Integrating Genomics Into Management of Fibrotic Interstitial Lung Disease

Ayodeji Adegunsoye, MD; Rekha Vij, MD; and Imre Noth, MD

Fibrotic interstitial lung diseases (ILDs) have a high mortality rate with an unpredictable disease course and clinical features that frequently overlap. Recent data indicate important roles for genomics in the mechanisms underlying susceptibility and progression of pulmonary fibrosis. The impact of these genomic markers on pharmacotherapy and their contribution to outcomes is increasingly recognized. Interstitial lung abnormalities, frequently considered representative of early ILD, have been consistently associated with the *MUC5B* promoter polymorphism, a common gene variant. Other rare gene variant mutations, including *TERT*, *TERC*, *SFTPC*, and *DKC1*, may be present in patients with familial interstitial pneumonia and are frequently associated with a usual interstitial pneumonia pattern of fibrosis. The minor allele of the *MUC5B* rs35705950 genotype is prevalent in several sporadic forms of ILD, including idiopathic pulmonary fibrosis and chronic hypersensitivity pneumonitis. Gene mutations that characterize familial pulmonary fibrosis may be present in patients with connective tissue disease-related ILD, such as rheumatoid arthritis-ILD. Additionally, shorter telomere lengths and mutations in telomere biology-related genes have been demonstrated in both familial and sporadic ILD, with significant implications for disease progression, lung function, and survival. An improved understanding of the impact of genetic and genomic risk factors on disease progression would better guide personalized therapeutic choices in persons with fibrotic ILD.

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The fibrotic interstitial lung diseases (ILDs) are a diverse group of pulmonary disorders characterized by parenchymal inflammation, scarring, and limitation in the gas exchange capacity of the lungs.¹ These pulmonary diseases have a high mortality rate with an unpredictable disease course and clinical features that frequently overlap.¹

The field of genomics in ILD has made tremendous progress in the last decade. An increasing body of evidence now points to important roles for genomics in the mechanisms underlying its development. Recent data indicate that common genetic variants and short telomere lengths account for a large fraction of the risk for developing

ABBREVIATIONS: CHP = chronic hypersensitivity pneumonitis; FIP = familial interstitial pneumonia; FPF = familial pulmonary fibrosis; GWAS = genome-wide association study; HLA = human leukocyte antigen; ILA = interstitial lung abnormality; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; NAC = N-acetylcysteine; PBMC = peripheral blood mononuclear cell; RA = rheumatoid arthritis; SNP = single nucleotide polymorphism; TNF = tumor necrosis factor; UIP = usual interstitial pneumonia; WES = whole exome sequencing

AFFILIATIONS: From the Section of Pulmonary & Critical Care (Drs Adegunsoye and Vij), Department of Medicine; The University of

Chicago, Chicago, IL; and the Division of Pulmonary & Critical Care & Sleep Medicine (Dr Noth), Department of Medicine, University of Virginia, Charlottesville, VA.

CORRESPONDENCE TO: Ayodeji Adegunsoye, MD, 5841 South Maryland, MC 6076, Chicago, IL 60637; e-mail: deji@uchicago.edu

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sporadic or familial ILD. Additionally, rare genetic variants are associated with ILD susceptibility. Bioinformatics research investigating the prognostic value of these genomic markers across diverse ILD phenotypes and their potential role in clinical decision-making continues to elucidate the approach to ILD management. The potential for these genomic markers to influence pharmacotherapy and their contribution to outcomes is increasingly recognized. This review discusses state-of-the-art contributions of genetics and genomics to our understanding of the pathogenesis of ILD over the past 5 years.

Genetic Variants in Interstitial Lung Abnormalities

Interstitial lung abnormalities (ILAs) are specific patterns of radiologic abnormalities identified on chest CT scans.^{2,3} These high attenuation areas on chest CT scan are associated with cigarette smoking, reduced lung function, and worsened survival.^{4,5} Because ILAs and ILDs share similar measures of spirometric restriction, diminished exercise capacity, and increased mortality, ILAs are frequently considered representative of early ILD.^{4,5} The minor allele of the *rs35705950* single nucleotide polymorphism (SNP) in the *MUC5B* gene promoter region has been consistently associated with risk for ILD in the general population.^{3,6,7}

In a large cohort study of participants enrolled in the Age Gene/Environment Susceptibility (AGES)-Reykjavik study and subjects within the Genetic Epidemiology of COPD (COPDGene) study, Putman et al⁸ found a consistent association of the *MUC5B* promoter polymorphism with defined radiologic ILA patterns, and minimal heterogeneity in this association among specific overlapping ILA subtypes. Their findings consolidated previous reports³ linking the *MUC5B* genotype to increased risk for ILAs, even in populations with low allelic frequency such as black subjects.⁸ Unlike idiopathic pulmonary fibrosis (IPF), their study suggested that *MUC5B* had no independent prognostic value in ILAs.⁸ Ash et al.⁹ evaluated 6,827 participants enrolled in the Genetic Epidemiology of COPD (COPDGene) study with mortality data available. They found that in non-Hispanic whites, the presence of each copy of the *MUCB* SNP conferred a 0.64% absolute increase in the percentage of objectively identified lung parenchymal interstitial changes.⁹ Similarly, Araki et al¹⁰ assessed 1,867 participants with serial chest CT scans available from the Framingham Heart Study and found that ILA progression was associated with increasing

copies of the *MUC5B* promoter polymorphism. These studies highlight the association between *MUC5B* and objectively identified interstitial changes and suggest that these radiographic changes may indicate early ILD.

Genetic Variants in Familial ILD

A family history of ILD is present in up to 20% of patients with IPF.¹¹ The diagnosis of an idiopathic ILD in two or more first-degree relatives constitutes the syndrome of familial interstitial pneumonia (FIP). Unlike sporadic ILD, the practical utility of genetic data is more evident in patients with FIP. Genetic testing in FIP may reveal information critical to diagnosis of other distinct etiologies for ILD. These include multisystem genetic disorders such as Hermansky-Pudlak syndrome and short telomere syndromes.

Gene mutations are frequently studied in a group of genetically related individuals referred to as kindred. About 15% of familial kindreds with ILD have rare coding mutations in *TERT*, a gene locus that encodes the protein component of telomerase (Table 1).¹²⁻³³ These individuals demonstrate autosomal dominant transmission with incomplete penetrance.¹²⁻¹⁴ Other rare gene mutations less frequently found but carrying large effect include *TERC*,^{15,34} which encodes the human telomerase RNA component; *SFTPC*^{15,34} and *SFTPA2*^{15,34} encoding surfactant proteins; and *DKC1*, which encodes dyskerin.^{15,33} Stuart et al¹⁴ recently studied 99 unrelated patients with familial pulmonary fibrosis (FPF) of unknown genetic cause. Using whole exome sequencing (WES) of genomic DNA samples, they identified new gene variants in 78 European probands with ILD in comparison with 2,816 European control subjects. Gene burden analysis of this cohort implicated an exoribonuclease, *PARN*, with five new heterozygous mutations shared by all affected relatives ($P = 1.3 \times 10^{-8}$).¹⁴ Damaging and missense variants were also present in the gene encoding *RTEL1*, an established locus for dyskeratosis congenita, at significantly greater frequencies than in control subjects ($P = 1.6 \times 10^{-6}$).¹⁴

Cogan et al³⁵ performed WES of genomic DNA from 25 kindreds enrolled in an ongoing FIP registry. They confirmed the presence of candidate rare variants and performed additional sequencing of affected individuals among a separate group of 163 kindreds. Similar to Stuart et al,¹⁴ their study identified a potentially damaging rare variant in *RTEL1*, and showed that 4.7% of FIP kindreds had heterozygous rare variants of *RTEL1* that segregated with the presence of clinical FIP.

TABLE 1] Gene Function of Common and Rare Gene Variants Associated With Fibrotic Interstitial Lung Disease

Common Gene Variants (Risk Allele)	Chromosome	Gene Function	Phenotype	References
<i>MUC5B</i> (rs35705950) ^a	11p15.5	Affects airway mucus properties, mucociliary transport, and airway defense	IPF, CHP, RA-ILD	3,6,7,15-17
<i>TOLLIP</i> (rs111521887, rs5743894, rs2743890)	11p15.5, 1q32.2	Regulates TLR-mediated immune responses, and TGF- β signaling pathway	IPF	15,18-21
<i>IL1RN</i> (rs408392, rs419598)	2q14.1	Inhibits proinflammatory effect of IL-1 α and IL-1 β	IPF	15,22
<i>IL8</i> (rs4073, rs2227307)	4q13	Proinflammatory cytokine	IPF	15,22
<i>FAM13A</i> (rs2609255) ^a	4q22	Affects signal transduction	IPF	15,19,21,22
<i>TLR3</i> (rs3775291)	4q35	Influences recognition of pathogens and activation of innate immunity	IPF	15,22
<i>TERT</i> (rs2736100)	5p15.33	Telomerase complex enzyme that maintains telomere length	IPF, CPFE	15,22-24
<i>HLA-DRB1</i> (rs2395655)	6p21.2	Major histocompatibility complex, critical to immune system	IPF, CHP, CTD-ILD	22,25-27
<i>DSP</i> (rs2076295) ^a	6p24	Cell adhesion, integrity, and mechanotransduction	IPF	15,19,21,22,28
<i>OBFC1</i> (rs11191865) ^a	10q25.1	Stimulates DNA polymerase- α -primase activity	IPF	15,19,21,22
<i>MUC2</i> (rs7934606)	11p15.5	Mucin production	IPF	15,22
<i>ATP11A</i> (1278769) ⁺	13q34	Phospholipid translocation	IPF	15,19,21,22
<i>MDGA2</i> (rs7144383)	14q21	Cell-cell interaction	IPF	15,22
<i>MAPT</i> (rs1981997)	17q21.3	Promotes microtubule assembly and stability	IPF	15,22
<i>SPPL2C</i> (rs17690703)	17q21.3	Protein cleavage	IPF	15,22
<i>DPP9</i> (rs12610495) ^a	19p13.3	Cell adhesion, integrity, and mechanotransduction	IPF	15,19,21,22,28
<i>TGFB1</i> (rs1800470)	19q13.2	Controls proliferation and differentiation of diverse cell types	IPF	15,22
<i>TP53</i> (rs12951053, rs12602273)	17p13	Production of tumor suppressor protein p53	IPF	22,29

(Continued)

TABLE 1] (Continued)

Common Gene Variants (Risk Allele)	Chromosome	Gene Function	Phenotype	References
<i>CDKN1A</i> (<i>rs2395655</i>)	6p21.2	Critical in cell cycle and response to DNA damage	IPF	22,29
<i>IVD</i> (<i>rs2034650</i>)	15q15	Production of isovaleryl-CoA dehydrogenase mitochondrial matrix enzyme	IPF	22,30
<i>LRRC34</i> (<i>rs6793295</i>)	3q26.2	Production of leucine-rich repeat protein for pluripotent stem cells	IPF	22,30
<i>AKAP13</i> (<i>rs62025270</i>)	15q25	Regulates activation of profibrotic signaling pathways	IPF	22,31
Rare Gene Variants (Risk Allele)	Chromosome	Gene Function	Phenotype	References
<i>SFTPC</i> ^b	8p21.3	Protein C component of surfactant fluid	IPF, CPFE	15,22,24,29
<i>SFTPA2</i> ^c	10q22.3	Pulmonary surfactant-associated protein A2 affects immunomodulation	IPF	15,22,29
<i>ABCA3</i> ^c	16p13.3	Lipid transport across plasma membrane	IPF, CPFE	15,22,24,29
<i>TERT</i> ^c	5p15.33	Telomerase complex reverse transcriptase enzyme	IPF, IPAF, CHP, CTD-ILD, PPFE, NSIP, DIP, CPFE	15,22-24,29,32
<i>TERC</i> ^c	3q26.2	Maintenance of telomerase RNA complex template	IPF, CHP, CTD-ILD, PPFE, CPFE	15,22,24,32
<i>DKC1</i> ^c	Xq28	Telomerase complex template stabilization	IPF	15,22,29,33
<i>TINF2</i> ^c	14q12	Maintenance of telomeres	IPF	15,22,29
<i>RTEL1</i> ^c	20q13.33	DNA helicase activity	IPF, IPAF, CHP, PPFE	15,22,23,29,32
<i>PARN</i> ^c	16p13.12	Stability of mRNA	IPF, IPAF, CHP	15,22,23,32

Gene data obtained from U.S. National Library of Medicine (<https://ghr.nlm.nih.gov/gene/> and <https://www.ncbi.nlm.nih.gov/genome/gdv/>). CHP = chronic hypersensitivity pneumonitis; CPFE = combined pulmonary fibrosis and emphysema; CTD-ILD = connective tissue disease-associated interstitial lung disease; DIP = desquamative interstitial pneumonia; IPAF = interstitial pneumonia with autoimmune features; coA = coenzyme A; IPF = idiopathic pulmonary fibrosis; mRNA = messenger RNA; NSIP = nonspecific interstitial pneumonia; PPFE = pleuroparenchymal fibroelastosis; RA-ILD = rheumatoid arthritis-associated interstitial lung disease; TGF- β = transforming growth factor- β ; TLR = toll-like receptor.

^aMinor allele frequency > 5%.

^bMinor allele frequency 2% to 25%.

^cMinor allele frequency < 1%.

Figure 1 – A-F, Clinical features frequently observed in patients with short telomeres. A, Early onset gray hair. B, Hepatic Doppler ultrasonographic image depicting enlarged caliber of portal vein in noncirrhotic portal hypertension. C, High-resolution hematoxylin and eosin stain depicting squamous cell carcinoma of the tonsil. D, Coronal image of MRI depicting splenomegaly in noncirrhotic portal hypertension. E, CD34 immunostain histologic image of bone marrow aspirate depicting occasional mast cells and plasma cells in a patient with aplastic anemia. F, Chest high-resolution CT axial image depicting usual interstitial pneumonia in a patient with pulmonary fibrosis. Digital enhancements applied to representative images for emphasis on clinical features.

Evaluation of peripheral blood mononuclear cells (PBMCs) from probands and unaffected carriers of the identified rare variants demonstrated telomere lengths that were below the 10th percentile for age, suggesting impaired function of *RTEL1*.³⁵ Mechanistically, *RTEL1* functions as a DNA helicase responsible for unwinding the T-loop structure of telomeres at chromosomal ends.³⁶ Therefore, impaired *RTEL1* function results in release of circular telomeric DNA fragments (T circles) and progressively shortened telomeres as successive rounds of DNA replication ensue.³⁵ The loss of *RTEL1*

function also leads to genomic instability and global genome replication defects.^{37,38} Ultimately, these observations imply that alteration of *RTEL1* function or expression leads to disrupted cell cycle progression.

The usual interstitial pneumonia (UIP) pattern on chest CT scans and environmental risk factors that often characterize FPF are also frequently observed in patients with rheumatoid arthritis (RA)-ILD,³⁹⁻⁴¹ where pulmonary involvement is the leading cause of mortality.⁴² Similarities in the UIP pattern, male

Figure 2 – Recommendations for diagnostic genetic testing for familial interstitial pneumonia-associated genetic variants. IIP = idiopathic interstitial pneumonia; PBMC = peripheral blood mononuclear cell. *Rare genetic variants exist in a small fraction of patients with telomere length greater than the 10th percentile. (Adapted with permission from Kropski et al.⁴⁵)

preponderance, greater prevalence in cigarette smokers, and poor survival shared by both conditions suggest that FPF-linked genes may constitute common genetic risk factors in both disease states.^{41,42} Juge et al⁴³ performed WES of nine FPF-linked genes in 101 well-phenotyped cases of RA-ILD in comparison with 1,010 control subjects without known autoimmune, inflammatory, or pulmonary disease. In those with telomere-maintenance candidate gene mutations within their RA-ILD cohort, they measured telomere lengths and assessed excess-risk mutations using a classical burden test.⁴³ Their study showed that 12% of patients with RA-ILD had heterozygous mutations in the coding regions for *TERT*, *RTEL1*, *PARN*, or *SFTPC* gene loci.⁴³ These mutations were present in excess among patients with RA-ILD when compared with healthy control subjects (OR, 3.17; $P = 9.45 \times 10^{-4}$), suggesting the contribution of these FPF-linked genes to RA-ILD susceptibility.⁴³

Except for *DKC1* which is X-linked, and *ABCA3* which is autosomal recessive, the heritability of these nine FPF-linked rare genetic variants is autosomal dominant with

a single (heterozygous) mutation present in affected individuals.^{15,44,45} Although no clear guidelines exist for pursuing genetic testing in FIP or incorporating test results into patient care, we and others recommend updating the family history for patients with IPF at every visit because a diagnosis of idiopathic interstitial pneumonia subsequently occurs in up to 10% of bloodline relatives.⁴⁵ A family history of neonatal respiratory distress, childhood ILD, aplastic anemia, cryptogenic cirrhosis, or premature graying before 25 years of age could be indicative of short telomeres (Figs 1 and 2).^{45,46} Because a positive genetic diagnosis may carry prognostic value, promote risk stratification in lung transplant candidates,⁴⁷ and aid in risk estimation for close relatives, genetic testing may be of benefit in patients with FIP and a high likelihood of positive genetic diagnosis (Fig 3).⁴⁵

Genetic Variants in Sporadic ILD

Patients with fibrotic ILD without a known family history are deemed to have sporadic pulmonary

Figure 3 – Conceptual model of recurrent inflammation/injury/repair at the bronchoalveolar junction in pulmonary fibrosis depicting gene variant and cells affected from alteration of gene function.

fibrosis.⁴⁸ Despite recent reports identifying common SNPs and rare missense variants associated with ILD,⁴⁸ there are no large multicenter studies that assess the clinical value of screening for rare ILD-linked genetic variants in patients with sporadic pulmonary fibrosis. Although rare variants have a much lower frequency than common variants and account for a comparatively smaller proportion of overall disease risk, they tend to be highly penetrant and have a greater effect size.¹⁵ Conversely, common variants (gene variants with a minor allele frequency of > 5%) appear to contribute to a larger proportion of disease risk in patients with pulmonary fibrosis but generally have a smaller effect size than rare variants.¹⁵ A notable exception is the *MUC5B* SNP, a common variant with a large effect size, that may account for up to 35% of risk for developing IPF.⁴⁹ Unlike rare gene variants, several genetic association studies performed to date indicate that the contribution of common genetic variants to disease risk in sporadic pulmonary fibrosis is similar to that in patients with FPF.^{19,20,45}

IPF

The genetic basis of IPF is incompletely understood, and the relationship between mutations, intrinsic pulmonary microinjury, and ecogenetic factors remains unclear.⁵⁰

Common variants such as loci adjacent to *MUC5B* explain a significant fraction of disease risk.^{30,51} Two landmark genome-wide association studies (GWASs) evaluating subjects with IPF in conjunction with control subjects were published in 2013.^{19,21} Both studies confirmed the known roles of *MUC5B* in disease susceptibility. In addition to the known association of *TERT* with IPF, the GWAS by Fingerlin et al²¹ identified novel gene loci including *DSP*, *FAM13A*, *OBFC1*, *ATP11A*, *DPP9*, among several others. Although the GWAS by Noth et al¹⁹ did not find an association in *TERT* or *TERC*, they identified the association of *TOLLIP* and *SPPL2C* with IPF susceptibility, and linked the *TOLLIP* gene to mortality in IPF (Table 2).^{3,6-9,14,16-19,21,23,26,27,30-33,35,43,52-54} To further understand the genetic architecture of pulmonary fibrosis and similarities between familial and sporadic IPF, Petrovski et al²³ conducted a case-control collapsing analysis using WES in 262 unrelated patients with pulmonary fibrosis (IPF = 81.3%) and 4,141 control subjects of European ancestry. Across 18,668 protein-coding genes evaluated, they found that qualifying variants in *TERT*, *RTEL1*, and *PARN* were significantly enriched in case subjects within their cohort ($P < 4.5 \times 10^{-7}$). Subgroup analysis of sporadic IPF case subjects identified *TERT*, *RTEL1*, and *PARN* as significant

TABLE 2] Recent Studies Evaluating the Association of Fibrotic Interstitial Lung Disease With Common and Rare Gene Variants

Study	Year	FLD/Abnormality Included	Study Type	Top Gene Polymorphisms	Results
Borie et al ⁷	2013	IPF, SSc-ILD	Targeted genotyping of <i>MUC5B</i>	<i>MUC5B</i>	<i>MUC5B</i> T allele associated with IPF risk but not with SSc-ILD
Hunninghake et al ³	2013	ILA	Targeted genotyping of <i>MUC5B</i>	<i>MUC5B</i>	<i>MUC5B</i> promoter polymorphism associated with ILA
Noth et al ¹⁹	2013	IPF	Genome-wide association study and gene-expression profiling	<i>TOLLIP</i> , <i>MDGA2</i> , and <i>SPPL2C</i>	<i>TOLLIP</i> and <i>SPPL2C</i> associated with IPF susceptibility; <i>TOLLIP</i> associated with mortality
Stock et al ⁵²	2013	IPF, SSc-ILD, sarcoidosis	Targeted genotyping of <i>MUC5B</i>	<i>MUC5B</i>	<i>MUC5B</i> associated with IPF but not with lung fibrosis of SSc or sarcoidosis
Fingerlin et al ²¹	2013	IPF, FIP, DIP, RB-ILD, unclassifiable IIP	Genome-wide association study	<i>FAM13A</i> , <i>DSP</i> , <i>OBFC1</i> , <i>ATP11A</i> , <i>DPP9</i> , <i>TERT</i> , and <i>MUC5B</i>	<i>FAM13A</i> , <i>DSP</i> , <i>OBFC1</i> , <i>ATP11A</i> , <i>DPP9</i> , <i>TERT</i> , and <i>MUC5B</i> associated with fibrotic IIP risk
Falfan-Valencia et al ²⁶	2014	CHP	Molecular genotyping with PCR amplifications	<i>HLA-DRB1</i> (1*04:07, 1*04:05, 1*11:01, and 1*13:01)	<i>HLA-DRB1</i> *04 alleles and <i>TNF</i> -238 GG increased in familial HP
Kropski et al ³³	2014	FIP	PCR-based sequencing	<i>NOP10</i> , <i>TINF2</i> , <i>NHP2</i> , and <i>DKC1</i>	<i>DKC1</i> variant identified as a genetic cause of FIP
Cogan et al ³⁵	2015	FIP	Whole exome and Sanger sequencing of genomic DNA	<i>RTEL1</i>	<i>RTEL1</i> associated with very short telomeres in FIP
Horimasu et al ⁶	2015	IPF	Targeted genotyping of <i>MUC5B</i>	<i>MUC5B</i>	Association between <i>MUC5B</i> T allele and IPF in Japanese subjects
Oldham et al ¹⁸	2015	IPF	Targeted genotyping of <i>TOLLIP</i> and <i>MUC5B</i> SNPs	<i>TOLLIP</i> , <i>MUC5B</i>	NAC associated with risk reduction in patients with <i>TOLLIP</i> (TT) genotype
Peljto et al ³⁰	2015	IPF	Targeted genotyping of 12 SNPs inc. <i>MUC5B</i> and IVD	<i>MUC5B</i> , <i>IVD</i>	<i>MUC5B</i> & <i>IVD</i> SNPs associated with IPF in Mexicans, <i>IVD</i> associated with PF in Koreans
Stuart et al ¹⁴	2015	FPF	Exome sequencing of familial PF kindreds	<i>PARN</i> , <i>RTEL1</i>	<i>PARN</i> and <i>RTEL1</i> mutation carriers had shortened leukocyte telomere lengths
Fingerlin et al ²⁷	2016	IIP	Genome-wide association study and RNA sequencing	<i>HLA DRB1</i> *15:01, <i>HLA DQB1</i> *06:02	Novel locus in the HLA region of chromosome 6 associated with FIP
Newton et al ³²	2016	IPF, CHP	Whole exome sequencing and analysis of genomic DNA	<i>TERT</i> , <i>TERC</i> , <i>RTEL1</i> , <i>PARN</i>	Earlier ILD in subjects with <i>TERC</i> mutations than in those with <i>PARN</i>
Allen et al ³¹	2017	IPF	Genome-wide association study	<i>AKAP13</i> , <i>MUC5B</i> , <i>DSP</i>	<i>AKAP13</i> expressed in alveoli, lymphoid follicles, and associated with IPF susceptibility
Ash et al ⁹	2017	ILA	Targeted genotyping of <i>MUC5B</i>	<i>MUC5B</i>	Increased copies of <i>MUC5B</i> minor allele associated with CT interstitial changes
Johnson et al ⁵³	2017	AIM-ILD	Targeted genotyping of <i>MUC5B</i>	<i>MUC5B</i>	<i>MUC5B</i> polymorphism was not associated with myositis-ILD risk

(Continued)

TABLE 2] (Continued)

Study	Year	FLD/Abnormality Included	Study Type	Top Gene Polymorphisms	Results
Juge et al ⁴³	2017	RA-ILD, FPF	Whole exome sequencing and burden test of FPF-linked genes	<i>TERT</i> , <i>RTEL1</i> , <i>PARN</i> , and <i>SFTPC</i>	Patients with RA-ILD with a <i>TERT</i> , <i>RTEL1</i> , or <i>PARN</i> mutation had shorter telomeres
Ley et al ¹⁶	2017	CHP	Targeted genotyping of <i>TOLLIP</i> and <i>MUC5B</i> ; TL measurement	<i>TOLLIP</i> , <i>MUC5B</i>	Greater <i>MUC5B</i> MAF in CHP; <i>MUC5B</i> and TL associated with extent of radiographic fibrosis
Petrovski et al ²³	2017	IPF	Whole-exome sequencing with collapsing analysis	<i>TERT</i> , <i>RTEL1</i> , and <i>PARN</i>	<i>TERT</i> , <i>RTEL1</i> , and <i>PARN</i> identified as significant contributors to sporadic IPF
Putman et al ⁸	2017	ILA	<i>MUC5B</i> promoter genotyping and ILA phenotyping	<i>MUC5B</i>	<i>MUC5B</i> associated with specific radiologic ILA subtypes
Dressen et al ⁵⁴	2018	IPF	Whole-genome sequencing and TL measurement	<i>TERT</i> , <i>PARN</i> , <i>TERC</i> , and <i>RTEL1</i>	Enrichment of <i>TERT</i> , <i>PARN</i> , <i>TERC</i> , and <i>RTEL1</i> variants in patients with IPF
Juge et al ¹⁷	2018	RA-ILD	Targeted genotyping of <i>MUC5B</i>	<i>MUC5B</i>	<i>MUC5B</i> polymorphism was associated with RA-ILD risk and UIP imaging pattern

Gene data obtained from U.S. National Library of Medicine (<https://ghr.nlm.nih.gov/gene/> and <https://www.ncbi.nlm.nih.gov/genome/gdv/>). AIM-ILD = autoimmune myositis-associated interstitial lung disease; FIP = familial interstitial pneumonia; FPF = familial pulmonary fibrosis; HP = hypersensitivity pneumonitis; IIP = idiopathic interstitial pneumonia; ILA = interstitial lung abnormalities; MAF = minor allele frequency; NAC = N-acetylcysteine; PCR = polymerase chain reaction; PF = pulmonary fibrosis; RB-ILD = respiratory bronchiolitis-associated interstitial lung disease; SNP = single nucleotide polymorphism; SSC-ILD = systemic sclerosis-associated interstitial lung disease; TL = telomere length; UIP = usual interstitial pneumonia. See Table 1 legend for expansion of other abbreviations.

contributors to disease susceptibility in sporadic IPF.²³ A qualifying variant in one of these three genes was more prevalent in cases compared with control subjects (11.3% vs 0.3%, respectively; OR, 47.7; $P = 5.5 \times 10^{-22}$). Their findings lend further credence to the involvement of telomere dysfunction in pathogenesis of sporadic IPF.

In some European populations, about one in five individuals carry the *MUC5B* promoter polymorphism,³ and this increases in certain groups to as high as 42%.⁵⁵ In both sporadic and familial IPF, additional copies of this minor allele increase the risk, up to 8.3-fold and 6.2-fold respectively.⁵⁵ Peljto et al³⁰ recently evaluated two IPF cohorts (Mexican and Korean) for 12 candidate SNPs common in non-Hispanic whites with IPF. They found that the *MUC5B* promoter SNP was a very strong risk factor for IPF in Mexican subjects (OR, 7.36; $P = .0001$) but not in Korean subjects ($P = 0.99$).³⁰ Additionally, the minor allele of the *rs2034650* gene for *IVD*, a mitochondrial matrix enzyme, was associated with IPF in both Mexicans (OR = 0.40; $P = .01$) and Koreans (OR = 0.13; $P = .0008$).³⁰ Their findings suggest that future targeted therapies may also be applicable to Hispanics with IPF given their shared risk profile.

The *MUC5B* gene is located on chromosome 11p15.5, in close proximity to the gene encoding toll-interacting protein (*TOLLIP-rs5743890/rs5743894/rs5743854/rs3750920*), an inhibitory adaptor protein that is important to lung immunity, and which acts downstream from the *TLR* genes.¹⁸ Multiple authors have shown that similar to *MUC5B*, SNPs within *TOLLIP* are associated with IPF susceptibility and survival.¹⁹⁻²¹ Because *MUC5B* and *TOLLIP* are critical to both the pulmonary immunologic response and presence of antioxidants, Oldham et al¹⁸ studied whether the effect of antioxidant therapy and immunosuppressive agents would be modified by polymorphisms in *MUC5B* and *TOLLIP*. Analysis of genotyped SNPs within *TOLLIP* and *MUC5B* in non-Hispanic white subjects with IPF demonstrated significant interaction between N-acetylcysteine (NAC) therapy and *TOLLIP* ($P = .001$). Among patients with IPF who had a TT genotype, NAC therapy was associated with a reduced composite end point risk (hazard ratio, 0.14; $P = .03$).¹⁸ Conversely, there was a nonsignificant increase in the composite end point risk (hazard ratio, 3.23; $P = .10$) among those with IPF and a CC genotype.¹⁸ These findings were replicated in an independent cohort of patients enrolled in the A Study of Interferon Gamma-1b for Idiopathic Pulmonary Fibrosis (INSPIRE) trial.^{18,56} This suggests a genotype-

stratified risk profile in IPF where presence of the *TOLLIP* polymorphism might influence response to NAC therapy.

Allen et al³¹ conducted GWAS to identify genetic variants associated with disease susceptibility in IPF and provide mechanistic insight using gene and protein expression analyses. In their study, patients with IPF recruited from nine different UK centers (n = 602) were matched to control subjects (n = 3,366) obtained from the UK Biobank. Identified genetic variants were analyzed in two independent datasets with patients with IPF (n = 2,158) and control subjects (n = 5,195).³¹ Using large transcriptomic and genomic datasets, and analyses of IPF lung tissue samples, they confirmed previously described associations of IPF with *MUC5B* (OR, 2.89; $P = 1.12 \times 10^{-66}$) and *DSP rs2076295* (desmoplakin; OR, 1.44; $P = 7.81 \times 10^{-28}$).³¹ Additionally, they identified *AKAP13 rs62025270* (encoding A-kinase-anchoring-protein-13; OR, 1.27; $P = 1.32 \times 10^{-9}$) a Rho guanine nucleotide exchange factor critical to profibrotic signaling. Their findings hold promise for potential therapies targeting RhoA pathway inhibitors in IPF.

Chronic Hypersensitivity Pneumonitis

A combination of genetic and environmental factors influences the pathogenesis of chronic hypersensitivity pneumonitis (CHP) in individuals exposed to inhaled environmental antigens.⁵⁷ Although studies assessing genetic susceptibility are scant, and genome studies have failed to completely explain heritability of the disease, multiple gene polymorphisms have recently been associated with disease susceptibility in affected individuals. Previous reports evaluating patients with sporadic CHP have linked disease susceptibility to a gene polymorphism in the tumor necrosis factor (TNF)-alpha-308 promoter, and increased TNF-alpha serum bioactivity (farmer's lung).²⁵

In individuals with sporadic CHP, disease susceptibility has been associated with genes located within the major histocompatibility complex, including *HLA-DR3* alleles (pigeon-breeder's lung), *HLA-DQ3* alleles (Japanese summer-type HP), and *HLA-A*, *HLA-B*, and *HLA-C* loci antigens (farmer's lung disease).²⁶ To explore the role of major histocompatibility complex class II gene polymorphisms and TNF-alpha promoter polymorphisms, Falfan-Valencia et al²⁶ evaluated 19 related Mexican patients with HP in comparison with 25 healthy first-degree relatives and 246 healthy unrelated individuals. Using polymerase chain reaction, they

identified an increase in the frequency of *HLA-DRB1*04:07*, *DRB1*04:05*, *DRB1*11:01*, and *DRB1*13:01* alleles in individuals with HP compared with control subjects ($P < .05$). Although *TNF-308* was not significantly different between cohorts, *TNF-238* GG genotype was found to be more frequent in the HP group compared with control subjects.²⁶ Their study suggests that the pathophysiology of sporadic and familial CHP may be similarly influenced by *HLA* gene polymorphisms.

With increasing interest in understanding the link between heterozygous mutations of telomere-related genes and disease progression in CHP, Newton et al³² analyzed 115 patients with such genetic mutations (*TERT* n = 75, *TERC* n = 7, *RTEL1* n = 14, and *PARN* n = 19). Among the 77 subjects with sufficient data for multidisciplinary diagnosis of ILD, 12% had CHP. They found no significant difference in time to death or lung transplantation for patients across gene mutation groups or across ILD subtype.³² The absence of differential outcomes among the seemingly heterogeneous ILD subtypes in their study may indicate that the prognostic importance of background genetics supersedes that of the currently used ILD diagnostic classification.

More recently, Ley et al¹⁶ sought to determine if genomic risk factors previously associated with IPF susceptibility and progression were also associated with CHP susceptibility and reduced survival. They measured *MUC5B* and *TOLLIP* SNPs with telomere lengths in PBMCs from two independent CHP cohorts (n = 217) and assessed outcomes and other morphologic features in comparison with healthy control subjects.¹⁶ The minor allele frequency for *MUC5B* in both CHP cohorts (24.4% and 32.3%) was greater than in healthy control subjects (10.7%; $P < .0001$), but the minor allele frequency for *TOLLIP* was not different.¹⁶ They also found that the extent of radiographic fibrosis was associated with the *MUC5B* minor alleles (adjusted OR, 1.91; $P = .045$) in the combined cohort, and telomere lengths below the tenth percentile for age were associated with reduced survival ($P = .006$).¹⁶ Their findings suggest a shared pathobiology in the disease processes underlying CHP and IPF.

Connective Tissue Disease-Associated ILD

Multiple studies suggest a complex interaction between genetic and environmental factors in connective tissue disease-associated ILD.⁵⁸ Fingerlin et al²⁷ performed a genome-wide genotype imputation association analyses and targeted gene expression in non-Hispanic whites

with pulmonary fibrosis (1,616 cases and 4,683 control subjects) and replicated their findings in an independent cohort (878 cases and 2,017 control subjects). They identified a novel locus in the human leukocyte antigen (HLA) region of chromosome 6 (rs7887 $P_{\text{meta}} = 3.7 \times 10^{-09}$) and two HLA alleles in high linkage disequilibrium associated with pulmonary fibrosis (*DRB1*15:01*; $P = 1.3 \times 10^{-7}$ and *DQB1*06:02*; $P = 6.1 \times 10^{-8}$).²⁷ These susceptibility genes were similar to loci previously linked to polymyositis-/dermatomyositis-associated ILD.²⁵ Evaluation of this HLA locus with targeted RNA sequencing identified 21 differentially expressed genes, most of which play key roles in immune and inflammatory response regulation.²⁷ In patients with RA-ILD, several IPF-linked mutations are present in coding regions for *TERT*, *RTEL1*, *PARN*, or *SFTPC* gene loci, similar to findings in patients with familial IPF.⁴³ Recently, Juge et al¹⁷ performed *MUC5B* genotyping in 1,234 patients with RA and 5,448 unaffected control subjects and demonstrated a strong association of the *MUC5B* promoter variant with pulmonary fibrosis. Their results underscore the pathobiologic similarity of RA-ILD with a UIP pattern to IPF and herald the potential future utility of *MUC5B* for early ILD detection and prognostication in patients with RA, particularly when preventive or effective therapies can be mandated.¹⁷ Interestingly, in their study, *MUC5B* was not a risk factor for RA-ILD without UIP, suggesting differences in the underlying pathobiology between RA-UIP and RA-ILD without UIP.¹⁷

Telomere Length, Disease Progression, and Survival in Fibrotic ILD

Mutations in *TERT*, *TERC*, *DKC1*, *RTEL1*, *TINF2*, and *PARN* have been associated with short telomeres and ILD.^{32,35,54,59} Presence of two copies of the deleterious mutations in *TERT*, *RTEL1*, or *PARN* occur in individuals with dyskeratosis congenita, a syndrome of multiorgan disease that includes pulmonary fibrosis.³² Although the underlying mechanisms through which telomerase dysfunction contribute to ILD are yet to be fully elucidated, shorter telomere lengths have been demonstrated in both familial and sporadic ILD when compared with control subjects, implicating telomere biology-related genes in susceptibility to pulmonary fibrosis.⁶⁰

Using next-generation sequencing, Cogan et al³⁵ examined PBMC telomeres in 54 subjects with familial ILD across 25 families. They found that telomere lengths from individuals with *RTEL1* mutations were extremely

short (< 10th percentile), similar to PBMC telomere lengths in individuals with known *TERT*, *TERC*, and *DKC1* mutations.³⁵ Although they found short telomeres in about one-third of patients with familial ILD, their study demonstrated the association of rare *RTEL1* gene variants with the development of familial ILD, especially in the subset of patients with short telomeres in PBMCs.³⁵ Snetselaar et al⁶⁰ used a multiplex quantitative polymerase chain reaction approach to measure telomere lengths in 359 patients with sporadic and familial ILD in comparison with 173 healthy control subjects. In their study, all cases of ILD had significantly shorter telomere lengths than control subjects. Among patients with sporadic pulmonary fibrosis, individuals with IPF had the shortest telomere lengths, whereas in the cohort with FPF, telomeres were shortest among those with *TERT* mutations.⁶⁰ Individuals with surfactant protein mutations (*SFTPA2* or *SFTPC*) within the familial ILD subset had telomere lengths similar to patients with sporadic ILD, potentially implicating stress-induced, acquired telomere shortening in the pathogenesis of ILD.⁶⁰

Recently, telomere lengths were evaluated in alveolar cells from fibrotic and nonfibrotic regions of IPF lung tissue using fluorescence in situ hybridization.⁶¹ Measured alveolar telomere lengths in fibrotic lung correlated with PBMC telomere lengths among those with *TERT* mutations and were significantly longer in nonfibrotic regions than in fibrotic regions.⁶¹ Studies of patients with heterogeneous telomere-related gene mutations demonstrate short telomeres (< 10th percentile) and an annual mean reduction in FVC of 300 mL.³² Comparatively, patients in the placebo arms of multiple IPF clinical trials have an average annual FVC decline of 130 to 210 mL. Short telomeres have also been linked to worse transplant-free survival, grade 3 primary graft dysfunction, and faster onset of chronic lung allograft dysfunction in patients with ILD.^{62,63} These results in IPF are similar to those in CHP where short telomeres have been associated with extent of fibrosis, histologic pattern, and increased mortality.¹⁶ These data support telomere function as related to the development and progression of pulmonary fibrosis.

Clinical Implications and Future Directions

The recognition of genomic factors that impact the development and prognosis of pulmonary fibrosis has spurred increasing interest in assessing their clinical implications for individuals at risk. This is further compounded by the heterogeneity present in subclasses of

Figure 4 – Heterogeneity in classification of fibrotic interstitial lung disease depicting overlap in gene variants (red) and clinical phenotypes (black).

ILD, because phenotypic and genomic markers frequently overlap, with differing ILD manifestations observed in persons with identical mutations, highlighting the need for improved understanding of the underlying pathobiologic pathways (Fig 4). Although there are no standardized guidelines that address when to perform genetic testing for patients with ILD,⁵⁰ there is general agreement among experts on the need to individualize genetic testing based on the specific situation.^{15,24,45,55}

Genetic abnormalities should be sought in patients with familial IPF.⁶⁴ Experts recommend that patients with ILD who have a personal or family history of telomere-linked features should undergo genetic testing because these features are frequently present in patients with telomere-linked ILD.^{45,65} These include premature hair graying, aplastic anemia/myelodysplasia, thrombocytopenia, and unexplained portal hypertension (Figs 1, 2).⁴⁵ Importantly, the association of these peripheral blood abnormalities with significant bone marrow pathology and regenerative hepatic changes could potentially influence the choice of planned immunosuppressive therapy in transplant candidates with hypocellular bone marrow.

In patients < 50 years of age who lack a family history or telomere-linked features, some ILD centers offer genetic testing if no identifiable cause for sporadic ILD is found.²⁴ Specific gene polymorphisms may be targeted when chorea and hypothyroidism (*NFKX2-1*) or oculocutaneous albinism is present. Rigorous attention to detail should be given to teamwork involving the pulmonologist, geneticist, genetics counselor, patient, and caregivers.^{24,50}

Role of Genetics in Early Detection of ILD and Prognostication

Genetic information may hold potential value in selected at-risk populations and for early detection of IPF; however, it is yet to be adopted for routine use in the clinical setting. Although common polymorphisms such as *MUC5B* and *TOLLIP* are promising prognostic indicators,^{18,52} there are no genetics-themed clinical trials demonstrating a beneficial effect on patient survival.

Carefully phenotyped subjects with a high risk for progression of fibrosis should be enrolled in longitudinal follow-up studies to determine relevant

physiologic and genetic traits predictive of disease progression.^{55,66} With increasing GWAS identification of novel risk variants, deeper understanding of associated comorbid disorders predictive of ILD progression is needed.⁵⁵ Likewise, the contribution of identified genetic risk variants to known epidemiologic risk factors such as race and ethnicity needs further elucidation.^{55,67,68} Because multiple biologic pathways carry prognostic value in pulmonary fibrosis, the complex relationship among risk genes, microbiome diversity, host defense pathways, and the link to disease progression deserve further study.^{28,69}

Immunosuppressive and Antifibrotic Therapies

The paucity of validated biomarkers and an inability to predict disease progression at baseline evaluation has limited the identification of novel therapies in ILD.⁷⁰ Identifying distinct genetic pathways that confer treatment benefit would improve precision in choosing therapies for individual patients.^{15,18,45} With widespread use of immunosuppressive therapies in non-IPF ILDs,^{1,71} and as antifibrotic therapy use for IPF gains traction,²⁸ differing responses to therapy among patients with ILD have become increasingly evident. Although pirfenidone demonstrates treatment benefit regardless of telomere length,⁵⁴ it is suggested that this beneficial effect may be more pronounced in the rapidly progressive form of IPF.⁷² Besides the recent pharmacogenomics influence of *TOLLIP* polymorphisms on IPF treatment response,¹⁸ recent reports indicate a high rate of adverse reactions with use of immunosuppressive therapy in the postlung transplant population with rare *TERT* and *TERC* variants.^{47,73,74} Therefore, the safety and efficacy of these therapies among patients with short telomeres and known genetic risk variants should be systematically assessed in elegantly conducted large controlled studies.

Conclusions

The growing body of evidence, which shows that genetic polymorphisms impact pulmonary fibrosis risk and meaningful clinical outcomes, necessitates the incorporation of genetic data into clinical trial design. An improved understanding of the impact of genetic and genomic risk factors on disease progression would better guide personalized therapeutic choices in persons with fibrotic ILD. Accounting for these genetic variations when evaluating therapeutic response in prospective studies will be vital to precision medicine in the management of ILD.

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