evaluated 73 families from the Vanderbilt FIP registry for mutations in *TERC* and *TERT*. In this study, we observed that 5 families had mutations in *TERT* and 1 family had a mutation in *TERC*.¹⁴ None of these families had the typical manifestations of DKC, and the probands from each family had a

lung biopsy pattern of UIP (5 cases) or a nonspecifically described IIP (1 case). Since then, we have evaluated additional families and have observed that approximately 10% of our FIP cohort have *TERT* or *TERC* mutations. *In vitro* functional analyses of the original mutations from the Armanios report indicated that these mutations had decreased telomerase activity. Furthermore, telomere shortening was severe in peripheral blood leukocytes, including many individuals with telomere lengths less than 10% predicted based on their age.¹⁴ Shortly after this report, Tsakiri and colleagues reported another study, identifying 5 FIP families with mutations in *TERT* and 1 FIP family with a mutation in *TERC* from a cohort of 45 families.¹⁵ As with the Armanios study, *in vitro* analyses revealed decreased telomerase activity with the mutations, and telomere shortening was observed in peripheral blood leukocytes.

Based on their observations in the FIP studies, both groups speculated that telomerase mutations lead to telomere shortening in the alveolar epithelium, and that it is the telomere shortening in this AEC population that is critical for disease. With that thought in mind, both groups performed telomere length analyses of peripheral blood samples from individuals with non-telomerase mutation FIP or sporadic IPF. In the first study by Cronkhite and colleagues, 59 probands from non-telomerase FIP kindreds and 73 individuals with sporadic IPF were analyzed, and it was observed that 24% of the FIP subjects and 24% of the sporadic IPF cases had peripheral blood leukocyte telomere length measurements that were less than the 10th percentile compared to age matched controls.³² In the second study, Alder and colleagues reported that in 62 individuals with sporadic IPF, 60 (97%) had peripheral blood leukocyte telomere length measurements that were below the median measurements of normal controls, with 6 of the 62 individuals having telomere length measurements below the 1st percentile compared to healthy controls.³³ In addition, in this second study, using fluorescent *in situ* hybridization techniques, the authors demonstrated that telomere shortening could be observed in alveolar epithelium as well.

ELMOD2

In 2002, Hodgson and colleagues performed linkage analyses on 24 families, with hierarchical fine mapping narrowing their search to a region on chromosome 4q31 in 8 of the 24 families.¹⁶ The region of the shared haplotype encompassed a gene known only as *LOC152586* and the first three exons of a gene known as *ELMOD2*. Analysis of expression of these two genes revealed that *LOC152586* was expressed in the testis but not in other tissues. *ELMOD2* expression, on the other hand, was detected in alveolar macrophages and the alveolar epithelium. Given that observation, it was thought that *ELMOD2* would be the more likely candidate, but sequencing of the nine exons and exon-intron boundaries failed to reveal any mutations in these regions. Little else is known about *ELMOD2*, including the function of the protein which it encodes. Nevertheless, given their findings, *ELMOD2* remains a candidate gene for FIP and warrants further investigation.

Using FIP to Gain Clues to the Pathogenesis of IPF

Understanding FIP has significant promise in allowing us to gain an improved understanding of the pathogenesis of IPF. First, the presence of *SFTPC* and *SFTPA2* mutations suggest that type II AECs are the cell population that is central to the initiation and progression of disease. Second, mutations in *TERC* and *TERT* point toward possible problems with cellular turnover. Taken together, it can be hypothesized that IPF occurs due to increased cell death in the type II AEC population and/or inability of this cell population to regenerate the alveolar epithelium following injury. With such impairments, dysregulated alveolar repair in combination with fibroblast activation could then lead to progressive fibrosis.

Looking to the Future

Taken together, mutations in *SFTPC*, *SFTPA2*, *TERT*, and *TERC* likely account for only 15-20% of all cases of FIP. Thus, the majority of FIP cases have yet to have their genetic mutations identified, and it is likely that many other genes are responsible across different families. Interestingly, this observation may impact development of future therapies for FIP and IPF, since individual aberrant genes may require specific targeted treatment strategies. While genetic heterogeneity across families and the fact that most FIP families are not highly genetically informative have limited genetic studies to date, the recent development of powerful new genetic approaches, including whole exome sequencing, genome wide association studies, high throughput candidate gene sequencing, and whole genome sequencing, is expected to rapidly escalate the number of genes linked to FIP and IPF. Identification of these genetic links to disease will further improve understanding of the pathogenesis of IPF, from which important new therapies for this devastating disease can be developed.

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Figure 1.

Pedigree of a family with familial interstitial pneumonia (FIP), condensed from a larger pedigree in the Vanderbilt FIP Registry. This pedigree represents a four generation pedigree in which individuals from two generations (II and III) had documented cases of pulmonary fibrosis (PF). Two individuals in generation III had documented usual interstitial pneumonia (UIP) on surgical lung biopsy. Individuals in the fourth generation remain asymptomatic to date with no documented case of pulmonary fibrosis. This pedigree demonstrates an autosomal dominant pattern of inheritance with a single parent passing an aberrant gene on to children, including male to male transmission. While the genetic mutation responsible for pulmonary fibrosis is not known in this family, two individuals (denoted with gray) are obligate carriers for the gene in question (female in generation I, and second male in generation II). Squares denote males; circles denote females. Black filling denotes individuals affected with pulmonary fibrosis; gray filling denotes individuals that are obligate carriers for the dysfunctional gene in this family; empty squares and circles denote unaffected individuals. Strikethrough symbol (/) denotes individuals who are no longer living. Bx = biopsy.