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Familial Interstitial Lung Disease

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Abstract

The interstitial lung diseases (ILDs) are a group of progressive disorders characterized by chronic inflammation and/or fibrosis in the lung. While some ILDs can be linked to specific environmental causes (i.e. asbestosis, silicosis), in many individuals no culprit exposure can be identified; these patients are deemed to have “idiopathic interstitial pneumonia”, or IIP. Family history is now recognized as the strongest risk factor for IIP, and IIP cases that run in families comprise a syndrome termed “Familial Interstitial Pneumonia” (FIP). Mutations in more than 10 different genes have been implicated as responsible for disease in FIP families. Diverse ILD clinical phenotypes can be seen within a family, and available evidence suggests underlying genetic risk is the primary determinant of disease outcomes. Together, these FIP studies have provided unique insights into the pathobiology of ILDs, and brought focus on the unique issues that arise in the care of patients with FIP.

Keywords

IPF; Pulmonary fibrosis; Genetics; Telomere; Surfactant; Alveolar epithelial cell

Introduction

The diffuse parenchymal lung diseases (DPLDs, also commonly referred to as interstitial lung diseases, ILDs) are a group of disorders characterized by subacute or chronic inflammation and/or fibrosis in the lung.[1] Patients with ILD typically present with symptoms of cough and/or dyspnea, which frequently progresses over time. There are numerous different risk factors that have been linked to different forms of ILD, including occupational and environmental exposures, systemic diseases, and more recently, genetic risk factors.[2] Family history is now recognized as the strongest risk factor for ILD,[3] and candidate gene-based, linkage, and next-generation sequencing-based approaches have now implicated mutations in more than 10 different genes as responsible for disease families with ILD. Studies of families with ILD (Familial Interstitial Pneumonia, FIP) have provided

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unique insights into the pathobiology of ILDs, and brought focus on the unique issues that arise in the care of patients with FIP.

Epidemiology

The syndrome of FIP is defined by the presence of ILD among two or more closely related individuals, including at least one family member with an idiopathic interstitial pneumonias (IIPs).[4,5] The earliest reports of interstitial lung disease clustering in families dates to the early 1950's, with a report by Peabody and colleagues described idiopathic pulmonary fibrosis in twin sisters.[6] Through the following several decades, there were scattered reports of familial ILD,[7–10] but it was generally believed these families were quite rare. As of the early 2000's, it was generally believed that FIP reflected a very small subset of patients with ILD, with most estimates ranging from 2–5%.[11,12] Several more recent studies employing intensive ascertainment strategies have reported that approximately 20% of ILD patients report a family history of ILD at referral centers in Mexico,[3] the United States,[13] and Canada.[14] An important limitation of studies to date is a focus on populations of European ancestry; while case reports of FIP in populations of non-European ancestry are common, there have been no large-scale studies estimating the prevalence of FIP in a non-European population.

Clinical considerations

Among unselected FIP patients, clinical features including age at diagnosis, histopathologic patterns, and disease progression are generally similar to those seen in patients with "sporadic" forms of ILD.[4] While usual interstitial pnuemonia (UIP) is the most common ILD phenotype in FIP kindreds, 50% or more of families have more than one ILD phenotype among affected family members.[4] In addition, imaging patterns may not conform to typical ILD patterns; in one report comparing HRCT images from FIP and sporadic ILD patients, more than 50% of FIP HRCT images did not fit UIP or nonspecific interstitial pnuemonia (NSIP) criteria, related in part to a relative increase in apical and mid-lung involvement.[15]

The evaluation of patients with suspected FIP should focus on features that may suggest a specific genetic diagnosis. While the majority of FIP cases occur in middle-aged and older adults, it has become clear through time that FIP presentations can occur across the lifetime, ranging from the neonatal period to late adulthood. As described below, mutations in genes related to surfactant biology in have been linked to diverse presentations of ILD in children and adults within a family.[16,17] A focused family history specifically inquiring about neonatal respiratory distress or neonatal death is advised evaluating all suspected cases of FIP. A personal or family history of unexplained chronic liver disease, bone marrow disease, or early greying suggests a potential short-telomere syndrome.[18,19] The presence of abnormal bleeding and/or ocular albinism in a family should raise suspicion for Hermansky-Pudlak Syndrome.[20,21] Hypothyroidism alone or in combination with movement disorders may suggest "brain-lung-thyroid syndrome" associated with mutations in the transcription factor *NKX2–1.*[22,23] Interstitial lung disease associated with pulmonary hemorrhage and/or highly elevated autoantibodies may suggest a *COPA* mutation.[24]

Genetics of FIP

Kindreds with FIP most commonly involve multiple affected individuals across successive generations, consistent with an autosomal dominant inheritance pattern with incomplete penetrance,[4,25] although in rare cases, X-linked[26] and recessive[27,28] disease patterns have been described. An autosomal dominant inheritance pattern indicates that a single copy of a mutant allele (a heterozygous variant) may be sufficient to confer disease risk. Consequently, most familial studies investigating genetic risk for FIP have focused on rare variants (RVs) with very low frequency in the general population (minor allele frequency <0.001 or lower). Studies to date have implicated rare genetic variants in more than 10 genes in FIP kindreds (Table 1). FIP genes identified to date comprise into two distinct groups: 1) genes related to surfactant production or processing, and 2) telomere-related genes.

Surfactant-related genes

In 2001, Nogee and colleagues reported the first recognized genetic cause of FIP; in this case a heterozygous mutation in the gene encoding for surfactant protein-C (*SFTPC*) in a mother and infant with NSIP and desquamative interstitial pneumonia (DIP), respectively.[17] This was soon followed by a report of a different *SFTPC* mutation in a very large multiplex kindred including adults with UIP pattern.[16] Subsequent studies indicated that *SFTPC* mutations are a rare cause of FIP[29–31] outside selected populations influenced by founder effects,[14,32] and very uncommon among ILD patients outside the context of FIP.[31,33–35]

The implication of *SFTPC* mutations in FIP led to a search for mutations in other genes related to surfactant biology in FIP kindreds. These studies have led to reports of mutations in the gene encoding for surfactant protein A2 (*SFTPA2*)[36,37] and surfactant protein A1 (*SFTPA1*)[38,39] in FIP kindreds. There are also a number of reports of FIP kindreds heterozygous for rare genetic variants in the gene encoding for ATP-binding cassette subfamily member A3 (*ABCA3*).[40,41] These findings are intriguing, although it is not yet certain that heterozygous *ABCA3* variants alone are sufficient to confer FIP risk. Biallelic *ABCA3* mutations cause severe and often fatal neonatal respiratory distress syndrome,[42,43] with severity of neonatal phenotypes closely associated with degree of retained ABCA3 enzymatic activity.[42] The reported *ABCA3* variants are found at low, but detectable frequency in the general population, and studies to date have not yet been large enough to determine whether *ABCA3* RVs are statistically overrepresented in FIP kindreds. It may be that penetrance of heterozygous *ABCA3* variants is influenced by other genetic loci; for example, in one family, an *ABCA3* RV appeared to influence disease natural history in a family carrying the I73T *SFTPC* mutation.[44]

Studies using heterologous cell lines and transgenic mouse models indicate that surfactant pathway mutations act predominantly through toxic gain-of-function mechanisms. The most common of the surfactant mutations, I73T *SFTPC*, leads to a trafficking defect wherein the proprotein is misprocessed, directed to the plasma membrane (rather than secreted), leads to alterations in protein quality-control associated with a block in the autophagy pathway.[45] Transgenic mice inducibly expressing this mutation develop a macrophage-rich alveolitis[46] and progressive parenchymal fibrosis.[47] In contrast, mutations affecting the BRICHOS domain generally lead to failure of proprotein processing, retention and aggregation of the

misfolded proprotein in the endoplasmic reticulum, activation of the unfolded protein response (UPR).[48–53] Severe or prolonged UPR activation then leads to AT2 apoptosis, patchy parenchymal inflammation, and fibrotic remodeling.[54] A similar phenotype has been described in mice homozygous for an *Sftpa1* mutation.[55] A mouse model expressing an *Abca3* mutation (*Abca3*^{E292V}) also develop alveolar inflammation, although surprisingly, with aging this is associated with an emphysema-phenotype.[56]

There is considerable heterogeneity among the clinical features and phenotypes observed in families with surfactant-related mutations, ranging from neonatal/pediatric presentations to disease detection late in adulthood. The factors responsible for this phenotypic variability are not well understood. While there are exceptions, compared to "sporadic" interstitial lung disease in adults, adults with surfactant-related mutations tend to have earlier disease onset, but progress somewhat more slowly - over the course of decades in some cases. Together, these available data indicate while surfactant-related mutations are a rare cause of FIP (comprising 1–3% of families), studying these mutations has yielded important insights into disease mechanisms with relevance to broad groups of patients with pulmonary fibrosis.[25,51,57] It is not yet clear whether currently approved antifibrotic therapies[58,59] have efficacy in patients with surfactant mutations, however recent studies demonstrating benefit of pirfenidone[60] and nintedanib[61] in broad groups of ILD patients suggest there is reason to consider antifibrotic therapy in the appropriate clinical context. Similar to the approach used in cystic fibrosis,[62–64] *in-vitro* models indicate potential benefit of pharmacologic chaperones designed to improve trafficking of misfolded proproteins.[53,65]

Telomere-related genes

Dyskeratosis congenita (DC) is a syndrome characterized by abnormal skin pigmentation, oral leukoplakia, and nail dystrophy,[66] often accompanied by bone marrow failure, chronic liver disease and other multisystem complications. Historically, it was recognized that pulmonary fibrosis occurred occasionaly in families with DC.[67–70] In the late 1990's into the early 2000's, linkage studies identified mutations in the three genes related to telomere biology in families with DC: dyskerin (*DKC1),*[71,72] telomerase RNA component (*TERC*),[73,74] and telomerase reverse transcriptase (*TERT*).[70,75]

These observations led several groups to test for mutations in telomere-related genes in FIP kindreds. In 2007, two independent groups reported heterozygous *TERT* or *TERC* mutations in 6/7376 and 7/4677 FIP families. These mutations were associated with short peripheral blood telomeres and reduced telomerase enzymatic activity, but notably were not exclusively found in families with classic DC features. Subsequent studies using candidate gene and next-generation sequencing approaches have implicated mutations in the genes encoding for *DKC1,*[26,78] TERF1 interacting factor 2 (*TINF2*),[79,80] regulator of telomere elongation helicase 1 (*RTEL1*),[29,30,81] poly-A-specific ribonuclease (*PARN*),[30,82] nuclear assembly factor 1 (*NAF1*),[83], and zinc finger CCHC-type containing 8 (*ZCCHC8*),[84] in FIP kindreds. In contrast to the surfactant pathway, mutations in telomere-related genes generally lead to alterations in cellular homeostasis through a haploinsufficiency mechanism. To date, it appears that nearly all of the mutations in telomere related genes converge upon a phenotype of reduced functional telomerase activity through a variety of different mechanisms. *TERT*

mutations directly lead to reduced catalytic activity of the reverse transcriptase enzyme,[76,77] while *TERC* mutations reduce levels or impair the function of the RNA template required for addition of telomere repeats. DKC1,[26,85] PARN,[86] NAF1,[83] and ZCCHC8[84] regulate RNA stability and are associated with reduced *TERC* levels. RTEL1 mutations do not directly affect telomerase enzymatic activity, but impair unwinding of T-loops, a crucial step required for telomerase to physically interact with telomere DNA-sequences.[87] In aggregate, estimates from across studies suggest that mutations in telomere-related genes are found in 25–30% of FIP kindreds, and more than 50% of families with short peripheral blood telomeres.

While the genetic evidence implicating defects in telomerase to pulmonary fibrosis is strong, the mechanisms linking telomere dysfunction to chronic lung disease are not yet well understood. The prevailing hypothesis has been that telomerase dysfunction leads to stem cell failure in the lung, although direct evidence to support this hypothesis is limited. In the lung, telomerase expression and activity is low and cell turnover relatively slow under homeostatic conditions,[18] and recent single-cell genomic studies have demonstrated only rare *TERT* expressing cells[88–92] in control or disease lungs, consequently, it remains unclear which cell type(s) are central to mediating disease pathogenesis. Studies using global *Tert* and/or *Terc* null mice have reported contradictory results with regard to the development of spontaneous lung pathology and response to injury.[93–98] Several groups have demonstrated that deletion of shelterin components (Trf1 or Trf2) in type II alveolar epithelial cells is sufficient to trigger a telomere DNA-damage response,[95,99,100] leading to chronic inflammation and/or progressive fibrosis.

Compared to other FIP patients and ILD patients without a family history, families with mutations in telomere related genes appear to develop disease at a somewhat earlier age (5–10 years younger than IPF trials populations).[29,76,77,101,102] A family history of premature greying, cryptogenic cirrhosis, or bone marrow dyscrasias (aplastic anemia, myelodysplastic syndrome, acute myeloid leukemia) is suggestive of a “short-telomere syndrome.” However, it should be noted that some families with mutations in telomere-related genes lack other systemic manifestations of short telomere syndromes. Genetic anticipation may be one mechanism driving the phenotypic heterogeneity of disease manifestations in these families,[70] although genetic and/or environmental factors also likely contribute.

Diverse imaging and histopathologic disease patterns (ILD phenotypes) have been described in patients and families with mutations in telomere-related genes,[101–104] and discordant ILD phenotypes are commonly observed within the same family.[29,101,102] Importantly, the available data suggest that disease natural history among patients in these families is similar regardless of imaging or histopathologic ILD pattern.[101] The efficacy of antifibrotic treatments in patients with telomere-related gene mutations is not known. A retrospective analysis of patients in the pirfenidone clinical trials suggested a similar, if not larger, effect size in IPF patients with the short-telomeres as estimated by whole-genome sequencing[35] compared to those with longer telomeres, however no studies to date have reported genotype stratified treatment effects. Due to the risk of occult chronic liver disease, careful monitoring of liver function is required in antifibrotic therapies are initiated.

There are unique considerations around lung transplantation required for patients with telomere-related gene mutations. While lung transplant can be successfully performed, patients with mutations in telomere-related genes may be at increased risk for complications related to immunosuppresion,[105,106] and at higher risk for acute rejection.[106]

Pulmonary fibrosis associated with other systemic disorders

In addition to short telomere syndromes, interstitial lung disease can be a feature of several other systemic disorders (Table 2).

Hermansky-Pudlak Syndrome (HPS) is an autosomal-recessive multisystem disorder related to defects in lysosomal biogenesis,[20] leading to clinical manifestations related to dysfunction of lysosomal-derived organelles. HPS is characterized by platelet dysfunction, oculocutaneous albinism, and pulmonary fibrosis.[20] In the appropriate clinical context, a diagnosis of HPS required demonstration of absent dense granules by platelet electron microscopy. There are at least 10 different subtypes of HPS caused by mutations in different factors related to lysosomal biogenesis and trafficking. Pulmonary fibrosis is highly penetrant in patients with HPS1, HPS2, and HPS4, but not other HPS subtypes.[20,21] As a result, in patients with HPS, genetic testing provides important information as to risk for interstitial lung disease, the most life-threatening complication of this syndrome. Two clinical trials have tested the antifibrotic pirfenidone in HPS patients;[107,108] while these studies did not detect differences in their primary endpoints, it is recognized that these studies were likely underpowered to detect clinically important effects, and there are now reports demonstrating safety and tolerability of long-term pirfenidone therapy in HPS-associated pulmonary fibrosis.[109] HPS has been considered a contraindication to treatment with nintedanib due to concern of excess bleeding risk.

“Brain-lung-thyroid syndrome”, a disorder caused by heterozygous mutations in the transcription factor *NKX2–1,*[110] is characterized by hypothyroidism, chorea-form movement disorders, and respiratory disease. A spectrum of interstitial lung disease phenotypes have been described in families with *NKX2–1* mutations. The majority of cases have been described in pediatric populations, and include neuroendocrine hyperplasia of infancy (NEHI),[111] pathology similar to surfactant-related disease,[112] and pulmonary alveolar proteinosis,[22,112,113] however there are now multiple reports of interstitial lung disease in adults with *NKX2–1* mutations.[23,113] Corticosteroids, hydroxychloroquine, and azithromycin have been used to treat patients with *NKX 2–1* mutations, but the efficacy of these therapies is not yet established.[113]

Diffuse lung disease has also been described in families with “COPA Syndrome”, a recently described disorder characterized by high-titer autoantibodies, inflammatory arthritis, and interstitial lung disease associated with mutations in the gene encoding for *coatamer subunit alpha (COPA).*[24] While initial report described pulmonary hemorrhage and/or interstitial and ground-glass infiltrates primarily in children,[24] several recent reports suggest there may be a broader spectrum of ILD-phenotypes associated with *COPA* mutations.[114–117] Immunsuppressive treatment with corticosteroids and/or other agents is generally recommended and beneficial in these patients.[24]

Common genetic variation in FIP

Family-based cohort studies have focused primarily on rare genetic variants of large effect in families, however common genetic variation also contributes to FIP risk.[118–120] The available data suggest that common genetic variants linked to IPF risk by linkage[118] or genome-wide association studies,[119] including the *MUC5B* promoter polymorphism and more than 15 additional loci[119,121–123] have similar effect sizes in familial and sporadic IPF patients.[119,120] As common genetic variants follow complex rather than Mendelian inheritance patterns, genetic testing for common genetic variants does not currently have a role in the clinical evaluation or care of patients with FIP.

Genetic testing

The role of genetic testing in the evaluation of patients and families with FIP is evolving, and at present there are no established guidelines for the use of genetic testing in adults with interstitial lung disease. There are two primary considerations when considering genetic testing in a patient with FIP: 1) What is the likelihood of finding a culprit variant, and 2) What, if any, action would result from a positive test?

Detection of a germline risk variant in a patient with FIP has implications not only for the patient, but also for siblings, children, and other family members, thus any consideration of genetic testing should be performed in coordination with experienced genetic counselors.[19] If testing is performed, testing an affected patient (rather than an unaffected relative) is highly recommended in order to determine whether a potentially pathogenic mutation segregates with disease within the family. Current estimates suggest that likely or definitely pathogenic rare variants are found in 20–30% of unselected FIP patients, thus in the majority of patients with FIP, a culprit variant will not be found. As a result, when considering a genetic test, it is important to recognize that only a positive result is informative. A negative genetic test does not indicate absence of genetic risk. One approach that maximizes the likelihood of an informative genetic test is to use clinical features and family history to identify patients with a high pretest probability of identifying a culprit variant,[19] and to restrict testing to genes in which a culprit variant is anticipated. For example, in a 35 year old with ILD who has a child with unexplained chronic lung disease, testing for a surfactant-related mutations would be appropriate. In contrast, this scenario is not suggestive of a short-telomere syndrome, so testing for mutations in telomere-related genes would likely have low utility.

If a genetic test is performed, the American College of Medical Genetics offers guidance as to interpretation of variants that are identified.[124] In broad terms, a variant may be reported as likely pathogenic, a variant of uncertain significance, or likely benign. Variants that lead to truncated proteins or null alleles (nonsense variants), variants altering splicing, or insertions/deletions may be considered pathogenic in the absence of prior reports of the same variant in disease, however missense variations (leading to changes in a single amino acid) are more challenging to classify. Many FIP-associated mutations reported to date are private (reported in only a single family), thus these variants would be considered variants of uncertain significance in the absence of data demonstrating the mutation alters protein function. In some cases, functional assays or corroborative measurements (such as

measurement of peripheral blood telomere length)[19,125] can aid in the interpretation of variants of uncertain significance.

There are several scenarios where a genetic test is likely to yield clinically actionable results. Among patients with Hermansky-Pudlak Syndrome, genetic testing to determine HPS subtype can inform with high confidence whether or not a patient will develop pulmonary fibrosis. Patients with *COPA* mutations appear to respond to immunosuppression, which is not recommended for most ILD patients. Detection of a mutation in a telomere-related gene has prognostic implications, and may also inform immunosuppression strategies in patients who require lung transplantation. A positive genetic test also provides the opportunity for subsequent generations to undergo targeted testing. For children of FIP patients, knowledge of risk variant status may inform approaches to screening for ILD, and can also influence reproductive considerations.

Implications for relatives of FIP patients

It is clear that bloodline relatives of FIP patients are at markedly elevated risk for ILD compared to the general population[4]. With the availability of effective antifibrotic therapies[58–61,126] that slow disease progression and appear to have similar efficacy in patients with relatively preserved pulmonary function,[127–129] a compelling case can be made for screening and early disease detection strategies for individuals at high risk for disease. The timing, modality, and interval for such a strategy remains an area of active investigation.

Data from multiple studies have demonstrated that 10–25% of close relatives of FIP patients have detectable early interstitial changes on HRCT despite having no known lung disease, [130–132] and this prevalence increases with age. Among these individuals with early interstitial changes, pulmonary function tests (PFTs) including diffusing capacity for carbon monoxide are typically normal,[130] indicating that PFT-based screening alone is not sufficiently sensitive to detect early disease. The *MUC5B* promoter variant has been associated with interstitial lung abnormalities in both families[132] and population-based cohorts.[133–135] A number of peripheral blood biomarkers have been associated with early interstitial changes in families[131] or general-population based cohorts,[136–139] however none of these biomarkers are currently approved or available for clinical use. The role of environmental exposures as a determinant of disease penetrance and phenotype has not been well-studied; identifying modifiable risk factors could enable preventive strategies in high-risk individuals. Advanced machine-learning and artificial-intelligence-based image analysis techniques hold promise for defining high-risk features,[132] but it remains to be seen whether the use of such techniques can detect subtle evidence of disease progression before symptoms or pulmonary function tests change. As longitudinal data become available, there will be opportunities to develop individualized models of risk for interstitial lung abnormaitiies (ILA) progression integrating genetic information, biomarkers, and physiologic measurements.

Conclusion

It has become clear through the past two decades that pulmonary fibrosis is a heritable syndrome, and studies of FIP have yielded new insights into the pathobiology of ILD with broad relevance. With increasing evidence indicating that known genetic risk factors for sporadic and familial ILD are much more similar than different,[35,118–120] considerations that inform the approach to and care of patients and families with FIP are likely to become increasingly relevant to broad groups of patients with ILD and their families.

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Table 1.

Rare genetic variants linked to FIP

Gene	Percent of FIP	References
TERT	8–15%	76,77,140
RTEL1	5–7%	29,30,81
PARN	3–5%	30,82
TINF2	<1%	79,80
TERC	<1%	76,77
DKC1	<1%	26,78
NAF1	<1%	83
ZCCHC8	<1%	84
SFTPC	2–25%	14,16,32,141,142
SFTPA2	<1%	36,37
SFTPA1	<1%	38,39
ABCA3	<1%	40,41
Unknown	70–80%	

Table 2.

Monogenic syndromes associated with ILD

Syndome	Genes associated	Key Clinical Features
Surfactant-related	*SFTPC, SFTPA1, SFTPA2, ABCA3*	Neonatal respiratory distress syndrome Waxing-and-waning ground glass and reticulation Diagnosis at <1 year to >70 years
Short telomere	*TERT, RTEL1, PARN, TERC, NAF1, TINF2, DCK1, ZCCHC8*	Premature greying (early 20's or younger) Cryptogenic cirrhosis Macrocytosis Bone marrow dyscrasias (aplastic anemia, MDS, AML)
Brain-lung-thyroid	*NKX2–1*	Movement disorders Hypothyroidism NEHI
COPA	*COPA*	Inflammatory arthritis Elevated autoantibodies Pulmonary hemorrhage Interstitial and ground glass infiltrates
Hermansky-Pudlak Syndrome	***HPS1***, ***AP3B1***, *HPS3,* ***HPS4***, *HPS5, HPS6, DNTBP1, BLOC1S3, BLOC1S6, AP3D1*	Bleeding diathesis - platelet dysfunction Oculocutaneous albinism Pulmonary fibrosis (subtypes 1, 2, 4)

Bold indicates HPS genes associated with pulmonary fibrosis