



HAL
open science

Impact of genetic factors on fibrosing interstitial lung diseases. Incidence and clinical presentation in adults

Raphael Borie, Caroline Kannengiesser, Clairelyne Dupin, Marie-Pierre Debray, Aurélie Cazes, Bruno Crestani

► To cite this version:

Raphael Borie, Caroline Kannengiesser, Clairelyne Dupin, Marie-Pierre Debray, Aurélie Cazes, et al.. Impact of genetic factors on fibrosing interstitial lung diseases. Incidence and clinical presentation in adults. La Presse Médicale, 2020, 49, pp.104024 -. 10.1016/j.lpm.2020.104024 . hal-03490716

HAL Id: hal-03490716

<https://hal.science/hal-03490716>

Submitted on 22 Aug 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Impact of genetic factors on fibrosing interstitial lung diseases Incidence and clinical presentation in adults

Raphael Borie¹, Caroline Kannengiesser², Clairelyne Dupin¹, Marie-Pierre Debray³, Aurélie Cazes⁴, Bruno Crestani¹

1. Service de Pneumologie A, Centre de Référence des Maladies Pulmonaires Rares; DHU FIRE, Hôpital Bichat, APHP and INSERM, Unité 1152; and Université Paris Diderot, Paris, France
2. Laboratoire de Génétique, APHP, Hôpital Bichat; and Université Paris Diderot, Paris, France and INSERM, Unité 1152; and Université Paris Diderot, Paris, France
3. Service de Radiologie, Hôpital Bichat, APHP, Paris, France and INSERM, Unité 1152
4. Service d'Anatomopathologie, Hôpital Bichat, APHP and INSERM, Unité 1152; and Université Paris Diderot, Paris, France

Corresponding author:

Raphael Borie, Service de pneumologie A, hôpital Bichat, 46 rue Henri Huchard, 75877

Paris CEDEX 18, France

Phone: +33 1 40 25 68 00

Fax: + 33 1 40 25 88 18

Mail: raphael.borie@aphp.fr

Abstract

At least 10% of patients with pulmonary fibrosis, whether idiopathic or secondary, present heritable pulmonary fibrosis suspected on familial aggregation of pulmonary fibrosis, specific syndromes or early age of diagnosis. Approximately 30% of those patients have an identified mutation mostly in telomere related genes (TRG) more rarely in surfactant homeostasis or other genes.

TRG mutation may be associated with hematological and hepatic diseases that may worsen after lung transplantation requiring a specific care and adapted immunosuppression. Surfactant genes mutations are usually associated with ground glass opacities and cysts on CT scan and may improve with steroids, hydroxychloroquine or azithromycin. Moreover relatives should benefit from a genetic analysis associated with a clinical evaluation according to the gene involved.

Genetics of pulmonary fibrosis raise specific problems from diagnosis, therapy or genetic counseling varying from one gene to another.

1 Introduction

Genetic predisposition to interstitial lung disease (ILD) in adults was first suggested by a 10-fold increase in prevalence of the disease in families of patients with a diagnosis of idiopathic pulmonary fibrosis (IPF) (1,2). Genetic studies of familial forms of ILD led to the discovery initially of mutations in surfactant homeostasis (*SFTPC*, *ABCA3*, *NFKX2.1*) then in telomeres related genes (TRG: *TERT*, *TERC*, *RTEL1*, *PARN*, *DKC1*, *TINF2*, *NAF1*) and more recently associated with complex syndromes (*COPA*, *TMEM173*, *HPS1 to 8*, *FAM111B*). Mutation associated with alveolar proteinosis such as *MARS* or *GATA2*, although sometimes associated with fibrosing ILD won't be discussed herein (Table 1 and Figure 1) (3–9).

While international recommendation for clinical practice are needed, we describe herein how genetic analysis can be added to the ILD diagnosis.

2. General characteristics of familial pulmonary fibrosis (FPF)

2.1 Epidemiology and risk factors

The prevalence of IPF is estimated at 1/5000 people (10), whereas the prevalence of ILD in a first-degree relative of a patient with IPF is ≈10% which indicates a familial linkage (1,11,12). The pedigree features an autosomal-dominant transmission in 80% of cases, with cases occurring in several successive generations (vertical transmission) without known consanguinity (2,13). In a case–control Mexican study, family history of pulmonary fibrosis was a risk factor for IPF (odds ratio [OR] = 6.1 [95% CI 2.3–15.9])(12). The risk of death with pulmonary fibrosis is increased 4.7-fold in first-degree relatives (14). Also, the risk of developing secondary ILD such as hypersensitivity pneumonitis (HP) is increased in the same family: in a Japanese series of 114 patients with chronic HP, 17.5% had a family history of pulmonary fibrosis (15).

In ILD families, the presence of ILD is more frequent in men, smokers and older adults (mean age 68) in one study (13).

2.2 Radiographic and pathological pattern and evolution

Two retrospective series reported discordant prevalence of chest CT pattern in FPF (13,16). While a series of 289 FPF patients reported a prevalent unclassifiable radiological pattern (50%), followed by usual interstitial pneumonia (UIP)(22%), nonspecific interstitial pneumonia (NSIP)(12%) and organizing pneumonia (1%), another series of 309 patients showed a prevalent pattern of UIP (80%), followed by unclassifiable (12%) and NSIP (6%) (13,16).

Different pathological patterns may be observed in FPF, although UIP is the most frequent (25-50% of cases) (16,17). A pattern of NSIP, fibroelastosis, organizing pneumonia or HP may be observed. However, in a series of 30 cases re-evaluated by 3 pathologists, the histology pattern was unclassifiable in 17 (16,17).

In most series, the evolution of FPF was comparable to that of sporadic IPF forms and the causes of death were similar to those observed with sporadic IPF forms (18,19). As observed in sporadic pulmonary fibrosis a definite radiological or histological UIP pattern is associated with a worst prognosis in FPF (13,17).

2.3 Asymptomatic involvement

Systematic high-resolution chest CT performed in asymptomatic members of families with FPF revealed ILD in 14% to 25% (2,13,20). The most commonly observed anomalies were thickening of septal lines, peribronchovascular thickening, subpleural reticular opacities and ground-glass opacities (2,13,20).

The transbronchial biopsies from 71 asymptomatic relatives of FPF patients presented histological abnormalities in 26 (36.6%) including interstitial fibrosis (n=12,

16.9%), peribronchiolar fibrosis (n=15, 21.1%), chronic inflammation (n=10, 14.1%), respiratory bronchiolitis (n=2, 2.8%) or granulomas (n=6, 8.5%) (2).

2 Rare variants associated with pulmonary fibrosis

2.1 Surfactant protein mutations

2.1.1 Genetic

Surfactant is secreted by type II alveolar epithelial cells. Surfactant is composed of 90% lipids and 10% proteins (surfactant (SP-)A, B, C and D) (21). The corresponding genes are *SFTPA*, *SFTPB*, *SFTPC* and *SFTPD* (21). SP-B and SP-C are transported to the cell membrane in lamellar bodies by the ATP binding cassette family A, member 3 (ABCA3) transporter encoded by *ABCA3* (22).

Homozygous *SFTPB* mutations have been associated with a neonatal respiratory distress syndrome but not with adult ILD (21). *SFTPD* mutations have not been associated with lung disease.

Among surfactant genes, *SFTPC* mutations were the first described in adult familial ILD (23)(24). Transmission is autosomal dominant. Neomutations are frequent and may explain as much as 50% of cases (25). Though *SFTPC* mutations were first linked to pediatric cases of ILD, adult FPF is associated with mutations in this gene. In 2002, Thomas and colleagues described a family in which 11 adults had ILD, 6 with biopsy-confirmed UIP/IPF and five with clinical diagnoses of IPF, as well as 3 pediatric cases of NSIP (26). Subsequently, additional mutations in *SFTPC* have been found in other FPF cohorts (27,28), up to 25% of FPF cases in a Dutch cohort, a much higher proportion than what has been observed elsewhere, and their frequency is usually less than 5% of FPF (29)

SFTPC mutations are rarely found in sporadic IPF cases. In a cohort of 89 patients with UIP, 46 with NSIP, only one coding mutation in *SFTPC* was found (24).

Given the numerous findings of *SFTPC* mutations in FPF cases, investigators soon examined other surfactant proteins in terms of their role in FPF. In 2009, Wang and colleagues analyzed a large family with 15 affected subjects with FPF and/or lung adenocarcinoma with bronchoalveolar cell carcinoma features (30). Genetic sequencing of surfactant proteins found a heterozygous mutation in *SFTPA2*. Additional 58 families were studied, and one different *SFTPA2* mutation was found. *In vitro* study of these mutations suggests that the resultant protein becomes retained in the ER and causes ER stress (30,31). More recently Nathan and colleagues analyzed 12 families affected by IPF and lung cancer. They identified, in one family, 9 members carrying heterozygous missense mutation of *SFTPA1* located in the carbohydrate recognition domain that impairs SP-A1 secretion (32).

Biallelic *ABCA3* mutations were first reported in children with ILD and are associated with adult ILD in cases of biallelic missense and nonsense mutations (33–35). Although homozygous *ABCA3* mutations are usually associated with respiratory failure in newborn (35), one teenage ILD patient with UIP pattern and one 41 year-old patient with combined pulmonary fibrosis and emphysema, carriers of mutations of *ABCA3*, have been reported (36)(37).

Thyroid transcription factor 1 (TTF1), a transcription factor encoded by *NKX2-1*, expressed in the lung, thyroid and central nervous system, is implicated in surfactant genes transcription (22)(38). Heterozygous mutations are classically associated with the triad of ILD, hypothyroidism, and neurologic anomalies (hypotonia, delayed development, chorea) (39). These mutations may be associated with ILD without hypothyroidism and neurologic anomalies in up to 1/3 of cases, including adult cases (39).

2.1.2 Clinical presentation

Biallelic *ABCA3* mutations and heterozygous *SFTPC* mutations in adults may have a similar clinical and radiological presentation (40,41).

The most frequent radiological pattern associates predominant diffuse ground-glass opacities, septal thickening and cysts of variable size with a preferential distribution in the upper lobes and in sub-pleural areas (Figure 3) (41–43). Differentiating emphysema from cysts is sometimes difficult, and *SFTPC* mutation must be evoked in a young patient presenting combined pulmonary fibrosis and emphysema (44). However, at a later stage of disease, honeycombing can predominate.

Histologically, the most frequently described pattern in adults is UIP, but NSIP, organizing pneumonia or desquamative interstitial pneumonia have also been reported. Granulomas have not been reported, but moderate inflammation and centrilobular fibrosis can be observed (41).

The HRCT pattern of ILD associates with *NKX2-1*, *SFTPA1* or *SFTPA2* mutation is atypical for UIP and usually associated predominant diffuse ground-glass opacities and septal thickening (39).

2.1.3 Treatment

In children, successful treatments reported in case reports or short series include methylprednisolone, hydroxychloroquine or azithromycin (9,22,33,45). In a retrospective study of 40 children carriers of *ABCA3* mutation, 10/32 patients (31%) were improved with with steroids, 9/15 (60%) were improved with hydroxychloroquine and 1/3 patients (33%) with azithromycin (46). An international, phase 2a, randomized, double-blind, placebo-controlled, parallel-group, multinational study investigating the initiation or withdrawal of hydroxychloroquine in subjects with chILD is acutally recruiting (NCT02615938).

In any case, no treatment appears to reduce disease in a patient with predominant honeycombing lesions. The effect of antifibrotic drugs, such as pirfenidone or nintedanib, is unknown. The disease does not appear and should not recur after pulmonary transplantation.

2.2 TRG mutations

2.2.1 Genetic mutations and complex inheritance

The telomerase complex catalyzes the addition of repeated DNA sequences in the telomere region, thereby protecting chromosomes against loss of material (47). The activity of the telomerase complex requires the activity of several proteins including telomerase reverse transcriptase (*TERT*), dyskerin (encoded by the *DKC1* gene), telomere binding protein (TIN2, encoded by the *TINF2* gene), interaction with the telomerase repeat binding factor (TERF1) and the telomerase RNA component (TERC, encoded by the *TERC* gene, also known as *TR* or *hTR* abbreviation), a specialized RNA that contains a template for telomere repeat addition [28]. In addition to the telomerase complex, other proteins such as regulator of telomere elongation 1 (RTEL1), poly(A) specific ribonuclease (PARN) and nuclear assembly factor 1 (NAF1), have been implicated in telomere maintenance and pulmonary fibrosis (5,48).

Heterozygous mutations have been detected in familial forms of pulmonary fibrosis involving *TERT* (≈15%), *RTEL1* (5-10%), *PARN* (≈5%) and *TERC* (≈3%). Mutations in *DKC1*, *NAF1*, and *TINF2* are much rarer (Figure 1) (5,8,29,49–55). *TERT* or *TERC* mutations have initially been found in about 1% to 3% of sporadic IPF cases (3,4). However rare variants within *TERT*, *TERC*, *PARN*, *RTEL1* have been reported in 149 (9%) of 1739 IPF patients included in 4 clinical trials (INSPIRE, CAPACITY, ASCEND and RIFF) and 29 (11.3%) of 262 IPF patients evaluated in one center before lung transplantation (56,57). However the

pathogenicity of the variants was for most of them not confirmed, and the IPF populations were selected and younger than usual sporadic IPF population.

None of the TRG is the site of a frequent mutation, and new genetic variants are continually being identified (<http://telomerase.asu.edu/diseases.html#tr>). The penetrance (risk of pulmonary fibrosis developing in a carrier of *TERT* and *TERC* mutations) depends on several factors, including environmental exposure (49,58). The gene–environment interaction reported for carriers of *TERT* or *TERC* mutations may also be implicated for carriers of *RTEL1* mutations (8,59).

When evaluated from blood cells (granulocytes or monocytes), patients with mutations in TRG show shortened telomeres in 80-90% of the cases (49,60). Patients with ILD have shorter telomere than age-matched controls, and patients with IPF have shorter telomere length than patients with other ILD (60). Within patients from FPF, patients with *TERT* mutations have the shorter telomere (60). Telomere length may be measured on circulating leucocytes, Flow-FISH, qPCR and Southern blot are different methods that are used for diagnostic purposes, but all of them require a well-defined control population (61). Telomere length shortens with age and the decrease is accelerated on exposure to toxins (tobacco, pesticides) and with numerous chronic diseases (62). Fifteen percent of the *TERT* mutation carriers presented normal telomere length in one study (49). In another study, almost all pulmonary fibrosis patients, older than 60 years, with *TERT*, *TERC* or *RTEL1* mutations, had a telomere length >1st percentile and half of them had a telomere length >10th percentile (63).

Telomeres shorten from generation to generation in patients with *TERT*, *TERC* or *RTEL1* mutations because of transmission of the short telomeres independent of transmission of the mutation (8,49). This epigenetic-like inheritance in human disorders of telomerase explains the phenomenon of genetic anticipation, defined by an earlier onset of the disease

with each generation (Figure 2) (8,64,65). Because telomere shortening varies depending on the involved gene and its impact on telomere length, genetic anticipation may be more pronounced for carriers of *TERC* than *PARN* mutations (8).

Eventually telomere length could be assessed from lung tissue of ILD patients and particularly from alveolar type 2 cells (AT2). Indeed telomere length is also reduced in AT2 from *TERT* mutation carriers, though telomere length might differ in AT2 from fibrotic or from non-fibrotic region (66).

2.2.2 Pulmonary involvement

Prevalence of ILD in carriers of TRG mutations increases with age (49). In an American cohort of *TERT* mutation carriers, none of the patients younger than 40 years showed ILD, but the prevalence was greater than 60% in those older than 60 (49). Patients with *TERC* mutations may be relatively younger at ILD diagnosis than cases of mutations in other genes (8). In a series of 114 patients with ILD associated with TRG mutation, the ILD was diagnosed at a mean age of 51 years (n=7) for *TERC* mutation carriers, 58 years (n=75) for *TERT* mutation carriers, 60 years (n=14) for *RTEL1* mutation carriers and 65 years (n=19) for *PARN* mutation carriers ($p=0.03$) (8,58). The male/female ratio of patients with ILD varies from 0.5 to 0.7. In one series, men were younger than women (54 vs 63 years) at ILD diagnosis [30]. Smoking and other pneumotoxic exposures are frequently observed in patients with ILD (40-96%) (8,49,58).

A typical UIP pattern on chest CT is observed in 46-74% of cases (Figure 4) (8,49,58). Unusual features found in 13% to 20% of cases includes upper-lung predominance of fibrosis, centrilobular fibrosis, or a pleuro-parenchymal fibroelastosis pattern (8,49,58). In all, 14% to 40% of cases show a combined pulmonary fibrosis and emphysema pattern (67). *TERT* and *NAF1* mutations have been associated with severe chronic obstructive pulmonary

disease and emphysema, particularly in female smokers, with an increased risk of pneumothorax (5,68).

IPF is the most frequent diagnosis in ILD patients with TRG mutation (86% in one cohort, 45-47% in recent cohorts) [9, 30, 38]. Pleuroparenchymal fibroelastosis (up to 10%), chronic HP (7-11%) and unclassifiable fibrosis (19-30%) are also frequent (8,49,58).

A rapid decline of pulmonary function is observed in patients with ILD associated with TRG mutations in IPF clinical trials (130-210 mL/year) (69). Newton and al. recently reported a 300 mL/year decline of FVC whatever the gene involved (*TERC*, *TERT*, *RTEL1* or *PARN*), and the ILD entity (IPF or not) (8).

Pulmonary fibrosis associated with *TERT* mutation is lethal, and most patients die of respiratory causes (8,49,58). The mean survival for symptomatic patients is 2.8 to 5.2 years after diagnosis. However, the evolution can be longer, particularly in asymptomatic patients (70). Transplant-free survival could be lower for carriers of *TERT* or *TERC* mutations than patients with familial ILD without *TERT* or *TERC* mutation (58).

2.2.3 Extra-pulmonary manifestations

Pulmonary fibrosis and extra-pulmonary manifestations associated with TRG mutations are variably called “telomere disease”, “telomeropathy” or “short telomere syndrome”, with lack of a consensual definition.

Mucocutaneous involvement

Dyskeratosis congenita (DKC), was the first telomeropathy associated with TRG mutations (71,72)(73). DKC is classically defined by a triad of mucocutaneous manifestations: reticular skin pigmentation, nail dystrophy and oral mucosal leukoplakia (73). The triad is present in childhood, and bone-marrow failure usually appears in the second decade of life (73). Lung fibrosis is also a feature that may spontaneously appear in DKC, and these

patients show severe pulmonary complications after hematopoietic stem-cell transplantation (74).

In patients with *TERT* mutation and pulmonary fibrosis, the classical triad of DKC is usually absent. However 15% to 40% of mutation carriers present premature hair graying (before the age of 30) (58,75). The same gene mutation can lead to different phenotypes: descendants from patients with pulmonary fibrosis and TRG mutation may present typical DKC (8).

Haematological involvement

TRG mutations have been described in patients with bone-marrow failure, myelodysplasia, or acute leukaemia in the absence of mucocutaneous DKC signs (76–78). In a young patient, the coexistence of pulmonary fibrosis and bone-marrow failure suggests TRG mutation. This is probably not the case in older patients (personal observation and (79)).

In patients with TRG mutations and pulmonary fibrosis, anaemia is present in 17% to 27%, macrocytosis in 24% to 41% and thrombocytopenia in 8% to 54% (8,58). *DKC1*, *TINF2* and *TERC* mutation carriers seem more prone to the development of haematological involvement than *TERT* or *RTEL1* mutation carriers (personal observation and (8)).

Liver involvement

Elevated liver enzyme levels or liver involvement was reported in 5% to 27% of patients with ILD and TRG mutation (8,58). Patients also present liver cirrhosis — cryptogenic, viral or alcoholic. In a series of 10 patients with liver cirrhosis and *TERT* or *TERC* mutations, all were considered to have cirrhosis secondary to hepatitis C, alcohol consumption, Wilson’s disease, nonalcoholic steatohepatitis, or primary biliary cirrhosis (80,81).

The presence of a *TERT* or *TERC* mutation increases the risk of liver cirrhosis in cases of hepatitis C infection and probably with equivalent alcohol consumption (80,81). Patients with the same mutation even in the same family may present normal or elevated liver enzyme levels with variable degrees of necrosis, inflammation, fibrosis and regeneration on liver histology (80).

Gorgy et al. highlighted the high frequency of hepatopulmonary syndrome associated with TRG mutations (82). In a retrospective series of 42 patients with dyspnea and TRG mutation, 9 patients had minimal or absent ILD and a hepatopulmonary syndrome, defined as liver disease with evidence of intrapulmonary vascular dilatation resulting in pulmonary gas exchange abnormalities and hypoxemia. Genetic analysis showed mutations in *TERT* (n=4), *RTEL1* (n=1), or *DKC1* (n=1) but no mutations in 3 patients despite their typical DKC phenotype. Among the 6 patients with available liver biopsies, the most common abnormality was nodular regenerative hyperplasia (n=4/6). The final diagnosis was non-cirrhotic portal hypertension. Two patients underwent liver transplantation, and lung fibrosis developed 18 months and 12 years later (82).

Other manifestations

Other manifestations linked to telomere disease include cellular or humoral immunodeficiency, exudative retinopathies, central neurological involvement with cerebral calcifications, gastrointestinal bleeding, radiation sensitivity, infertility, osteoporosis or renal insufficiency [54]. Indeed whole sequencing was done in a cohort of 92 patients with chronic kidney disease of unknown cause and identified loss-of-function mutations in *PARN* in 2 probands with tubulointerstitial fibrosis (83). Immunodeficiency has been mainly been described in children. However an opportunistic infection with *Pneumocystis jivocii* in a

TERC mutation carrier had been reported and patients with TRG mutations present an increased risk of CMV infection after lung transplantation (84,85).

2.2.4 Treatment

The safety and efficacy of pirfenidone has recently been reported. One European multicentric retrospective study was not able to show an effect of pirfenidone on lung function decline, with a decline of FVC of 161.8 ± 31.2 mL/year before and 235.0 ± 49.7 mL/year after pirfenidone initiation (86). A post-hoc analysis of 2 prospective phase 3 clinical trials (CAPACITY, ASCEND), showed 102 patients with IPF carriers of rare variants within one of the TRG. Those patients had a more rapid decline in predicted FVC than patients without a rare variant (1,66% vs 0,83% per month), and pirfenidone reduced the decline of FVC in this subgroup of severe patients (56). No data have been published concerning nintedanib in those patients.

Additionally, danazol, a synthetic sex hormone with androgenic properties, showed promise for pulmonary fibrosis associated with TRG mutation, with stabilization of diffusing capacity of the lung for CO (DLCO), FVC and CT scan findings during the 2-year treatment in a prospective 2 years study involving 10 patients with “overt” pulmonary fibrosis and 15 patients with “subclinical” pulmonary fibrosis (48). Moreover treatment with danazol was associated with telomere elongation and hematological response in 79% of the cases (19/24). However this drug is poorly tolerated in many patients, with liver adverse effects and increased risk of venous thrombosis. Indeed a phase I/II trial (ANDROTELO, NCT03710356) with danazol in lung fibrosis has been set up in France.

Given the young age of most patients, lung transplantation is often discussed. Three retrospective series reported the outcome of lung transplantation in 26 patients with *TERT* and *TERC* mutations (87–89). Most patients required adjustment of immunosuppression

because of haematologic toxicity. Thrombocytopenia and a need for platelet transfusion were frequent, and myelodysplastic syndrome and/or bone-marrow failure occurred in some patients. Acute kidney failure requiring dialysis support seemed unexpectedly frequent in two series (22-50%) (87,88). Study in post-transplant pulmonary fibrosis patients show that telomere length < 10th percentile before transplant was associated with worse survival and also a shorter time to onset of chronic lung allograft dysfunction (90). Comparison of the <10th percentile telomere length group with the >10th percentile group showed a higher rate of primary graft dysfunction, but there were no differences in the incidence of acute rejection, cytopenias, infection, or renal dysfunction (90).

2.3 Other Genetic Diseases that Can Cause fibrosing ILD

2.3.1 Hermansky-Pudlak Syndrome

Hermansky-Pudlak Syndrome (HPS) refers to a group of heterogeneous autosomal recessive disorders. To date, eight different subtypes have been described associated with different genetic abnormalities. HPS is diagnosed clinically in patients with oculocutaneous albinism, clotting dysfunction secondary to defective platelets, and, in some subtypes that affect Type II AECs, ILD. It is thought that genetic mutations in HPS lead to abnormal protein trafficking with associated lysosome-related organelles (91). HPS is the most commonly encountered genetic disease in Puerto Rico, with 1/1800 individuals in regions of Puerto Rico affected (92).

HPS-1 is the most common subtype of this disease, accounting for approximately 50% of HPS cases outside the Puerto Rican population. Over 20 disease-causing mutations have been reported in HPS1 (93). Among HPS subtypes, ILD and pulmonary fibrosis occur in HPS-1 and HPS-4.

In most individuals with HPS-1 and HPS-4 who survive to adulthood, ILD can be found, with many patients having severe progressive pulmonary fibrosis resulting in respiratory failure (94,95). Patients who present with lung fibrosis have a mean age of onset of symptoms of 35 and an average age of death related to respiratory failure of 37—therefore, these patients experience rapidly progressive disease (95).

Clinical presentations for HPS-1- and HPS-4-related pulmonary fibrosis have much in common with what can be seen with some IIPs. Lung biopsy in HPS can reveal a pathologic pattern similar to UIP, but can also show hyperplastic AECs filled with phospholipid-rich droplets and enlarged lamellar bodies, pointing to possible defects in the secretory pathway (96). Compared to HPS-1, HPS-4 is much less common, but lung manifestations occur in the same pattern as noted in HPS-1 (97). Two small trials evaluated the effect of pirfenidone vs placebo in these patients and contradictory results were reported. One report with 35 patients did not find a difference between the two groups. The other with 21 patients reported a slowing of lung function decline in treated patients(98,98)

2.3.2 Heritable Forms of Pulmonary Fibrosis with auto-immune features

Recently, 10 pediatric and young adult patients with systemic inflammation, peripheral vascular inflammation with skin involvement, and ILD, associated with gain-of-function *TMEM173* gene mutations, have been reported (99,100). The *TMEM173* gene encodes the stimulator of interferon gene (STING). The mutations are associated with a strong interferon signature in blood monocytes with increased interferon-induced cytokines levels in the serum. Screening for autoantibodies shows variable lupus-like positivity (antinuclear or antiphospholipid antibodies) and ANCA positivity has also been reported (99,100). Pulmonary fibrosis may lead to respiratory insufficiency, lung transplantation, or death

(100). Janus kinase inhibitors (tofacitinib or ruxolitinib) have shown promising results on systemic inflammation (101,102) .

Otherwise, 21 patients from five families were initially reported with arthritis, renal disease, and ILD that were associated with heterozygous *COPA* mutations, impairing endoplasmic–Golgi transport (7). Similarly to patients carriers of *TMEM173* gene mutations, *COPA* mutations induce a strong upregulation of interferon-stimulated genes (103). Most of the patients (76%) were under 5 years, 95% had joint pain, and all had ILD or alveolar hemorrhage (7). Screening for autoantibodies showed positivity for ANCA (71%), antinuclear antibodies (67%), and rheumatoid factor (43%). Specificity of ANCA was initially not reported.

Alveolar hemorrhage generally occurs before the age of 5 years and may be life threatening. After the second decade of life, patients develop ILD. Chest CT scans initially show diffuse ground-glass opacities with septal thickening and honeycomb cysts. The number of cyst then increases as the ground-glass opacities decrease, with a pattern suggestive of NSIP or lymphocytic interstitial pneumonia (103). Cysts are commonly observed on CT (104). Recently, two other patients were reported, one with a CT pattern suggestive of NSIP and the other with a CT showing cysts and tree-in-bud opacities (103,105). Histopathological evaluation shows initially alveolar hemorrhage and pulmonary capillaritis with necrosis of the capillary walls, and neutrophils along the capillaries, but also lymphoid aggregates around airways (106). Lung biopsies of older patients show NSIP and follicular bronchiolitis or diffuse interstitial pulmonary neuroendocrine cell hyperplasia (104,106).

All patients have at least a partial response to immunosuppression particularly in case of alveolar hemorrhage but several patients died during acute exacerbation of the disease and one patient required lung transplantation(106).

2.3.3 FAM111B and NDUFAF6

At least 5 families presented poikiloderma associated with tendon contractures and pulmonary fibrosis were associated with *FAM111B* mutations (6). In this series, CT seems also to be inconsistent with UIP.

Acadian variant of Fanconi syndrome refers to a specific condition characterized by proximal tubular dysfunction in newborn, resulting in chronic kidney disease and pulmonary interstitial fibrosis. It has been associated with biallelic intronic variants of *NDUFAF6* coding for a mitochondrial enzyme. Pulmonary data are sparse, but age of the patients varied from 19 to 50 and patients presented lung fibrosis (107).

3 Common variants associated with fibrosing ILD

3.1 MUC5B

In 2011, with the benefit of a large study cohort, Seibold and colleagues discovered that rs35705950 a variant located in the promoter region of *MUC5B* with both FPF and IPF (108). *MUC5B* encodes mucin 5B (MUC5B), a glycosylated macromolecular component of mucus. Heterozygous (GT) and homozygous (TT) carriers had increased odds ratios (ORs) for disease—6.8 (95% confidence interval [CI], 3.9-12.0) and 20.8 (95% CI, 3.8-113.7) for FPF and 9.0 (95% CI, 6.2 to 13.1) and 21.8 (95% CI, 5.1 to 93.5) for IPF, respectively (108). This initial study revealed that the rs35705950 minor allele frequency (MAF) was 0.338 in FPF subjects and 0.375 in sporadic IPF subjects, indicating a similar influence in disease risk in the two conditions. The minor allele rs35705950 is associated with an increased expression of MUC5B in the lung (108).

Numerous groups have validated the association between rs35705950 genotype and IPF, making this variant the strongest and most well-replicated single genetic risk factor for disease (108–115). The presence of the variant alone is insufficient to cause disease. In the

non-Hispanic white population, the rs35705950 variant is pretty common, found in 9% (MAF=0.09) of those without disease (116). Since IPF does not occur in 10% of this population. Approximately half of the IPF patients do not carry this variant. Therefore, the rs35705950 variant is neither necessary nor sufficient to cause the disease, suggesting interplay between rs35705950 and other genetic or environmental factors to cause disease development; this remains an area of active research (117).

The *MUC5B* promoter polymorphism also appears to be linked to the risk of UIP pattern, and then most frequently associated with IPF, but eventually also associated with UIP in the context of hypersensitivity pneumonitis (HP) or the context of rheumatoid arthritis-ILD (RA-ILD). A recent study of two separate cohorts with chronic HP showed that minor allele at rs35705950 was associated with disease and the MAFs observed were similar to those previously published in IPF cohorts (118). The rs35705950 was also shown to be associated with the risk of RA-ILD compared to controls (OR=4.7 95%CI[3.9-5.8]; $P=1.3 \times 10^{-49}$), and more interestingly associated with an increased risk of ILD among RA patients (OR=3.1 95%CI[1.8-5.4]; $P=7.4 \times 10^{-5}$). The association of the *MUC5B* promoter variant with RA-ILD increased significantly when restricted to UIP pattern (OR=6.1 95%CI[2.9-13.1]; $P=2.5 \times 10^{-6}$) (119).

Otherwise rs35705950 has not been associated with ILD without UIP pattern such as systemic sclerosis-ILD (110,112), or sarcoidosis (110), or with chronic obstructive pulmonary disease, and asthma (120). A subsequent GWAS that examined numerous genetic loci as well as rs35705950 in a fibrotic IIP cohort that largely contained IPF subjects but also contained other forms of fibrotic IIP confirmed the association between *MUC5B* genotype and the fibrotic IIP phenotype (121).

Studies of diverse ethnic groups suggest that rs35705950 is a genetic risk factor for IPF in Mexican cohorts (OR 7.36, $p=0.0001$), but is rare in Korean IPF cohorts (115). The overall rs35705950 frequency is low in Asian populations, yet the variant had higher prevalence in IPF cases compared to controls in Japanese and Chinese cohorts (114,122). Overall, the MAF for rs35705950 appears to be associated with populations in which IPF is more commonly diagnosed; non-Hispanic whites appear to be at higher risk of developing IPF than Hispanics or Asians, and the disease is thought to be rare in African populations (123) where the rs35705950 MAF is extremely low (NCBI dbSNP [h\[https://www.ncbi.nlm.nih.gov/projects/SNP/\]](https://www.ncbi.nlm.nih.gov/projects/SNP/): rs35705950). The examination of rs35705950 in the context of other disease-associated SNPs and rare variants will be critical to understand its relative importance to disease in different populations.

3.2 Other Common Genetic Variants and IPF

More recent investigations have used genome-wide approaches and discovered common genetic variants (defined as a MAF in the relevant population as > 0.05) associated with pulmonary fibrosis. In 2008, researchers from Japan analyzed a cohort of patients with IPF and controls and identified an association of a common *TERT* variant with susceptibility to IPF (124). Among 242 IPF cases and 1469 controls, the MAF in diseased subjects was 0.277 versus 0.409 in controls ($p = 2.9 \times 10^{-8}$), indicating that the more common A was the risk allele in this cohort (124,125).

In 2013, Fingerlin and colleagues performed a case-control GWAS in 1,616 fibrotic IIP and 4,683 control subjects. This large GWAS confirmed several known disease-associated loci (chromosome 5p15 which contains *TERT*; 11p15 which contains *MUC5B*; 3q25 near *TERC*), but also identified seven new loci, including *FAM13A* (4q22), *DSP* (6p24), *OBFC1* (10q24), *ATP11A* (13q4), *DPP9* (19p13), and regions on chromosomes 7q22 and 15q14-15

(121). The implicated genes span a wide variety of biological functions, but could be categorized into the following: host defense (*MUC5B* and *ATP11A*), cell-cell adhesion (*DSP* and *DPP9*), and DNA repair (*TERT*, *TERC*, and *OBFC1*) (117,121,126,127). It has been estimated that these loci, excluding the *MUC5B* variant, may account for up to one-third of disease risk, emphasizing the importance of genetic predisposition in fibrotic ILD (121,127).

Another GWAS performed by an independent group compared IPF subjects to non-diseased controls, confirming the *MUC5B* promoter polymorphism association, but also noted further risk alleles, including one in Toll-interacting protein (*TOLLIP*) and another in signal peptidase-like 2C (*SPPL2C*) (111). Importantly, this study not only identified risk variants, but also drew connections between specific variants (rs5743890) in *TOLLIP* and differential mortality from disease (111,128).

More recently a GWAS performed in 2760 IPF patients and 8561 controls identified a new locus associated with IPF near A-kinase anchoring protein 13 (*AKAP13*; rs62025270, OR=1.27 [95% CI 1.18–1.37], $p=1.32 \times 10^{-9}$). The allele associated with increased susceptibility to IPF was also associated with increased expression of *AKAP13* mRNA in control lung tissue (129).

Interestingly, as was observed in the initial *MUC5B* promoter polymorphism study (108), the ORs for loci identified by the 2013 GWAS by Fingerlin and colleagues did not differ between FPF and sporadic IPF cases (121). The same was true in a secondary analysis of the data that compared non-IPF fibrotic IIPs to the cases of diagnosed IPF, suggesting that genetic risk factors for fibrotic IIPs in general, whether recognized as familial or not, are similar.

3.3 Common variants associated with secondary ILD

Numerous auto-immune disorders are associated with fibrosing ILD, and for many of them it is a prominent finding with significant implications for morbidity and mortality.

Systemic sclerosis (SSc), or scleroderma, is an autoimmune disease that is not inherited in a Mendelian fashion; however, having a relative with SSc increases an individual's risk of disease (130). SSc has a strong association with pulmonary fibrosis, which is a frequent cause of mortality in this disease (130). Various lung pathologies are observed in SSc-ILD: NSIP is commonly found on histologic pattern (77.5% in one observational study), though UIP is also observed (15%) (131). Though treatment with immunosuppressive medications is generally pursued in these patients, clinical course is variable, and there are many patients with progressive and fatal lung disease. A study in Greece found associations with HLA-DRB1*11, specifically finding that the allelic subtype *1104 was associated with the presence of anti-topoisomerase antibodies and lung fibrosis (132). Numerous other genes have been analyzed as well using a candidate gene approach. In a study by Sato and colleagues, tumor necrosis factor (*TNF*) alleles were not associated with lung fibrosis, but the *TNF* -863A allele was strongly associated with anticentromere antibody disease, in which pulmonary fibrosis is observed less frequently (133). Two haplotypes (Hap-5 and Hap-6) in the fibrillin 1 gene (*FBN1*) have been associated with SSc, with Hap-5 specifically associated with pulmonary fibrosis (134). Two separate studies detailed an association between the *TGF-β* L10P codon and lung fibrosis in systemic sclerosis (135,136). In a study by Beretta and colleagues (137), 104 subjects with systemic sclerosis were followed longitudinally, with 25 (12.3%) of these individuals developing severe lung fibrosis. In this cohort, the interleukin-1β (*IL-1β*) C+3962T polymorphism was found to be associated with the presence of severe restrictive lung disease (137).

The connective tissue growth factor (*CTGF*) locus was one of many loci significantly associated with SSc in a genome-wide study of a cohort enriched for the disease (138). Subsequent study of this locus through targeted sequencing in cases and follow-up larger-scale genotyping found that genotype at rs6918698, a SNP in the *CTGF* promoter region, was found to be significantly associated with SSc (139). Additionally the G allele at this variant was associated with SSc-ILD (139). Subsequent study of a Japanese cohort confirmed this association between the G allele at rs6918698 and SSc as well as SSc-ILD. Though there have been attempts to replicate these findings in diverse ethnic groups, these studies have not always validate earlier findings, suggesting that different genetic risk factors may be at play in different sub-groups of disease.

3.5 Disease severity

Retrospective analyses of large clinical trials data reveals that IPF patients with the minor allele (T) at rs35705950 in *MUC5B* had improved survival when compared to wild-type (GG) subjects of the safe cohort (140). This survival difference is significant even when controlling for age, sex, lung function, and treatment status. Therefore, while the minor allele at rs35705950 increases risk of disease, IPF patients with the risk allele appear to have improved survival (140), suggesting that the *MUC5B* promoter variant identifies a subset of patients with IPF who have a distinct phenotype/prognosis.

A post-hoc analysis of CAPACITY and ASCEND trials showed that patients with the at risk *MUC5B* allele were older (68.1 years vs 65.5 years) and had a slower disease progression than the patient without the at risk allele. Pirfenidone was though still associated with a decrease decline of FVC (56). Nintedanib has not been examined in terms of efficacy by genotype.

Genotype at the variant in *TOLLIP* first associated with IPF by Noth and colleagues (rs5743890) is also associated with differential survival (111). In the case of rs5743890, the minor allele (G) is associated with decreased disease severity within diseased subjects, minor-allele carriers with IPF have increased mortality (111). Retrospective analysis of the PANTHER-IPF clinical trial data showed that when *TOLLIP* (rs5743890/rs5743894/rs5743854/rs3750920) and *MUC5B* (rs35705950) variants were examined, of those who received oral N-acetylcysteine (NAC), those with TT genotype at rs3750920 (*TOLLIP*) had decreased risk of the trial's composite endpoint of death, transplantation, hospitalization, or greater than 10% decrease in FVC (128). Patients with the CC genotype at rs3750920, on the other hand, had an increased risk of the composite endpoint. These findings suggest that though NAC has not been shown to be efficacious in treating IPF in general (141), it is possible that a subset of patients defined by their rs3750920 genotype could benefit from the drug.

4 Clinical application of genetic analysis

4.1 Genetic analysis

We don't offer genetic testing to every patient with ILD, but limited to some specific situations though specific recommendations are still pending (2)(142). Telomere length analysis is the first step analysis for some teams (2), though it is not our clinical practice and we propose genetic analysis for:

- Every patients with familial pulmonary fibrosis regardless of patient age
- Pulmonary fibrosis and personal or familial telomeropathy features i. e. patients with ILD and haematological anomalies (unexplained macrocytosis/thrombocytopenia or myelodysplasia/aplastic anemia), or unexplained liver disease (particularly

unexplained portal hypertension) or cutaneous findings suggestive of DKC, including premature hair graying (Table 2).

- Patients with ILD and extra-pulmonary manifestation suggestive of specific syndrome such as chorea and hypothyroidism (*NFKX2-1*) or oculocutaneous albinism (*HPS*) (Table 1).
- Sporadic cryptogenic pulmonary fibrosis occurring before 50. In these cases, *SFTPC* and *ABCA3* mutations are more common than is *TERT* or *TERC* mutation, in the absence of a telomere syndrome or familial ILD (143).
- Before lung transplantation (57).

4.2 Genetic multidisciplinary discussion

In Bichat hospital with the RESPIFIL and ORPHALUNG networks we have developed a monthly multidisciplinary discussion involving pulmonologists specialized in ILD and lung transplantation, pediatricians specialized in ILD, geneticists, radiologists, pathologists and psychologists. Hematologists, hepatologists, dermatologists, and immunologists, are involved in discussion when a specific question is raised. This monthly multidisciplinary discussion produces for each patient 3 questions:

- Molecular diagnosis: is a mutation identified and how likely is the mutation pathogenic?
- Therapeutic management: what treatment can be proposed for the lung disease: anti-fibrotic treatment, lung or medullar transplantation, others?
- Genetic counseling: what is the proposed advice for the relatives, and is there a place for a prenatal diagnosis, if asked for by the family?

4.3 Genetic counseling

Genetic counseling must be performed by physicians with specific expertise. Furthermore specific rules may apply in each country. For instance, in France, physicians are not allowed to contact relatives without the proband's agreement.

Relatives should be evaluated in a specific outpatient clinic including a pneumologist with ILD expertise, geneticist, hematologist and psychologist. First consultation includes interview with a pneumologist, a psychologist and a clinical geneticist. According to the nature of the mutation and the possible associated phenotypes, evaluation may be scheduled with a hematologist, a rheumatologist, a dermatologist, a gastro-enterologist, a gynecologist, or a neurologist. Currently, genetic analysis takes several months. Results of genetic analysis are given and explained to the subject in our specialized outpatient clinic in a dedicated appointment scheduled 3 to 6 months after the DNA sampling.

5. Conclusions

FPF is relatively frequent and raises specific problems. Approximately 25% of families have an identified mutation and should benefit from specific genetic counseling. Current studies aim to identify new genes by whole-genome sequencing to increase this percentage and to develop specific therapies. These molecular progresses come along with specific questions such as the significance of numbers of VUS identified.

In adults, the most frequently detected mutations are within *TERT*, *PARN* and *RTEL1*. Beyond pathophysiological knowledge, detection of these mutations has practical consequence for patients. For instance, mutations in *TERT* and *TERC* are associated with haematological complications after lung transplantation and may require adapted immunosuppression but are also associated with genetic anticipation and different phenotypes even in the same family.

Prospective clinical trials are needed to evaluate the therapeutic options for these patients depending on the genetic background. Regarding the rarity of the disease and the limited evidence to set up specific diagnostic counseling, international collaboration is mandatory to address these crucial issues

Figure 1. Prevalence of (A) main genes and (B) corresponding pathways (TRG, telomeres related genes) with mutations associated with monogenic pulmonary fibrosis in adults.

Figure 2 Pedigree suggestive of a telomeres related genes mutation. Filled in blue, patients with interstitial lung disease (ILD), filled in green patients with hematological disease (MDS, myelodysplastic syndrome)

Figure 3 Representative CT scan of patients carriers of (A) homozygous non null *ABCA3* mutation, (B) *SFTPC* mutation and (C) *SFTPA2* mutation all inconsistent with UIP pattern

Figure 4 Representative CT scan of patients with *TRG* mutations and (A) UIP pattern (A) hepatopulmonary syndrome and (C) inconsistent with UIP pattern suggestive of pleuroparenchymal fibroelastosis.

Disease or associated signs	Gene	Transmission	Reference
IPF, Dyskeratosis congenital	<i>TERT-TERC-TINF2- PARN-NAF1-RTEL1/DKC1</i>	AD/X	(144)(145)(146)(147)(148)
IPF, Lung cancer Combined pulmonary fibrosis and emphysema Alveolar proteinosis	<i>SFTPA1-SFTPA2-SFTPC/ ABCA3</i>	AD/AR	(32)(28)(149)
Chorea, hypothyroidism	<i>NKX2.1 (TITF1)</i>	AD	(39)
Hermansky Pudlak syndrome	<i>HPS-1 to 8/AP-3B1</i>	AR	(150)
STING associated vasculopathy with onset in infancy	<i>TMEM173/ COPA</i>	AD	(99,100)(7)
Poikiloderma Lung fibrosis	<i>FAM111B</i>	AD	(6)
Acadian variant of Fanconi syndrome	<i>NDUFAF6</i>	AR	(107)

Table 1 Main genes with rare variant associated with pulmonary fibrosis

IPF Idiopathic pulmonary fibrosis; AR, autosomal recessive; AD, autosomal dominant; X X linked

References

1. Hodgson U, Laitinen T, Tukiainen P. Nationwide prevalence of sporadic and familial idiopathic pulmonary fibrosis: evidence of founder effect among multiplex families in Finland. *Thorax*. avr 2002;57(4):338-42.
2. Kropski JA, Young LR, Cogan JD, Mitchell DB, Lancaster LH, Worrell JA, et al. Genetic Evaluation and Testing of Patients and Families with Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med* [Internet]. 27 oct 2016;[Epub ahead of print]. Disponible sur: <http://www.ncbi.nlm.nih.gov/pubmed/27786550>
3. Tsakiri KD, Cronkhite JT, Kuan PJ, Xing C, Raghu G, Weissler JC, et al. Adult-onset pulmonary fibrosis caused by mutations in telomerase. *Proc Natl Acad Sci U A*. 1 mai 2007;104(18):7552-7.
4. Armanios MY, Chen JJ, Cogan JD, Alder JK, Ingersoll RG, Markin C, et al. Telomerase mutations in families with idiopathic pulmonary fibrosis. *N Engl J Med*. 29 mars 2007;356(13):1317-26.
5. Stanley SE, Gable DL, Wagner CL, Carlile TM, Hanumanthu VS, Podlevsky JD, et al. Loss-of-function mutations in the RNA biogenesis factor NAF1 predispose to pulmonary fibrosis-emphysema. *Sci Transl Med*. 10 août 2016;8(351):351ra107.
6. Mercier S, Kury S, Shaboodien G, Houniet DT, Khumalo NP, Bou-Hanna C, et al. Mutations in FAM111B cause hereditary fibrosing poikiloderma with tendon contracture, myopathy, and pulmonary fibrosis. *Am J Hum Genet*. 5 déc 2013;93(6):1100-7.
7. Watkin LB, Jessen B, Wiszniewski W, Vece TJ, Jan M, Sha Y, et al. COPA mutations impair ER-Golgi transport and cause hereditary autoimmune-mediated lung disease and arthritis. *Nat Genet*. juin 2015;47(6):654-60.
8. Newton CA, Batra K, Torrealba J, Kozlitina J, Glazer CS, Aravena C, et al. Telomere-related lung fibrosis is diagnostically heterogeneous but uniformly progressive. *Eur Respir J*. déc 2016;48(6):1710-20.
9. Kroner C, Reu S, Teusch V, Schams A, Grimmelt AC, Barker M, et al. Genotype alone does not predict the clinical course of SFTPC deficiency in paediatric patients. *Eur Respir J*. juill 2015;46(1):197-206.
10. Harari S, Madotto F, Caminati A, Conti S, Cesana G. Epidemiology of Idiopathic Pulmonary Fibrosis in Northern Italy. *PLoS One*. 2016;11(2):e0147072.
11. Marshall RP, Puddicombe A, Cookson WO, Laurent GJ. Adult familial cryptogenic fibrosing alveolitis in the United Kingdom. *Thorax*. févr 2000;55(2):143-6.
12. Garcia-Sancho C, Buendia-Roldan I, Fernandez-Plata MR, Navarro C, Perez-Padilla R, Vargas MH, et al. Familial pulmonary fibrosis is the strongest risk factor for idiopathic pulmonary fibrosis. *Respir Med*. déc 2011;105(12):1902-7.
13. Steele MP, Speer MC, Loyd JE, Brown KK, Herron A, Slifer SH, et al. Clinical and pathologic features of familial interstitial pneumonia. *Am J Respir Crit Care Med*. 1 nov 2005;172(9):1146-52.

14. Scholand MB, Coon H, Wolff R, Cannon-Albright L. Use of a genealogical database demonstrates heritability of pulmonary fibrosis. *Lung*. oct 2013;191(5):475-81.
15. Okamoto T, Miyazaki Y, Tomita M, Tamaoka M, Inase N. A familial history of pulmonary fibrosis in patients with chronic hypersensitivity pneumonitis. *Respiration*. 2013;85(5):384-90.
16. Lee HY, Seo JB, Steele MP, Schwarz MI, Brown KK, Loyd JE, et al. High-resolution CT scan findings in familial interstitial pneumonia do not conform to those of idiopathic interstitial pneumonia. *Chest*. déc 2012;142(6):1577-83.
17. Leslie KO, Cool CD, Sporn TA, Curran-Everett D, Steele MP, Brown KK, et al. Familial idiopathic interstitial pneumonia: histopathology and survival in 30 patients. *Arch Pathol Lab Med*. nov 2012;136(11):1366-76.
18. Ravaglia C, Tomassetti S, Gurioli C, Piciocchi S, Dubini A, Casoni GL, et al. Features and outcome of familial idiopathic pulmonary fibrosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2014;31(1):28-36.
19. Lee HL, Ryu JH, Wittmer MH, Hartman TE, Lymp JF, Tazelaar HD, et al. Familial idiopathic pulmonary fibrosis: clinical features and outcome. *Chest*. juin 2005;127(6):2034-41.
20. Rosas IO, Ren P, Avila NA, Chow CK, Franks TJ, Travis WD, et al. Early interstitial lung disease in familial pulmonary fibrosis. *Am J Respir Crit Care Med*. 1 oct 2007;176(7):698-705.
21. Whitsett JA, Wert SE, Weaver TE. Alveolar surfactant homeostasis and the pathogenesis of pulmonary disease. *Annu Rev Med*. 2010;61:105-19.
22. Thouvenin G, Abou Taam R, Flamein F, Guillot L, Le Bourgeois M, Reix P, et al. Characteristics of disorders associated with genetic mutations of surfactant protein C. *Arch Child*. juin 2010;95(6):449-54.
23. Nogee LM, Dunbar AE, Wert SE, Askin F, Hamvas A, Whitsett JA. A mutation in the surfactant protein C gene associated with familial interstitial lung disease. *N Engl J Med*. 2001;344(8):573-9.
24. Lawson WE, Grant SW, Ambrosini V, Womble KE, Dawson EP, Lane KB, et al. Genetic mutations in surfactant protein C are a rare cause of sporadic cases of IPF. *Thorax*. 2004;59(11):977-80.
25. Kröner C, Reu S, Teusch V, Schams A, Grimmelt AC, Barker M, et al. Genotype alone does not predict the clinical course of SFTPC deficiency in paediatric patients. *Eur Respir J*. 2015;46(1):197-206.
26. Thomas AQ, Lane K, Phillips J, Prince M, Markin C, Speer M, et al. Heterozygosity for a surfactant protein C gene mutation associated with usual interstitial pneumonitis and cellular nonspecific interstitial pneumonitis in one kindred. *Am J Respir Crit Care Med*. 2002;165(9):1322-8.
27. van Moorsel CHM, Ten Klooster L, van Oosterhout MFM, de Jong PA, Adams H, Wouter van Es H, et al. SFTPA2 Mutations in Familial and Sporadic Idiopathic Interstitial Pneumonia. *Am J Respir Crit Care Med*. 15 nov 2015;192(10):1249-52.

28. Van Moorsel CHM, Van Oosterhout MFM, Barlo NP, De Jong P a., Van Der Vis JJ, Ruven HJT, et al. Surfactant protein C mutations are the basis of a significant portion of adult familial pulmonary fibrosis in a dutch cohort. *Am J Respir Crit Care Med.* 2010;182(11):1419-25.
29. Fernandez BA, Fox G, Bhatia R, Sala E, Noble B, Denic N, et al. A Newfoundland cohort of familial and sporadic idiopathic pulmonary fibrosis patients: clinical and genetic features. *Respir Res.* 2012;13:64.
30. Wang Y, Kuan PJ, Xing C, Cronkhite JT, Torres F, Rosenblatt RL, et al. Genetic Defects in Surfactant Protein A2 Are Associated with Pulmonary Fibrosis and Lung Cancer. *Am J Hum Genet.* 2009;84(1):52-9.
31. Maitra M, Wang Y, Gerard RD, Mendelson CR, Garcia CK. Surfactant protein A2 mutations associated with pulmonary fibrosis lead to protein instability and endoplasmic reticulum stress. *J Biol Chem.* 2010;285(29):22103-13.
32. Nathan N, Giraud V, Picard C, Nunes H, Dastot-Le Moal F, Copin B, et al. Germline *SFTPA1* mutation in familial idiopathic interstitial pneumonia and lung cancer. *Hum Mol Genet.* 2016;25(8):1457-67.
33. Flamein F, Riffault L, Muselet-Charlier C, Pernelle J, Feldmann D, Jonard L, et al. Molecular and cellular characteristics of ABCA3 mutations associated with diffuse parenchymal lung diseases in children. *Hum Mol Genet.* 15 févr 2012;21(4):765-75.
34. Thouvenin G, Nathan N, Epaud R, Clement A. Diffuse parenchymal lung disease caused by surfactant deficiency: dramatic improvement by azithromycin. *BMJ Case Rep [Internet].* 2013;2013. Disponible sur: <http://www.ncbi.nlm.nih.gov/pubmed/23814005>
35. Wambach JA, Casey AM, Fishman MP, Wegner DJ, Wert SE, Cole FS, et al. Genotype-phenotype correlations for infants and children with ABCA3 deficiency. *Am J Respir Crit Care Med.* 15 juin 2014;189(12):1538-43.
36. Young LR, Nogee LM, Barnett B, Panos RJ, Colby T V, Deutsch GH. Usual interstitial pneumonia in an adolescent with ABCA3 mutations. *Chest.* juill 2008;134(1):192-5.
37. Epaud R, Delestrain C, Louha M, Simon S, Fanen P, Tazi A. Combined pulmonary fibrosis and emphysema syndrome associated with ABCA3 mutations. *Eur Respir J.* févr 2014;43(2):638-41.
38. Hamdan H, Liu H, Li C, Jones C, Lee M, DeLemos R, et al. Structure of the human Nkx2.1 gene. *Biochim Biophys Acta.* 13 mars 1998;1396(3):336-48.
39. Nattes E, Lejeune S, Carsin A, Borie R, Gibertini I, Balinotti J, et al. Heterogeneity of lung disease associated with NK2 homeobox 1 mutations. *Respir Med.* 2017;129.
40. Campo I, Zorzetto M, Mariani F, Kadija Z, Morbini P, Dore R, et al. A large kindred of pulmonary fibrosis associated with a novel ABCA3 gene variant. *Respir Res.* 2014;15(1):43.
41. van Moorsel CH, van Oosterhout MF, Barlo NP, de Jong PA, van der Vis JJ, Ruven HJ, et al. Surfactant protein C mutations are the basis of a significant portion of adult familial pulmonary fibrosis in a dutch cohort. *Am J Respir Crit Care Med.* 1 déc 2010;182(11):1419-25.

42. Mechri M, Epaud R, Emond S, Coulomb A, Jaubert F, Tarrant A, et al. Surfactant protein C gene (SFTPC) mutation-associated lung disease: high-resolution computed tomography (HRCT) findings and its relation to histological analysis. *Pediatr Pulmonol.* oct 2010;45(10):1021-9.
43. Ono S, Tanaka T, Ishida M, Kinoshita A, Fukuoka J, Takaki M, et al. Surfactant protein C G100S mutation causes familial pulmonary fibrosis in Japanese kindred. *Eur Respir J.* oct 2011;38(4):861-9.
44. Cottin V, Reix P, Khouatra C, Thivolet-Bejui F, Feldmann D, Cordier JF. Combined pulmonary fibrosis and emphysema syndrome associated with familial SFTPC mutation. *Thorax.* oct 2011;66(10):918-9.
45. Klay D, Hoffman TW, Harmsze AM, Grutters JC, van Moorsel CHM. Systematic review of drug effects in humans and models with surfactant-processing disease. *Eur Respir Rev Off J Eur Respir Soc.* 30 sept 2018;27(149).
46. Kroner C, Wittmann T, Reu S, Teusch V, Klemme M, Rauch D, et al. Lung disease caused by ABCA3 mutations. *Thorax.* 11 août 2016;72(3):213-20.
47. Calado RT, Young NS. Telomere diseases. *N Engl J Med.* 10 déc 2009;361(24):2353-65.
48. Townsley DM, Dumitriu B, Liu D, Biancotto A, Weinstein B, Chen C, et al. Danazol Treatment for Telomere Diseases. *N Engl J Med.* 19 mai 2016;374(20):1922-31.
49. Diaz de Leon A, Cronkhite JT, Katzenstein AL, Godwin JD, Raghu G, Glazer CS, et al. Telomere lengths, pulmonary fibrosis and telomerase (TERT) mutations. *PLoS One.* 2010;5(5):e10680.
50. Alder JK, Parry EM, Yegnasubramanian S, Wagner CL, Lieblisch LM, Auerbach R, et al. Telomere phenotypes in females with heterozygous mutations in the dyskeratosis congenita 1 (DKC1) gene. *Hum Mutat.* nov 2013;34(11):1481-5.
51. Fukuhara A, Tanino Y, Ishii T, Inokoshi Y, Saito K, Fukuhara N, et al. Pulmonary fibrosis in dyskeratosis congenita with TINF2 gene mutation. *Eur Respir J.* déc 2013;42(6):1757-9.
52. Alder JK, Stanley SE, Wagner CL, Hamilton M, Hanumanthu VS, Armanios M. Exome Sequencing Identifies Mutant TINF2 in a Family With Pulmonary Fibrosis. *Chest.* 1 mai 2015;147(5):1361-8.
53. Stuart BD, Choi J, Zaidi S, Xing C, Holohan B, Chen R, et al. Exome sequencing links mutations in PARN and RTEL1 with familial pulmonary fibrosis and telomere shortening. *Nat Genet.* mai 2015;47(5):512-7.
54. Cogan JD, Kropski JA, Zhao M, Mitchell DB, Rives L, Markin C, et al. Rare variants in RTEL1 are associated with familial interstitial pneumonia. *Am J Respir Crit Care Med.* 15 mars 2015;191(6):646-55.
55. Kannengiesser C, Borie R, Menard C, Reocreux M, Nitschke P, Gazal S, et al. Heterozygous RTEL1 mutations are associated with familial pulmonary fibrosis. *Eur Respir J.* août 2015;46(2):474-85.
56. Dressen A, Abbas AR, Cabanski C, Reeder J, Ramalingam TR, Neighbors M, et al. Analysis of protein-altering variants in telomerase genes and their association with MUC5B common

variant status in patients with idiopathic pulmonary fibrosis: a candidate gene sequencing study. *Lancet Respir Med*. août 2018;6(8):603-14.

57. Petrovski S, Todd JL, Durheim MT, Wang Q, Chien JW, Kelly FL, et al. An Exome Sequencing Study to Assess the Role of Rare Genetic Variation in Pulmonary Fibrosis. *Am J Respir Crit Care Med* [Internet]. 18 janv 2017; Disponible sur: <http://www.ncbi.nlm.nih.gov/pubmed/28099038>
58. Borie R, Tabeze L, Thabut G, Nunes H, Cottin V, Marchand-Adam S, et al. Prevalence and characteristics of TERT and TERC mutations in suspected genetic pulmonary fibrosis. *Eur Respir J*. déc 2016;48(6):1721-31.
59. Borie R, Bouvry D, Cottin V, Gauvain C, Cazes A, Debray M-P, et al. Regulator of telomere length 1 (RTEL1) mutations are associated with heterogeneous pulmonary and extra-pulmonary phenotypes. *Eur Respir J*. 5 déc 2018;
60. Snetselaar R, van Moorsel CH, Kazemier KM, van der Vis JJ, Zanen P, van Oosterhout MF, et al. Telomere length in interstitial lung diseases. *Chest*. oct 2015;148(4):1011-8.
61. Gutierrez-Rodrigues F, Santana-Lemos BA, Scheucher PS, Alves-Paiva RM, Calado RT. Direct comparison of flow-FISH and qPCR as diagnostic tests for telomere length measurement in humans. *PLoS One*. 2014;9(11):e113747.
62. Cronkhite JT, Xing C, Raghu G, Chin KM, Torres F, Rosenblatt RL, et al. Telomere shortening in familial and sporadic pulmonary fibrosis. *Am J Respir Crit Care Med*. 1 oct 2008;178(7):729-37.
63. Alder JK, Hanumanthu VS, Strong MA, DeZern AE, Stanley SE, Takemoto CM, et al. Diagnostic utility of telomere length testing in a hospital-based setting. *Proc Natl Acad Sci U S A*. 06 2018;115(10):E2358-65.
64. Alder JK, Cogan JD, Brown AF, Anderson CJ, Lawson WE, Lansdorp PM, et al. Ancestral mutation in telomerase causes defects in repeat addition processivity and manifests as familial pulmonary fibrosis. *PLoS Genet*. mars 2011;7(3):e1001352.
65. Collopy LC, Walne AJ, Cardoso S, de la Fuente J, Mohamed M, Toriello H, et al. Triallelic and epigenetic-like inheritance in human disorders of telomerase. *Blood*. 9 juill 2015;126(2):176-84.
66. Snetselaar R, van Batenburg AA, van Oosterhout MFM, Kazemier KM, Roothaan SM, Peeters T, et al. Short telomere length in IPF lung associates with fibrotic lesions and predicts survival. *PLoS One*. 2017;12(12):e0189467.
67. Nunes H, Jeny F, Bouvry D, Picard C, Bernaudin JF, Menard C, et al. Pleuroparenchymal fibroelastosis associated with telomerase reverse transcriptase mutations. *Eur Respir J* [Internet]. mai 2017;49(5). Disponible sur: <http://www.ncbi.nlm.nih.gov/pubmed/28495689>
68. Stanley SE, Chen JJ, Podlevsky JD, Alder JK, Hansel NN, Mathias RA, et al. Telomerase mutations in smokers with severe emphysema. *J Clin Invest*. févr 2015;125(2):563-70.
69. Karimi-Shah BA, Chowdhury BA. Forced vital capacity in idiopathic pulmonary fibrosis--FDA review of pirfenidone and nintedanib. *N Engl J Med*. 26 mars 2015;372(13):1189-91.

70. El-Chemaly S, Ziegler SG, Calado RT, Wilson KA, Wu HP, Haughey M, et al. Natural history of pulmonary fibrosis in two subjects with the same telomerase mutation. *Chest*. mai 2011;139(5):1203-9.
71. Heiss NS, Knight SW, Vulliamy TJ, Klauck SM, Wiemann S, Mason PJ, et al. X-linked dyskeratosis congenita is caused by mutations in a highly conserved gene with putative nucleolar functions. *Nat Genet*. mai 1998;19(1):32-8.
72. Zinsser F. Atrophia Cutis Reticularis cum Pigmentations, Dystrophia Unguium et Leukoplakis oris (Poikiodermia atrophicans vascularis Jacobi). *Ikonographia Dermatol*. 1910;5:219-23.
73. Savage S, Cook EF. *Dyskeratosis Congenita and Telomere Biology Disorders: Diagnosis and Management Guidelines*. Dyskeratosis Congenita Outreach I, éditeur. 2015. 446 p.
74. Langston AA, Sanders JE, Deeg HJ, Crawford SW, Anasetti C, Sullivan KM, et al. Allogeneic marrow transplantation for aplastic anaemia associated with dyskeratosis congenita. *Br J Haematol*. mars 1996;92(3):758-65.
75. Diaz de Leon A, Cronkhite JT, Yilmaz C, Brewington C, Wang R, Xing C, et al. Subclinical lung disease, macrocytosis, and premature graying in kindreds with telomerase (TERT) mutations. *Chest*. sept 2011;140(3):753-63.
76. Ball SE, Gibson FM, Rizzo S, Tooze JA, Marsh JC, Gordon-Smith EC. Progressive telomere shortening in aplastic anemia. *Blood*. 15 mai 1998;91(10):3582-92.
77. Yamaguchi H, Baerlocher GM, Lansdorp PM, Chanock SJ, Nunez O, Sloan E, et al. Mutations of the human telomerase RNA gene (TERC) in aplastic anemia and myelodysplastic syndrome. *Blood*. 1 août 2003;102(3):916-8.
78. Yamaguchi H, Calado RT, Ly H, Kajigaya S, Baerlocher GM, Chanock SJ, et al. Mutations in TERT, the gene for telomerase reverse transcriptase, in aplastic anemia. *N Engl J Med*. 7 avr 2005;352(14):1413-24.
79. Parry EM, Alder JK, Qi X, Chen JJ, Armanios M. Syndrome complex of bone marrow failure and pulmonary fibrosis predicts germline defects in telomerase. *Blood*. 26 mai 2011;117(21):5607-11.
80. Calado RT, Regal JA, Kleiner DE, Schrupp DS, Peterson NR, Pons V, et al. A spectrum of severe familial liver disorders associate with telomerase mutations. *PLoS One*. 2009;4(11):e7926.
81. Hartmann D, Srivastava U, Thaler M, Kleinhans KN, N'Kontchou G, Scheffold A, et al. Telomerase gene mutations are associated with cirrhosis formation. *Hepatology*. mai 2011;53(5):1608-17.
82. Gorgy AI, Jonassaint NL, Stanley SE, Koteish A, DeZern AE, Walter JE, et al. Hepatopulmonary syndrome is a frequent cause of dyspnea in the short telomere disorders. *Chest*. oct 2015;148(4):1019-26.
83. Lata S, Marasa M, Li Y, Fasel DA, Groopman E, Jobanputra V, et al. Whole-Exome Sequencing in Adults With Chronic Kidney Disease: A Pilot Study. *Ann Intern Med*. 16 2018;168(2):100-9.

84. Borie R, Kannengiesser C, Sicre de Fontbrune F, Boutboul D, Tabeze L, Brunet-Possenti F, et al. Pneumocystosis revealing immunodeficiency secondary to TERC mutation. *Eur Respir J.* 2017;50(5).
85. Popescu I, Mannem H, Winters SA, Hoji A, Silveira F, McNally E, et al. Impaired CMV Immunity in Idiopathic Pulmonary Fibrosis Lung Transplant Recipients with Short Telomeres. *Am J Respir Crit Care Med.* 8 août 2018;
86. Justet A, Thabut G, Manali E, Molina Molina M, Kannengiesser C, Cadranel J, et al. Safety and efficacy of pirfenidone in patients carrying telomerase complex mutation. *Eur Respir J.* mars 2018;51(3).
87. Borie R, Kannengiesser C, Hirschi S, Le Pavec J, Mal H, Bergot E, et al. Severe hematologic complications after lung transplantation in patients with telomerase complex mutations. *J Heart Lung Transpl.* avr 2015;34(4):538-46.
88. Silhan LL, Shah PD, Chambers DC, Snyder LD, Riise GC, Wagner CL, et al. Lung transplantation in telomerase mutation carriers with pulmonary fibrosis. *Eur Respir J.* juill 2014;44(1):178-87.
89. Tokman S, Singer JP, Devine MS, Westall GP, Aubert JD, Tamm M, et al. Clinical outcomes of lung transplant recipients with telomerase mutations. *J Heart Lung Transpl [Internet].* 11 mai 2015; Disponible sur: <http://www.ncbi.nlm.nih.gov/pubmed/26169663>
90. Newton CA, Kozlitina J, Lines JR, Kaza V, Torres F, Garcia CK. Telomere length in patients with pulmonary fibrosis associated with chronic lung allograft dysfunction and post-lung transplantation survival. *J Heart Lung Transplant.* 2017;36(8):845-53.
91. Wei ML. Hermansky-Pudlak syndrome: A disease of protein trafficking and organelle function. *Pigment Cell Res.* 2006;19(1):19-42.
92. Oh J, Ho L, Ala-Mello S, Amato D, Armstrong L, Bellucci S, et al. Mutation analysis of patients with Hermansky-Pudlak syndrome: a frameshift hot spot in the HPS gene and apparent locus heterogeneity. *Am J Hum Genet.* mars 1998;62(3):593-8.
93. Wei ML. Hermansky-Pudlak syndrome: a disease of protein trafficking and organelle function. *Pigment Cell Res.* févr 2006;19(1):19-42.
94. Shimizu K, Matsumoto T, Miura G, Shimizu A, Awaya H, Matsunaga N, et al. Hermansky-Pudlak syndrome with diffuse pulmonary fibrosis: radiologic-pathologic correlation. *J Comput Assist Tomogr.* 1998;22(2):249-51.
95. Reynolds SP, Davies BH, Gibbs AR. Diffuse pulmonary fibrosis and the Hermansky-Pudlak syndrome: clinical course and postmortem findings. *Thorax.* juin 1994;49(6):617-8.
96. Nakatani Y, Nakamura N, Sano J, Inayama Y, Kawano N, Yamanaka S, et al. Interstitial pneumonia in Hermansky-Pudlak syndrome: significance of florid foamy swelling/degeneration (giant lamellar body degeneration) of type-2 pneumocytes. *Virchows Arch Int J Pathol.* sept 2000;437(3):304-13.
97. Anderson PD, Huizing M, Claassen DA, White J, Gahl WA. Hermansky-Pudlak syndrome type 4 (HPS-4): clinical and molecular characteristics. *Hum Genet.* juill 2003;113(1):10-7.

98. Gahl WA, Brantly M, Troendle J, Avila NA, Padua A, Montalvo C, et al. Effect of pirfenidone on the pulmonary fibrosis of Hermansky-Pudlak syndrome. *Mol Genet Metab.* juill 2002;76(3):234-42.
99. Liu Y, Jesus AA, Marrero B, Yang D, Ramsey SE, Montealegre Sanchez GA, et al. Activated STING in a vascular and pulmonary syndrome. *N Engl J Med.* 7 août 2014;371(6):507-18.
100. Picard C, Thouvenin G, Kannengiesser C, Dubus JC, Jeremiah N, Rieux-Laucat F, et al. Severe Pulmonary Fibrosis as the First Manifestation of Interferonopathy (TMEM173 Mutation). *Chest.* sept 2016;150(3):e65-71.
101. Frémond M-L, Rodero MP, Jeremiah N, Belot A, Jeziorski E, Duffy D, et al. Efficacy of the Janus kinase 1/2 inhibitor ruxolitinib in the treatment of vasculopathy associated with TMEM173-activating mutations in 3 children. *J Allergy Clin Immunol.* 2016;138(6):1752-5.
102. Seo J, Kang J-A, Suh DI, Park E-B, Lee C-R, Choi SA, et al. Tofacitinib relieves symptoms of stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy caused by 2 de novo variants in TMEM173. *J Allergy Clin Immunol.* avr 2017;139(4):1396-1399.e12.
103. Volpi S, Tsui J, Mariani M, Pastorino C, Caorsi R, Sacco O, et al. Type I interferon pathway activation in COPA syndrome. *Clin Immunol Orlando Fla.* févr 2018;187:33-6.
104. Tsui JL, Estrada OA, Deng Z, Wang KM, Law CS, Elicker BM, et al. Analysis of pulmonary features and treatment approaches in the COPA syndrome. *ERJ Open Res.* avr 2018;4(2).
105. Noorelahi R, Perez G, Otero HJ. Imaging findings of Copa syndrome in a 12-year-old boy. *Pediatr Radiol.* 2018;48(2):279-82.
106. Vece TJ, Watkin LB, Nicholas S, Canter D, Braun MC, Guillerman RP, et al. Copa Syndrome: a Novel Autosomal Dominant Immune Dysregulatory Disease. *J Clin Immunol.* 2016;36(4):377-87.
107. Hartmannova H, Piherova L, Tauchmannova K, Kidd K, Acott PD, Crocker JF, et al. Acadian variant of Fanconi syndrome is caused by mitochondrial respiratory chain complex I deficiency due to a non-coding mutation in complex I assembly factor NDUFAF6. *Hum Mol Genet* [Internet]. 27 juill 2016; Disponible sur: <http://www.ncbi.nlm.nih.gov/pubmed/27466185>
108. Seibold MA, Wise A, Speer M, Steele M, Brown K, Lloyd JE, et al. A common MUC5B promoter polymorphism and pulmonary fibrosis. *N Engl J Med.* 2011;364(16):1503-12.
109. Zhang Y, Noth I, Garcia JGN, Kaminski N. A Variant in the Promoter of MUC5B and Idiopathic Pulmonary Fibrosis NT5E Mutations and Arterial Calcifications. *N Engl J Med.* 2011;364(16):1576-7.
110. Stock CJ, Sato H, Fonseca C, Banya W a S, Molyneaux PL, Adamali H, et al. Mucin 5B promoter polymorphism is associated with idiopathic pulmonary fibrosis but not with development of lung fibrosis in systemic sclerosis or sarcoidosis. *Thorax.* 2013;68(5):436-41.
111. Noth I, Zhang Y, Ma S-F, Flores C, Barber M, Huang Y, et al. Genetic variants associated with idiopathic pulmonary fibrosis susceptibility and mortality: a genome-wide association study. *Lancet Respir Med.* 2013;1(4):309-17.

112. Borie R, Crestani B, Dieude P, Nunes H, Allanore Y, Kannengiesser C, et al. The MUC5B variant is associated with idiopathic pulmonary fibrosis but not with systemic sclerosis interstitial lung disease in the European Caucasian population. *PLoS One*. janv 2013;8(8):e70621.
113. Wei R, Li C, Zhang M, Jones-Hall YL, Myers JL, Noth I, et al. Association between MUC5B and TERT polymorphisms and different interstitial lung disease phenotypes. *Transl Res*. 2014;163(5):494-502.
114. Horimasu Y, Ohshimo S, Bonella F, Tanaka S, Ishikawa N, Hattori N, et al. MUC5B promoter polymorphism in Japanese patients with idiopathic pulmonary fibrosis. *Respirology*. 2015;20(3):439-44.
115. Peljto AL, Selman M, Kim DS, Murphy E, Tucker L, Pardo A, et al. The MUC5B promoter polymorphism is associated with idiopathic pulmonary fibrosis in a mexican cohort but is rare among asian ancestries. *Chest*. 1 févr 2015;147(2):460-4.
116. Hunninghake GM, Hatabu H, Okajima Y, Gao W, Dupuis J, Latourelle JC, et al. MUC5B promoter polymorphism and interstitial lung abnormalities. *N Engl J Med*. 6 juin 2013;368(23):2192-200.
117. Mathai SK, Schwartz DA, Warg LA. Genetic susceptibility and pulmonary fibrosis. *Curr Opin Pulm Med*. 2014;20(5):429-35.
118. Ley B, Newton CA, Arnould I, Elicker BM, Henry TS, Vittinghoff E, et al. The MUC5B promoter polymorphism and telomere length in patients with chronic hypersensitivity pneumonitis: an observational cohort-control study. *Lancet Respir Med*. 2017;5(8):639-47.
119. Juge P-A, Lee JS, Ebstein E, Furukawa H, Dobrinskikh E, Gazal S, et al. MUC5B Promoter Variant and Rheumatoid Arthritis with Interstitial Lung Disease. *N Engl J Med*. 6 déc 2018;379(23):2209-19.
120. Yang I V., Schwartz DA. Epigenetics of idiopathic pulmonary fibrosis. *Transl Res*. 2015;165(1):48-60.
121. Fingerlin TE, Murphy E, Zhang W, Peljto AL, Brown KK, Steele MP, et al. Genome-wide association study identifies multiple susceptibility loci for pulmonary fibrosis. *Nat Genet*. juin 2013;45(6):613-20.
122. Wang C, Zhuang Y, Guo W, Cao L, Zhang H, Xu L, et al. Mucin 5B Promoter Polymorphism Is Associated with Susceptibility to Interstitial Lung Diseases in Chinese Males. *PLoS One*. 2014;9(8):e104919.
123. Ley B, Collard HR. Epidemiology of Idiopathic Pulmonary Fibrosis. *Clin Epidemiol*. 2013;5:483-92.
124. Mushiroda T, Wattanapokayakit S, Takahashi a, Nukiwa T, Kudoh S, Ogura T, et al. A genome-wide association study identifies an association of a common variant in TERT with susceptibility to idiopathic pulmonary fibrosis. *J Med Genet*. 2008;45(10):654-6.
125. Snetselaar R, van Oosterhout MFM, Grutters JC, van Moorsel CHM. Telomerase Reverse Transcriptase Polymorphism rs2736100: A Balancing Act between Cancer and Non-Cancer Disease, a Meta-Analysis. *Front Med*. 2018;5:41.

126. Yang I V, Fingerlin TE, Evans CM, Schwarz MI, Schwartz DA. MUC5B and Idiopathic Pulmonary Fibrosis. *Ann Am Thorac Soc.* nov 2015;12 Suppl 2:S193-9.
127. Mathai SK, Yang I V, Schwarz MI, Schwartz DA. Incorporating genetics into the identification and treatment of Idiopathic Pulmonary Fibrosis. *BMC Med.* 2015;13(1):191.
128. Oldham JM, Ma SF, Martinez FJ, Anstrom KJ, Raghu G, Schwartz DA, et al. TOLLIP, MUC5B, and the response to N-acetylcysteine among individuals with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med.* 2015;192(12):1475-82.
129. Allen RJ, Porte J, Braybrooke R, Flores C, Fingerlin TE, Oldham JM, et al. Genetic variants associated with susceptibility to idiopathic pulmonary fibrosis in people of European ancestry: a genome-wide association study. *Lancet Respir Med.* 2017;5(11):869-80.
130. Tochimoto A, Kawaguchi Y, Yamanaka H. Genetic Susceptibility to Interstitial Lung Disease Associated with Systemic Sclerosis. *Clin Med Insights Circ Respir Pulm Med.* 2015;9s1:135-40.
131. Bouros D, Wells AU, Nicholson AG, Colby T V., Polychronopoulos V, Pantelidis P, et al. Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. *Am J Respir Crit Care Med.* 2002;165(12):1581-6.
132. Vlachoyiannopoulos PG, Dafni UG, Pakas I, Spyropoulou-Vlachou M, Stavropoulos-Giokas C, Moutsopoulos HM. Systemic scleroderma in Greece: Low mortality and strong linkage with HLA-DRB1*1104 allele. *Ann Rheum Dis.* 2000;59(5):359-67.
133. Sato H, Lagan AL, Alexopoulou C, Vassilakis DA, Ahmad T, Pantelidis P, et al. The TNF-863A Allele Strongly Associates with Anticentromere Antibody Positivity in Scleroderma. *Arthritis Rheum.* 2004;50(2):558-64.
134. Tan FK, Wang N, Kuwana M, Chakraborty R, Bona CA, Milewicz DM, et al. Association of fibrillin 1 single-nucleotide polymorphism haplotypes with systemic sclerosis in Choctaw and Japanese populations. *Arthritis Rheum.* avr 2001;44(4):893-901.
135. Sugiura Y, Banno S, Matsumoto Y, Niimi T, Yoshinouchi T, Hayami Y, et al. Transforming growth factor beta1 gene polymorphism in patients with systemic sclerosis. *J Rheumatol.* juill 2003;30(7):1520-3.
136. Crilly A, Hamilton J, Clark CJ, Jardine A, Madhok R. Analysis of transforming growth factor beta1 gene polymorphisms in patients with systemic sclerosis. *Ann Rheum Dis.* août 2002;61(8):678-81.
137. Beretta L, Bertolotti F, Cappiello F, Barili M, Masciocchi M, Toussoun K, et al. Interleukin-1 gene complex polymorphisms in systemic sclerosis patients with severe restrictive lung physiology. *Hum Immunol.* juill 2007;68(7):603-9.
138. Zhou X, Tan FK, Wang N, Xiong M, Maghidman S, Reveille JD, et al. Genome-wide association study for regions of systemic sclerosis susceptibility in a Choctaw Indian population with high disease prevalence. *Arthritis Rheum.* sept 2003;48(9):2585-92.
139. Fonseca C, Lindahl GE, Ponticos M, Sestini P, Renzoni EA, Holmes AM, et al. A polymorphism in the CTGF promoter region associated with systemic sclerosis. *N Engl J Med.* 20 sept 2007;357(12):1210-20.

140. Peljto AL, Zhang Y, Fingerlin TE, Ma S-F, Garcia JGN, Richards TJ, et al. Association between the MUC5B promoter polymorphism and survival in patients with idiopathic pulmonary fibrosis. *JAMA J Am Med Assoc.* 5 juin 2013;309(21):2232-9.
141. The Idiopathic Pulmonary Fibrosis Network. Randomized Trial of Acetylcysteine in Idiopathic Pulmonary Fibrosis. *N Engl J Med.* 2014;1-9.
142. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med.* 1 sept 2018;198(5):e44-68.
143. Nathan N, Borie R, Kannengiesser C, Dastot Le Moal F, Nunes H, Valeyre D, et al. Contribution of Mutations in Genes Encoding Proteins of the Surfactant Metabolism to Idiopathic Interstitial Pneumonia and Idiopathic Pulmonary Fibrosis in a Cohort of 265 Families. *Am J Respir Cell Mol Biol.* 2016;193:A2605.
144. Borie R, Tabèze L, Thabut G, Nunes H, Cottin V, Marchand-Adam S, et al. Prevalence and characteristics of TERT and TERC mutations in suspected genetic pulmonary fibrosis. *Eur Respir J.* 2016;48(6).
145. Hoffman TW, van der Vis JJ, van Oosterhout MF, van Es HW, van Kessel DA, Grutters JC, et al. TINF2 Gene Mutation in a Patient with Pulmonary Fibrosis. *Case Rep Pulmonol.* 2016;2016:1310862.
146. Alder JK, Parry EM, Yegnasubramanian S, Wagner CL, Lieblich LM, Auerbach R, et al. Telomere phenotypes in females with heterozygous mutations in the dyskeratosis congenita 1 (DKC1) gene. *Hum Mutat.* 2013;34(11):1481-5.
147. Stuart BD, Choi J, Zaidi S, Xing C, Holohan B, Chen R, et al. Exome sequencing links mutations in PARN and RTEL1 with familial pulmonary fibrosis and telomere shortening. *Nat Genet.* 2015;47(5):512-7.
148. Stanley SE, Gable DL, Wagner CL, Carlile TM, Hanumanthu VS, Podlevsky JD, et al. Loss-of-function mutations in the RNA biogenesis factor NAF1 predispose to pulmonary fibrosis-emphysema. *Sci Transl Med.* 2016;8(351):1-10.
149. Bullard JE, Wert SE, Whitsett JA, Dean M, Nogee LM. ABCA3 mutations associated with pediatric interstitial lung disease. *Am J Respir Crit Care Med.* oct 2005;172(8):1026-31.
150. Young LR, Gulleman PM, Bridges JP, Weaver TE, Deutsch GH, Blackwell TS, et al. The alveolar epithelium determines susceptibility to lung fibrosis in Hrmansky-Pdlak syndrome. *Am J Respir Crit Care Med.* 2012;186(10):1014-24.

Figure 1

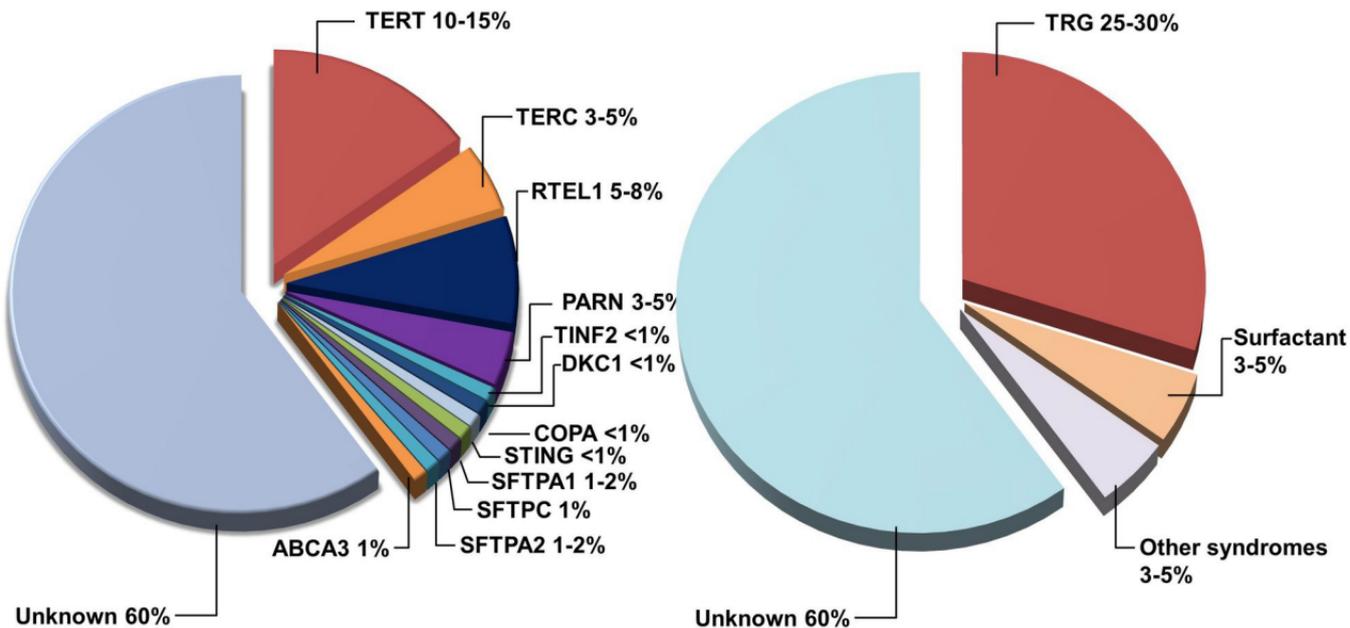


Figure 2

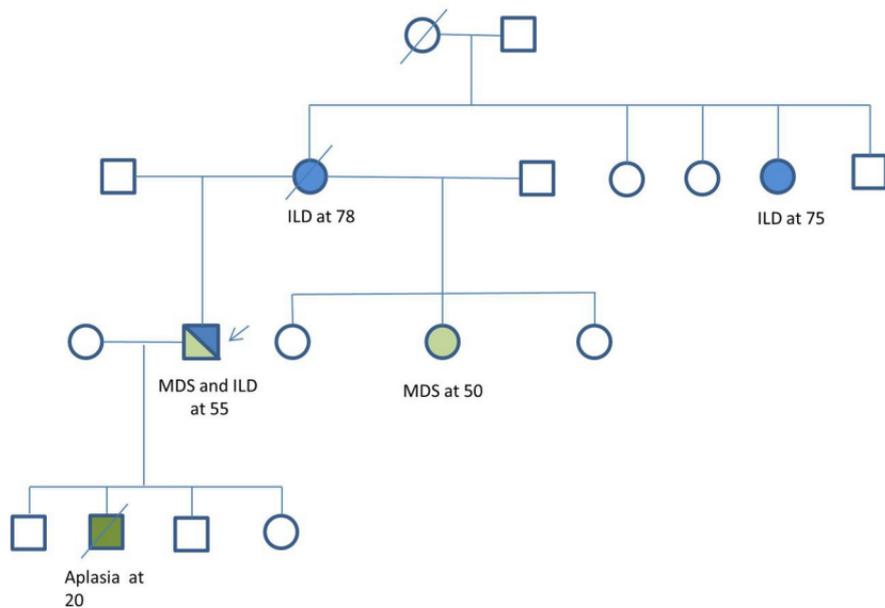


Figure 3

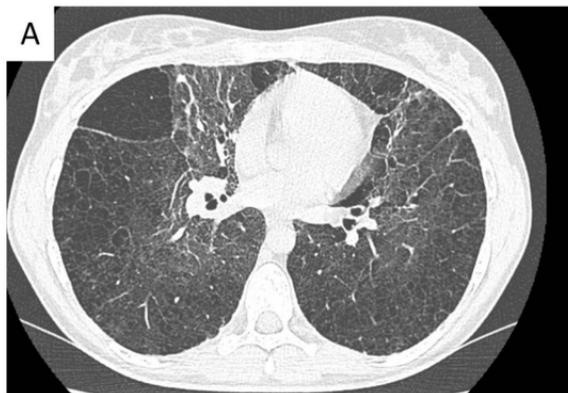


Figure 4

