Genetics and Early Detection in Idiopathic Pulmonary Fibrosis

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Abstract

Genetic studies hold promise in helping to identify patients with early idiopathic pulmonary fibrosis (IPF). Recent studies using chest computed tomograms (CTs) in smokers and in the general population have demonstrated that imaging abnormalities suggestive of an early stage of pulmonary fibrosis are not uncommon and are associated with respiratory symptoms, physical examination abnormalities, and physiologic decrements expected, but less severe than those noted in patients with IPF. Similarly, recent genetic studies have demonstrated strong and replicable associations between a common promoter polymorphism in the mucin 5B gene (*MUC5B*) and both IPF and the presence of abnormal imaging

findings in the general population. Despite these findings, it is important to note that the definition of early-stage IPF remains unclear, limited data exist to definitively connect abnormal imaging findings to IPF, and genetic studies assessing early-stage pulmonary fibrosis remain in their infancy. In this perspective we provide updated information on interstitial lung abnormalities and their connection to IPF. We summarize information on the genetics of pulmonary fibrosis by focusing on the recent genetic findings of *MUC5B*. Finally, we discuss the implications of these findings and suggest a roadmap for the use of genetics in the detection of early IPF.

Keywords: interstitial lung disease; interstitial lung abnormalities; *MUC5B*; subclinical; idiopathic pulmonary fibrosis

Scars have the strange power to remind us that our past is real.

—Cormac McCarthy, *All The Pretty Horses*

It is the extensive scarring that reminds us that idiopathic pulmonary fibrosis (IPF) has had a past. Although current definitions of IPF require either radiologic or pathologic features consistent with end-stage fibrosis (e.g., honeycombing) (1), there is almost certainly a stage of this disorder that precedes these changes. What does early-stage IPF look like? How common is it? How long does it take to transition from early-stage IPF to end-stage fibrotic lung disease? Could interventions targeted at early stages prevent the progression to clinically apparent IPF? These are questions

that have been difficult to answer, because the evolutionarily adaptive reserve capacity of the human lung often precludes the development of respiratory symptoms, and subsequently patients present to our hospitals and clinics when signs of advanced disease are present.

Should we ignore these questions because they are difficult to answer? The answer to these questions would be “yes” if IPF was a disease that could improve or stabilize with medical treatment. Unfortunately, this has not been the case. IPF remains a disorder that is minimally responsive to pharmacotherapy (2, 3) and has a mortality rate comparable to that of many end-stage malignancies (2–5). As

adroitly presented in a prior editorial (6), although most of the efforts aimed at improving the morbidity and mortality of IPF have focused on previously diagnosed symptomatic patients, much of the progress in reducing the morbidity and mortality of other diseases, such as cardiovascular disease, have come from efforts shifted toward the study of asymptomatic patients, risk factors, and secondary prevention. Given this information, confronting the natural history of IPF seems more urgent and answering the difficult questions about early IPF a more prescient task.

How do we put the past of IPF into focus? One lens we can use to sharpen the past of IPF is to perform studies of genetic association. Genetic studies are unique in

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that we know that most of these mutations are present at birth (e.g., germline mutations) and therefore predate disease development; thus, they can provide insights into early stages. Although most genetic association studies are used for discovery (e.g., identifying variants in unique genes that are associated with the development of a known, or clinically apparent, disease or trait), genetic studies also hold promise in teaching us about the connections between early-stage and advanced disease (7). In addition, genetic association studies can suggest pathologic links between seemingly disparate diseases (8) and in some cases can result in a blurring of apparent disease boundaries (9).

In this perspective we frame the topic of genetic detection in early IPF by reviewing updated information on interstitial lung abnormalities (ILA) and their connection to IPF. We summarize information on the genetics of pulmonary fibrosis by focusing on the recent genetic findings of *MUC5B*. Finally, we discuss the implications these findings and suggest a roadmap for the use of genetics in the detection of early IPF.

ILA and IPF

To have a discussion about the use of genetics in early IPF detection, it is important to have some concept about what the phenotype of early IPF might be. In this section we examine similarities and differences between subjects in research studies with ILA and patients with IPF. A more comprehensive review of early stages of interstitial lung disease (ILD) in a variety of contexts has been published previously (10). It should be noted that various terms (e.g., “dirty-lung” [11], preclinical [12], and subclinical [10, 13] ILD) and methodologies for detection (13–18) have been used in the literature when referring to the use of imaging studies to identify early stages of pulmonary fibrosis. To some degree, these differences cloud the field by limiting comparisons between studies. For the purposes of clarity, we maintain use of the term ILA (14, 16) to highlight a phenotype that is defined by specific patterns of increased lung densities on imaging studies without the benefit of additional clinical information. To date, studies attempting to identify ILA have primarily relied on chest computed tomograms (CTs) and have included subjects from population samples

(13, 15, 16) and smokers participating in research studies (14, 17, 18). Reading methodologies for ILA have included quantitative density metrics (13) and visual reads relying on selected imaging features (13–16, 18) and global pattern identification (10, 14–18). As noted in Table 1, there is now accumulating information about the similarities between the radiologic and clinical phenotype of patients with IPF and research subjects with ILA.

ILA and IPF: Radiology

Thoracic CT findings considered to be “classic” for usual interstitial pneumonia (UIP, the histopathologic equivalent of IPF) include subpleural reticular changes, honeycombing, and traction bronchiectasis with a predominantly posterior and basilar distribution (1). Ground-glass abnormalities are common among patients with IPF but are typically less extensive than the reticular abnormalities (1). It should be noted that “classic” CT findings are only noted to be present in approximately half of patients ultimately diagnosed with IPF by histopathology (19). With that in mind, it is worth comparing the imaging features of ILA to those reported in patients with IPF.

As noted in Table 1, comparable to patients with IPF, reticular abnormalities are among the most common radiologic features noted in subjects with ILA in some (14–16) but not all studies (13, 17, 18). Ground-glass abnormalities, occasionally identified in patients with IPF, are commonly reported in subjects with ILA in most studies (13–18). Although all studies document honeycombing in some subjects with ILA, in contrast to IPF (1), this feature is more rarely identified. Additional radiologic features atypical for IPF are also noted in subjects with ILA.

Of note, one difficulty with this field is trying to convey the extent of abnormalities present on chest CT imaging to readers with single or small sets of axial and coronal images. As demonstrated in Figure 1, although partly transparent three-dimensional reconstructions demonstrate more extensive radiologic abnormalities (subjects from the Framingham Heart Study [FHS] without ILA [Figure 1A], with ILA but without fibrotic changes [Figure 1B], and with ILA with fibrotic changes [Figure 1C]), single planar images

do not often convey the full extent of these radiologic findings (Figure 1C3) and in some cases, due to the selection of a comparable image, can miss critical radiologic abnormalities entirely (Figure 1B3). In short, although most patients with ILA do not meet radiologic criteria for IPF, the description of ILA as a set of subtle radiologic findings is often a misconception.

ILA and IPF: Clinical Syndrome and Physiology

Comparable to the similarities we have noted in radiologic findings, many similarities exist between the clinical syndrome and physiologic abnormalities apparent in both subjects with ILA and patients with IPF (Table 1).

Advanced age, a common feature of patients with IPF (1), is strongly associated with the presence of ILA and has been a consistent finding across most studies (14–18). Smoking, an increasingly accepted risk factor for IPF (20, 21), has now been associated with ILA in multiple independent populations and is currently the most well-replicated risk factor for ILA (14–18). Subjects with ILA have been demonstrated to have an increase in respiratory symptoms (14–16) and physical examination findings noted in patients with IPF (15). In addition, statistically significant reductions in total lung, exercise, and diffusion capacity have been noted in subjects with ILA when compared with subjects without ILA (Table 1) (14, 16, 22).

Although relative increases in age, respiratory symptoms, and physical examination findings, and relative reductions in physiologic parameters suggestive of an early restrictive ventilatory deficit with impaired exercise capacity and gas exchange, all suggest that, in some cases, ILA may be an early stage of pulmonary fibrosis, it is also important to comment on the differences noted between these two phenotypes. Respiratory symptoms are less common among subjects with ILA than in patients with IPF (Table 1). As ILA is a phenotype defined by radiologic abnormalities in research subjects, none whom have been diagnosed with an ILD by a clinician, this difference is not surprising. In addition, for most of the physiologic parameters, the median values noted in subjects with ILA are greater than those

Table 1: Comparisons of the Features Noted in Subjects with Interstitial Lung Abnormalities to Those in Patients with Idiopathic Pulmonary Fibrosis

Variable	Percent or Median/Means Where Appropriate and Noted						Patients with IPF**
	Research Subjects with ILA						
	MESA*	Nagano, Japan†	COPDGene‡	MILD§	FHS	NLST¶	
Prevalence of ILA, %	2	3	8	4	7	10	0.01–0.04
Radiologic features, %							
Reticular markings	4–9	62	85	21	97	24	All
Ground glass	61–93	15	97	90	100	78	Occasional
Centrilobular nodules	—	—	28	28	20	—	Rare
Cysts	—	—	51	—	47	27	Rare
Traction bronchiectasis	—	—	30	21	50	—	Common
Honeycombing	2–13	9	9	7	3	10	Common
High-attenuation areas in >10% of the lung	100% (by definition)	—	—	—	—	—	Unknown (but likely elevated)
Demographic parameters							
Age, yr	—	62	64	60	70	62	66
Sex, female, %	—	26	50	14	52	28	41–49
History of smoking, current or former, %	—	70	100	100	62	100	60–72
Respiratory symptoms, %							
Chronic cough, yes	—	13	41	—	12	—	73–86
Chronic shortness of breath, yes	—	15	60	—	18	—	Present in most patients
Physical examination findings							
Fine crackles, %	—	26	—	—	—	—	Present in most patients
Pulmonary physiologic testing							
FVC % predicted	—	113–116	88	101	101	—	68–89
Total lung capacity % predicted	—	—	95	—	79	—	46–78
Diffusion capacity of carbon monoxide, % predicted	—	—	—	—	86	—	46–61
6-min walk distance, m	—	555–573	403	—	—	—	373–392
Radiologic progression, %, follow-up time							
Improvement	—	16, 4 yr	—	0, 3 yr	—	33, 2 yr	The median survival of IPF patients is 3 yr
Unchanged	—	40, 4 yr	—	75, 3 yr	—	47, 2 yr	
Overall progression	—	46, 4 yr	—	25, 3 yr	—	20, 2 yr	
Progression to UIP pattern	—	5, 4 yr	—	8, 3 yr	—	—	—

Definition of abbreviations: FHS = Framingham Heart Study; ILA = interstitial lung abnormalities; MESA = The Multi-Ethnic Study of Atherosclerosis—Lung Study; MILD = The Multicentric Italian Lung Detection trial; NLST = National Lung Screening Trial.

*Data in the MESA column from Reference 13. The range of values noted in the column refers to the differences in expected prevalence depending on the threshold of high attenuation areas used to define ILA.

†Nagano, Japan: Subjects participating in a health screening program from Nagano prefecture, Japan. Data from Reference 15.

‡Data from References 14 and 22.

§Data from Reference 17. Estimates of prevalence, frequency, and median values refer to those with interstitial abnormalities but limited to either a usual interstitial pneumonia or another chronic interstitial pneumonia pattern on chest computed tomography.

||Data from Reference 16.

¶Data from Reference 18.

**Data on IPF prevalence, the expected sex prevalence, and smoking prevalence from Reference 1. Data on the radiologic features expected among patients with IPF from Reference 62. Data on the median age of IPF from Reference 63. Data on the expected sex prevalence of IPF from Reference 64. Data on the prevalence of smoking in patients with IPF from Reference 20. Data on the prevalence of chronic cough in patients with IPF from References 65 and 66. There are limited data on the expected prevalence of chronic shortness of breath and fine crackles on physical examination in patients with IPF, but it is generally assumed that some degree of shortness of breath and rales on examination occur in most patients with IPF (1). Data on the range of expected medians for FVC, total lung capacity, and diffusing capacity of carbon monoxide from Reference 23. Data on the expected median range of 6-min-walk distance in meters in patients with IPF from References 67 and 68. Data on the median survival of patients with IPF from Reference 3.

noted in patients with IPF (Table 1). Reductions in FVC have not been noted in subjects with ILA, although they are common among patients with IPF (23). Perhaps the most striking difference between ILA and IPF is the difference in prevalence, a finding we address in more detail later in this article.

ILA and IPF: Longitudinal Evaluation

Although reports of improvement and stability of radiologic findings have been noted in some patients with ILA, radiologic progression of ILA over a 2- to 4-year period has now been described in multiple studies (Table 1) (15, 17,

18). The presence of underlying fibrotic imaging features appears to predispose to radiologic progression in subjects with ILA (15, 17, 18). It is also important to note that although a UIP pattern on chest CT has been noted in subjects with ILA from multiple studies (13–15, 17, 18), two articles have additionally demonstrated radiologic

Figure 1. Each row represents data from a single subject. On the vertical axis are representative examples including (A) a subject without interstitial lung abnormalities (ILA), (B) a subject with ILA but without fibrotic changes, and (C) a subject with ILA with fibrotic changes. On the horizontal axis we present both three-dimensional (3D) reconstructions ([1] an anterior-to-posterior view; [2] a rotated anterior-to-posterior view with an axial section at the right inferior pulmonary vein) and (3) axial high-resolution chest computed tomographic images approximately at the level of the right inferior pulmonary vein. As demonstrated, single planar images do not often convey the full extent of the radiologic findings (C3) noted on 3D reconstructions (C1). B3 demonstrates an example of when selecting a comparable image can result in missing the critical radiologic abnormalities entirely (a review of the 3D reconstruction in B1 reveals a significant number of increased reticular markings at the lung bases). Figures were made using AZE VirtualPlace workstations (AZE Inc., Tokyo, Japan).

progression of ILA from a non-UIP pattern to a UIP pattern in small numbers of subjects over a 3- to 4-year period (Table 1) (15, 17). Although these findings suggest that, in some cases, ILA can lead to radiologic evidence of IPF, the differences in prevalence between these two disorders suggest that most research subjects with ILA will not develop IPF and/or that some subjects with ILA may have a similar but distinct syndrome from IPF.

Genetics of Pulmonary Fibrosis: *Muc5b*

Rather than providing an exhaustive review of the genetics of pulmonary fibrosis

(24–26), this section focuses primarily on the genetics of *MUC5B* and notes comparisons with some of the more extensively studied and well-replicated genes and genomic regions that contain variants that have been associated with an increased risk for pulmonary fibrosis. Although it might initially seem more logical to discuss the genetics of IPF specifically, rather than the genetics of pulmonary fibrosis more broadly, a review of the literature demonstrates that, in many cases, genetics studies of ILD do not conform neatly to the current disease boundaries defined by expert consensus (i.e., most well-replicated genetic association findings for

UIP are also associated with additional histopathologic disorders).

In 2011, a landmark article was published that changes our understanding of the genetics of pulmonary fibrosis (27). This article, published in the *New England Journal of Medicine* by Seibold and colleagues, demonstrated, through the use of a genome-wide linkage analysis, that a variant (rs35705950) on the short arm of chromosome 11, in the promoter region of the mucin 5b gene (*MUC5B*), was strongly associated with familial pulmonary fibrosis (FPF), sporadic IPF, and increased expression of *MUC5B* in the lung (27). Despite the relatively recent identification, the association between the *MUC5B* promoter variant and pulmonary fibrosis is currently the most consistently reproducible finding in the genetics of pulmonary fibrosis (28–30) and remains the dominant genetic finding for pulmonary fibrosis identified by two recent genome-wide association studies (Table 2) (31, 32).

What makes the association between the *MUC5B* promoter variant and pulmonary fibrosis unique, both in terms of pulmonary fibrosis and in the genetic epidemiology literature in general, is that this is a rare example (33) of a common variant with a very large genetic effect. The minor allele of rs35705950 is present in approximately 20% of the European CEPH (Centre D'étude du Polymorphisme Humain) population (34) and has been noted in approximately 31–42% of patients with IPF (27–32). Each copy of the minor allele of rs35705950 confers a 1.6- to 8.3-fold increase in the odds of developing IPF (the 1.6 odds ratio is an outlier and is the only effect estimate that is the result of imputation) (31) and a 6.2-fold increase in the risk of FPF (27) (Table 2). This large genetic effect is even more remarkable considering that the vast majority of the highly reproducible findings of genetic association identified in the genome-wide association era typically increase the odds of disease by 1.1- to 1.5-fold (35).

Despite these findings, important aspects of the *MUC5B* story still remain unclear. For example, a recent study suggests that there may be a genetic dose-response relationship toward improved survival among patients with IPF (36) with increasing copy numbers of the same *MUC5B* promoter variant that also increases IPF risk (27–32). One possible conclusion of these seemingly discordant findings is that the *MUC5B* promoter variant

Table 2: Association between Interstitial Lung Diseases (and Abnormalities) and the *MUC5B* Genotype (rs35705950)

Study	Diseases or Abnormalities Included	Study Type	Minor Allele Frequency (%)	Effect Size (Allelic Odds Ratio)	P Value
Seibold <i>et al.</i> , 2011 (27)	IPF	Genome-wide linkage study with fine mapping	34	8.3	<0.001
	FPF (also NSIP, COP, RB-ILD, and unclassified IIP)		38	6.2	<0.001
Zhang <i>et al.</i> , 2011 (28)	IPF	Case-control replication	34	4.2*	<0.001
Stock <i>et al.</i> , 2013 (29)	IPF	Case-control replication	36	4.9	<0.001
	Systemic sclerosis		12	1.2	0.36
	Sarcoidosis		11	1.1	0.60
Peljto <i>et al.</i> , 2012 (41)	Systemic sclerosis	Case-control replication	11	1.1	0.80
Borie <i>et al.</i> , 2013 (30)	IPF	Case-control replication	42	6.2	<0.001
	Systemic sclerosis		10	1.0	0.64
Noth <i>et al.</i> , 2013 (31)	IPF (discovery)	Genome-wide association study	14	1.6*	<0.001
	(replication)		31–33	3.1–3.7	<0.001
Fingerlin <i>et al.</i> , 2013 (32)	IPF and FIP (also NSIP, COP, DIP, RB-ILD, and unclassified IIP)	Genome-wide association study	NR	4.5	<0.001
Hunninghake <i>et al.</i> , 2013 (16)	ILA (all) [†]	Case-control replication	19	2.8	<0.001
	ILA (definite fibrosis) [‡]		23	6.3	<0.001

Definition of abbreviations: COP = cryptogenic organizing pneumonia; DIP = desquamative interstitial pneumonia; FPF = familial pulmonary fibrosis; IIP = idiopathic interstitial pneumonia; ILA = interstitial lung abnormalities; IPF = idiopathic pulmonary fibrosis; NR = not reported; NSIP = nonspecific interstitial pneumonia; RB-ILD = respiratory bronchiolitis-associated interstitial lung disease.

*Allelic odds ratio from Zhang *et al.* have been calculated from the data provided, and the allelic odds ratio from Noth *et al.* is the only effect estimate that is based on the imputation of rs35705950 rather than genotyping.

[†]ILA (all) = interstitial lung abnormalities including all subjects diagnosed. Analysis includes a multivariate logistic regression model adjusted for familial relationship, and additional covariates including age, sex, body mass index, pack-years of smoking, and current or former smoking status.

[‡]ILA (definite fibrosis) = interstitial lung abnormalities limited to those with the presence of architectural distortion highly suggestive of a fibrotic lung disease. Analysis includes a multivariate logistic regression model adjusted for familial relationship, and additional covariates including age, sex, body mass index, pack-years of smoking, and current or former smoking status.

confers a strong increase in the risk of a less severe form of pulmonary fibrosis. Additionally and/or alternately, survival bias could be an explanation for these findings (e.g., an increase in the risk of death resulting from an increase in the risk of pulmonary fibrosis conferred by the *MUC5B* variant resulted in a biased inclusion of relatively healthier patients with IPF with the *MUC5B* variant in these trials). In addition, increases in *MUC5B* levels have been noted in many respiratory diseases besides pulmonary fibrosis (37–39), and the mechanism by which increases in *MUC5B* expression could lead to pulmonary fibrosis is not currently known. Some evidence for the important role *MUC5B* might play in the pulmonary system comes from a recent study in mice demonstrating that *MUC5B* may be critical for normal macrophage homeostasis and for mucociliary clearance after respiratory infections (40).

Finally, it is important to note that although studies have suggested that the *MUC5B* promoter variant is not associated with additional ILDs such as sarcoidosis (29) or with rheumatologic conditions associated with pulmonary fibrosis (e.g., systemic sclerosis) (29, 30, 41), both the original

genome-wide linkage study (27) and the follow-up genome-wide association study (32) have included patients with additional forms of idiopathic interstitial pneumonia (IIP) (e.g., ~77% of cases in the genome-wide association study discovery sample were believed to have IPF; the remainder included cases of nonspecific interstitial pneumonia [NSIP], cryptogenic organizing pneumonia, desquamative interstitial pneumonia [DIP], respiratory bronchiolitis-associated ILD, and unclassified IIP; Table 2) (32). It remains unclear how much the non-IPF IIP cases contributed to the results in these studies. Additional variants in the promoter of *MUC5B* (rs885454, rs17235353, and rs7115457) have been associated with diffuse panbronchiolitis in a Korean population (42).

Associations with multiple histopathologic findings in those with similar genetic backgrounds should be familiar to those who have been following genetic studies of pulmonary fibrosis. For example, heterozygous mutations of the surfactant protein C gene (*SFTPC*) were originally described in 2001 in a case of familial interstitial pneumonia, including in

an infant who was diagnosed with NSIP and whose mother had DIP (43). Since that time, multiple other mutations in *SFTPC* have been described in children, which have been noted to cause NSIP, DIP, and pulmonary alveolar proteinosis (44–48), whereas adults with similar mutations are often diagnosed with IPF and to a lesser degree NSIP and unclassified fibrosis (44, 49–53). Similarly, many manuscripts have demonstrated that variants in genes involved in the control of telomere length (e.g., telomerase [TERT], telomerase RNA component [TERC], oligonucleotide/oligosaccharide-binding fold containing 1 [OBFC1]) (32, 54–56) may confer an increase in the risk of UIP; however, some of these studies have also included additional histopathologic forms of IIP in their analyses (32, 54–56). In summary, although the extent of histopathologies associated with the *MUC5B* variant have not been assessed to date, the data from genetic variants of *SFTPC* and for multiple genes controlling telomere length suggest that the *MUC5B* variant might be expected to increase the risk for multiple histopathologies in addition to UIP.

Genetics of ILA

Based on the similarities between ILA and IPF, we hypothesized that some of the genetic risk of IPF and ILA might be shared. Although further longitudinal follow-up studies and/or lung biopsies would help to definitively establish the connections between ILA and IPF, demonstrating similar genetic backgrounds between these two phenotypes is an important step in establishing if ILA are in some cases an early stage of IPF. Given that the *MUC5B* promoter variant was both common and had a large effect on disease risk, we chose to evaluate the association between this genotype and ILA in the FHS.

Our study demonstrated that ILA were present among 7% of FHS subjects (9% among subjects > 50 yr of age), and after adjusting for covariates, for each copy of the *MUC5B* promoter variant (rs35705950) an individual had a 2.8-fold increase in their odds to have ILA. For each copy of the *MUC5B* promoter variant there was an even greater risk (6.3-fold increase in the odds) when ILA was limited to those with definite CT evidence of pulmonary fibrosis (definite CT evidence of fibrosis was present in ~25% of subjects with ILA and 2% of the population overall) (16). The latter finding was particularly remarkable, given that the risk of definite CT evidence of pulmonary fibrosis associated with increasing copies of the *MUC5B* promoter variant was similar to the risk noted with this variant in IPF (Table 2) (27–32). Although this study, through a demonstration of similarities in radiologic, physiologic, and genetic features, suggests that ILA may in some cases represent an early stage or mild form of IPF, it important to recognize limitations and unresolved questions raised by these findings.

First, as noted above, although recent studies demonstrate that not all forms of ILD are associated with the *MUC5B* promoter polymorphism (29, 30, 41), further studies will be needed to determine the extent of histopathologies that are more likely among those with the *MUC5B* promoter variant and, by association, the extent of histopathologies expected among those with ILA. Second, despite the large effect sizes and consistent replication of the *MUC5B* promoter variant and pulmonary fibrosis, it should be noted that single genetic markers alone are not likely to be helpful

Figure 2. A schematic demonstrating the potential outcomes of subjects with interstitial lung abnormalities (ILA). Circle sizes in those with ILA and IPF reflect the minimum relative differences in prevalence we have noted between these two conditions. IIP = idiopathic interstitial pneumonia; ILA = interstitial lung abnormalities; IPF = idiopathic pulmonary fibrosis. Adapted by permission from Reference 14.

in screening for pulmonary fibrosis in the general population. Finally, the prevalence of ILA (13–18) is much greater than the reported prevalence of IPF (Table 1; even if limited to those with definite pulmonary fibrosis, ILA remains a disorder that is ~50–200 times more prevalent than IPF) (1, 57). Although there is some evidence that IPF may be underdiagnosed (58), our findings are consistent with the concept that IPF may represent an advanced stage of a relatively common and often minimally symptomatic pulmonary fibrosis syndrome that progresses at various rates in some individuals (Figure 2).

Suggested Roadmap for the Use of Genetics in Early IPF Detection

Are we ready to use genetic information for early IPF detection in the clinical setting? Not yet, at least not routinely. It is not known if genetic information will ultimately change the clinical course of IPF even if it can help us to detect IPF at an early stage. However, if genetic information can help us to detect an early stage of IPF, we should also not let the results of disappointing clinical trials in patients with advanced fibrotic disease lead us to believe that we know for certain that patients at a much earlier stage of the

disease will be similarly recalcitrant to medical therapy. As noted above, although progression has been demonstrated in small longitudinal follow-up studies of subjects with ILA, clinical stability is not uncommon, even among subjects with fibrotic features at baseline. No intervention study has evaluated large numbers of subjects with pulmonary fibrosis recruited at early stages of disease.

Of note, in selected at-risk populations, genetic information is already known to be clinically useful. For example, genetic testing in FPF, which can reveal information suggesting unique clinical syndromes (e.g., dyskeratosis congenita in families with *TERT* mutations) (55), is something we offer to our patients (59). To move more efficiently and confidently toward a goal of determining if genetic information will be helpful in early IPF detection, we suggest the following simple roadmap.

Define the Early IPF Phenotype

We need to determine the combination of demographic, clinical, imaging, and physiologic traits that predict a substantially increased risk of progression to IPF. Longitudinal follow-up studies including larger numbers of carefully phenotyped subjects followed for longer periods of time will be required. Some measure of consistency across studies will be important.

Determination of Genetic Variants Predicting IPF Diagnosis and Severity

Although the IPF genetics field has made significant progress in identifying common variants that are confidently associated with IPF diagnosis (27, 31, 32), further studies that include rare variants and assess clinical outcomes (31, 36, 60) will also be important. We need to understand what other diseases or additional phenotypic manifestations (61) are expected in those with particular IPF risk variants. We should require strong evidence for statistical significance, independent replication, and/or functional validity for confident identification of novel IPF risk variants.

involving rare variants and IPF risk variants with effect sizes comparable to those reported in many common diseases will need large sample sizes. Although novel genetic variant identification in early IPF is not without merit (e.g., variants predicting regression or clinical stability), the clinical justification for these analyses should be strong. Ultimately, genetic analyses should combine information from multiple variants (as well as including additional epidemiologic and molecular risk factors) and should move beyond association analyses to analyses that examine risk prediction and stratification. Predictive analyses should also focus on high-risk groups for whom genetic testing might be more likely to prove clinically valuable.

IPF, the use of genetics in early IPF detection remains a field of research in its infancy. Previous studies have demonstrated that ILA are relatively common radiologic abnormalities on chest CT imaging studies that are associated with imaging findings, respiratory symptoms, physical examination abnormalities, physiologic decrements, and both epidemiologic and genetic risk factors frequent in patients with IPF. However, to move this field more confidently forward, further work, including longitudinal studies, will be needed to add precision to the early IPF phenotype and depth to our understanding of the genetics of pulmonary fibrosis. ■

Determination of Genetic Variants Predicting Early IPF Diagnosis and Progression

Initial studies should focus on replicating confidently identified IPF risk variants. Studies

Conclusions

Although genetic studies hold promise in providing definition to the blurry past of

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