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Pulmonary Fibrosis Predisposition Overview

Christine Kim Garcia, MD, PhD[1] and Janet L Talbert, MS, CGC, LGC[2]

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Summary

The goals of this overview on pulmonary fibrosis predisposition are the following.

Goal 1

Briefly describe the clinical characteristics of pulmonary fibrosis.

Goal 2

Review genetic causes of pulmonary fibrosis.

Goal 3

Review the differential diagnosis of pulmonary fibrosis.

Goal 4

Provide an evaluation strategy to identify the genetic cause of pulmonary fibrosis in a proband.

Goal 5

Inform genetic counseling of family members of an individual with a genetic predisposition to pulmonary fibrosis.

Goal 6

Review management of pulmonary fibrosis.

Author Affiliations: 1 Columbia University Medical Center, New York, New York; Email: ckg2116@cumc.columbia.edu. 2 Vanderbilt University Medical Center, Nashville, Tennessee; Email: janet.talbert@vumc.org.

1. Clinical Characteristics of Pulmonary Fibrosis

Clinical Features of Pulmonary Fibrosis

Individuals with pulmonary fibrosis typically present with shortness of breath with exertion and a dry cough. Disease onset during adulthood is most common, but onset can range over multiple decades. Most individuals with pulmonary fibrosis have had a history of smoking or fibrogenic environmental exposures [Borie et al 2016, Newton et al 2016, Salisbury et al 2020]. The prevalence of fibrotic lung disease increases with age.

Dry rales are identified on pulmonary auscultation. Hypoxemia with exertion is usually one of the earliest signs. With disease progression, hypoxemia occurs at rest. Symptoms worsen over time as lung scarring progresses. Later findings include finger clubbing, signs of pulmonary hypertension, and sequelae of right heart failure.

Degradation of pulmonary function occurs over time, with progressive decline of forced vital capacity and diffusion capacity. Most individuals die of respiratory causes. Transplant-free survival appears to be lower for individuals with *TERC* or *TERT* pathogenic variants than for those without identifiable pathogenic variants in these two genes [Borie et al 2016].

Radiographic Features of Pulmonary Fibrosis

The distribution and extent of specific radiographic features of pulmonary fibrosis can vary, but generally pulmonary fibrosis is characterized by reticulations, traction bronchiectasis, and honeycombing. Individual interstitial lung diseases are associated with different radiographic patterns and features. Radiographic patterns of lung involvement in individuals with certain pathogenic variants may be atypical (see Table 1).

2. Genetic Causes of Pulmonary Fibrosis

Suggestive Features of a Genetic Cause of Pulmonary Fibrosis

The presence of a genetic cause of predisposition to pulmonary fibrosis can be suggested by family history or by clinical features of a known genetic cause of pulmonary fibrosis (see Table 1 and Table 2).

Family history. Familial pulmonary fibrosis (FPF) describes the occurrence of fibrotic interstitial lung disease (ILD) in at least two related family members. The specific ILD diagnosis may vary in affected individuals from the same family [Lee et al 2012, Newton et al 2016]. Individuals with FPF may be clinically diagnosed with any of the following disorders:

- Idiopathic pulmonary fibrosis (~50% of individuals with FPF) [Borie et al 2016, Newton et al 2016]
- Chronic hypersensitivity pneumonitis (~10% of individuals with FPF) [Okamoto et al 2013, Borie et al 2016, Newton et al 2016]
- Progressive pulmonary fibrosis [Newton et al 2016]
- Idiopathic interstitial pneumonia (IIP) (e.g., unclassifiable IIP, nonspecific interstitial pneumonia, pleuroparenchymal fibroelastosis, among others) [Reddy et al 2012, Borie et al 2016, Newton et al 2016, Nunes et al 2017]
- Connective tissue disease-associated ILD, including rheumatoid arthritis ILD and scleroderma ILD [Juge et al 2017]
- Drug-induced ILD [Borie et al 2016]
- Pulmonary fibrosis and adenocarcinoma of the lung
- Combined pulmonary fibrosis and emphysema [Nunes et al 2014, Stanley et al 2015, Stanley et al 2016]

Adenocarcinoma of the lung. Individuals with familial pulmonary fibrosis are at a threefold greater risk of developing adenocarcinoma of the lung compared to the general population [Yoon et al 2018]. A variant of non-

small cell lung cancer previously described as bronchoalveolar cancer, arising from the alveolar acinar epithelial with a lepidic growth pattern in the presence or absence of minimally invasive disease, suggests an *SFTPA1* or *SFTPA2* pathogenic variant [Wang et al 2009, van Moorsel et al 2015, Nathan et al 2016].

Clinical features of a short telomere syndrome (e.g., dyskeratosis congenita) include skin reticular pigmentation, nail dystrophy, oral mucosal leukoplakia, premature graying of hair (age <30 years), thrombocytopenia, macrocytosis, aplastic anemia, bone marrow failure, immunodeficiency, myelodysplasia, acute leukemia, elevated liver enzymes, liver cirrhosis, gastrointestinal disease, radiation sensitivity, and infertility [Newton et al 2016]. Hepatopulmonary syndrome and the development of pulmonary fibrosis after liver transplantation have been reported in individuals with short telomere syndrome [Gorgy et al 2015]. Features of short telomere syndrome are more common in individuals with pathogenic variants in *DKC1*, *TINF2*, and *TERC* than *TERT*, *RTEL1*, or *PARN*.

Prognosis for Those with a Predisposition to Pulmonary Fibrosis

Median survival for those with *TERT*- or *TERC*-related pulmonary fibrosis was 3.7 years in a European cohort; this was shorter than the life expectancy of the entire cohort of individuals with a suspected genetic cause of pulmonary fibrosis (6.3 years) [Borie et al 2016]. Median life expectancy for a United States cohort with pulmonary fibrosis due to pathogenic variants in *TERT, TERC, RTEL1,* and *PARN* was 2.9 years.

Influence of Environmental Exposures

Cigarette smoking and exposures to inhaled agents are frequently reported by individuals with an identified genetic predisposition to pulmonary fibrosis, suggesting that the combination of genetic predisposition and environmental exposures are particularly injurious [Diaz de Leon et al 2010, Borie et al 2016, Newton et al 2016, Salisbury et al 2020].

Pulmonary Fibrosis – Associated Genes and Syndromes

See Table 1 and Table 2.

Table 1. Predisposition to Pulmonary Fibrosis: Genes and Distinguishing Clinical Features

	Gene [1]	% of all FPF	MOI	Age of Onset of Pulmonary Fibrosis	Distinguishing Features
Genes associated w/ telomere maintenance [2]	*DKC1*	~1% [3]	XL [4]	Adult	Short telomere syndrome features
	NAF1	~1% [5, 6]	AD	Adult	Combined PF & emphysema; short telomere syndrome features
	PARN	4%-5% [5, 7]	AD AR	Mean: 64 yrs	
	RTEL1	4%-9% [5, 8]	AD	Mean: 60 yrs	
	TERC	2%-5% [9]	AD	Mean: 51 yrs	Short telomere syndrome features
	TERT	15%-20% [5, 10, 11]	AD	>40 yrs (mean: 58 yrs; PF in >60% of those age >60 yrs)	Some persons have combined PF & emphysema
	TINF2	~1% [12]	AD	Adult	Short telomere syndrome features
	ZCCHC8	<1%	AD	Adult	± bone marrow failure

Table 1. continued from previous page.

	Gene [1]	% of all FPF	MOI	Age of Onset of Pulmonary Fibrosis	Distinguishing Features
Genes associated w/ surfactant metabolism	*ABCA3*	<1% [13]	AR	Rare in adults, more common in childhood-onset PF	Lung radiographs show ground glass opacities, reticulations, & cysts of variable size, predominantly involving upper lobes
	SFTPA1	<1% [14, 15]	AD	Adult	Lung adenocarcinoma
	SFTPA2	<1% [14, 16]	AD	Adult	Lung adenocarcinoma
	SFTPC	1%-5% [14, 17]	AD	Infancy to late adulthood	Wide array of radiographic abnormalities, incl combined PF & emphysema, & atypical upper lobe involvement [18]

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; PF = pulmonary fibrosis

1. Genes are listed alphabetically.

2. Persons w/predisposition to PF associated with a gene involved in telomere maintenance may have additional features within the spectrum of telomere biology disorders (of which classic dyskeratosis congenita is the most severe phenotype; see Table 2).

3. Alder et al [2013], Kropski et al [2014]

4. Heterozygous females can be variably affected [Alder et al 2013].

5. Loss-of-function variants in *NAF1, PARN, RTEL1,* and *TERT* are typically pathogenic.

6. Stanley et al [2016]

7. OMIM 616371; rarely associated with AR inheritance [Zhang et al 2019]

8. OMIM 616373

9. OMIM 614743

10. OMIM 614742

11. Individuals with germline pathogenic variants in genes associated with short telomere syndrome, especially those older than age 60 years, may acquire somatic *TERT* promoter pathogenic variants in circulating leukocytes [Maryoung et al 2017, Gutierrez-Rodrigues et al 2019].

12. Alder et al [2015]

13. OMIM 610921; Campo et al [2014], Epaud et al [2014]

14. Pathogenic variants in the surfactant metabolism genes (*SFTPA1*, *SFTPA2*, *SFTPC*) are typically missense variants that lead to increased endoplasmic reticulum stress.

15. Nathan et al [2016]

16. OMIM 178642

17. OMIM 610913

18. Mechri et al [2010], van Moorsel et al [2010]

Table 2. Syndromes in which Pulmonary Fibrosis is a Common Feature: Genes and Distinguishing Clinical Features

Gene(s)	Disorder	MOI	Pulmonary Phenotype	Other Clinical & Laboratory Features
ACD *CTC1* *DKC1* *NAF1* *NHP2* *NOP10* *PARN* *RTEL1* *STN1* *TERC* *TERT* *TINF2* *WRAP53* *ZCCHC8*	Dyskeratosis congenita and related telomere biology disorders (DC/TBD)	XL AR AD	PF may be a presenting sign or may develop over time. Note: Some genes assoc w/DC may cause PF w/o other features of DC (see Table 1).	Variable: skin reticular pigmentation, nail dystrophy, oral mucosal leukoplakia, premature graying of hair, bone marrow failure, myelodysplastic syndrome, acute myelogenous leukemia, liver cirrhosis, immunodeficiency, gastrointestinal disease, radiation sensitivity, infertility, shortened telomere length

Table 2. continued from previous page.

Gene(s)	Disorder	MOI	Pulmonary Phenotype	Other Clinical & Laboratory Features
AP3B1 *HPS1* *HPS4* [1]	Hermansky-Pudlak syndrome (HPS)	AR	Onset of PF is typically in 4th decade & fatal w/in 10 yrs; PF is most common in *HPS1*-related HPS.	Tyrosinase-positive oculocutaneous albinism; bleeding diathesis resulting from a platelet storage pool deficiency
FAM111B	Hereditary fibrosing poikiloderma w/tendon contractures, myopathy, & pulmonary fibrosis	AD	± adult-onset progressive PF, can be life threatening	Early-onset poikiloderma, hypotrichosis, hypohidrosis, mild lymphedema, multiple contractures, myopathy, scoliosis, exocrine pancreatic insufficiency, liver impairment, hematologic abnormalities

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; PF = pulmonary fibrosis; XL = X-linked
1. To date, convincing evidence of pulmonary fibrosis has not been reported in affected individuals with pathogenic variants in other HPS-related genes.

3. Differential Diagnosis of Pulmonary Fibrosis

Acquired (non-genetic) causes of pulmonary fibrosis

- Fibrogenic environmental exposures, including smoking, radiation, asbestosis, inhaled metal and fine inorganic particulates, coal, bird antigens and droppings, certain organic dusts
- Inflammation, such as arising from respiratory infections
- Associated with other medical conditions (sarcoidosis, rheumatoid arthritis, scleroderma, dermatomyositis, connective tissue disorders, immunodeficiency, and others)
- Medications, especially chemotherapy and antiarrhythmia medications

Other **genetic disorders** that exhibit diffuse parenchymal lung disease as a clinical feature are summarized in Table 3.

Table 3. Inherited Disorders that Exhibit Diffuse Parenchymal Lung Disease as a Clinical Feature

Gene(s)	Disorder	MOI	Pulmonary Phenotype	Other Clinical & Laboratory Features
CFTR	Cystic fibrosis	AR	Progressive obstructive lung disease, bronchiectasis, recurrent pulmonary infections, PF, respiratory failure	Pancreatic insufficiency, malnutrition, recurrent sinusitis & bronchitis, male infertility, meconium ileus
COPA	Autoimmune interstitial lung, joint, & kidney disease (OMIM 616414)	AD	Affects children & young adults; lymphocytic lung infiltrates	High-titer autoantibodies, inflammatory arthritis, kidney disease
GBA1 (*GBA*)	Gaucher disease type 1	AR	<5% w/interstitial lung involvement characterized by infiltration of Gaucher cells	Childhood presentation of hepatosplenomegaly, pancytopenia, & bone disease
NF1	Neurofibromatosis 1	AD	± adult-onset parenchymal lung disease (bullae ± interstitial fibrosis) often in assoc w/pulmonary hypertension	Multiple café au lait macules, axillary & inguinal freckling, cutaneous neurofibromas, Lisch nodules, plexiform neurofibromas, ID
NKX2-1	Brain-lung-thyroid syndrome (See *NKX2-1*-Related Disorders.)	AD	Infant respiratory distress is common w/recurrent pulmonary infections, chronic ILD, respiratory failure	Choreoathetosis & congenital hypothyroidism
RNF168	RIDDLE syndrome (OMIM 611943)	AR	Radiation sensitivity, PF	Immunodeficiency, ID, dysmorphic features, short stature

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Pulmonary Phenotype	Other Clinical & Laboratory Features
SMPD1	Niemann-Pick disease type B (See Acid Sphingomyelinase Deficiency.)	AR	Most affected persons develop widespread ILD, recurrent lung infections, respiratory failure	Hepatosplenomegaly w/progressive hypersplenism & stable liver dysfunction; atherogenic lipid profile
TMEM173	STING-associated vasculopathy (OMIM 615934)	AD	Infantile or childhood-onset ILD	Autoinflammatory vasculopathy, severe ulcerative skin lesions (face, ears, nose, digits), arthritis, autoantibodies, immune complex deposition

AD = autosomal dominant; AR = autosomal recessive; ID = intellectual disability; ILD = interstitial lung disease; MOI = mode of inheritance; PF = pulmonary fibrosis

4. Evaluation Strategies to Identify the Genetic Cause of Pulmonary Fibrosis in a Proband

Establishing a specific genetic cause of pulmonary fibrosis:

- Can aid in discussions of prognosis (which are beyond the scope of this *GeneReview*) and genetic counseling;
- Usually involves a medical history, physical examination, family history, pulmonary function testing, imaging, lung biopsy, and molecular genetic testing.

Medical history

- **Age of onset.** Onset of pulmonary fibrosis in childhood or adults younger than age 30 years suggests an *SFTPC* or *ABCA3* pathogenic variant (a surfactant metabolism disorder).
- **Evaluate for features of a short telomere syndrome** (e.g., dyskeratosis congenita; see Table 2), including premature graying of hair (often diffuse and before age 30 years), oral cancer, bone marrow failure, myelodysplasia, acute leukemia, aplastic anemia, leukopenia, macrocytosis, thrombocytopenia, avascular necrosis/osteoporosis, liver cirrhosis, elevated liver enzymes, immunodeficiency, radiation sensitivity, and infertility.

Physical examination. Physical features of a **short telomere syndrome** (e.g., dyskeratosis congenita; see Table 2) include dermal reticular pigmentation, nail dystrophy, oral mucosal leukoplakia, and premature graying of the hair.

Family history. A three-generation family history should be taken, with attention to relatives with features of pulmonary fibrosis, age of onset, clinical features of a short telomere syndrome, evidence of anticipation suggestive of a short telomere syndrome (see Related Genetic Counseling Issues, **Anticipation**), evidence of X-linked inheritance (*DKC1* should be considered if all affected individuals are males younger than age 50 years), and documentation of relevant findings through direct examination or review of medical records, including results of molecular genetic testing.

Laboratory features. Shortened telomere length is seen in blood leukocytes measured by flow cytometry with fluorescent in situ hybridization (flow FISH).

Note: (1) Telomere length measurement should be offered to individuals with pulmonary fibrosis and extrapulmonary manifestations of a short telomere syndrome (e.g., dyskeratosis congenita; see Table 2). (2) This testing may be useful to help establish a diagnosis in individuals with inconclusive results on molecular genetic testing.

- If the age-adjusted neutrophil or lymphocyte telomere length is <10th percentile, molecular genetic testing of genes associated with a short telomere syndrome should be considered (see Table 2) [Diaz de Leon et al 2010, Snetselaar et al 2015].
- If the age-adjusted neutrophil or lymphocyte telomere length is >10th percentile, panels that include surfactant metabolism genes (*SFTPC*, *SFTPA1*, *SFTPA2)* or other genetic syndromes (see Table 1 and Table 2) should be considered.
- Note: Shortened telomeres can be inherited independently of the associated pathogenic variant and result in a clinical phenocopy of the short telomere syndrome in offspring who do not inherit the associated pathogenic variant [Alder et al 2011] (see Related Genetic Counseling Issues).

Molecular genetic testing. A multigene panel is recommended [Borie et al 2017, Kropski et al 2017]. Sequence analysis should be performed first. If no pathogenic variant is found, deletion/duplication analysis can be considered, although large deletions/duplications have not been reported.

- *SFTPC* and *ABCA3* should be included if disease onset is before age 30 years or if there is a wide range in age among affected individuals in the family.
- Panels that include genes associated with a short telomere syndrome (e.g., dyskeratosis congenita; see Table 2) should be included when clinical and/or laboratory features of a short telomere syndrome are present.
- Panels should include *SFTPA1* and *SFTPA2* if there is a personal or family history of adenocarcinoma of the lung, especially non-small cell lung cancer (previously described as bronchoalveolar cancer), arising from the alveolar acinar epithelial with a lepidic growth pattern in the presence or absence of minimally invasive disease.
- Additional gene panels should be considered if there is overlap with clinical features associated with related disorders (see Table 3).

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

5. Genetic Risk Assessment

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Almost all germline pathogenic variants known to be associated with predisposition to pulmonary fibrosis (see Table 1) are associated with autosomal dominant inheritance. Less commonly, predisposition to pulmonary fibrosis is inherited in an autosomal recessive manner (*ABCA3*-related pulmonary fibrosis) or an X-linked manner (*DKC1*-related pulmonary fibrosis).

Genetic counseling for pulmonary fibrosis associated with a pathogenic variant(s) in a gene involved in telomere maintenance (see Table 1) may be complicated by factors such as anticipation and clinical phenocopies (see Related Genetic Counseling Issues); it is recommended that individuals and their families undergo genetic counseling with a healthcare provider who has experience with monogenic short telomere syndromes.

Note: Individuals with germline pathogenic variants in genes associated with short telomere syndrome, especially those older than age 60 years, may acquire somatic *TERT* promoter pathogenic variants in circulating

leukocytes [Maryoung et al 2017, Gutierrez-Rodrigues et al 2019]. Somatic *TERT* promoter pathogenic variants are not transmitted to offspring.

Syndromic pulmonary fibrosis. If a proband has syndromic pulmonary fibrosis (e.g., dyskeratosis congenita or features suggestive of a syndrome listed in Table 2), genetic counseling for the specific syndrome is appropriate.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Some individuals diagnosed with predisposition to pulmonary fibrosis inherited a pathogenic variant from an affected parent. Because some genetic causes of pulmonary fibrosis can be associated with anticipation, an affected parent may have a later age of onset than the proband.
- Alternatively, a proband with predisposition to pulmonary fibrosis may have a *de novo* pathogenic variant. The overall proportion of individuals with predisposition to pulmonary fibrosis caused by a *de novo* pathogenic variant is unknown.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for both parents to ascertain their genetic status and to allow reliable recurrence risk counseling. (Note: Because individuals with predisposition to pulmonary fibrosis are often diagnosed late in the adult years, parental genetic testing is not feasible in many families.)
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with predisposition to pulmonary fibrosis may appear to be negative because of failure to recognize the disorder in affected family members (due to lack of appropriate radiographic imaging) and/or reduced, age-related penetrance (i.e., late onset of the disease in the affected parent or early death of the parent before onset of symptoms). Therefore, an apparently negative family history cannot be confirmed without appropriate clinical evaluation (including radiographic imaging) of the parents and/or molecular genetic testing (to establish that neither parent is heterozygous for the pathogenic variant identified in the proband).

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected or is known to have a pulmonary fibrosis-related pathogenic variant, the risk to the sibs of inheriting the pulmonary fibrosis-related pathogenic variant is 50%. Because predisposition to pulmonary fibrosis is associated with reduced penetrance and intrafamilial clinical variability, the age of onset and clinical manifestations in a sib who inherits a familial pathogenic variant cannot be predicted.
- In families segregating a pathogenic variant in a gene associated with telomere maintenance (see Table 1), sibs of a proband are at risk of inheriting the familial pathogenic variant and are at risk for epigenetic inheritance of shortened telomere length. The inheritance of shortened telomere length (with or without the familial pathogenic variant) can result in manifestations of a short telomere syndrome (including pulmonary fibrosis) (see Related Genetic Counseling Issues).

- If the proband has a known pulmonary fibrosis pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

Offspring of a proband. Each child of an individual with a germline pathogenic variant associated with predisposition to pulmonary fibrosis has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on their biological relationship with the proband and the genetic status of the proband's parents.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one *ABCA3* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for one *ABCA3* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *ABCA3* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with *ABCA3*-related nonsyndromic pulmonary fibrosis are obligate heterozygotes (carriers) for a pathogenic variant in *ABCA3*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *ABCA3* pathogenic variant.

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the *ABCA3* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management of Pulmonary Fibrosis, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment

Genetic counseling for short telomere syndrome. It is recommended that individuals with a pathogenic variant(s) in a gene associated with telomere maintenance (see Table 1) and their families undergo genetic counseling with a healthcare provider who has experience with monogenic short telomere syndromes and complicating factors including the following:

- **Epigenetic inheritance.** Shortened telomere length is transmitted from parent to offspring independently of the familial short telomere syndrome-causing pathogenic variant (i.e., the offspring of a heterozygous individual may inherit shortened telomere length but not the pathogenic variant).

- **Clinical phenocopies.** An individual who inherits a shortened telomere length but not the familial pathogenic variant may have manifestations of a short telomere syndrome (i.e., a clinical phenocopy) because of epigenetic inheritance of shortened telomere length [Alder et al 2011]. Consequently, assessment of recurrence risk based on family history (rather than molecular genetic testing and telomere length measurement) is unreliable.
- **Anticipation.** Anticipation (the occurrence of increasing disease severity and decreasing age of onset in successive generations) may be observed in pulmonary fibrosis caused by a pathogenic variant(s) in a gene associated with telomere maintenance (see Table 1). This phenomenon is the result of epigenetic transmission of progressively shorter telomere lengths in conjunction with autosomal dominant transmission of the familial pathogenic variant (i.e., offspring of an affected individual who inherit both the familial pathogenic variant and a shorter telomere length than that in their transmitting parent) [Armanios et al 2005, Armanios 2009, Newton et al 2016, Borie et al 2017].
- **Variant interpretation.** The lack of cosegregation of a familial genetic variant and clinical manifestations (resulting from epigenetic inheritance and phenocopies) raises the possibility that the variant is not pathogenic (see Evaluation Strategies to Identify the Genetic Cause of Pulmonary Fibrosis in a Proband, **Molecular genetic testing**).

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the pulmonary fibrosis-causing pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible. Note: Age of onset, severity of disease, specific symptoms, and rate of disease progression are variable and cannot be accurately predicted by the family history or prenatal molecular genetic testing.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Lung Association**
  55 West Wacker Drive
  Suite 1150
  Chicago IL 60601
  Phone: 1-800-LUNGUSA
  Understanding Pulmonary Fibrosis

- **American Thoracic Society Patient Information Series**
  General Information About Pulmonary Fibrosis
- **MedlinePlus**
  Idiopathic pulmonary fibrosis (IPF)
- **National Heart, Lung, and Blood Institute**
  Idiopathic Pulmonary Fibrosis (IPF)
- **Pulmonary Fibrosis Foundation**
  230 East Ohio Street
  Suite 500
  Chicago IL 60611
  Phone: 844-825-5733 (toll-free)
  Fax: 866-587-9158 (toll-free)
  Email: info@pulmonaryfibrosis.org
  www.pulmonaryfibrosis.org

6. Management of Pulmonary Fibrosis

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a predisposition to pulmonary fibrosis, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) should be considered.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Predisposition to Pulmonary Fibrosis

System/Concern	Evaluation	Comment
Pulmonary fibrosis	• Clinical history & exam for comorbidities • Chest radiograph • HRCT scan of chest • Pulmonary function studies • Eval by pulmonologist, preferably one w/experience in PF	Comorbidities that may affect disease course (e.g., pulmonary hypertension, obstructive sleep apnea, emphysema, GERD, & obesity)
Dyskeratosis congenita [1]	See Dyskeratosis Congenita and Related Telomere Biology Disorders, Evaluations Following Initial Diagnosis.	
Genetic counseling	By genetics professionals [2]	To inform affected persons & families re nature, MOI, & implications of FPF to facilitate medical & personal decision making

FPF = familial pulmonary fibrosis; GERD = gastroesophageal reflux disease; HRCT = high-resolution computed tomography; MOI = mode of inheritance; PF = pulmonary fibrosis

1. Most often associated with pathogenic variants in *TERC* or *TERT*

2. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse.

Treatment

Clinical management of pulmonary fibrosis due to a genetic cause is similar to that for individuals with other causes of fibrotic interstitial lung disease and depends on the subtype of interstitial lung disease. It is recommended that individuals be evaluated by a pulmonologist, preferably one with experience in treating familial pulmonary fibrosis.

Table 5. Treatment of Manifestations in Individuals with Predisposition to Pulmonary Fibrosis

Manifestation/Concern	Treatment	Considerations/Other
Idiopathic PF	Antifibrotic medications [1] (nintedanib, [2] pirfenidone [3])	Monitoring of side effects
Progressive PF	Nintedanib [4]	
Unclassifiable progressive PF	Pirfenidone [5]	
Any progressive PF	Consideration of lung transplantation: • In persons w/primarily lung limitations & few manifestations of other organ failure • Often an option because most persons w/hereditary PF are age <70 yrs	In persons w/short telomere: • Adjustment of immunosuppressive medication may be required to avoid drug toxicities in those w/hematologic abnormalities. [6] • Subclinical bone marrow abnormalities may affect immunosuppression at time of lung transplantation. [7] • Cytomegalovirus-related morbidity after lung transplantation has been reported. [8]
	Oxygen	May improve exercise tolerance & prevent or delay onset of pulmonary hypertension & right heart failure
	Treatment of comorbid conditions	Eval (as clinically indicated) & treatment of pulmonary embolism, lung cancer, pulmonary hypertension, GERD, obstructive sleep apnea
	Pulmonary rehab	May improve exercise tolerance
Short telomere syndrome	See Dyskeratosis Congenita and Related Telomere Biology Disorders, Treatment of Manifestations.	

GERD = gastroesophageal reflux disease; PF = pulmonary fibrosis

1. Treatment with antifibrotic medications (e.g., nintedanib, pirfenidone), was associated with an improved trajectory in lung function (i.e., less forced vital capacity decline) in individuals with short telomere-related pathogenic variants. A European study did not find a difference between the two medications in terms of efficacy [Justet et al 2021]. A US study found that individuals taking pirfenidone had less lung function decline, regardless of the degree of telomere shortening [Dressen et al 2018].

2. Richeldi et al [2014]

3. King et al [2014]

4. Flaherty et al [2019]

5. Maher et al [2020]

6. Silhan et al [2014], Borie et al [2015], Tokman et al [2015]

7. George et al [2015]

8. Popescu et al [2019]

Surveillance

Table 6. Recommended Surveillance for Individuals with Predisposition to Pulmonary Fibrosis

System/Concern	Evaluation	Frequency
Pulmonary fibrosis	• PFTs: spirometry (incl FVC), plethysmography, & DLCO • High-resolution chest CT • Oxygen saturation by pulse oximetry at rest & w/exertion (exercise-related hypoxemia precedes development of hypoxemia at rest) • 6-MWT distance & oxygen saturation measurements	The frequency of surveillance has not been established. It is common to obtain baseline testing at age ~40 yrs. Those w/ features of early disease need frequent follow up (every 3-12 mos) to determine durability & progression of findings. Those w/no evidence of early disease could have less frequent repeat testing. Since early initiation of antifibrotic therapeutics is recommended, surveillance testing at regular intervals is strongly recommended. Repeat PFTs, oxygen desaturation studies, & 6-MWT incur less radiation exposure than repeat chest CTs.
Dyskeratosis congenita	See Dyskeratosis Congenita and Related Telomere Biology Disorders, Surveillance.	

6-MWT = six-minute walk test; DLCO = diffusion capacity of the lung for carbon monoxide; FVC = forced vital capacity; PFT = pulmonary function test

Agents/Circumstances to Avoid

Environmental exposures. Every effort should be made to remove and avoid environmental exposures linked to the development of pulmonary fibrosis. Deleterious environmental exposures include but are not limited to: smoking, metal fumes/dust, wood dust, stone and sand particulates, certain agricultural, farming and livestock exposures, bird feather and droppings, aerosolized molds, as well as certain medications including chemotherapeutics, antiarrhythmia agents, and nitrofurantoin.

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger first-degree relatives of an affected individual in order to identify as early as possible those who would benefit from avoidance of environmental risks and initiation of antifibrotic medications to slow down the rate of progression of disease in those with early findings of lung fibrosis. Evaluations can include the following:

- Molecular genetic testing if a molecular diagnosis has been established in the proband
- If a molecular diagnosis has not been established in the proband but there is a family history of pulmonary fibrosis, the following evaluations are recommended:
  - Baseline high-resolution chest CT and PFTs for all individuals at age 40 years or ten years before the earliest diagnosis in affected family members
  - If any abnormality is discovered in a first-degree relative, it is recommended that testing be repeated to determine the durability and progression of findings. Although the frequency of testing has not been established, it is the author's clinical practice to repeat pulmonary function tests (PFTs), oxygen desaturation studies, or six-minute walk testing (6-MWT) every three to 12 months. Frequency of testing depends on symptoms and trend. Repeat PFTs, oxygen desaturation studies, and 6-MWT incur less radiation exposure than repeat chest CTs (see Table 6).
  - Telomere length testing can be considered, especially if there is a personal or family history to suggest a short telomere syndrome.

Environmental exposures. Development and progression of interstitial lung abnormalities in family members have been associated with environmental exposures. Progression of radiographic abnormalities occurred in most individuals who had detectable early radiographic abnormalities [Salisbury et al 2020].

Every effort should be made to remove and avoid environmental exposures linked to the development of pulmonary fibrosis. Deleterious environmental exposures include but are not limited to: smoking, metal fumes/dust, wood dust, stone and sand particulates, certain agricultural, farming and livestock exposures, bird feather and droppings, aerosolized molds, as well as certain medications including chemotherapeutics, antiarrhythmia agents, and nitrofurantoin.

Note: It is recommended that individuals with a pathogenic variant(s) in a gene associated with telomere maintenance (see Table 1) and their families undergo genetic counseling with a healthcare provider who has experience with monogenic short telomere syndromes and related complications (see Related Genetic Counseling Issues).

Therapies under Investigation

Many therapies are under investigation for the treatment of pulmonary fibrosis. Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Chapter Notes

Author Notes

Dr Garcia is the Frode-Jensen Professor of Medicine at Columbia University Irving Medical Center, as well as the Chief of the Division of Pulmonary, Allergy, and Critical Care Medicine, and the Acting Director of the Interstitial Lung Disease Program. She obtained her MD and PhD degrees, as well as completed residency in Internal Medicine and fellowship in Pulmonary and Critical Care Medicine, at the University of Texas Southwestern Medical Center in Dallas. Her laboratory has discovered rare pathogenic variants in several genes (*TERT, TERC, SFTPA2, PARN, RTEL1*) in patients with familial pulmonary fibrosis. These discoveries have linked the telomere and surfactant pathways to adult-onset fibrotic interstitial lung diseases. She and her colleagues have shown that leukocyte telomere length is a biomarker that predicts clinical outcomes for patients, including survival, rate of progression, and response to immunosuppressive medications. Dr Garcia holds appointments in the Department of Medicine, the Institute for Genomic Medicine, and the Center for Precision Medicine and Genomics.

Janet Talbert earned her Master of Science (MS) in Biophysics and Genetics at the University of Colorado Medical Campus. She became a Diplomate of the American Board of Genetic Counselors (ABGC) in 2009. She is a member of the National Society of Genetic Counselors (NSGC) and the American Board of Genetic Counselors (ABGC). She worked in the Interstitial Lung Disease Program at National Jewish Health from 2003 to 2020 in roles that included oversight of a national familial pulmonary fibrosis genetic study that lead to discovery of several SNPs associated with IPF/FPF, providing genetic counseling services for the institution at large and to patients and families with FPF, genetic services manager (molecular laboratory report writing, provider-to-provider genetic services, and genetic test development) and a genetic advisor to the institution. She was the director of the Familial Pulmonary Fibrosis Genetic Counseling telephone line at National Jewish Health from 2008 to 2020. She serves on the Medical Advisory Board of the Pulmonary Fibrosis Foundation (PFF) and is part of an education outreach Ambassador Program for the PFF. From 2014 to 2015 she worked as faculty at the University of Colorado in the Hereditary Cancer clinic and from 2015 to 2020 at InformedDNA as a Senior Genetic Counselor performing genetic counseling via telehealth to patients nationwide with personal or family histories of cancer, inherited retinal disease, neurologic disorders, and FPF. As of 2021 she is an Associate Faculty member in Pediatrics, Division of Medical Genetics and Genomic Medicine, Vanderbilt University and Vanderbilt University Medical Center.

Author History

Christine Kim Garcia, MD, PhD (2021-present)
David Schwartz, MD; National Jewish Health (2005-2021)
Janet Talbert, MS, CGC (2010-present)
Anastasia Wise, PhD; National Jewish Health (2005-2010)

Revision History

- 12 May 2022 (aa) Revision: edited information on DC/TBD in Table 2
- 11 February 2021 (sw) Comprehensive update posted live; scope changed to overview
- 19 March 2015 (me) Comprehensive update posted live
- 19 October 2010 (me) Comprehensive update posted live
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