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Genetic Interstitial Lung Disease

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The interstitial lung diseases (ILDs), or diffuse parenchymal lung diseases, are a heterogeneous collection of over 100 different pulmonary disorders that affect the tissue and spaces surrounding the alveoli. For many of the ILDs, this delicate tissue is filled with inflammatory cells, proliferating fibroblasts, collagen, fibronectin, laminin and other macromolecules, which cause irreversible architectural distortion and impaired gas exchange. Patients affected by ILD usually present with shortness of breath or cough; for many, there is evidence of pulmonary restriction, decreased diffusion capacity and radiographic appearance of alveolar and/or reticulonodular infiltrates. Here we review the inherited ILDs, with a focus on the diseases that may be seen by pulmonologists caring for adult patients. We will conclude the review by briefly discussing the utility of genetic testing in this population.

Inherited ILDs are those that result from the transmission of genetic mutations from a parent or ancestor. We have subdivided the inherited ILDs into two major categories: systemic disorders affecting multiple organs and disorders that primarily affect the lung. For both of these groups, thorough past medical and family histories provide essential clues about the exact nature of the ILD. First, the pattern of inheritance provides important information; for example, the inborn errors of metabolism that are associated with an ILD demonstrate an autosomal recessive pattern of inheritance. Second, some diseases show a predisposition for affecting a certain gender; for example, lymphangiomyomatosis (LAM) occurs exclusively in women. The age of onset of disease is yet another important hint. Younger and more severely affected individuals seen in later generations may reflect genetic anticipation, which can be seen in autosomal dominant kindreds with inherited telomerase mutations and progressively shortened telomere lengths. Finally, the spectrum of disease in the patient and related family members provides important clues to the etiology of ILD. If

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there is reduced penetrance and variable expressivity, the proband may demonstrate only a subset of all possible clinical findings.

Genetic Disorders Affecting Multiple Organs, Including the Lung

Table 1 lists the defined genetic disorders that are associated with interstitial lung diseases, with the lung being only one of many different affected organs.

Dyskeratosis congenita (DC)

Dyskeratosis congenita is a rare multisystem disorder characterized by the triad of lacy reticular pigmentation on the upper chest and neck, nail dystrophy and mucosal leukoplakia. The prevalence is approximately 1 in 1,000,000, with death occurring at a median age of 16 years¹. Patients are usually healthy at birth and then develop the mucocutaneous findings during infancy, bone marrow failure during the 1st or 2nd decade, followed by various organ dysfunction, including pulmonary fibrosis, eye, tooth, gastrointestinal, endocrine, skeletal, urologic, and immunologic abnormalities^{2,3}. Because clinical features include premature graying, testicular atrophy, an increased predisposition to cancer, and a shortened lifespan, DC has been considered a syndrome of premature aging. There is wide variation in the mode of inheritance, severity and spectrum of clinical findings, which is only partly explained by locus and allelic heterogeneity. Most patients in a large international registry are male with X-linked recessive inheritance². For this subgroup of patients, the classic skin and nail findings are present in ~90% of affected males. Bone marrow failure is very common (>85%) and accounts for the leading cause of death. Pulmonary fibrosis develops in 20%. DC families with autosomal recessive and autosomal dominant patterns of inheritance are less common.

Telomeres are specialized nucleoprotein structures that protect chromosomal ends and telomerase is the multisubunit enzyme that extends telomeres to offset the shortening that accompanies DNA replication due to lagging strand synthesis. In the setting of insufficient telomerase, telomere shortening limits tissue renewal by impairing the function of tissue stem cells and progenitor cells⁴. Genetic anticipation, or the finding of more severe and earlier onset disease in later generations, has been described in DC kindreds with mutations in the genes encoding telomerase (*TERC* and *TERT*)^{5,6}. Inheritance of progressively shorter telomere lengths in each subsequent generation of mutation carriers provides a molecular explanation for the genetic anticipation.

ILD associated with DC has been characterized as a progressive restrictive lung disease with interstitial fibrosis, often with histopathologic lesions suggestive of hypersensitivity^{7,8}. Over 30% of DC patients develop a rapidly progressive interstitial fibrosis following bone marrow transplantation^{9,10}. Pulmonary disease was 2.2-fold more common and apparent at a younger age (14 years vs. 37 years) in patients who had undergone hematopoietic stem cell transplantation, than those who did not¹¹. Clinical survival of DC patients after the development of ILD is poor, with death 12–40 months after the onset of dyspnea⁸. Some patients with mutations in dyskerin (*DKC1*), the gene encoding a nucleolar protein that co-purifies with telomerase¹², have evidence of pulmonary fibrosis^{13,14}. Mutations in either of the telomerase genes (*TERT*, *TERC*) or *TINF2*, a component of the shelterin complex, have been found in patients with autosomal dominant DC and ILD^{6,11,15}. Homozygous mutations in *NOLA2*, *NOLA3*, and *TCAB1* are rare causes of DC^{16–18}; so far none of the affected individuals have been described with pulmonary fibrosis.

Neurofibromatosis, type 1 (NF1)

Type 1 neurofibromatosis is an autosomal dominant disorder that affects all ethnic groups and is caused by heterozygous loss of function mutations in the gene encoding

neurofibromin, *NF1*. It is characterized by multiple (>6) *café au lait* spots, axillary and inguinal freckling, multiple cutaneous neurofibromas, Lisch nodules, optic gliomas and osseous lesions. The incidence of ILD in NF1 has been estimated at 6–12%^{19–21}. It is characterized by lower lobe predominant diffuse interstitial fibrosis and honeycombing. Thin-walled bullae are present in almost all patients with ILD or may be seen in isolation; these are large, asymmetric and typically involve the upper lobes²¹. Interestingly, histologic evidence of an alveolitis and interstitial fibrosis have been found in patients with normal chest x-rays or those with only apical bullae²⁰. Although there is near complete penetrance of the disease after childhood, the ILD is not observed until adulthood and is typically seen in patients older than 40 years of age²⁰. The disease is often progressive and may lead to pulmonary hypertension and right heart failure. The pathogenesis of NF1-associated ILD is unknown. Other manifestations of the disease include large airway obstruction, mediastinal, bronchial or intraparenchymal neurofibromas, abnormal curvature of the spine and intercostal tumors²².

Lymphangioleiomyomatosis (LAM) and tuberous sclerosis complex (TSC)

Pulmonary LAM is a rare disease that almost exclusively affects women. It is caused by proliferating smooth muscle-like cells, the so-called “LAM cells”, which can involve small airways, the pulmonary vasculature and intrathoracic and extrathoracic lymphatic structures. The hallmark of the disease is a radiographic pattern of diffuse, numerous, round, thin-walled cysts, generally between 2 and 60 mm in diameter. Other pulmonary abnormalities include pneumothorax and pleural effusions. Eighty percent of patients develop a pneumothorax sometime during the course of their disease. Pleural effusions are almost always chylous. Both obstructive and mixed obstructive-restrictive ventilatory defects are observed in LAM.

LAM can occur as an isolated disorder or in 1–3% of patients with tuberous sclerosis complex (TSC), an autosomal dominant multisystem disorder characterized by hamartomas affecting brain, skin, heart, kidneys and lungs. The pulmonary ILD of TSC patients is indistinguishable from LAM²³; those affected are usually women over 30 years of age with little or no mental retardation. Major and minor criteria exist to diagnose the disease; two major features (or one major plus two minor features) are needed for diagnosis²⁴. The major features include facial angiofibromas, non-traumatic ungula or periungual fibromas, three or more hypomelanotic macules (which are most easily visualized with a Wood’s light), a rough, yellow thickening of skin over the lumbosacral area (known as a Shagreen patch), multiple retinal nodular hamartomas, cortical tubers, subependymal nodules or giant-cell astrocytomas, cardiac rhabdomyomas, LAM and/or renal angiomyolipomas. TSC patients with LAM have a high incidence of renal angiomyolipomas (>90%) compared to those with isolated LAM (~30%)²⁵.

Although TSC is characterized by its autosomal dominant inheritance, about two-thirds of patients have new mutations. Mutations in *TSC1* are found in 15–30% of all families and 10–15% of sporadic cases, whereas mutations in *TSC2* occur more frequently, accounting for 75–80% of all sporadic cases^{24,26,27}. Inactivation of both alleles of *TSC1* or *TSC2* through loss of heterozygosity is found in renal angiomyolipomas and supports Knudson’s two-hit model of tumor suppressor pathogenesis²⁸. Most sporadic LAM renal angiomyolipomas are characterized by two mutations in *TSC2*; a few are caused by *TSC1* mutations^{29–31}. In contrast with TSC patients whose germline mutations are present in tumor and normal tissues, genetic mutations are found only in abnormal lung and kidney cells in LAM patients.

The proteins encoded by *TSC1* and *TSC2* regulate the mammalian target of rapamycin (mTOR) pathway. Inhibition of the mTOR complex causes shrinkage of renal or

retroperitoneal angiomyolipomas and subependymal giant-cell astrocytomas in TSC patients^{32–34}. In addition, sirolimus, a mTOR inhibitor, stabilizes lung function, reduces respiratory symptoms and improves the quality of life of LAM patients³⁵.

Birt-Hogg-Dubé Syndrome (BHDS)

This rare disorder, initially described in 1977 by three dermatologists, is characterized by the autosomal dominant inheritance of multiple benign skin tumors including fibrofolliculomas. Approximately 90% of affected individuals have evidence of lung cysts³⁶, and ~10% have renal malignancy, usually with a hybrid oncocytic-chromophobe histology³⁷. The disease is caused by loss-of-function mutations in the folliculin (*FLCN*) gene³⁸. Two different studies, one using whole genome linkage analysis and the other a candidate gene approach, independently found that kindreds presenting solely with familial spontaneous pneumothorax and/or lung cysts have mutations in *FLCN* and represent a lung-limited form of BHDS^{39,40}. Overall 24% of patients have a history of spontaneous pneumothorax³⁶. The pulmonary cysts are generally bilateral, usually located in the mid-and lower-lung zones, of varying sizes, and ranging from round, oval, lentiform to multiseptated shapes^{41,42}. Since the skin findings typically appear in the 4th decade and the renal malignancy can be a late finding (mean age of 48 years), a spontaneous pneumothorax may be the presenting manifestation of this disease^{37,40}. Genetic testing is indicated for all individuals suspected of having BHDS, including those with multiple facial or truncal papules histologically characterized as fibrofolliculomas or angiofibromas, those with multiple or bilateral renal tumors and those with a family history of autosomal dominant primary spontaneous pneumothorax.

Hyper IgE syndrome (AD-HIES)

Autosomal dominant hyper IgE syndrome is an immune deficiency disorder characterized by the triad of recurrent staphylococcal skin abscesses, cyst-forming pneumonias and extreme elevations of IgE (usually > 2000 IU/ml). Survival is typically into adulthood and death is usually secondary to infection. Diagnosis requires a high level of suspicion due to variability of phenotypic features⁴³. A clinical scoring system has been developed that combines immunologic (elevated IgE, eosinophilia > 700/ μ L, decreased T_H17 cells, recurrent infections) and non-immune features (retained primary teeth, scoliosis, joint hyperextensibility, bone fractures following minimal trauma, a characteristic facial appearance and vascular abnormalities)⁴⁴. Pneumatocoeles and bronchiectasis, the result of the frequent pneumonias, are seen in approximately 70% of patients⁴⁵. The most common pathogens are *S. aureus*, *S. pneumoniae*, and *H. influenzae*. Although purulent sputum may be present, most patients with pneumonia often lack systemic signs of inflammation. The pneumatocoeles may be sites of fungal and gram negative infections, which lead to the significant mortality⁴⁶. Patients' purified native T cells are unable to differentiate *in vitro* into IL-17 producing (T_H17) T helper cells, which play a critical role in the clearance of fungal and extracellular bacterial infections of the lung and skin⁴⁷. Over 95% of patients have heterozygous missense, splice site or intragenic deletions of the *STAT3* gene⁴⁸. Most patients represent sporadic cases but autosomal dominant transmission has been seen in some kindreds.

Hermansky-Pudlak syndrome (HPS)

HPS is an autosomal recessive disease first described in 1959⁴⁹. It is characterized by oculocutaneous albinism, a bleeding diathesis resulting from platelet storage pool deficiency, and other organ involvement, including pulmonary fibrosis⁵⁰. Other clinical features of the disease include inflammatory bowel disease, cutaneous malignant melanomas, renal failure and cardiomyopathy. It is now known that HPS is caused by defects of multiple cytoplasmic organelles, including melanosomes, platelet-dense granules

and lysosomes. Currently the diagnosis is confirmed by the absence of dense bodies on whole mount electron microscopy of platelets⁵¹. Mutations in eight different genes cause this disease. Each of these genes functions in trafficking of vesicular cargo proteins to cytoplasmic organelles (*HPS2*)⁵² or organelle biogenesis and maturation (*HPS1*, *HPS3*, *HPS4*, *HPS5*, *HPS6*, *HPS7* and *HPS8*)^{53–57}. HPS is the most common single-gene disorder in Puerto Rico with an estimated frequency of about 1 in 1,800 and a carrier frequency of 1 in 21⁵⁸. Mutations in *HPS1* and *HPS3* are found in 75% and 25% of Puerto Rican HPS patients, respectively.

The clinical, physiologic and radiographic features of the pulmonary fibrosis associated with HPS are similar to those of idiopathic pulmonary fibrosis (IPF). Pulmonary fibrosis has been described most frequently in patients with *HPS1* mutations, and more rarely in patients with *HPS4* mutations^{59–63}. In one of the largest studies to date, the mean age of onset was 35 years with a range of 15 to 53 years⁵⁹. The variability of pulmonary findings was not attributable to prior environmental exposures (13% were prior smokers). Over 80% of patients had abnormalities on CT scans, which were generally predictive of the degree of physiologic impairment and mortality. Most patients demonstrate a peripheral distribution of HRCT reticulations with a trend toward increasing involvement of the central portions of the lungs. The amount of the interstitial reticulation, bronchiectasis and peribronchial thickening seen by HRCT correlates well with patient age and extent of pulmonary dysfunction⁶⁰. Surgical lung biopsies demonstrate lung remodeling, numerous chronic inflammatory cells and distinctive clusters of clear vacuolated type II pneumocytes with florid foamy swelling and degeneration (“giant lamellar body degeneration”)^{64,65}.

Mice homozygous for both *HPS1* and *HPS2* mutations (double mutant) develop spontaneous pulmonary fibrosis⁶⁶. The abnormalities begin with subpleural disease at 3 months and develop into extensive fibrosis by 9 months⁶⁷. The histology of the mouse lung replicates the human phenotype with “giant lamellar body degeneration” of the type II cells and demonstrates decreased phospholipid, surfactant protein B and C secretion^{66,68}.

Gaucher's disease

Gaucher's disease is an autosomal recessive lysosomal storage disease characterized by the accumulation of the glycolipid glucosylceramide due to the deficiency of the enzyme acid-beta glucosidase. Diagnosis relies on the demonstration of deficient enzyme activity in cells or the identification of two disease causing mutations in the *GBA* gene. Patients can display a large variety of symptoms, ranging from patients who are completely asymptomatic to those who present with perinatal lethality. The usual clinical findings include hepatosplenomegaly, anemia, thrombocytopenia, and bone manifestations including osteopenia, lytic lesions, bone crisis and skeletal deformities. Infiltration of Gaucher cells into the alveoli, interstitium and pulmonary capillaries can lead to lung involvement. Over 65% of patients with type I disease have pulmonary function abnormalities, but only a fraction (<5%) have diffuse lower-lobe linear infiltrates, restrictive physiological impairment and a reduced diffusion capacity consistent with ILD^{69,70}. Enzyme replacement therapy can reduce organ volumes, improve the hematologic parameters and bone pain, but are usually poorly effective in treating the lung manifestations of this disease⁷¹.

Niemann-Pick disease

Niemann-Pick disease types A and B are caused by an inherited deficiency of acid sphingomyelinase activity. Patients demonstrate a range of phenotypes from infantile death (type A) to later-onset with survival to adulthood (type B). Nearly all type B patients have hepatosplenomegaly and lung disease⁷². By thin-section chest CT scans, 98% have evidence of a basal-predominant ILD, with thickened interlobular septa, interlobular lines and ground

glass opacities; however, the radiographic appearance of the lung is not a good predictor of lung function⁷³.

Lysinuric Protein Intolerance (LPI)

LPI is an autosomal recessive disease caused by an inherited defect of cationic amino acid transport. Most patients present in infancy with failure to thrive, growth retardation, protein aversion, muscular hypotonia, hepatosplenomegaly and osteoporosis. In one study, all patients who developed a fatal respiratory insufficiency were children less than 15 years of age⁷⁴. Adult patients have evidence of an ILD on computed tomography (CT) scans of the chest with inter- and intralobular septal thickening and subpleural cysts, but only a few are symptomatic⁷⁴.

Genetic Diseases Primarily Affecting the Lung

Table 2 lists the genetic disorders in which an ILD is the dominant clinical feature. Within the last decade, a group of genetic disorders involving the production, processing and clearance of surfactant has been recognized as an important cause of neonatal and pediatric respiratory illness. This group, collectively referred to as Surfactant Dysfunction Disorders⁷⁵, encompasses a variety of mutations involving the genes that encode surfactant protein B (*SFTPB*), surfactant protein C (*SFTPC*), the ATP-binding cassette transporter A3 (*ABCA3*), and the receptor for granulocyte-macrophage colony stimulating factor (*CSF2R*). There are several good reviews of the surfactant dysfunction disorders in infants and children, and we refer you to these for more detail^{76–78}.

Surfactant metabolism dysfunction, type 1, and SP-B Deficiency

Surfactant protein B deficiency is inherited in an autosomal recessive manner, and the majority of affected patients develop respiratory failure in the neonatal period with rapid progression of disease and death at 3 to 6 months^{79–83}. Children with mutations associated with partial expression of the SP-B protein survive longer and go on to develop a chronic ILD^{84,85}.

Surfactant metabolism dysfunction, type 2, and SP-C Deficiency

Autosomal dominant lung disease due to mutations in the gene encoding surfactant protein C (SP-C), *SFTPC*, was first described by Noguee and colleagues in a mother and infant with heterozygous splice site mutations resulting in skipping of exon 4 and deletion of 37 amino acids⁸⁶. A large five generation kindred was later described with 14 affected family members, including four adults with surgical lung biopsy evidence of usual interstitial pneumonitis (UIP) and three children with nonspecific interstitial pneumonitis (NSIP), with a rare heterozygous missense SP-C mutation (L188Q)⁸⁷. Many other mutations in *SFTPC* have been identified, including the I73T missense variant, which may be one of the more common abnormal alleles^{88–90}. The lung disease associated with *SFTPC* mutations is characterized by marked phenotypic heterogeneity. Manifestations range from severe respiratory distress in infants to idiopathic pulmonary fibrosis (IPF) in older adults. Mutations of *SFTPC* are rare in individuals without a family history of pulmonary fibrosis^{91,92}. At present, the disease phenotype is thought to be caused by aberrant surfactant protein folding, decreased endogenous SP-C secretion, endoplasmic reticulum (ER) stress and apoptosis of alveolar epithelial cells^{93–96}.

Surfactant metabolism dysfunction, type 3, and ABCA3 mutations

There is a significant amount of phenotypic overlap between patients with *SFTPB* mutations and those with defects in *ABCA3*. This gene encodes for an ATP-binding cassette transporter that facilitates the translocation of phospholipids into lamellar bodies for the production of

surfactant in type II epithelial cells^{97–100}. Like SP-B deficiency, the disease is inherited in an autosomal recessive manner. Since the first mutation was discovered in 2004¹⁰¹, more than 100 distinct mutations have been found, and mutations in *ABCA3* may be the most common cause of inherited defects in surfactant metabolism^{102,103}. Initially, the *ABCA3* mutations were thought to cause only severe respiratory distress and death in infants. Recently it has been found that mutations in *ABCA3* are associated with a wider continuum of disease. Some patients have a more indolent course with the development of a chronic ILD in late childhood or during the adult years^{104–106}. One particular mutation resulting in the substitution of a valine residue for glutamic acid at position 292 (E292V) has been found in multiple, unrelated patients with a milder phenotype^{103,104}.

Surfactant metabolism dysfunction, type 4, and the GM-CSF Receptor Dysfunction

Pulmonary alveolar proteinosis (PAP) is a rare form of lung disease characterized by intra-alveolar overaccumulation of surfactant, which results in respiratory insufficiency. Histopathology specimens from affected patients demonstrate distal airspaces filled with foamy alveolar macrophages and a granular, eosinophilic material that stains positive with periodic acid-Schiff reagent. In general, the underlying lung architecture is normal, unless altered by infection¹⁰⁷. Approximately 90% of PAP cases are acquired (also referred to as primary) and are associated with the presence of antibodies against the GM-CSF receptor^{108–110}. These antibodies block GM-CSF signaling *in vivo*, reduce alveolar macrophage surfactant catabolism and impair surfactant clearance^{111–113}. Secondary PAP occurs in several different clinical settings, such as in association with hematologic malignancies, immunosuppression, inhalation of inorganic dusts and certain infections.

The GM-CSF receptor is composed of an α and a β chain, encoded by the *CSF2RA* and *CSF2RB* genes, respectively. The chains dimerize and activate downstream signaling *via* the signal transducer and activator of phosphorylation (STAT)5 protein. Mice with deletion of the gene encoding the GM-CSF receptor or GM-CSF itself demonstrate a phenotype very similar to adults with acquired PAP^{114,115}. To date, mutations in both *CSF2RA* and *CSF2RB* have been identified in children with PAP^{78,116}. In 2011, a case of adult-onset hereditary PAP was reported in a 36-year-old Japanese woman with a homozygous, single-base deletion at nucleotide 631 in exon 6 of *CSF2RB*¹¹⁷. Multiple hereditary PAP kindreds demonstrate autosomal recessive pattern of inheritance.

Familial adult-onset pulmonary fibrosis

The prototype of the adult-onset ILDs is idiopathic pulmonary fibrosis, IPF. This disease preferentially affects older males of white and Hispanic ethnicities, and smokers^{118,119}. The mean life expectancy is 2–3 years after diagnosis¹²⁰. In 2000, Marshall and colleagues published the first large collection of IPF kindreds and estimated that 0.5–2.2% of IPF cases are familial¹²¹. In 2005, Steele et al published an even larger number of kindreds with familial IPF; the largest ones demonstrated autosomal dominant inheritance with reduced penetrance¹²². Multiple studies have been performed investigating genetic associations with common single nucleotide polymorphisms (SNPs)¹²⁰. The most significant result has been found for a variant located within the cluster of mucin genes on chromosome 11, which is present in ~35% of subjects with familial or sporadic IPF and in 9% of controls¹²³.

Familial pulmonary fibrosis associated with telomerase mutations

Both a candidate gene approach and a whole genome linkage approach have led to the discovery of mutations in the genes encoding telomerase (*TERT* and *TERC*) in kindreds with familial pulmonary fibrosis (defined as kindreds with 2 or more cases of an idiopathic interstitial pneumonia or unclassified pulmonary fibrosis)^{124,125}. Heterozygous mutations in *TERT* are more common and are found in ~18% of familial pulmonary fibrosis kindreds and

~3% of sporadic idiopathic interstitial pneumonia patients^{125–127}. Mutations in *TERC* are more rare. As was seen in the dyskeratosis congenita patients with telomerase mutations, each of the *TERT* or *TERC* mutations is associated with short telomere lengths and decreased *in vitro* activity of telomerase^{125,126}. The mutations are loss-of-function frameshift, splice site or missense changes that span the length of the gene; most are private for the family in which they are found¹²⁷.

The penetrance of pulmonary fibrosis in the *TERT* mutation carriers is age and gender-dependent (Figure 1A)¹²⁷. Disease is rare in subjects less than 40 years of age. However the penetrance of pulmonary fibrosis increases with age and is higher in men than women. 60% of men >60 years of age have a self-reported diagnosis of ILD; for women of this age, 50% have pulmonary fibrosis.

The ILD subtype most commonly found in *TERT* mutation carriers is idiopathic pulmonary fibrosis (IPF). CT scans of the chest were evaluated for 39 different cases of *TERT* associated pulmonary fibrosis¹²⁷. For 74% of patients, their CT scan was typical of usual interstitial pneumonitis (UIP) and IPF, with reticulation concentrated at the periphery and bases accompanied by honeycombing (Figure 1C). For 13% of cases the CT scans were consistent with UIP except for an absence of honeycombing. For the remaining cases (13%), the CT scans were atypical of UIP because the fibrosis was predominantly located in the mid or upper lung fields or it was located along the bronchi. The majority of surgical lung biopsies specimens (86%) had histologic features of UIP (Figure 1D). Small, loosely-formed non-necrotizing granulomas were seen in 17%; these are not typically seen in IPF.

Over 95% of *TERT* mutation carriers with pulmonary fibrosis report past cigarette smoking or an exposure to a fibrogenic environmental or occupational agent, suggesting that alveolar epithelial damage in conjunction with the underlying inherited genetic predisposition leads to the lung disease¹²⁷. Overall, the clinical course of the *TERT*-associated pulmonary fibrosis mirrored that of IPF, with a mean survival of 3 year after diagnosis (Figure 1B)¹²⁷.

Familial pulmonary fibrosis, adult-onset, due to mutations in surfactant protein A

Whole-genome linkage analysis led to the mapping and identification of heterozygous mutations in the gene encoding surfactant protein (SP-)A2 (*SFTPA2*) in two kindreds with familial adult-onset pulmonary fibrosis and/or lung adenocarcinoma with features of bronchoalveolar cell carcinoma¹²⁸. Both mutations (G231V and F198S) reside within the highly conserved carbohydrate-recognition domain of the protein and are predicted to disrupt protein structure. Recombinant proteins carrying these mutations are retained within the ER and are not secreted into the culture media. In addition, the mutant proteins form fewer intracellular oligomers, demonstrate greater sensitivity to proteolytic digestion, and increase markers of ER stress¹²⁹. Family members with the heterozygous G231V mutation secrete comparable amounts of total surfactant protein A (encoded by two human paralogs, *SFTPA1* and *SFTPA2*) into the alveolar space, as compared with control family members¹²⁹. The mechanism of disease is not likely related to an overt lack of SP-A within the alveolar space, but instead related to pathogenic effects to epithelial cells expressing the mutant protein.

Familial pulmonary alveolar microlithiasis

Pulmonary alveolar microlithiasis (PAM) is a rare disorder characterized by laminated calcium-phosphate concretions within the alveoli. PAM is inherited in an autosomal recessive manner and is particularly prevalent in Turkey, Italy, the U.S. and Japan^{130–132}. The chest radiographs of patients with PAM show diffuse, bilateral, micro-nodular opacities, which obscure the heart border, mediastinum and diaphragmatic surfaces. Despite the

“sandstorm-like” appearance, the clinical presentation of PAM is variable^{130,131,133,134}. Early in the disease course, patients are often asymptomatic, but over time develop cough, dyspnea and a restrictive defect with reduced diffusion. At present, treatment is supportive and the overall prognosis is poor.

In 2006, Corut et al. reported the discovery of several mutations in the gene encoding the type IIb sodium-phosphate cotransporter protein (*SCL34A2*) in individuals with PAM¹³⁵. The group used linkage analysis of a large consanguineous family and ultimately identified six homozygous mutations in *SCL34A2* that predict loss of protein function. Using genome-wide single-nucleotide polymorphism (SNP) association mapping, a Japanese group independently identified mutations in *SCL34A2*¹³⁶. Two patients had homozygous frameshift mutations and four had splice-site mutations. None of the mutations were identified in normal controls. Since these initial discoveries, additional missense and frameshift mutations as well as intragenetic deletions have been identified^{137–139}. The *SCL34A2* gene is expressed in high levels in the lung, predominantly in type II epithelial cells^{140–142}. Its hypothesized role is to remove phosphate from the alveolar space^{135,136}.

Familial sarcoidosis

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology that affects the lungs in over 90% of patients; lymph nodes, liver, bone, spleen and other organs can also be involved¹⁴³. The development and progression of the ILD appear to result from the complex interaction of various genetic and environmental factors. The importance of genetic predisposition is indicated by observation of familial clustering¹⁴⁴, increased concordance in monozygotic twins as compared to dizygotic or non-twin siblings¹⁴⁵ and variations among different racial and ethnic groups^{146,147}. In a twin study from Finland and Denmark, monozygotic twins had an 80-fold increased risk for developing sarcoidosis compared to a 7-fold increased risk among dizygotic twins¹⁴⁵. Although there were statistically more concordant pairs among monozygotic twins compared to dizygotic twins, the majority of monozygotic twins were actually discordant for the presence of disease. Strong genetic associations are found with polymorphisms within the major histocompatibility complex (MHC)¹⁴⁸; some of these are also associated with disease phenotype and progression. For other, well-studied associations we refer the reader to the following references^{149,150}.

Clinical Management of Genetic Interstitial Lung Diseases

The ILDs are a clinically heterogeneous group of pulmonary disorders and the genetic underpinnings of this group demonstrate that aberrations of multiple different pathways can lead to interstitial disease. Given the increasing volumes of data generated by novel genetic and genomic techniques, how does the clinician make sense of all these genetic discoveries? For all these various genetic polymorphisms and mutations, what information is clinically significant or will influence patient care?

The risk to benefit ratio for genetic screening is specific for each disorder and is related to its pre-test probability and the availability of therapeutic actions. Given the current cost of genetic screening for mutations or intragenic deletions and the possibility of identifying genetic variants of unknown clinical significance, this approach is generally reserved for those diseases that show low genetic locus heterogeneity and those diseases for which a particular genetic diagnosis would impact clinical care. The following case illustrates both of these points.

The proband of kindred F42 is a 37 year old white female who was referred for evaluation of familial spontaneous pneumothorax (Figure 2). She had suffered four spontaneous pneumothoraces and underwent bilateral video-assisted thoracic surgery with bleb resection

and mechanical pleurodesis. Her family history was significant for a great uncle who also had multiple spontaneous pneumothoraces. Because her CT scan of the chest showed multiple subpleural and intraparenchymal lung cysts, a diagnosis of Birt-Hogg-Dubé syndrome (BHDS) was considered. Genetic sequencing of the *FLCN* gene of the proband revealed a heterozygous deletion of a coding nucleotide that predicts the premature termination of the protein; this variant has been previously described in families with BHDS³⁷. Her available family members were screened for this deleterious variant and three other mutation carriers were identified. Each individual underwent genetic counseling and screening for kidney cancer. Renal ultrasound of the 35 year sister revealed a 3cm right mass and she was referred for partial nephrectomy.

This case illustrates how the pulmonary phenotype (here, familial spontaneous pneumothorax) may be the presenting symptom that provides the clue for the underlying disorder. This case also demonstrates that mutations in a single gene may result in a spectrum of clinical manifestations. The characteristic skin lesions for BHDS are frequently not seen until the 4th decade and were not apparent in the proband or her younger sister, who had also inherited the same *FLCN* mutation. Genetic analysis is recommended in the work up of BHDS because there is no locus heterogeneity (only one culprit gene is known) and the presence of a mutation necessitates screening for renal cancer, which is found in ~10%. In this case, nephrectomy was curative.

Is genetic screening indicated for the other inherited ILDs? Certainly, in many cases the identification of a genetic mutation clarifies the underlying diagnosis and may explain a variety of seemingly unrelated clinical phenotypes. However, in some cases genetic screening yields a rare variant of unknown clinical significance. The variant may be so rare that it has not been previously described or its functional effects on the resulting protein are unpredictable. Penetrance of clinical phenotypes is another key issue. Predictions of genetic risk for first degree family members are tenuous for dominant genetic mutations of low penetrance. Genetic counseling of patients prior to mutation analysis needs to be specific for each disease and clinical scenario.

The ultimate goal of genetic investigations is to identify the underlying molecular pathogenesis of the disease. The identification of new targets for therapeutic intervention may lead to successful treatments of the ILDs. The success of sirolimus in stabilizing lung function, reducing respiratory symptoms and improving the quality of life of tuberous sclerosis/LAM patients is proof of concept that therapy targeting defective genetic and biochemical pathways can be successful³⁵. Let us hope that other personalized medical therapies will be soon in coming for other inherited ILDs. Until that time, the genetic work up for some of these conditions may clarify the diagnosis for the proband and in some situations provide clinical predictions for related family members.

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Figure 1. Characteristics of ILD associated with telomerase (*TERT*) mutations

(A) Penetrance of self-reported pulmonary fibrosis is shown for men (yellow) and women (blue bars) of different ages. Penetrance of pulmonary fibrosis for men vs. women 40–49, 50–59 and >60 years of age is 14% vs. 2%, 38% vs. 14% and 60% vs. 50%. (B) Kaplan-Meier survival curve of 47 different *TERT* mutation carriers with ILD demonstrate a mean survival of three years after diagnosis. (C) Computed tomography (CT) scans of three different *TERT* mutation carriers with ILD. Representative cases are shown with a pattern typical of Usual Interstitial Pneumonia (UIP) with peripheral, basal-predominant fibrosis and moderate to severe honeycombing (a,b), a pattern consistent with UIP except for the absence of honeycombing (c,d) and a pattern atypical of UIP with fibrosis predominantly affecting the upper lobes and along the bronchi (e,f). Scans are shown at the level of the carina (a, c, e) and the lung base (b, d, f). The majority of carriers (74%) had a CT scan typical of UIP, 13% had a CT scan consistent with UIP except for the absence of honeycombing and 13% had a CT scan atypical of UIP. (D) Histology of surgical lung biopsies from *TERT* mutation carriers with ILD. The majority of cases (86%) of *TERT* mutation carriers with lung specimens available for review had diagnostic histologic features of UIP. In this low magnification view of UIP (g), typical variegated honeycomb areas are seen alternating with normal areas and scarred lung. The cases shown in (h) shows increased inflammation and a small, loosely aggregated non-necrotizing granuloma (arrows) that is characterized by a cluster of epithelioid histiocytes and multinucleated giant cells surrounded by chronic inflammation in the interstitium. Panels g and h are shown at 40 and 100-fold magnification, respectively. Adapted from figures originally published in reference¹²⁷.

Figure 2. Birt-Hogg-Dubé (BHD) syndrome presenting as recurrent spontaneous pneumothoraces

(A) Condensed pedigree of kindred F42 presenting with familial spontaneous pneumothorax. Circles represent females; squares represent males. Individuals with a pneumothorax, lung cysts as detected by high resolution CT scans of the chest, fibrofolliculomas, and renal cancer are indicated by blue, green, yellow and red symbols, respectively. The presence of a heterozygous frameshift mutation in the gene encoding folliculin (*FLCN*) predicting the premature termination of the protein is indicated by the plus signs. The sequence variant is described according to recommended guidelines¹⁵¹. Of the four mutation carriers, only the two elder family members had histopathologic evidence of multiple fibrofolliculomas, the characteristic skin lesion of BHD syndrome. The proband, her sister and mother have evidence of at least one pulmonary cyst by high resolution computed tomograph (HRCT). A 3 cm renal mass was detected in the proband's sister and she was referred for partial nephrectomy. (B) HRCT scan of the proband reveals multiple subcentimeter cysts (indicated by the arrows) within the lower lobes.

Table 1**Inherited ILD: Disorders with Multiple Organ Pathology**

Disease	Inheritance	Gene^I	Pathogenesis	Presentation
Dyskeratosis congenita	XLR, AD, AR	<i>DKC1</i> <i>TERC</i> <i>TERT</i> <i>TINF2</i>	Telomere shortening	ILD
Neurofibromatosis, type I	AD	<i>NF1</i>	Loss of function of tumor suppressor	ILD, Bullae
Tuberous Sclerosis/LAM	AD	<i>TSC1</i> <i>TSC2</i>	Proliferation of LAM cells	Multiple cysts
Birt-Hogg-Dubé Syndrome	AD	<i>FLCN</i>	Loss of folliculin	Multiple cysts
Hyper IgE syndrome	AD	<i>STAT3</i>	Lack of T _H 17	Pneumatoceles, bronchiectasis
Hermansky-Pudlak syndrome	AR	<i>HPS1</i> <i>HPS4</i>	Defects of cytoplasmic organelles	ILD
Gaucher disease, type I	AR	<i>GBA</i>	Deficiency of acid β -glucosidase	ILD, PAH
Niemann-Pick disease, type B	AR	<i>SMPD1</i>	Deficiency of acid sphingomyelinase	ILD
Lysinuric protein intolerance	AR	<i>SLC7A7</i>	Defect of cationic amino acid transport	PAP, ILD

^I Mutations in these gene(s) have been found in patients with the following disorders and an ILD. Abbreviations: AD, autosomal dominant; AR, autosomal recessive; XLR, x-linked recessive; ILD, interstitial lung disease; PAH, pulmonary arterial hypertension; PAP, pulmonary alveolar proteinosis; LAM, lymphangioleiomyomatosis; IgE, immunoglobulin E; T_H17, T helper 17 cells.

Table 2**Inherited ILD: Disorders with Primary Lung Pathology**

Disease	Inheritance	Gene	Pathogenesis	Presentation
Surfactant Metabolism Dysfunction 1	AR	<i>SFTPB</i>	Absent SP-B	Neonatal respiratory failure
Surfactant Metabolism Dysfunction 2	AD	<i>SFTPC</i>	Lack of SP-C and ER stress	ILD, PAP
Surfactant Metabolism Dysfunction 3	AR	<i>ABCA3</i>	Defective transport of phospholipid into lamellar bodies	PAP, ILD
Surfactant Metabolism Dysfunction 4	AR	<i>CSF2RA</i> <i>CSF2RB</i>	Defective GM-CSF signaling	PAP
Familial Pulmonary Fibrosis	AD	<i>TERT</i>	Telomere shortening	ILD
		<i>TERC</i>		
	AD	<i>SFTPA2</i>	ER stress of alveolar epithelium	ILD
Pulmonary Alveolar Microlithiasis	AR	<i>SLC34A2</i>	Reduced phosphate clearance from alveolar space	Micronodules

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; ILD, interstitial lung disease; PAP, pulmonary alveolar proteinosis; SP-B, surfactant protein B; SP-C, surfactant protein C; ER, endoplasmic reticulum; GM-CSF, granulocyte macrophage colony stimulating factor.