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The genetic basis of idiopathic pulmonary fibrosis

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Abstract

Throughout the past decade, there have been substantial advances in understanding the pathogenesis of idiopathic pulmonary fibrosis (IPF). Recently, several large genome-wide association and linkage studies have identified common genetic variants in more than a dozen loci that appear to contribute to IPF risk. In addition, family-based studies have led to the identification of rare genetic variants in genes related to surfactant function and telomere biology, and mechanistic studies suggest pathophysiologic derangements associated with these rare genetic variants are also found in sporadic cases of IPF. Current evidence suggests that rather than existing as distinct syndromes, sporadic and familial cases of IPF (Familial Interstitial Pneumonia, FIP) likely reflect a continuum of genetic risk. Rapidly evolving bioinformatic and molecular biology techniques, combined with next-generation sequencing technologies, hold great promise for developing a comprehensive, integrated approach to defining the fundamental molecular mechanisms that underlie IPF pathogenesis.

Introduction

Idiopathic Pulmonary Fibrosis (IPF), the most common of the idiopathic interstitial pneumonias (IIPs), is characterized by clinical symptoms of cough and dyspnea, restrictive pulmonary function tests with impaired gas exchange, and progressive lung scarring [1]. Recently, two modestly effective drugs for treating IPF have been identified [2, 3]; however, the prognosis of IPF remains grave, emphasizing a need for a more complete understanding of the mechanisms of disease pathogenesis. Available data indicate that both genetic and environmental factors contribute to risk of IPF and other IIPs [1, 4, 5]. The first insights into IIP genetics came from studies of families with heritable cases of IIP, a syndrome termed Familial Interstitial Pneumonia (FIP). As early as the 1950's, it was recognized that on occasion, IIP cases clustered in families [6, 7], suggesting a genetic basis to at least a subset

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of disease. By the 1990's, it was reported that FIP represented a rare subset of IIP, comprising 3-5% of cases [8]. More recently, estimates from several independent groups have suggested that as many as 20% of IIP cases are familial [9-12]. Studies in families have uncovered rare genetic variants in eight genes that are linked to FIP, including three surfactant-related proteins [surfactant protein C, *SFTPC* [13-16] and surfactant protein A2, *SFTPA2* [17] and ATP-binding cassette member A3 (*ABCA3*)[18, 19]] as well as five genes linked to telomere function [telomerase reverse transcriptase, *TERT* [20, 21], human telomerase RNA component, *hTR* [20, 21], dyskerin, *DKC1* [22-24], telomere interacting factor 2, *TINF2*[25-27] and regulator of telomere elongation helicase, *RTEL1*[28]]. Rare genetic variants in FIP-associated genes can be found in some cases of sporadic IPF[12], and investigations into the mechanisms through which these mutated genes contribute to disease have uncovered common underlying pathobiological changes that likely contribute to progressive fibrotic remodeling in FIP and sporadic IPF[4, 5].

Common genetic variants in IPF

Several studies since the early 2000's have investigated the role of functional polymorphisms in a variety of genes in relationship to IPF risk (Table 1). Variants in several genes related to inflammation and immune response, including transforming growth factor beta-1 (*TGFB1*)[29, 30], interleukin-1 receptor alpha (*IL1RN*)[31-33], interleukin 8 (*IL8*) [34], toll-like receptor 3 (TLR3)[35], *HLA DRB1*1501*[36], as well as cell-cycle progression related genes *CDKN1A* and *TP53* [37], have been nominally associated with IPF risk or progression. However, results from these small studies have not yet been validated in independent cohorts. More recently, several large genome-wide linkage and association studies have been completed and identified numerous additional loci that appear to confer risk for IPF.

MUC5B

In 2011, a genome-wide linkage study identified a locus on chromosome 11 that was significantly associated with IPF risk[38]. Resequencing of this region subsequently identified a common single nucleotide polymorphism (SNP) (rs35705950) in the promoter of the gene encoding for Mucin 5B (Muc5B) that was associated with a 6-8 fold increased risk for IPF. The association of this *MUC5B* promoter polymorphism and IPF has since been confirmed in several independent cohorts, predominantly in Caucasians [39-44]. Interestingly, it appears the *MUC5B* SNP has a similar frequency in FIP and sporadic IPF cases[38]. This association, however, may be specific to IIP among interstitial lung diseases (ILD) since reports indicate rs35705950 does not confer increased risk of scleroderma-related ILD or sarcoidosis [39, 42, 45]. This association of rs35705950 with IPF was confirmed in a cohort of Mexican patients [46]; however, rs35705950 was found to be rare in a Korean cohort of IPF patients. Similarly, in a Chinese population, rs35705950 was rare in IPF patients but different *MUC5B* polymorphisms were associated with disease [47].

While the rs35705950 *MUC5B* SNP was associated with increased *MUC5B* mRNA expression in lungs of control subjects, *MUC5B* expression was uniformly increased in lungs of IPF patients compared to controls regardless of whether the *MUC5B* SNP was

present[38]. Consistent with this observation, increased numbers of *MUC5B* expressing cells have been detected in the distal airways of IPF patients[48]. *MUC5B* rs35705950 has also been reported as a risk factor for asymptomatic interstitial lung abnormalities detected on CT scan among subjects over age 50 in the Framingham cohort[49]. Surprisingly, although minor allele carriers of rs35705950 have increased risk of developing disease, IPF patients who carry the minor (risk) allele appear to have improved survival compared to noncarriers[50]. Previous animal studies have suggested that MUC5B regulates airway host defense[51], but the mechanisms by which MUC5B influences fibrotic remodeling are uncertain at present.

Insights from Genome Wide Association Studies

A major advance of the past several years has been the development of large, robust datasets with sufficient statistical power for genome wide association studies (GWAS). Two large independent GWAS of IPF patients have now been conducted and identified numerous genetic loci that confer IPF risk. The first, published in 2013[40], evaluated 1,616 IIP cases (the vast majority of which were IPF) and 4,683 controls subjects with replication in an additional 876 cases and 1,890 controls. In addition to confirming the previously reported association with *MUC5B*, 9 additional loci were significantly associated with IIP, predominantly IPF (summarized in Table 1), including SNPs near *TERT* and *hTR*. Ten SNPs on chromosome 11p15 nominally met genome-wide significance, but after controlling for *MUC5B* rs35705950 these loci no longer met genome-wide significance, suggesting weak linkage disequilibrium (LD) with the *MUC5B* promoter polymorphism was largely responsible for this association.

Results of a second GWAS again implicated a locus on chromosome 11p15 as significantly associated with IPF, but did not replicate other risk loci identified by Fingerlin and colleagues. This GWAS [41] performed a three-stage analysis, including a discovery and two replication cohorts, comprising in total 1410 IPF cases and 2934 control individuals. Five loci achieved genome-wide significance, including 4 SNPs on chromosome 11p15 and one on 17q21. Among the 11p15 SNPs were *MUC5B* rs35705950 and 3 SNPs within the Toll-interacting protein (*TOLLIP)* locus. LD was reported to be low with rs35705950, suggesting *TOLLIP* may represent an independent risk locus. Similar to *MUC5B* rs35705950, IPF cases with the *TOLLIP* risk allele (the major allele) had decreased mortality compared to minor allele carriers.

Deciphering the biological effects of common genetic variants identified by GWAS has proven challenging so far. It is possible that the relevant biological effect of most individual SNPs is subtle or manifests only in the context of unique additional genetic or environmental factors to confer disease risk. Despite challenges, future studies are needed to clarify the biological role of disease-associated common genetic variants.

Rare genetic variants in FIP and IPF

FIP and sporadic IPF share many clinical and histopathologic features[52], which has led to the hypothesis that similar mechanisms underlie the pathogenesis of sporadic and familial disease. Additionally, Scholand et al. employed an extensive genealogical database and

found unexpected relatedness among patients who died of what was believed to be sporadic IPF[53], further supporting the idea that the genetic landscapes of sporadic IPF and FIP overlap considerably. Together, studies to date suggest that sporadic and familial disease reflect of spectrum of genetic risk for pulmonary fibrosis (Figure 1). In this model, genetic risk factors of small and large effects interact with rare and common environmental stimuli to produce the phenotype of pulmonary fibrosis. Most FIP kindreds appear to have an autosomal dominant inheritance pattern with incomplete penetrance, suggesting an important role for genetic rare variants (RVs) of large effect. In contrast, sporadic IPF may occur more often in the setting of *de-novo* or low penetrance RVs, or a combination of more common, less severe genetic risk alleles. As described below, in some cases genetic RVs of large effect may be found in genes that lie within loci also containing common variants associated with IPF risk. Focusing on familial disease offers the ability to use Mendelian approaches to identify disease-associated RVs. This represents a promising approach to enhance mechanistic understanding of the impact of genetic risk factors on development of FIP and potentially sporadic IPF.

Telomerase and short telomeres

Pulmonary fibrosis occurs in approximately 20% of patients with dyskeratosis congenita (DC)[54], a rare inherited genetic disorder characterized by leukoplakia, bone marrow failure and dystrophic nails that typically affects young males. RVs in genes related to telomere biology have been implicated in DC[55]. In 2007, using candidate gene approaches, two groups identified heterozygous loss-of-function RVs in telomere-related genes in 7-15% of FIP families who did not have a history of DC[20, 21]. These variants in *TERT* and *hTR* lead to short telomeres in peripheral blood and in the lung [20, 21, 56, 57]. To date, *TERT* RVs are the most commonly identified mutations linked to FIP; however, *TERT* RVs are rarely identified in sporadic cases of IPF[56]. In addition to variants in *TERT* and *hTR*, two recent reports identified FIP patients with RVs in the gene encoding for dyskerin (*DKC1*)[22, 23], another component of the telomerase complex. Several reports have also identified pulmonary fibrosis in families with DC associated with RVs in *TINF2* [26, 27]. In one of these families, there was evidence of somatic or acquired mosaicism for a deletion which abolished expression of the missense variant [25]. This interesting observation suggests acquired genetic variation may represent one mechanism regulating the clinical spectrum of disease linked to telomere pathway RVs.

Using whole-exome sequencing in a cohort of >180 FIP kindreds, our group has identified heterozygous loss-of-function RVs in another telomere related gene, regulator of telomere elongation helicase (*RTEL1*) in 9 families with IPF[28]. Similar to *TERT*, *hTR* and *DKC1* RVs, these *RTEL1* RVs are associated with short telomeres in peripheral blood. In addition to a role in telomere maintenance, *RTEL1* appears to play a more general role in genome stability, DNA-repair, and replication[58-60], suggesting it may confer disease risk through additional mechanisms. As *TERT* deficiency has also been associated with abnormal DNA-repair[61], it is possible that this mechanism, rather than direct effects on telomere length, could be an important in mediating disease risk associated with telomerase pathway RVs. Cumulatively, RVs in these five telomere-related genes are reported in approximately 15-20% of FIP families.

Notably, the short telomere phenotype in peripheral blood mononuclear cells (PBMCs) is not limited to patients with loss of function RVs in telomerase complex genes. Approximately 1/3 of sporadic IPF and FIP patients have short telomeres (<10th percentile for age) in PBMCs [56, 57]. In addition, it appears that the majority of IPF patients have short telomeres in alveolar epithelial cells[23, 56], suggesting that additional factors (besides genetic risk) contribute to telomere shortening in lungs of patients with IPF and FIP. Interestingly, asymptomatic first-degree relatives of FIP patients have decreased alveolar epithelial cell telomere length compared to controls, and alveolar epithelial cell telomere length is significantly associated with the presence of interstitial changes on high-resolution chest CT [62]. In addition, it appears that PBMC telomere length within families with *TERT* RVs can be inherited at least in part independent of a known RV, producing a unique scenario of inherited genetic risk without the risk allele[21, 56, 63]. PBMC telomere length appears to be predictive of survival among patients with IPF, wherein IPF patients with short telomeres have reduced survival compared to those with “normal” length PBMC telomeres [64]. In addition to rare genetic variants in telomere related genes, common genetic variants in loci near *TERT*, *hTR* and telomere gene *OBFC1* have been linked to sporadic IPF by GWAS [40] and may be an important factor in determining telomere length. Environmental factors, including cigarette smoke exposure, may also play a role in telomere shortening in FIP and sporadic IPF[65].

Genetic and clinical evidence provide a compelling association between lung fibrosis and telomere biology. Although the mechanisms through which telomerase pathway RVs lead to lung fibrosis are uncertain, it has been suggested that these loss of function variants disrupt lung epithelial repair mechanisms[66]. Murine models of telomerase dysfunction have been developed but present a number of challenges that limit their utility for mechanistic studies [4]. In spite of these limitations, several studies have reported attempts to model telomerase deficiency in the lung. *Tert* null mice have decreased numbers of alveolar epithelial cells and modest architectural changes in the lung[67]. These mice have increased susceptibility to cigarette smoke induced-emphysema[68], but do not develop lung fibrosis. Studies using pro-fibrotic stimuli such as bleomycin to investigate fibrotic susceptibility in *Tert* and *Terc* null mice have yielded conflicting results[69, 70]. Together, it appears that recapitulating the biology of telomere dysfunction in humans using mouse models is problematic. Therefore, new approaches are needed in this area.

Surfactant Protein-Related Genes

Nogee and colleagues first described a heterozygous mutation in the gene encoding surfactant protein C (*SFTPC*) in a young woman and her child with IIP in 2001[13]. Soon after, we identified the first association between *SFTPC* and FIP in a large family with 11 affected individuals[14]. Subsequently, other groups have reported heterozygous RVs in *SFTPC* in 1-2% of FIP [9, 12, 14-16, 71]. Although one group reported *SFTPC* RVs in 25% of FIP kindreds [15], this high frequency was likely related to founder effects. The mechanisms through which *SFTPC* RVs contribute to disease pathogenesis were recently reviewed elsewhere[4, 72]. In brief, it appears that C-teminal BRICHOS domain mutants result in defects in folding of the propeptide within the endoplasmic reticulum (ER), leading to ER stress and activation of the unfolded protein response[73-77]. Linker domain mutants

(such as the I73T RV) appear to alter trafficking of the pro-peptide[78] and lead to dysregulated proteastasis.[79]. Animal modeling suggests induction of ER stress in alveolar epithelial cells is not sufficient to induce spontaneous fibrosis but results in an exaggerated fibrotic response following low-dose bleomycin challenge[80]. Induction of ER stress in alveolar epithelial cells increases susceptibility to apoptotic stimuli[80, 81], increases expression of mesenchymal markers, and enhances production of profibrotic mediators [82, 83]. In addition, RVs in another surfactant protein (*SFTPA2*)[17] has been linked to FIP. *SFTPA2* RVs also result in ER stress and may increase latent TGFβ activation[84, 85].

While the frequency of surfactant protein RVs in sporadic IPF appears to be low[86, 87], several groups have reported that ER stress and UPR activation is a common feature of FIP and sporadic IPF [74, 88], suggesting that environmental factors (such as herpesviruses [74, 89] and tobacco smoke[90-92]) may contribute to this phenotype. Promisingly, it has recently been shown that pharmacologic chaperones might improve processing of mutant surfactant proteins in alveolar epithelial cell lines[93]. These exciting developments raise the possibility of targeted therapies for at least a subset of patients with pulmonary fibrosis.

In addition, RVs in another gene involved in surfactant processing, ATP-binding cassette-type 3 (*ABCA3*) (previously linked to pediatric interstitial lung disease) have been reported in several FIP families[18, 19, 94], as well as in sporadic cases of IPF[12]. In one consanguineous family[18], homozygous RVs in *ABCA3* were identified. A heterozygous RV in *ABCA3* was also reported in a patient with “combined pulmonary fibrosis and emphysema”[19]. In another family carrying the I73T *SFTPC* RV, a second heterozygous RV in *ABCA3* modified disease penetrance [94]. The exact mechanisms by which *ABCA3* variants confer FIP risk are unclear at present, but presumably relate to epithelial cell dysfunction.

ELMOD2

A report using linkage in a cohort of Finnish FIP families suggested *ELMOD2* as a candidate FIP gene[95] and *in vitro* studies suggest *ELMOD2* may play a role in anti-viral responses[96]. Whether *ELMOD2* plays an important role in lung fibrosis has not yet been elucidated.

Missing heritability and future genetic discovery

Cumulatively, available literature suggests that rare-variants in FIP genes *SFTPC*, *SFTPA2*, *ABCA3*, *TERT*, *hTR*, *DKC1, TINF2* and *RTEL1* comprise 15-20% of FIP cases (Table 2). However, it is possible that selection of families for these candidate-based genetic studies, as well as founder effects in certain populations, may have overestimated the frequency of some variants among all FIP families. While common genetic variants also confer FIP risk and may explain as much as 30% of FIP risk [40], there remains substantial “missing heritability.” In an effort to identify novel FIP genes, recently, our group has performed extensive whole-exome sequencing of subjects from FIP kindreds. While this approach has implicated *RTEL1* as an FIP gene, ongoing analysis suggests that RVs in a single gene (or small group of related genes) do not account for disease in a majority of families [28]. Compared to other genetic lung diseases such as cystic fibrosis and familial pulmonary

arterial hypertension, it appears the genetic basis of FIP is substantially more heterogenous. Given the lack of a dominant gene in FIP, the principal challenge is one of power, both within families and across subjects. Linkage or co-segregation based approaches rely upon the power of large, multigenerational pedigrees with numbers of affected individuals, a well-established inheritance model, and ability to clearly ascertain affection status. Considering that each individual typically harbors 200 rare genetic variants in their exomes[97] and most FIP kindreds are small, dozens of RVs will be shared among affected individuals making it difficult to identify the culprit RV by this approach. In light of what appears to be substantial allelic heterogeneity, similar to what has been observed for other familial disorders including hypercholesterolemia [98], neurodegenerative diseases [99] and cardiomyopathies[100], functional testing and validation in cell and/or animal models will be critical to determine the pathogenicity of specific variants and genes tentatively linked to disease.

These challenges suggest that novel and creative approaches will be necessary to further genetic discovery in FIP and IPF. As elaborated further below, we anticipate that evolving bioinformatic approaches to variant prioritization [101, 102], coupled with network and pathway based analysis [103] hold promise for identifying, validating, and integrating disease-associated variants. In addition to rare coding variants, future studies investigating intronic variants or variants in more distant *cis*- and *trans*- regulatory regions should further inform understanding of the spectrum of genetic risk for FIP.

Implications for other IIPs

The evolving understanding of the genetic landscape of FIP and sporadic IPF leads to the question of whether the same genes and genetic variants confer risk for other ILDs, including other forms of IIP. Genetic predisposition for IIPs other than IPF has been poorly characterized; however, several clues suggest there are both conserved and distinct genetic risk factors. Within FIP pedigrees, it has been well recognized that individuals may harbor the same disease-associated RV yet present with different histopathologies [13, 52]. This finding indicates that differential environmental exposures overlaid on a common set of genetic risk factors may play a role in determining IIP phenotype. No study to date has been adequately powered to assess whether common genetic variants linked to IPF also confer risk to other IIPs. Future studies are required to address this important issue.

Implications for clinical management

Impact on clinical trial design and treatment

Although no clinical trials to date have stratified patients based on genetic risk, this strategy could prove useful in light of the now recognized associations of the 11p15 risk variants (*MUC5B* and *TOLLIP*) with reduced disease progression and improved survival. As additional genes and risk alleles are identified, more complex stratification schemes may be developed to enhance study design. With the recent publication of randomized controlled trials of two pharmacologic agents, pirfenidone [2] and nintedanib[3], that reduce lung function decline among IPF patients, a reasonable question for future study is whether genetic factors influence response to treatment with one or both of these medications.

Whether genetic factors influence outcomes after lung transplant remains an underexplored question. One small series described successful lung transplant in 8 patients with *TERT* RVs, however a high rate of hematologic and renal toxicities were noted[104]. The role of other rare or common genetic variants on outcome after lung transplant is not known.

Genetic testing

As our understanding of the influence of genetic factors on risk of IPF and its natural history, a potential role for clinical genetic testing emerges. At present, we suggest that evidence is not sufficient to recommend routine genetic testing for rare or common genetic variants for patients with sporadic IPF. In families with FIP, clinical testing for variants in *SFTPC*, *SFTPA2*, and telomerase-related genes including *TERT*, *hTR, DKC1 and RTEL1* is available from commercial and academic sources. Our practice is to offer genetic counseling and consideration of genetic testing to patients with FIP and a family history suggestive of a telomerase dysfunction syndrome (including diagnoses of aplastic anemia, cryptogenic cirrhosis, premature graying). Decisions to undergo genetic testing are complex and highly individual, and no studies have evaluated the impact of genetic testing on patients/families in the context of FIP. Extrapolating from our experience and literature from other disorders [105-107], continued close follow-up of patients who undergo genetic testing appears essential regardless of whether they are found to carry a disease-associated RV. In light of the incomplete penetrance and variable expressivity of FIP associated RVs, we recommend patients and their families confer with genetic counselors before consideration of genetic tests that are currently available or may become available in the future. Over time, we anticipate there may be a role for broader screening of common and rare genetic variants associated with IPF.

Overcoming challenges and future directions

To date, investigations of the genetic basis of FIP and sporadic IPF have provided crucial insights into underlying mechanisms of progressive pulmonary fibrosis. We suggest that there is likely not a single “road to IPF” but rather there are “multiple paths” that converge to a common phenotype. The development of exciting next-generation sequencing capabilities, along with continuously evolving bioinformatic approaches to analysis of large data sets and rapidly improving molecular biological techniques, offer unique possibilities to identify additional novel genes and pathways that contribute to the pathogenesis of progressive pulmonary fibrosis (Figure 2). Whole-genome sequencing is rapidly becoming feasible, and although it presents new and greater bioinformatic challenges, the possibility of analyzing non-coding variants, as well as interactions among variants holds promise in identifying as-of-yet unexplained heritability of FIP and sporadic IPF. In addition, the rapidly evolving field of stem-cell biology offers the possibility of studying the effects of genetic variants in primary human cell-types of interest using inducible pluripotent stem cell (iPSC) differentiation strategies[108, 109]. The development of improved gene-editing technologies including the CRISPR-Cas9-based system should facilitate enhanced ability to characterize genetic variants with functional testing *in vitro* and *in vivo*[110, 111].

We anticipate that by understanding the biological mechanisms through which individual genetic variants contribute to disease pathogenesis, key pathways will be identified that will clarify the crucial molecular mediators of IPF pathogenesis. We anticipate that a role for molecular genetics in the classification of IIPs will emerge. The ultimate challenge that lies ahead is to develop an integrated understanding of the role of genetic variants (rare and common) and to identify how these variants interact with each other and with environmental factors to produce the epigenetic, transcriptomic, proteomic, histopathologic, and clinical features of IPF. With increased understanding of the fundamental mechanisms of disease, the future is promising for development of new, targeted therapies to further improve treatment of IPF.

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Take home idea

Emerging genetic studies offer new insights into the fundamental mechanisms of pulmonary fibrosis.

Novel ideas

Through the past decade, rapid advances in genetic and genomic technologies have begun to reshape our understanding of the “idiopathic” interstitial pneumonias. Genome-wide association studies have identified more than a dozen common genetic variants associated with IPF risk, and may be linked to altered disease progression and survival. Rare genetic variants in 8 genes have been implicated in familial interstitial pneumonia (FIP), the familial form of IPF, which broadly fall into two categories: genes related to surfactant protein processing and trafficking and those linked to telomere biology. In addition to genetic links, unique disease phenotypes based on transcriptomic changes have been identified. As we go forward, we anticipate that advances in these genetic and genomic technologies will result in a re-organization of the way we define and classify interstitial lung disease based on molecular characterization. As we evolve from a system of diagnosis based on histopathology to one based on a specific genetic/genomic signature reflecting the fundamental biology of the disease, there will be unique opportunities to develop and test therapies in specific patient populations based on the molecular profiles. Coupled with advances in detection of early disease, the coming decade offers an unprecedented opportunity to dramatically change the lives of patients with idiopathic pulmonary fibrosis.

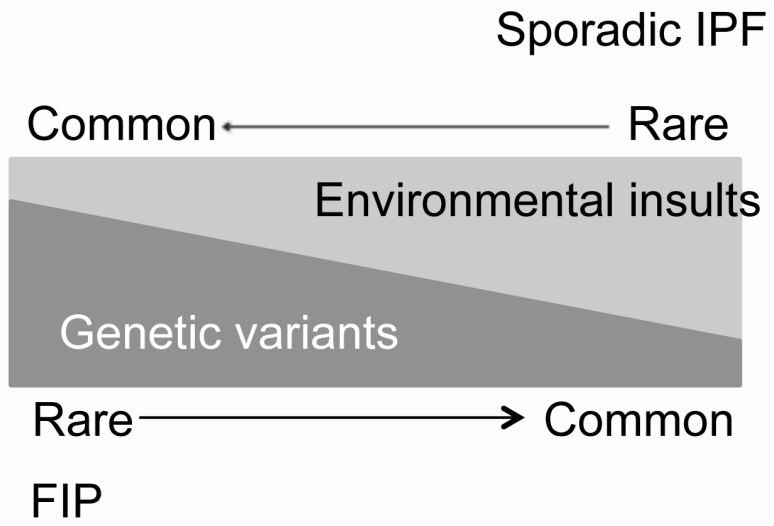

Figure 1.
Proposed model of gene × environment interactions in the pathogenesis of pulmonary fibrosis.

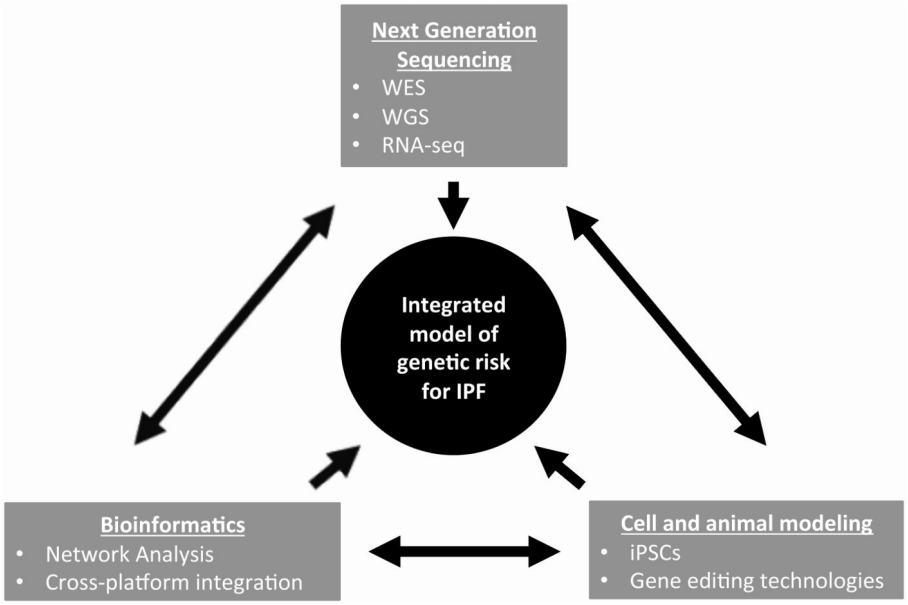

Figure 2. Paradigm to develop an integrated model of genetic risk for IPF

Future studies identifying and characterizing the role of genetic variants in IPF will require integration of next-generation sequencing technologies, bioinformatics, and use of state-of-the-art molecular biology in cell and animal models. Identification of variants by whole exome sequencing (WES) or whole-genome-sequencing (WGS) will require strategic bioinformatics approaches. These genetic variants will require functional validation in cell and animal models; characterizing the effects of these genetic variants on gene expression profiles will require integration of sequencing and bioinformatics technologies.

Table 1

Summary of common genetic variants linked to IPF

Locus	Gene	SNP	IPF Risk	IPF Survival	Reference
2q14	*IL1RN*	rs408392 rs419598 rs2637988	Y Y Y		[31-33]
3q26	*hTR*	rs6793295	Y		[40]
4q13	*IL8*	rs4073 rs2227307	Y Y		[34]
4q22	*FAM13A*	rs2609255	Y		[40]
4q35	*TLR3*	rs3775291		Harmful	[35]
5p15	*TERT*	rs2736100	Y		[40, 112]
6p21 6p21	*CDKN1A* *HLA-DRB1*	rs2395655	Y	Harmful Y	[37] [36]
6q24	*DSP*	rs2076295	Y		[40]
7q22	Intergenic	rs47274443	Y		[40]
10q24	*OBFC1*	rs11191865	Y		[40]
11p15	*MUC5B* *MUC2* *TOLLIP* *TOLLIP* *TOLLIP*	rs35705950 rs7934606 rs111521887 rs5743894 rs2743890	Y Y Y Y Y	Protective Protective	[38-43, 50] [40] [41] [41] [41]
13q34	*ATP11A*	rs1278769	Y		[40]
14q21	*MDGA2*	rs7144383	Y		[41]
15q14-15	Intergenic	rs2034650	Y		[40]
17q13	*TP53* *TP53*	rs12951053 rs12602273	N N	Harmful Harmful	[37]
17q21 17q21	*MAPT* *SPPL2C*	rs1981997 rs17690703	Y Y		[40] [41]
19q13 19q13	*DPP9* *TGFB1*	rs12610495 rs1800470	Y N	Harmful	[40] [29, 30]

Table 2

Rare genetic variants linked to FIP

Gene	Reported % of FIP	Reference
TERT	8-15%	[20, 21]
RTEL1	5%	[28]
hTR	<1%	[20, 21]
DKC1	<1%	[23, 24]
TINF2	<1%	[25-27]
SFTPC	2-25%	[13-16, 86, 87]
SFTPA2	<1%	[17]
ABCA3	<1%	[18, 19]
Unknown	75-85%	