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Familial Pulmonary Fibrosis
Genetic Features and Clinical Implications

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Pulmonary fibrosis comprises a wide range of fibrotic lung diseases with unknown pathogenesis and poor prognosis. Familial pulmonary fibrosis (FPF) represents a unique subgroup of patients in which at least one other relative is also affected. Patients with FPF exhibit a wide range of pulmonary fibrosis phenotypes, although idiopathic pulmonary fibrosis is the most common subtype. Despite variable disease manifestations, patients with FPF experience worse survival compared with their counterparts with the sporadic disease form. Therefore, ascertaining a positive family history not only provides prognostic value but should also raise suspicion for the inheritance of an underlying causative genetic variant within kindreds. By focusing on FPF kindreds, rare variants within surfactant metabolism and telomere maintenance genes have been discovered. However, such genetic variation is not solely restricted to FPF, as similar rare variants are found in patients with seemingly sporadic pulmonary fibrosis, further supporting the idea of genetic susceptibility underlying pulmonary fibrosis as a whole. Researchers are beginning to show how the presence of rare variants may inform clinical management, such as informing predisposition risk for yet unaffected relatives as well as informing prognosis and therapeutic strategy for those already affected. Despite these advances, rare variants in surfactant and telomere-related genes only explain the genetic basis in about one-quarter of FPF kindreds. Therefore, research is needed to identify the missing genetic contributors of pulmonary fibrosis, which would not only improve our understanding of disease pathobiology but may offer additional opportunities to improve the health of patients. CHEST 2021; 160(5):1764-1773

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Pulmonary fibrosis is a heterogeneous group of chronic lung conditions marked by aberrant inflammation and collagen deposition leading to progressive physiological impairment and death.[1] The inciting pathobiological events that lead to pulmonary fibrosis are largely unknown; however, it is believed that both environmental insults and genetic vulnerability confer disease susceptibility. Although sporadic forms of pulmonary fibrosis are predominant, familial clustering is relatively common. The recent explosion of genetics research has uncovered a host of risk variants implicating a variety of disease pathways, the effects of which are

ABBREVIATIONS: CHP = chronic hypersensitivity pneumonitis; CTD = connective tissue disease; DC = dyskeratosis congenita; FPF = familial pulmonary fibrosis; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; LTL = leukocyte telomere length; SNP = single nucleotide polymorphism; U-ILD = unclassifiable interstitial lung disease; VUS = variant of unknown significance

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most relevant in the inherited forms of pulmonary fibrosis.

Familial pulmonary fibrosis (FPF) is diagnosed when at least two relatives within the same family develop pulmonary fibrosis. This phenomenon was initially described more than a century ago.[2] However, in the 1950s and 1960s, clinicians began to astutely recognize that FPF likely represented a unique version of fibrotic lung disease resulting from inherited determinants.[3,4] Despite the advanced diagnostic and therapeutic tools at our disposal today, the diagnosis of FPF relies, almost entirely, on detailed patient-clinician discussions, as it did > 100 years ago. Accordingly, the current review discusses the importance of family history ascertainment and focuses on the clinical implications of the FPF entity. We outline syndromic features that suggest the presence of an underlying pathogenic rare variant and discuss their clinical ramifications. One unique form of FPF, the Hermansky-Pudlak syndrome, was recently reviewed[5] and therefore is not discussed here. Lastly, we review the utility of genetic testing and provide a prospective on how genetic information can be leveraged in the clinical setting.

Epidemiology of FPF

Defining the true prevalence of pulmonary fibrosis in the population is challenging. Epidemiologic studies estimate the prevalence of idiopathic pulmonary fibrosis (IPF) at 13.4 to 18.5 per 100,000 people,[6] which is orders of magnitude larger than the estimated FPF prevalence of 1.3 to 5.9 per 1,000,000 people.[7] In contrast, observational cohort studies indicate that FPF may be much more common, affecting up to 20% of patients with pulmonary fibrosis.[8-10] This discordance likely reflects differences in access to patient-level data for family history validation. Recent results from prospective pulmonary fibrosis screening programs suggest that the prevalence of FPF is likely still underappreciated. Three independent groups used radiographic screening for asymptomatic relatives of patients with pulmonary fibrosis and identified subclinical disease in 15% to 31% of cases.[11-13] Interestingly, Hunninghake et al[13] found that 31% of asymptomatic relatives of patients with seemingly sporadic pulmonary fibrosis had radiographic interstitial lung abnormalities, which is four times higher than community-dwelling adults.[14,15] Together, these studies confirm family history as a risk factor for pulmonary fibrosis in yet-unaffected relatives[9] and show that the burden of FPF may be much higher than previously suspected.

Importance of Family History Ascertainment

By definition, family history ascertainment is required to confer the FPF designation. This process should include a detailed assessment of each relative's medical history focusing primarily on FPF-associated pulmonary and extrapulmonary manifestations (Table 1). Age-dependent onset of disease and reduced penetrance can sometimes obscure familial cases. In fact, symptomatic pulmonary fibrosis often does not manifest until after the fifth decade of life, even in those with inherited pathogenic rare variants.[16] In addition, genetic anticipation has been reported in FPF families wherein subsequent generations develop more severe disease at an earlier age. Pedigree construction is a simple yet methodical approach to assess for inherited forms of pulmonary fibrosis, which can be updated as new information is obtained from kindreds.

Patients with FPF can manifest a spectrum of pulmonary fibrosis phenotypes. Although accurate pulmonary fibrosis classification relies heavily on radiographic characterization, FPF cases often do not conform to typical radiographic patterns,[17] making dogmatic etiology-based classification challenging. IPF is the most common phenotype of patients with FPF[9,18]; however, other subtypes commonly occur. Prior multicenter cohort studies have shown that 20% to 25% of patients with IPF, as well as 14% to 17% of patients with chronic hypersensitivity pneumonitis (CHP), 15% with unclassifiable interstitial lung disease (U-ILD), and 3% to 8% with connective tissue disease-ILD (CTD-ILD), have a family history of pulmonary fibrosis (Fig 1).[19-21] Furthermore, even relatives within

TABLE 1] Clinical Features That Increase Suspicion for Familial Pulmonary Fibrosis

History of pulmonary fibrosis for any reason in one or more family members
Age of pulmonary fibrosis onset within family
Pediatric onset (age < 18 y)
Younger age of onset with each generation affected (genetic anticipation)
Lung cancer and pulmonary fibrosis co-segregation within kindred
Extrapulmonary manifestations
Bone marrow failure (eg, aplastic anemia, myelodysplastic syndrome)
Macrocytosis with or without anemia
Cryptogenic cirrhosis or portal hypertension
Premature graying of the hair (by the third or fourth decade of life)

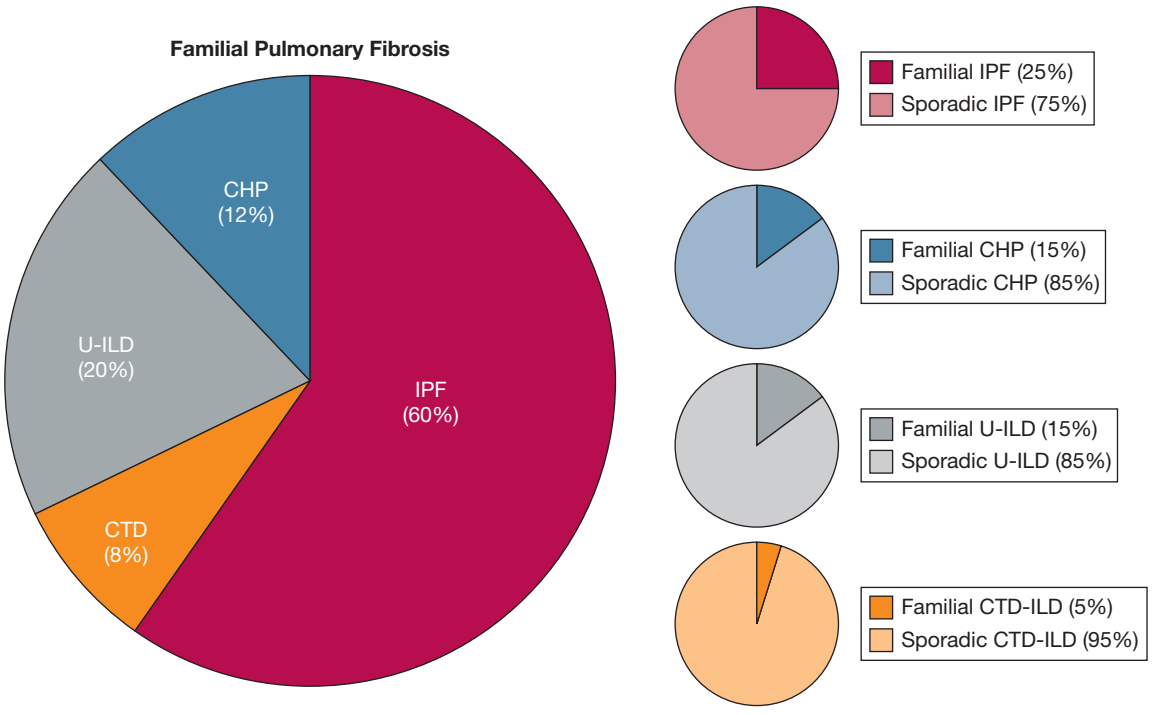

Figure 1 – *Estimated makeup of clinical diagnoses of patients with familial pulmonary fibrosis. CHP = chronic hypersensitivity pneumonitis; CTD = connective tissue disease; IPF = idiopathic pulmonary fibrosis; U-ILD = unclassifiable interstitial lung disease.*

the same family can manifest different pulmonary fibrosis subtypes.[18,22]

Although a positive family history may not inform the clinical diagnosis, the presence of familial disease does have prognostic value. Cutting et al[21] found that patients with a self-reported family history of pulmonary fibrosis experienced worse survival compared with their counterparts with sporadic disease (Fig 2). In this study, patients with familial IPF experienced an 80% higher mortality risk than those with sporadic IPF, whereas patients with familial non-IPF had a 200% higher mortality risk than their counterparts with sporadic disease. In addition, patients with FPF diagnoses that traditionally confer a better prognosis, such as CTD-

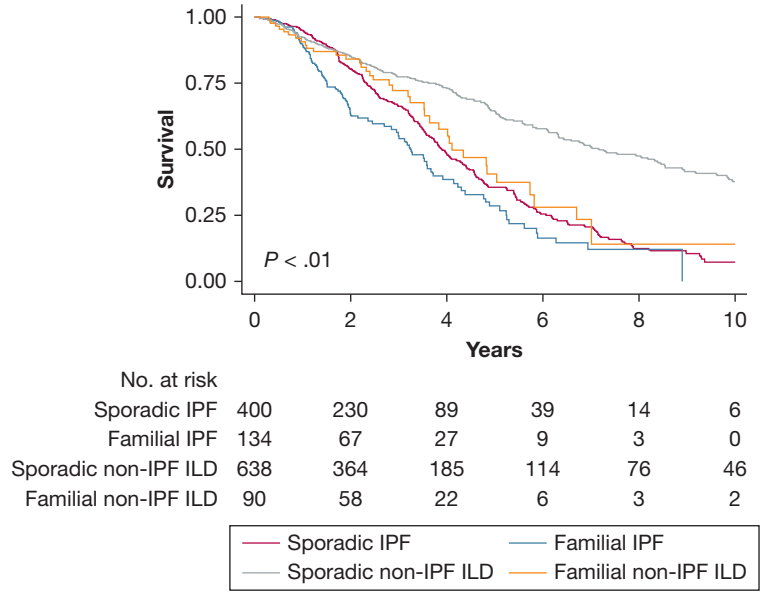

Figure 2 – *Decreased survival in familial forms of pulmonary fibrosis. ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis. (Reprinted from Cutting et al.[21])*

ILD, had similar survival characteristics as patients with sporadic IPF. Therefore, the FPF designation represents an easily identifiable supplement to the clinical pulmonary fibrosis diagnosis that signifies higher risk.

FPF Genetic Variation

Although a positive family history can provide broad information regarding heritability and disease course, identifying specific variants can improve predictive resolution. The known genetic variants that are associated with pulmonary fibrosis fall into two broad categories: common single nucleotide polymorphisms (SNPs) and rare damaging variants. Common SNPs are frequently found in the general population, defined by minor allele frequency $> 5\%$. By contrast, rare damaging variants are scarcely found in the general population, often with minor allele frequency $< 0.1\%$. The frequency with which a variant is present in the population is inversely related to the size of its effect on disease risk, such that common SNPs confer a smaller effect size compared with that of rare variants.[23] In this paradigm, SNPs may contribute to disease risk but alone are insufficient to cause disease. In contrast, co-segregation of rare variants with disease is often found in FPF kindreds with or without other risk factors, suggesting a causal relationship.

To date, rare variants within two distinct biologic pathways have been implicated in adult-onset FPF: surfactant metabolism (*SFTPC*,[24-26] *SFTPA1/2*,[27] *ABCA3*[28]) and telomere maintenance (*TERT*,[29,30] *TERC*,[29,30] *PARN*,[31,32] *RTEL1*,[31,33,34] *NAF1*,[35] *DKC1*,[36,37] *TINF2*,[38] *ZCCHC8*,[39] and *NOP10*[40]). Collectively, rare variants in these genes are found in about 25% of patients with FPF and, when present, can inform extrapulmonary manifestations, clinical course, and management considerations.

Clinical Implications of Surfactant-Related Gene Variants

Genetic profiling of large kindreds led to the discovery of rare surfactant-related gene variants that predispose to adult-onset FPF. The most common surfactant gene implicated in adult-onset FPF is *SFTPC*, which has been found in 2% to 25% of patients with FPF, although the larger estimates are likely related to founder effects.[25,41] Conversely, rare variants in *SFTPA1/2* are found in $<$ 1% of FPF cases. Rare biallelic variants in *ABCA3* have been described in FPF but more commonly present in infancy.[28,42] The link between rare heterozygous variants and adult-onset FPF is less clear. Kindreds harboring *SFTPC* and *SFTPA1/2* exhibit autosomal dominant inheritance, whereas inheritance of *ABCA3* is autosomal recessive.[43]

Surfactant-related gene variants have diverse molecular consequences depending on the gene and involved domain. The most common risk variant in *SFTPC*, encoding a missense mutation (I73T), causes altered surfactant protein C trafficking and proteostasis.[44] Damaging variants in the C-terminal BRICHOS domain of *SFTPC*, as well as damaging variants in *SFTPA1/2*, cause protein misfolding and endoplasmic reticulum stress.[45,46] Biallelic damaging variants in *ABCA3* cause reduced protein expression that disrupts surfactant metabolism, resulting in epithelial cell toxicity.[47,48]

From a clinical perspective, a unique hallmark of families that harbor a rare surfactant-related gene variant is the variable age of disease onset within the kindred, ranging from infancy to late adulthood. Surfactant variant-related neonatal syndrome is typical for *ABCA3* variant carriers but uncommonly occurs in *SFTPC* variant carriers.[42,49,50] From a pulmonary fibrosis phenotypic standpoint, adults harboring surfactant-related variants have varied radiographic and histologic patterns, including usual interstitial pneumonia, nonspecific interstitial pneumonia, and desquamative interstitial pneumonia.[26,50,51] Rare pathogenic variants within *SFTPA1* and *SFTPA2* are associated with both pulmonary fibrosis and lung adenocarcinoma.[27,52] Although these variants are rare among FPF kindreds, their presence should trigger diligent lung cancer surveillance. Because surfactant production is limited to the lung, rare surfactant variants do not cause extrapulmonary manifestations. The identification of a rare surfactant-related variant in a proband can help inform pulmonary fibrosis susceptibility in unaffected relatives who also inherited the rare variant, and radiographic screening can identify subclinical disease in this at-risk group.[53] However, given their low prevalence, it is unclear if the natural history for surfactant-related variants in adult-onset FPF differs from their sporadic counterparts.

Clinical Implications of Telomere-Related Gene Variants

Rare variants within telomere-related genes are found in about one-quarter of FPF kindreds, with variants in *TERT* affecting 8% to 15% of all FPF.[29,30,54] Comparatively, *PARN* and *RTEL1* variants each comprise about 5% to 10% of FPF cases,[31] followed by *TERC* at 1% to 2%.[54] Rare variants within *DKC1*, *TINF2*,

NAF1, NOP10, and *ZCCHC8* genes have been identified in few families, and their suspected prevalence is < 1%.[35,36,38-40] Telomeres comprise six-nucleotide repeats located at chromosomal ends that buffer against loss of protein-encoding DNA during cellular replication. Collectively, the telomere-related genes serve to protect, maintain, or elongate telomeres. Although telomere shortening is a normal function of aging, damaging variants within these genes often result in pathologic shortening. The majority of telomere-related gene variant carriers have age-adjusted telomere lengths below the 10th percentile, although gene-specific differences may occur; *PARN* variants tend to cause less extreme telomere shortening than *TERT, TERC*, or *RTEL1* variants.[22,31] Therefore, measurement of leukocyte telomere length (LTL) alone may be an imprecise screening tool for the presence of a pathogenic telomere-related gene variant.

Phenotypically, damaging variants in telomere-related genes are associated with multisystem abnormalities collectively referred to as telomeropathies, or short telomere syndromes. The prototypic telomeropathy is the pediatric disorder dyskeratosis congenita (DC), which is often due to homozygous telomere-related gene mutations and extreme telomere shortening. The classic manifestations of DC include abnormal skin pigmentation, oral leukoplakia, and nail dystrophy; however, bone marrow failure occurs in > 80% of DC cases and is the leading cause of death.[55] Pulmonary fibrosis develops in approximately 20% of patients with DC and often manifests in early adulthood or following bone marrow transplantation.[56] In contrast, pulmonary fibrosis is the most common manifestation in adults with heterozygous rare telomere-related gene variants, although extrapulmonary manifestations reminiscent of DC phenotypes can coexist within patients or relatives. Such manifestations include bone marrow dysfunction, liver disease, predisposition to malignancy, and premature hair graying.[57] Importantly, relatives within families harboring telomere-related gene variants may manifest different telomeropathy disorders. For example, the proband may only have pulmonary fibrosis while their relatives have only bone marrow disease or premature hair graying. In other cases, multiple telomeropathy features can manifest within a single individual. In addition, short telomere length itself is a heritable trait passed from generation to generation,[16,58] mediating genetic anticipation in which more severe disease phenotypes present at younger ages.[22,59,60] For these reasons, obtaining a detailed family history regarding possible telomeropathy manifestations and age of disease onset is critical.

Not only are the telomere-related gene variants associated with varied extrapulmonary manifestations, but their pulmonary fibrosis subtypes are also heterogeneous. Approximately one-half of rare telomere-related gene variant carriers develop IPF, whereas others develop CHP (7%-12%), CTD-ILD (2%-3%), U-ILD (8%-20%), and other idiopathic interstitial pneumonias (14%-18%).[22,54] Although the pulmonary fibrosis phenotype may be variable, rare telomere-related gene variant carriers experience uniformly progressive disease and poor survival.[22] Similar observations have been extended to those with sporadic forms of pulmonary fibrosis. Ley et al[61] found that patients with CHP and qualifying variants in *TERT*, *PARN*, and *RTEL1* experienced worse transplant-free survival compared with those without a variant. This finding suggests that the genetic diagnosis may be more prognostically informative than the specific pulmonary fibrosis diagnosis.

Patients with adult-onset sporadic pulmonary fibrosis are also enriched for rare telomere-related gene variants and short telomere length. Rare telomere-related gene variants are present in about 10% of sporadic IPF, CHP, and rheumatoid arthritis-ILD cases.[61-64] Although short age-adjusted telomere length is found in about one-half of patients with FPF,[31,65] it is also present in sporadic disease in about 20% to 60% of IPF,[66,67] 20% to 35% of CHP,[20] and 26% of rheumatoid arthritis-ILD.[19] Not only do short telomeres and pulmonary fibrosis coexist, but short telomere length is potentially causative of pulmonary fibrosis. Using a polygenic score of common SNPs associated with telomere length, Duckworth et al[68] used a Mendelian randomization strategy to show a causal relationship between short telomere length and IPF but not COPD.

Given this information, LTL has been evaluated as a potentially informative biomarker, and multiple studies have shown that short LTL consistently informs prognosis. Stuart et al[69] reported that shorter LTL was associated with worse mortality in patients with IPF, which has since been replicated in multiple ethnically diverse IPF cohorts.[64,70,71] Short LTL is similarly prognostic for other forms of pulmonary fibrosis, including CHP[20,72] and U-ILD.[73] Although extrapulmonary telomeropathy manifestations may contribute to their poor survival, patients with short LTL experience rapid lung function decline, indicating that

progressive lung fibrosis is a key contributor to their mortality.[19,64]

Interactions between medical therapies and telomere dysfunction may also influence clinical outcomes. We reported that patients with IPF and LTL below the 10th percentile disproportionally experienced worse outcomes when exposed to immunosuppressive medications.[66] Although immunosuppression is no longer used for IPF, it remains the mainstay for many non-IPF forms of pulmonary fibrosis in which short LTL and telomere-related gene mutations are prevalent. Adegunsoye et al[72] recently showed that mycophenolate therapy was associated with a mortality benefit for patients with CHP and longer LTL, which was absent in those with short LTL. Together, these studies suggest that the short LTL-immunosuppression interaction confers a phenotype-specific effect ranging from not beneficial to potentially harmful. The relative influence of telomere dysfunction within disease subtypes may partially explain these results; however, additional research is needed to understand the pathobiology underlying this potential interaction. Because the majority of patients with short LTL or rare variants in telomere-related genes either exhibit IPF or non-IPF progressive fibrotic interstitial lung disease, the use of antifibrotic therapies remains a safe and seemingly effective option to slow lung function decline.[64,74]

Heritability Gap in Familial Pulmonary Fibrosis

Causative rare genetic variants have been discovered in a subset of FPF kindreds, largely explaining the genetic risk within those families. In addition, common SNPs such as the *MUC5B* rs35705950 SNP, which was originally identified through family-based linkage scans, also likely contribute to FPF risk.[75] However, a large portion of FPF kindreds remain without a predominant genetic diagnosis. This heritability gap may be attributable to numerous causes. First, there are limitations to accurately predicting the pathogenic effects of any one specific variant. This is especially true for variants that lie within noncoding regions of the genome as well as silent, or synonymous, variants without a predicted amino acid change. Such variants often elude typical genetic screens and require in-depth functional analyses for identification. Second, due to the limited sample sizes of previously costly next-generation sequencing studies, discovery has been saturated with large effect risk genes; future studies aiming to identify novel risk genes may require much larger cohorts. Third, a portion of the missing heritability may be due to the additive or multiplicative effects of many variants, including both rare variants and common SNPs, rather than a single perturbation. Advancements in sequencing depth and analytic strategies may allow researchers to quantitate polygenic interactions, accounting for the differential risk of both common SNPs and rare variants. Fourth, epigenetic sources of heritability may explain a portion of disease risk. One source of epigenetic-mediated inheritance is telomere length itself, which is a heritable trait independent of telomere-related variant inheritance[29,76] and may alone explain a subset of the patients with FPF. Finally, shared environmental exposures may also contribute to the development of FPF. Small case series have described familial or community clusters of CHP through shared exposure to an occult antigen.[77-79] However, given the prevalence of risk gene mutations in CHP, it remains likely that shared exposures and underlying genetic susceptibility both contribute to these cases.

Clinical Genetic Testing Considerations

As the framework of FPF genetic heritability becomes clearer, clinicians should consider how genetic testing can be leveraged in patient care. Genomics-based testing options include genetic sequencing and telomere length measurement. Genetic sequencing aims to identify specific variants within risk genes. This can be accomplished via whole genome, whole exome, or panel sequencing in which only previously identified risk genes are assessed. In the correct clinical context (strong family history with syndromic manifestations), the rate of identification of a pathogenic or likely pathogenic variant in a known risk gene can be relatively high. Conversely, telomere length can be measured within peripheral blood leukocytes, and age-adjusted values are returned to the clinician and patient. Telomere length testing does not provide information about a specific gene or mutation, as short telomere length can occur independent of rare variants in telomere-related genes. Considerations of which test to perform depend on the pretest probability of an FPF genetic syndrome. For those with telomeropathy manifestations, telomere length measurement or genetic sequencing can be performed simultaneously or in series, as these tests provide different, yet complementary information. Those with clinical features of a surfactant-related variant should undergo genetic sequencing only.

Although genetic testing is available, the risks and benefits of testing should be considered prior to

embarking on this endeavor. Patients with a suggestive family history should undergo pretest counseling to better understand the shortcomings and potential consequences of genetic testing. First, sequencing results are often neither positive nor negative; instead, sequencing commonly reveals variants of unknown significance (VUS). Adjunctive testing, such as clinical telomere length measurement in the case of a telomere-related gene VUS, may help assess variant pathogenicity. Expansion of genetic testing in relatives, a process known as cascade testing, may be informative if the suspicious VUS co-segregates with disease, thus providing suggestive evidence of variant pathogenicity. In addition, it is possible that some patients who have a negative genetic test result may harbor yet-to-be-identified variants that predispose to disease. Second, the cost of genetic testing can be substantial and is often deferred to the patient. Third, genetic testing itself may have a psychological impact on patients and their relatives. This impact may not always be negative, and in fact some patients may be relieved by knowing their genetic status. Encouragingly, Carmichael et al[80] found that relatives of patients with pulmonary fibrosis who underwent clinical and genetic screening did not experience excessive decisional regret, but there are still many unknowns about the potential psychological ramifications of genetic testing that require exploration. Given the nuances and potential pitfalls of genetic testing, we recommend referring patients with FPF to certified genetic counselors who can offer invaluable insight through pretesting counseling, choosing the appropriate genetic test, interpreting the results, and providing posttesting counseling to patients and their relatives.

Prospect of Genetics-Informed FPF Management

The idea of precision medicine in pulmonary fibrosis leans heavily on genetics-informed decision-making. This is already being realized for the roughly 25% of FPF kindreds who harbor a rare variant in a risk gene, paving the way for patient and family-specific approaches to management. For instance, the presence of a rare telomere-related variant might sway the clinician and patient away from performing invasive diagnostic biopsies because the genetic abnormality informs disease course more than the specific pulmonary fibrosis subtype.[22] Furthermore, the presence of a rare telomere-related variant should trigger additional evaluations for extrapulmonary disorders such as occult cirrhosis, hematologic abnormalities, or oral leukoplakia (a precursor to squamous cell carcinoma). Due to the progressive nature of pulmonary fibrosis in patients with telomeropathy, early referral for lung transplant may be considered. However, small studies have suggested that these patients are at risk for bone marrow abnormalities, infections, and allograft dysfunction.[81-83] Additional studies are needed to outline optimal strategies for posttransplant management. For those with *SFTPA1/2* variants, screening for lung cancer should be performed. The identification of a rare variant in a proband also has ramifications for their relatives who may have inherited the variant. Therefore, relatives may opt to undergo genetic sequencing to improve risk stratification. Those relatives who are found to harbor the variant should be counseled to avoid potential fibrogenic exposures and undergo monitoring for development of clinical disease. In essence, relatives of FPF probands become patients in their own right.

Despite the growing recognition of genetic variants underlying FPF, genetic testing may not identify a causative rare variant in a known risk gene in up to 75% of FPF kindreds. Although a "negative" result may seem reassuring, these patients should still be considered at risk for developing disease and require close monitoring with radiographic and physiological screening.[11-13] In some cases, future re-assessment may be considered as new genetic discoveries are made, potentially resolving undiagnosed cases. If screening identifies subclinical disease, early initiation of antifibrotic therapy should be considered when symptoms develop or with any evidence of progression. Early recognition of disease offers a substantial opportunity to delay further disease progression and improve clinical outcomes in FPF kindreds.

Conclusions

Patients with FPF represent a uniquely vulnerable population. Their disease carries a high risk for mortality, manifests with atypical radiographic or histologic features, and poses challenging questions for their relatives. However, major advances in pulmonary fibrosis genetics have yielded a much greater understanding of the genetic architecture that informs these unique characteristics. Over the last few decades, around one-quarter of the heritability of FPF has been explained, which is no trivial task for a disease with such extreme phenotypic heterogeneity. FPF is becoming increasingly recognized, offering substantial opportunities to decipher the remaining sources of

heritability and unlock novel pathways that contribute to lung fibrosis. With the pace of discovery over the past decade, the future of FPF diagnostics and management has never been brighter.

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