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Recognizing genetic disease: A key aspect of pediatric pulmonary care

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Abstract

Advancement in technology has improved recognition of genetic etiologies of disease, which has impacted diagnosis and management of rare disease patients in the pediatric pulmonary clinic. This review provides an overview of genetic conditions that are likely to present with pulmonary features and require extensive care by the pediatric pulmonologist. Increased familiarity with these conditions allows for improved care of these patients by reducing time to diagnosis, tailoring management, and prompting further investigation into these disorders.

Keywords

bronchiectasis and primary ciliary dyskinesia; cystic fibrosis (CF); genetics/Genome-Wide Association Studies (GWAS); immunology and immunodeficiency; surfactant biology and pathophysiology

1 | INTRODUCTION

As primary care physicians are often comfortable handling more common diseases, referral to a pediatric pulmonologist is frequently based on the presence of unusual signs and symptoms or advanced progression of disease. In some cases, these uncommon presentations may be due to an underlying genetic etiology. Therefore, an understanding of genetic diseases that have a respiratory component is crucial for the pediatric pulmonologist.

Comfort with the principles of genetics and genetic counseling are important elements of caring for patients with genetic conditions; these key aspects are reviewed in the companion article by Hawley et al. The goal of this review is to provide a concise overview of monogenic diseases with pulmonary features that present in the pediatric setting, highlighting current understanding of these conditions. In this review, we focus on genetic diseases that cause acute respiratory distress of the newborn, bronchiectasis, pulmonary

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fibrosis, vascular abnormalities, pneumothorax, and central hypoventilation. Table 1 provides an overview of the genetic conditions discussed in this review. Many additional genetic conditions, such as neuromuscular disorders or chromosomal abnormalities, frequently require care by the pediatric pulmonologist but are outside of the scope of this review.

2 | ACUTE RESPIRATORY DISTRESS OF THE NEWBORN/SURFACTANT DYSFUNCTION DISORDERS/OTHER INFANTILE FORMS OF DIFFUSE LUNG DISEASE

- ABCA3, SFTPB, and SFTPC-related surfactant dysfunction
- Brain-lung-thyroid syndrome
- Pulmonary alveolar proteinosis

2.1 | Clinical overview

Acute respiratory distress during the neonatal period, as characterized by hypoxemia and retractions, is expected in preterm infants due to immature lung development. However, if these signs and symptoms present in a full-term infant, or to a more severe degree than would be explained by prematurity alone, surfactant deficiency or dysfunction should be considered. Surfactant dysfunction disorders result from abnormal production or transport of the phospholipids and proteins that comprise the pulmonary surfactant complex. Surfactant is produced by alveolar type II epithelial cells before birth and is required to reduce surface tension in the alveolar space.[1,2] Abnormal quantity or quality of surfactant results in alveolar collapse and insufficient gas exchange, leading to hypoxemia and hypercapnia. Infants with surfactant dysfunction display signs of respiratory distress often leading to respiratory failure in the newborn nursery.

In some cases, neonates may be well enough to be discharged home after delivery, but display chronic tachypnea, retractions, and failure to thrive. These infants are hypoxemic and often have crackles on exam. In milder disease, symptoms may present over time, occasionally even in adulthood. Symptoms include dyspnea and exercise intolerance with associated digital clubbing. These patients may have been diagnosed with interstitial lung disease or pulmonary fibrosis.[2] Patients can present with recurrent respiratory infections (ie, infectious exacerbations of the underlying surfactant dysfunction), and crackles or wheezing can be heard on physical exam. Chest X-rays often demonstrate low lung volumes and diffuse homogenous granular opacities.[3] Chest computed tomography (CT) findings include ground glass opacities, cysts, atelectasis, and fibrosis in older patients.[4,5]

Nongenetic causes of respiratory failure in a full-term newborn include infection, meconium aspiration, or aspiration due to an anatomic defect such as a tracheoesophageal fistula or laryngeal cleft must be considered before ordering genetic testing. The most common genetic causes, discussed in depth below, include surfactant deficiencies related to *ABCA3*, *SFTPB*, *SFTPC*, and *NKX2-1* mutations. Pulmonary alveolar proteinosis (PAP), which also disrupts surfactant homeostasis and may have a genetic etiology, does not typically present

in the newborn period, however, given its similarity in surfactant homeostasis dysfunction, it is also discussed below. Figure 1 shows cellular disease pathology of surfactant dysfunction, with corresponding genetic mutations.

Other causes of neonatal interstitial lung disease, including neuroendocrine hyperplasia of infancy (NEHI) and pulmonary interstitial glycogenosis (PIG), should also be considered. *NKX2-1* mutations have been described in NEHI, although this is a minority of cases, and no genetic mutations have been associated with PIG; further research into a likely genetic predisposition for these diseases is needed.[6,7]

Several additional genetic syndromes not included in this review that are associated with a disruption of surfactant homeostasis have been described, including interstitial lung and liver disease (associated with the *MARS* gene), lysinuric protein intolerance (associated with the *SLC7A7* gene), and Niemann-Pick disease type C2 (associated with the *NPC2* gene). Immunodeficiencies, specifically *GATA2*-deficiency and 22q11.2 microdeletion syndrome, also known as DiGeorge syndrome, can also exhibit surfactant abnormalities.[8,9]

Other genetic conditions can also cause respiratory distress in the full-term neonate, including primary ciliary dyskinesia (PCD) and alveolar capillary dysplasia with misalignment of pulmonary veins (ACD/MPV) which are discussed later in this review. Loss-of-function mutations in the *FLNA* gene which encodes filamin A, a key protein guiding cell shape and migration, can also result in lobar hyperinflation and respiratory failure in young infants.[10] Loss-of- function mutations in *FLNA* have also been associated with pulmonary hypertension and pneumothorax in older age groups, which are discussed later in this review.[10,11]

2.2 | Genetic conditions

2.2.1 | Surfactant dysfunction disorders—Surfactant dysfunction most often results from mutations in the *ABCA3*, *SFTPB*, or *SFTPC* genes. Surfactant dysfunction is associated with various inheritance patterns and clinical presentations depending on the underlying genetic defect. *ABCA3* and *SFTPB*-related surfactant deficiencies are inherited in an autosomal recessive pattern, while *SFTPC*-related surfactant dysfunction is inherited in an autosomal dominant pattern.

Mutations in the *ABCA3* gene, which encodes a protein involved in surfactant production and transport, are the most common genetic cause of surfactant dysfunction. *ABCA3*-related surfactant dysfunction can present in infancy, childhood, or rarely in adulthood.[2] Lung biopsy reveals PAP and desquamative interstitial pneumonitis in the neonatal period, and nonspecific interstitial pneumonitis in older children. On electron microscopy, dense abnormal lamellar bodies can be seen.[12] Loss of function or null mutations in *ABCA3* result in the complete absence of protein production and are associated with a more severe clinical presentation with lung transplantation or death within the first year of life being the usual outcome. Missense variants and other mutation types are associated with a more variable disease trajectory.[13]

Individuals with pathogenic changes in the *SFTPB* gene, which encodes surfactant protein B, can have a similar clinical course to those with *ABCA3* mutations, typically experiencing acute respiratory failure and death in the newborn period. Lung biopsy also shows PAP desquamative interstitial pneumonitis, but absent lamellar bodies on electron microscopy.[4]

The *SFTPC* gene encodes surfactant protein C and is associated with autosomal dominant inheritance, variable severity, and reduced penetrance. Individuals with *SFTPC* mutations can exhibit neonatal respiratory distress, but more frequently present with interstitial lung disease at varying ages of onset.[2,14,15] Lung biopsy shows differing degrees of PAP, fibrosis, and desquamative interstitial pneumonitis, and lamellar bodies may be normal or disorganized on electron microscopy.[4] The majority of *SFTPC* mutations occur as de novo changes, while others are inherited, often from unaffected or mildly affected parents. Some mutations in *SFTPC* result in loss of function of the protein, while others, usually missense variants, resulting in the production of an abnormal protein product that disrupts function.[2,16]

2.2.2 | Brain-lung-thyroid syndrome—Mutations in the *NKX2-1* gene, previously known as the thyroid transcription factor-1 (*TTF1*) gene, are also associated with neonatal or childhood-onset interstitial lung disease. However, in contrast to *ABCA3, SFTPB*, and *SFTPC*-related surfactant deficiencies, individuals with *NKX2-1* mutations often present with additional clinical features resulting from disruption of brain and thyroid development. About half of individuals exhibit involvement of all three organ systems, while the other half can manifest any combination of the associated features.[17,18] Most individuals have some neurological involvement, with childhood onset of chorea being one of the hallmark features of the disease. Patients may also have intention tremor, dysarthria, facial apraxia, sensorineural hearing loss, hypotonia, motor delay, attention deficit hyperactivity disorder, learning disabilities, myoclonus, dystonia, ataxia, and structural brain abnormalities.[19] Thyroid problems include congenital hypothyroidism, compensated hypothyroidism, and hypoplasia or aplasia.[17,20]

Lung disease is the leading cause of mortality in brain-lung-thyroid syndrome patients. Approximately, 50% of individuals with *NKX2-1* mutations have some degree of pulmonary dysfunction, although clinical presentation and age of onset of lung disease are variable.[5,17] Respiratory distress may occur in the neonatal period,[18,21,22] while other patients can present with interstitial lung disease or pulmonary fibrosis at any age.[5,17] CT findings in patients with lung disease can include mild to diffuse ground-glass opacities, cysts, atelectasis, and fibrosis. Data from lung biopsies in these patients are limited but can have an appearance typical of surfactant dysfunction disorders.[5,22] NEHI, a form of interstitial lung disease characterized by tachypnea, crackles, retractions, and hypoxemia in infancy, has been reported in rare cases in association with *NKX2-1* mutations.[7,23] Most cases of NEHI do not have a clear genetic cause; diagnosis relies on typical CT patterns or lung biopsy.[24] There have also been a few reports of individuals with *NKX2-1* mutations developing pulmonary carcinoma, although the association of *NKX2-1* related conditions with cancer remains unclear.[5,25]

Brain-lung-thyroid syndrome results from dysregulation of neuron development and migration in the brain, altered expression of surfactant genes in the lungs, and reduced hormone production in the thyroid gland. These functions all are attributable in part to the homeobox gene, *NKX2-1*, which encodes the Nkx-2.1 transcription factor.[21,26] Mutations in the *NKX2-1* gene resulting in reduced protein production or abnormal protein function are associated with brain-lung-thyroid disease and other *NKX2-1* related conditions, such as benign hereditary chorea. Deletions of the entire *NKX2-1* gene have also been reported. *NKX2-1* related conditions are inherited in an autosomal dominant pattern with markedly variable expressivity among affected individuals.[18]

2.2.3 | Pulmonary alveolar proteinosis—PAP also causes disruption of surfactant homeostasis. However, PAP usually presents in adolescents or adults, and rather than an absence of surfactant, there is an accumulation of surfactant in the alveolar space. Individuals with PAP may develop signs of interstitial lung disease, including dyspnea, exercise intolerance, and dry cough, with crackles on the exam and a “crazy paving” pattern on CT imaging of the chest. Bronchoalveolar lavage reveals copious frothy liquid, and lung biopsy is characterized by amorphous periodic acid-Schiff-positive fluid filling the alveolar space.[27,28]

Although PAP can occur following exposure to toxins or infection, autoimmune PAP is the most common cause of PAP, with autoantibodies targeting granulocyte-macrophage colony-stimulating factors (GM-CSF).[27] Genetic causes of PAP are rare but should be considered, especially in children. Mutations in *CSF2RA* and *CSF2RB* genes, which encode the target receptors for GM-CSF, have been reported in autosomal recessive PAP with reduced penetrance.[8]

3 | BRONCHIECTASIS

- Cystic fibrosis
- Primary ciliary dyskinesia
- Immune deficiencies
- Autosomal recessive pseudohypoaldosteronism-type 1

3.1 | Clinical overview

Bronchiectasis is irreversible dilation of the bronchial lumen, with resulting reduced mucus clearance. Bronchiectasis can be focal and isolated, or it can be progressive and become diffuse. Nongenetic causes of bronchiectasis can include chronic aspiration, allergic hypersensitivity, severe lung infection, and inhalation injury.[29] Areas of the lung affected by bronchiectasis are at increased risk for inflammation and infection. Clinical features include cough, sputum production, recurrent respiratory infections, and occasionally, hemoptysis. Genetic causes of bronchiectasis that should be considered in pediatric patients include cystic fibrosis (CF), PCD, immune defects, and pseudohypoaldosteronism (Figure 2). Bronchiectasis has also been reported as a rare complication of Marfan syndrome, which is discussed later in this review.[30]

3.2 | Genetic conditions

3.2.1 | Cystic fibrosis—CF, characterized by obstructive lung disease and pancreatic insufficiency, is one of the most common pediatric genetic conditions. It is an autosomal recessive condition associated with mutations in the *CFTR* gene, which encodes an epithelial chloride ion channel known as cystic fibrosis transmembrane conductance regulator (CFTR). Loss of CFTR expression leads to abnormal chloride transport which results in mucus obstruction in the pancreatic ducts and lungs.[31,32]

Recurrent infections in these patients can cause bronchiectasis, chronic cough, sputum production, dyspnea, airway obstruction, hemoptysis, and pneumothorax. Individuals with CF eventually progress to respiratory failure due to the accumulation of extensive lung damage, which is the principal cause of death in this patient population.[31] CF-associated bronchiectasis generally presents within the first few years of life and is progressive. It is usually bilateral and can be saccular or cystic in appearance.[33,34] Common infections in the CF population include various strains of *Pseudomonas*, *Staphylococcus aureus*, and *Haemophilus influenzae*. Additional manifestations include diabetes, sinusitis, gastrointestinal complications, and male infertility due to congenital absence of the vas deferens.[32]

CF is now universally screened for in the United States as a part of the newborn screening program; however, this screening does not identify all affected individuals, and clinical suspicion should guide additional diagnostic work-up. A positive newborn screen or high level of clinical suspicion at any age warrants quantification of sweat chloride through pilocarpine iontophoresis (“sweat test”), which should be completed at an accredited Cystic Fibrosis Center. Individuals found to have elevated sweat chloride levels (>60 mmol/L) should have full gene sequencing, with deletion and duplication analysis, at a clinical diagnostic laboratory.[35]

Pathogenic variants in *CFTR* are categorized into five classes based on the mechanism by which they cause disease. These mutation classes are associated with variable expressivity of symptoms. Mutations with a more severe impact result in the classical multisystemic presentation, while those at the mild end are associated with isolated congenital absence of the vas deferens or can be found in asymptomatic individuals.[31,36] An online database known as CFTR2 (https://www.cftr2.org/) is maintained by CF experts and provides detailed information about specific variants, including whether a variant is disease-causing and the clinical features of variant carriers.

CF occurs in patients of all ethnicities but has the highest prevalence in the Caucasian population with carrier rates of approximately 1:28 in individuals of Northern European descent.[37,38] The life expectancy of patients with CF has increased at a steady rate from 28 years in 1986 to 47.7 years in 2016 due to advances in treatment. The advent of CFTR modulators that can partially restore the function of the chloride channel in patients with specific mutations has been a major breakthrough for the treatment of patients with CF, particularly with the recent introduction of elexacaftor-tezacaftor-ivacaftor combination therapy that is indicated for nearly 90% of patients. These drugs, as well as other therapies

under development, should have a substantial impact on overall life expectancy and quality of life for these patients in the coming years.[32,39,40]

CF-related metabolic syndrome, CF screen positive inconclusive diagnosis, and CF-related disorders are terms that are used to describe individuals who do not meet the full criteria for CF. These individuals may develop isolated features of CF, such as bronchiectasis, sinus disease, or absence of the vas deferens, or they may remain asymptomatic. They may have an intermediate sweat chloride (30–59 mmol/L) with one or no CF-causing mutation, or a normal sweat chloride (<30 mmol/L) despite two *CFTR* mutations.[41,42] Although genotype-phenotype predictions are available for some combinations of mutations, additional factors, including environmental influences and genetic modifiers can impact disease expression. Therefore, this information is not predictive of clinical course on an individual level and patients with mild mutations should still receive periodic monitoring for clinical features of CF.[43]

3.2.2 | Primary ciliary dyskinesia—PCD, previously known as immotile cilia syndrome or, if in conjunction with situs inversus, Kartagener's syndrome, is one of a group of genetic conditions known as ciliopathies that are characterized by ciliary dysfunction.[44] PCD results from abnormalities in structure or function of motile cilia, which line the respiratory tract, the ventricles of the central nervous system, the Fallopian tubes, and are required for sperm mobility. The most common ultrastructure defects in individuals with PCD result in absent or shortened dynein arms of the cilia, which are essential for a proper beating. The pulmonary symptoms associated with PCD, including recurrent respiratory tract infections and bronchiectasis, are caused by inadequate mucociliary clearance leading to mucus retention.[45–47]

Individuals with PCD often present during the newborn period with nasal congestion and as full-term neonates with respiratory distress requiring supplemental oxygen; however, the diagnosis of PCD is rarely made in infancy.[48] PCD-associated respiratory distress is characterized by tachypnea, lobar collapse, hypoxemia, and atelectasis.[49] Most individuals develop bronchiectasis involving the right middle lobe and lower lobes. Chronic cough, recurrent infections, digital clubbing, and obstructive lung disease are also observed in these patients.[46,50]

Extrapulmonary features include recurrent sinusitis and chronic otitis media that, if severe, can lead to conductive hearing loss. Approximately, 50% of individuals with PCD are reported to have laterality defects, including situs inversus totalis, heterotaxy with or without polysplenia, and congenital heart defects. However, there may be ascertainment bias in these reported rates due to the high clinical suspicion for PCD when these laterality defects are identified.[50–52] Therefore, PCD should still be considered in the absence of laterality defects in individuals with consistent sino-pulmonary features. Most affected males are infertile due to abnormalities of sperm flagellar structure with the exception of those with *CCDC114* mutations. Females are typically fertile but can experience issues due to the role of cilia in egg transport.[47]

The American Thoracic Society recently published guidelines regarding the diagnosis of PCD.[53] Use of nasal nitric oxide (nNO) is suggested as the first line of testing, if possible, with reflex to genetic testing and/or ciliary biopsy to corroborate the diagnosis. When nNO is not possible, gene panel testing is recommended as the initial diagnostic study. Notably, negative gene panel does not definitively rule out PCD, as approximately 30% of individuals with high clinical suspicion have negative or inconclusive genetic testing results.[52] Transmission electron microscopic analysis of ciliary ultrastructure, obtained by sampling the nasal or carinal epithelium, is not recommended as a first-line study as structural changes can be subtle and ciliary biopsy can even appear unremarkable in many individuals with PCD.[54] However, ciliary ultrastructure analysis can be used to aid in clarifying a diagnosis, particularly in cases where genetic testing results are inconclusive.[53]

PCD is typically inherited in an autosomal recessive pattern, with biallelic pathogenic changes in the *DNAI1*, *DNAH5*, and *DNAH11* genes as the most common causes of disease.[55,56] Two genes, *OFD1* and *RPGR*, are associated with syndromic X-linked recessive forms of PCD. To date, over 40 genes have been associated with PCD.[49]

3.2.3 | Primary immunodeficiencies—Primary immunodeficiencies (PID) encompass over 180 monogenic disorders that cause an intrinsic defect in the immune system. PID can present with varying clinical severity or infection tendencies. The most severe types are lethal in infancy or early childhood, while milder types can cause minimal symptoms or be subclinical. Individuals with PID may develop recurrent and persistent infections caused by organisms that are rarely infectious in the general population, or they may develop inflammatory-mediated interstitial lung disease. The pulmonary phenotype of these conditions can be similar to what is observed in CF and PCD patients: bronchiectasis, asthma, chronic cough, and dyspnea.[57–59]

Severe combined immunodeficiency (SCID) is a rare severe condition affecting both cellular and humoral immunity, characterized by absent T lymphocytes with variable B and natural killer cell function that presents in infancy with life-threatening infections.[60] The most common type of SCID is inherited in an X-linked recessive pattern and caused by mutations in the *IL2RG* gene. The most common autosomal recessive causes of SCID result from mutations in the *ADA, CD3D, DCLRE1C, JAK3, RAG1*, and *RAG2* genes.[61] SCID is lethal without effective treatment, usually a bone marrow transplant, and is, therefore, included as a part of the national newborn screening program in the United States and several other countries.[62]

Common-variable immune deficiency (CVID) is one of the most prevalent PIDs and is characterized by B cell dysfunction resulting in low immunoglobulin levels. CVID can often be mild and may not be recognized until adulthood.[58,59] The majority of CVID cases occur in individuals with no apparent family history of the disorder and may have a multifactorial inheritance. When a genetic cause is identified, the most commonly mutated gene is *TNFRSF13B* (previously known as *TACI*). *TNFRSF13B*-associated CVID can be inherited in an autosomal dominant or recessive pattern.[63,64]

The majority of pediatric-onset PID is inherited in autosomal recessive or X-linked recessive patterns; however, in a large proportion of individuals with suspected immune deficiencies, underlying genetic causes are not identified. It is also important to note that several syndromic genetic conditions, including DiGeorge syndrome, trisomy 21, Noonan syndrome, ataxia-telangiectasia, and Wiskott-Aldrich syndrome, are also associated with immunodeficiency, and recurrent infections in these patient populations may warrant further immune work-up and treatment.[62]

Identification of unusual pathogens or recurrent/severe infections in a child should prompt an immune evaluation including measurement of immunoglobulin levels (including response to immunizations), complement function, neutrophil function, mitogen and antigen responses, and flow cytometry to measure immune cell populations, guided by the clinical suspicion of the underlying immune defect.

3.2.4 | Autosomal recessive pseudohypoaldosteronism-type 1—Autosomal recessive pseudohypoaldosteronism-type 1 (PHA1) is characterized by salt wasting leading to hyponatremia, hyperkalemia, and severe dehydration. Systemic PHA1 often presents within the first two weeks of life, with varying severity. Symptoms include failure to thrive, fatigue, nausea, vomiting, and muscle weakness. Individuals with autosomal recessive PHA1 have high plasma levels of aldosterone and renin. Additional features include cardiac arrhythmias, skin eruptions, cholelithiasis, and short stature. Life-long salt supplementation is usually necessary; however, salt-wasting episodes tend to decrease in frequency and severity over time.[65,66]

Respiratory symptoms of autosomal recessive PHA1 are similar to CF: cough, chest congestion, excessive, thick airway mucus, and recurrent lower respiratory infections. In addition, patients with PHA1 can have positive sweat chloride testing, which can lead to misdiagnosis of CF.[67,68] However, unlike the progressive clinical course of CF, respiratory symptoms in PHA1 tend to improve over time.[65,66,69]

Mutations in the *SCNN1A*, *SCNN1B*, and *SCNN1G* genes, encoding the alpha, beta, and gamma subunits of the epithelial sodium channel, respectively, result in autosomal recessive PHA1.[70] Loss of function of these genes results in reduced or absent function of the epithelial sodium channel, which is found in the kidneys, lungs, and sweat glands, leading to a reduced stimulatory response to aldosterone.[71] The autosomal dominant form of PHA1 is isolated to the renal manifestations.[65]

4 | PULMONARY FIBROSIS

- Short telomere syndromes
- Hermansky-Pudlak syndrome

4.1 | Clinical overview

Patients presenting with exercise intolerance, hypoxia, or desaturation with activity should prompt the consideration of pulmonary fibrosis. Crackles can be heard on auscultation of the lungs, and pulmonary function testing reflects restrictive patterns with a decreased diffusion

capacity. Chest CT shows patchy peripheral reticular abnormalities with intralobular linear opacities, irregular septal thickening, subpleural honeycombing, and traction bronchiectasis. Although in the adult population pulmonary fibrosis may be multifactorial, resulting from a combination of genetic and environmental risk factors,[72,73] it is exceedingly rare in the pediatric population and underlying causes are often identifiable, including genetic conditions, such as short telomere syndromes and Hermansky-Pudlak syndrome (HPS). Pulmonary fibrosis is also reported in several other conditions discussed in this review including, brain-lung-thyroid syndrome, Marfan syndrome, and surfactant deficiencies.

4.2 | Genetic conditions

4.2.1 | Short telomere syndromes—Eukaryotic chromosomes end in structures known as telomeres, which are repetitive sequences that protect the coding DNA and the integrity of the chromosome. With each mitotic cell division, telomere length normally shortens slightly. Once telomeres have shortened sufficiently, cell death occurs. While this is a natural part of aging, individuals with excessively short telomeres for age can have various clinical manifestations affecting multiple organ systems.[74] Short telomere syndromes occur when there are defects in telomere elongation or maintenance, resulting in a significant reduction in telomere length. In general, shorter telomere length correlates with increased severity of the disease, disproportionately impacting tissue types with high rates of cell proliferation, such as bone marrow, skin, and immune cells.[75–77]

Short telomere syndromes exhibit variable expressivity, including a wide range of clinical features and ages of onset. Dyskeratosis congenita (DC), a childhood-onset syndromic condition, represents the more severe end of the disease spectrum. Symptoms include the diagnostic triad of oral leukoplakia, nail dystrophy, and reticulated pigmentation. Epiphora (excessive watering of the eyes due to lacrimal duct obstruction), lymphopenia, dental abnormalities, short stature, developmental delay, premature hair loss or graying, esophageal stricture or narrowing, hyperhidrosis, brain abnormalities, intrauterine growth restriction, and genitourinary abnormalities may also be seen.[78,79] In rare cases, pulmonary arteriovenous malformations (AVMs) have been reported.[80]

Although pulmonary fibrosis can be seen in pediatric patients with DC, it is otherwise rare for children to develop pulmonary fibrosis as part of a short telomere syndrome. However, adult-onset pulmonary fibrosis may be the first life-threatening manifestation of short telomere syndromes, often presenting with comorbid aplastic anemia or liver cirrhosis.[75,76,81–84] If a family member presents with symptoms of short telomere syndrome, genetic evaluation of family members could be considered.

Genetic testing can confirm a diagnosis of DC in children with clinical features. Measurement of leukocyte telomere length by automated multicolor flow cytometry fluorescence in situ hybridization can confirm the diagnosis of short telomere syndromes when an underlying genetic mutation cannot be identified.[79,80] The most common genetic defects responsible for short telomere syndromes result in reduced activity of telomerase, the main enzyme involved in telomere elongation. *TERC*, *TERT*, and *DKC1*, which encode the proteins that make up the major subunits of the telomerase complex, are the most frequently reported mutations. Mutations in *TNIF2, RTEL1, CTC1, ACD, NOP10, NHP2, PARN,*

USB1, and *WRAP53* genes have also been identified as rare causes of short telomere syndromes.[76,79,80]

Families with *TERC* and *TERT*-related autosomal dominant forms of the disease can exhibit genetic anticipation, which means there may be increased severity of the clinical presentation with each subsequent generation. It is believed that the additive effect of inheriting a mutation that reduces telomere length in combination with inheriting cells with shorter baseline telomere length from an affected parent results in the increased severity of disease.[20,76]

4.2.2 | Hermansky-Pudlak syndrome—HPS is an autosomal recessive disease characterized by oculocutaneous albinism combined with a deficiency of platelet delta granules, resulting in a bleeding diathesis.[85] Individuals with HPS generally have lighter skin, hair, and eye color than other family members plus ocular abnormalities including nystagmus, photo-phobia, decreased visual acuity, and lack of visual attention. Individuals with HPS can also experience easy bruising, epistaxis, prolonged bleeding after minor procedures, postpartum hemorrhage, colonic bleeding, gingival bleeding, and prolonged menstruation.[86,87]

Pathogenic variants in *AP3B1, AP3D1, BLOC1S3, BLOC1S6, DTNBP1, HPS1, HPS3, HPS4, HPS5*, and *HPS6* genes are associated with HPS. These genes encode proteins involved in the biogenesis of lysosome-related organelle complexes (BLOCs). BLOCs traffic lysosome-related organelles, including melanosomes and platelet dense granules. Defective BLOC function results in improper trafficking of these organelles, leading to albinism and bleeding diathesis.[87,88]

Some subtypes of HPS are associated with specific clinical features. The *HPS1, HPS4*, and *AP3B1* genes are linked with the development of early-onset pulmonary fibrosis, typically occurring during the third decade of life, which can mimic idiopathic pulmonary fibrosis.[85,89] *HPS1* and *HPS4* are also associated with granulomatous colitis, while the *AP3B1* and *AP3D1* genes are associated with immunodeficiencies and severe neutropenia as well as increased neurological involvement.[85,90,91] Although HPS occurs across all ethnicities, there is an increased incidence of *HPS1* and *HPS3*-related disease in individuals of northwest Puerto Rican descent due to founder mutations in that population.[85]

5 | ABNORMALITIES OF THE PULMONARY VASCULATURE

- Alveolar capillary dysplasia
- Pulmonary arterial hypertension
- Hereditary hemorrhagic telangiectasia

5.1 | Clinical overview

Genetic conditions associated with abnormalities of the pulmonary vasculature should be considered when there is significant shortness of breath or hypoxemia without underlying pulmonary parenchymal or cardiac structural abnormalities. Genetic causes of pulmonary

vascular disease may alter either the structure or function of pulmonary veins and arteries and are often associated with abnormalities of the vasculature in other parts of the body or additional syndromic features. ACD, pulmonary arterial hypertension (PAH), and hereditary hemorrhagic telangiectasia (HHT) are discussed in this review; however, many other genetic syndromes that are associated with vascular abnormalities can impact pediatric pulmonary patients.

5.2 | Genetic conditions

5.2.1 | Alveolar capillary dysplasia with misalignment of pulmonary veins—

ACD/MVP is generally lethal within the neonatal period. Shortly after birth, infants develop severe hypoxemia and respiratory distress that is unresponsive to standard treatments, including mechanical ventilation and supplemental oxygen. An echocardiogram reveals persistent pulmonary hypertension that fails to improve with inhaled nitric oxide. Most individuals with ACD/MVP have extrapulmonary involvement.[92,93] Cardiovascular, gastrointestinal, and genitourinary malformations, including atrial septal defects, intestinal malrotation, Hirschprung's disease, imperforate anus, duodenal atresia, and omphalocele have all been identified. In rare cases with a milder phenotype, later onset of the disease has been reported.[94–96]

Respiratory issues result primarily from improperly positioned alveolar capillaries leading to the defective transfer of oxygen from the alveoli to the circulation. Histologically, lung tissue is characterized by reduced and malpositioned alveolar wall capillaries, abnormally located pulmonary veins, deficient pulmonary lobular development, and thickening of the muscle walls of small pulmonary arteries with possible pulmonary lymphangiectasis.[92]

Mutations in the *FOXF1* gene cause autosomal dominant ACD/MVP. *FOXF1* encodes a transcription factor that impacts the function of many genes, including those involved in the development of the pulmonary mesenchyme. Most pathogenic mutations result in loss of function of the *FOXF1* gene. Almost all cases of *FOXF1*-related ACD/MPV occur in individuals with no family history of the disease as a result of de novo changes.[97] In a few reported cases, variants in *FOXF1* were found to be inherited from an unaffected mother, suggesting a possible imprinting effect.[92] Some individuals have mutations within the *FOXF1* gene, while others have a microdeletion at position 16q24.1 resulting in loss of the entire *FOXF1* gene. Microdeletions in this region can encompass other nearby genes and be associated with additional features, such as heart defects.[95]

5.2.2 | Heritable PAH—

Patients who present with dyspnea, fatigue, syncope, chest pain, palpitations, and leg edema, and are found to have signs of pulmonary hypertension on echocardiogram or electrocardiogram, should be evaluated for hereditary PAH.[98,99] PAH results from the narrowing and obstruction of the pulmonary arterioles, causing increased pulmonary arterial pressure and right ventricular overload.[100] It can occur at any age and is often associated with a precipitous decline in health, with a mean survival of 2.8 years postdiagnosis.[101]

Most cases of hereditary PAH are caused by mutations in the *BMPR2* gene and are inherited in an autosomal dominant pattern. Variants resulting in loss of function of the *BMPR2* gene,

leading to an absent or truncated protein product are the most common cause of hereditary PAH. *BMPR2* encodes the bone morphogenetic protein receptor type 2, which is involved in the growth and differentiation of cartilage and bone; however, it remains unclear how pathogenic variants in this gene lead to the development of PAH.[102]

In rare cases, pathogenic variants in other genes have been identified in individuals with PAH. These genes include *ACVRL1, BMPR1B, CAV1, CBLN2, EIF2AK4, ENG, KCNA5, KCNK3*, and *SMAD9*. The *ACVRL1* and *ENG* genes are also associated with HHT, which is described in more detail below.[98,99] Additional genetic syndromes associated with PAH include *FLNA*-associated periventricular heterotopia, Gaucher disease, pulmonary veno-occlusive disease, and sickle cell anemia.[10,103–106]

Hereditary PAH is characterized by markedly reduced penetrance of approximately 20% and variable expressivity.[107] Females are more likely to be affected than males; however, affected males generally have a more severe disease course.[98,108] Pregnancy in individuals with hereditary PAH can be dangerous and is associated with high mortality.[102]

5.2.3 | Hereditary hemorrhagic telangiectasia—Similar to PAH, HHT should be considered in patients with dyspnea or hypoxemia with exertion. Distinctive features of HHT include recurrent, potentially severe epistaxis, usually beginning in childhood, and the presence of telangiectasias.[109,110] Telangiectasias occur on the mucocutaneous surfaces of the body, especially the lips, oral cavity, fingers, face, and chest. When present in the gastrointestinal mucosa, they can lead to gastrointestinal bleeding, a common complication in HHT.[110,111]

Larger AVMs occurring in the lungs, liver, and brain, can be life- threatening. Although pulmonary AVMs occur in only 30% to 50% of individuals with HHT, most individuals with pulmonary AVMs have HHT.[112] Pulmonary AVMs generally increase in size over time and serious complications include stroke, brain abscess, and transient ischemic attacks from paradoxical emboli.[113] They occasionally rupture causing hemoptysis and some individuals with pulmonary AVMs develop PAH.[112,114] CT imaging of the chest, completed with IV contrast, reveals well-circumscribed areas of increased blood supply, occasionally with a feeding vessel visualized. Hepatic AVMs are also common in individuals with HHT, although they are frequently asymptomatic.[115,116] Cerebral AVMs, which can lead to hemorrhage, occur in approximately 10% of individuals and are usually present from birth.[110,117]

HHT, inherited in an autosomal dominant pattern, is most often caused by pathogenic variants in the *ACVRL1, ENG*, and *SMAD4* genes. Mutations in *GDF2* have been identified as a rare cause of HHT. *SMAD4*-related HHT presents with the concurrence of HHT and juvenile polyposis syndrome, which is characterized by a predisposition to develop hamartomatous polyps in the gastrointestinal tract and an increased risk of gastrointestinal cancers.[111] A significant portion of individuals meeting clinical criteria for a diagnosis of HHT do not have identifiable mutations in one of these genes, suggesting that additional genetic etiologies of HHT have yet to be discovered or that these individuals have another syndrome with overlapping features.[111,118]

The *ACVRL1* and *ENG* genes encode proteins involved in the differentiation of blood vessels into veins and arteries and the coordination of smooth muscle cells in developing vessels. The *SMAD4* gene encodes a protein involved in signaling in the transforming growth factor-β pathway. It functions as both a transcription factor and tumor suppressor, although the exact mechanism by which *SMAD4* mutations cause HHT with juvenile polyposis is not well understood.[110]

6 | PNEUMOTHORAX

- Connective tissue diseases
- Birt-Hogg-Dubé syndrome

6.1 | Clinical overview

Although pneumothorax may develop spontaneously or following trauma, repeated occurrences of pneumothorax should prompt suspicion of an underlying genetic etiology, such as a connective tissue disorder or Birt-Hogg-Dubé (BHD), especially if there is a family history of pneumothorax. Additional clinical manifestations such as joint laxity, skin abnormalities, dysmorphic facial features, or the presence of lung blebs or cysts seen on chest imaging, should also prompt genetic evaluation.[119]

While recurrent pneumothorax may trigger genetic evaluation, it is not usually life-threatening. Associated extrapulmonary complications, namely the vascular issues common in connective tissue disorders and renal cancer associated with BHD are associated with high mortality if left undetected. Thus, efficient diagnosis is essential for proper screening and management of these patients. As the majority of the genetic conditions described below has an autosomal dominant inheritance and potentially life-threatening extrapulmonary features, it is important to consider the implications of these diagnoses for family members who may also need genetic testing and clinical screening.

Pneumothorax can also occur in conditions associated with chronic respiratory infections, such as CF and PCD,[120,121] and in other genetic conditions not described in detail in this review, such as autosomal recessive polycystic kidney disease, *FLNA*-associated periventricular heterotopia, homocystinuria, and tuberous sclerosis.[10,103,122–124]

6.2 | Genetic conditions

6.2.1 | Connective tissue disorders—Connective tissue disorders are a large genetically heterogeneous group of conditions that are associated with cutaneous, skeletal, and vascular abnormalities.[125] They typically result from mutations in genes involved in the structure or function of the primary proteins that comprise connective tissues including collagen, elastin, and glycosaminoglycans. A subset of connective tissue disorders is associated with the development of pneumothorax. Figure 3 highlights the overlap of clinical features and distinctions of the select connective tissue disorders described below.

Marfan syndrome: Marfan syndrome is an autosomal dominant condition caused by mutations in the *FBN1* gene, which encodes the fibrillin protein. Fibrillin is a structural

protein that makes up part of the structure of microfibrils, which form elastic fibers found in skin ligaments and blood vessels and provide support in nonelastic tissues including bone.[126]

Marfan syndrome can have variable features, but classically involves characteristic phenotypic changes of the skeletal, ocular, and cardiovascular systems. Individuals with Marfan syndrome are often taller than unaffected family members with long extremities, arachnodactyly, pectus deformities, scoliosis, and joint laxity. Ocular manifestations include ectopia lentis, retinal detachment, and myopia. Cardiovascular complications include aortic dilation, mitral valve prolapse, tricuspid valve prolapse, and enlargement of the pulmonary artery root, which can be life-threatening.[126,127]

Pneumothorax occurs in approximately 5% to 10% of individuals with Marfan syndrome and has been attributed to various underlying causes in different individuals, including the presence of apical pulmonary blebs or bullae, connective tissue abnormalities in the lung parenchyma, and mechanical stress on the lung apices due to tall habitus.[128] Individuals with Marfan syndrome can also have additional pulmonary manifestations including cystic changes, emphysema, bronchiectasis, congenital malformations, and fibrosis.[30]

Ehlers-Danlos syndromes: Ehlers-Danlos syndromes (EDS) are a group of 13 disorders characterized by joint hypermobility, skin hyperextensibility, and tissue fragility.[129] Spontaneous pneumothorax has primarily been described in patients with the vascular subtype of EDS, which is an autosomal dominant condition caused by mutations in the *COL3A1* gene. *COL3A1* encodes type III collagen, which is found in the skin, lungs, intestinal walls, and vascular walls.[130] Common features of the vascular form of Ehlers-Danlos syndrome (vEDS) include easy bruising, thin, translucent skin, characteristic facial features, and tissue fragility. Ruptures or dissection of arteries, gastrointestinal perforation, and organ rupture all lead to the high mortality associated with vEDS.[130] Several other forms of EDS can have genetic causes and overlapping features of vEDS but have not yet been associated with pneumothorax.

Pneumothorax in vEDS can present in childhood or adulthood and can be spontaneous or recurrent. Hemothorax and hemopneumothorax have been reported in individuals with vEDS and are often associated with pulmonary blebs, cystic legions, or lung nodules.[129] Individuals can also have hematomas and severe recurrent hemoptysis.[131]

Loeys-Dietz syndrome: Loeys-Dietz syndrome (LDS) is an autosomal dominant condition characterized by vascular, skeletal, craniofacial, and cutaneous features. Skeletal manifestations include pectus deformities, scoliosis, joint laxity, arachnodactyly, and talipes equinovarus. Vascular complications include aortic dilation, which is present in more than 95% of individuals with LDS and can lead to aortic dissection. Arterial aneurysms and tortuosity can also be present in other organs. Craniofacial features include hypertelorism, bifid uvula, cleft palate, and craniosynostosis, while cutaneous findings include velvety, translucent skin, easy bruising, and dystrophic scarring. The prevalence of pneumothorax and restrictive lung disease in LDS patients is unknown.[132,133] Most cases of LDS are

caused by mutations in the *TGFBR1* and *TGFBR2* genes with mutations in the *SMAD2, SMAD3, TGFB2*, and *TGFB3* genes accounting for rare causes.[132]

Cutis laxa: Cutis laxa is characterized by loose, saggy, and inelastic skin, that is particularly noticeable around the neck, armpits, and groin. Individuals with cutis laxa may also have inguinal, umbilical, and diaphragmatic hernia, visceral diverticula, joint hypermobility, developmental issues, and cardiovascular involvement. Pulmonary manifestations include neonatal or childhood-onset emphysema, which can be severe, progressive, and lead to pneumothorax, laryngomalacia, tracheomalacia, bronchomalacia, bronchiolitis, and pulmonary hypertension.

The *FBLN5*, *EFEMP2*, *LTBP4*, and *ELN* genes are associated with cutis laxa and the development of emphysema. *EFEMP2* and *LTBP4* are associated with autosomal recessive cutis laxa; *FBLN5* mutations can be inherited in an autosomal dominant or recessive pattern.[134–136] Mutations in the *ELN* gene may cause autosomal dominant cutis laxa. Notably, Williams syndrome, which results from a microdeletion at 7q11.23 and is characterized by unique personality features, distinct facial features, and intellectual disability, may also result in deletion of the *ELN* gene, with ensuing connective tissue complications, including possible emphysema or pneumothorax.[137]

6.2.2 | Birt-Hogg-Dubé syndrome—

BHD syndrome is an autosomal dominant condition caused by mutations in the *FLCN* gene, which encodes the folliculin protein. Although the exact function of folliculin is unknown, it is hypothesized to function at least in part as a tumor suppressor and is expressed in the brain, heart, lungs, kidneys, skin, and testes.[138] BHD primarily affects the skin, lungs, and kidneys. Although the penetrance of BHD is high, the clinical presentation and severity of the disease is variable, and BHD is thought in general to be underdiagnosed.[138,139]

Cutaneous hamartomas, including fibrofolliculomas, trichodiscomas, and acrochordons, are common and generally benign. Fibrofolliculomas, which are the most common skin finding, typically appear on the face, neck, and upper trunk and develop in adulthood.[140]

The majority of individuals with BHD has bilateral multifocal basal or medial lung cysts. Although these lung cysts are initially asymptomatic, these patients are at high risk to develop pneumothoraces that can be recurrent. Pneumothoraces primarily occur in adolescence or adulthood, and they can be the presenting feature of BHD.[141,142]

Importantly, individuals with BHD are at increased risk of developing renal tumors (an estimated 15%−30% lifetime risk), and thus the diagnosis of BHD should prompt kidney screening. Oncocytic hybrid tumors, chromophobe renal cell carcinoma, and renal oncocytomas are the most common tumors observed in patients with BHD. Clear cell renal cell carcinoma and papillary renal cell carcinoma have also been reported. While the renal tumors in BHD tend to be slow-growing, early detection in this high-risk population is essential to prevent malignancy. Many individuals with BHD are found to have renal cysts on imaging.[138,143]

7 | CONGENITAL CENTRAL HYPOVENTILATION SYNDROME

7.1 | Clinical overview

Congenital central hypoventilation syndrome (CCHS) is a disorder of the respiratory and autonomic nervous systems. CCHS classically presents in the newborn period with alveolar hypoventilation with increased episodes during non-rapid eye movement sleep. In severe cases, infants can have complete apnea during sleep as well as hypoventilation during wakefulness. Hypoventilation in individuals with CCHS often results in hypoxemia and hypercapnia and requires mechanical ventilation or placement of a diaphragmatic pacemaker. Some individuals require 24-hour mechanical ventilatory support. Although the respiratory issues associated with CCHS can be life- threatening, early diagnosis and aggressive management can significantly improve prognosis and quality of life.[144–146]

Individuals with CCHS have additional complications of autonomic nervous system dysfunction affecting multiple body systems. Symptoms include decreased heart rate variability, dysrhythmias, syncope, gastrointestinal issues, altered pain perception, ophthalmological abnormalities, temperature and sweating dysregulation, and urinary issues.[146,147] In addition, some individuals have altered the development of neural crest-derived structures which can lead to Hirschprung's disease or tumors of neural origin.[148] While most individuals present in the newborn period, later onset has been reported. Patients with later onset disease usually have a milder phenotype.[149]

7.2 | Genetic condition

CCHS is caused by mutations in the *PHOX2B* gene and is inherited in an autosomal dominant pattern. Most mutations in *PHOX2B* are expansions of the polyalanine repeat region in exon 3. Normally, individuals have 20 repeats of three nucleotides encoding the amino acid alanine. When this region expands to 25 or greater alanine repeats, individuals are affected by CCHS. Individuals with 24 repeats and some individuals with 25 repeats can have a mild clinical presentation. Due to the repetitive nature of the polyalanine region, these types of mutations can be difficult to detect by traditional sequencing methods and targeted fragment length analysis may be necessary to characterize these variations.[144] Some individuals with CCHS have other types of mutations in the *PHOX2B* gene, primarily frameshift variants.[149]

The majority of repeat expansions occur as de novo mutations; however, a subset of asymptomatic parents have been found to have somatic mosaicism for the polyalanine repeat variations identified in their children.[150,151] Somatic mosaicism can be difficult to detect, but this is an important finding because it suggests that the recurrence risk of CCHS in future children of these individuals may not be negligible as compared to most other conditions caused by primarily de novo mutations that are rarely known to recur in families.

PHOX2B encodes a homeobox domain transcription factor that is expressed during embryonic development and important for proper formation of the peripheral and central autonomic nervous systems. *PHOX2B* is essential for the development of hindbrain motor neurons and neural crest cells.[149] Although mutations in *PHOX2B* are generally repeated expansion variations or frameshift variants, which usually have a loss-of-function impact on

gene function, it is thought that pathogenic mutations in *PHOX2B* cause disease via a dominant-negative effect. This dominant-negative effect is hypothesized to occur when the abnormal protein product from the mutated allele dimerizes with the normal protein product of the wild type allele and disrupts its function.[144,152]

8 | CONCLUSION

The genetic determinants for a growing number of pediatric pulmonary diseases have been identified. Recent advances in genetic testing technology combined with the reduced cost of genetic testing have made genetic evaluation a routine and integral component of the diagnostic work-up. It is important that pediatric pulmonologist be aware of the latest developments in pulmonary genetic disease and how to obtain genetic testing in the most effective manner.

Genetic evaluation and diagnosis is the first step in caring for a patient with a genetic condition. Individuals with a confirmed genetic condition should be connected with the appropriate registries and guideline-directed care should be followed. In the future, genetic therapies for an increasing number of these conditions will become available. In summary, genetics is a crucial component of pediatric pulmonary medicine and understanding and properly incorporating genetic evaluation in the pulmonary clinic is becoming a standard of care.

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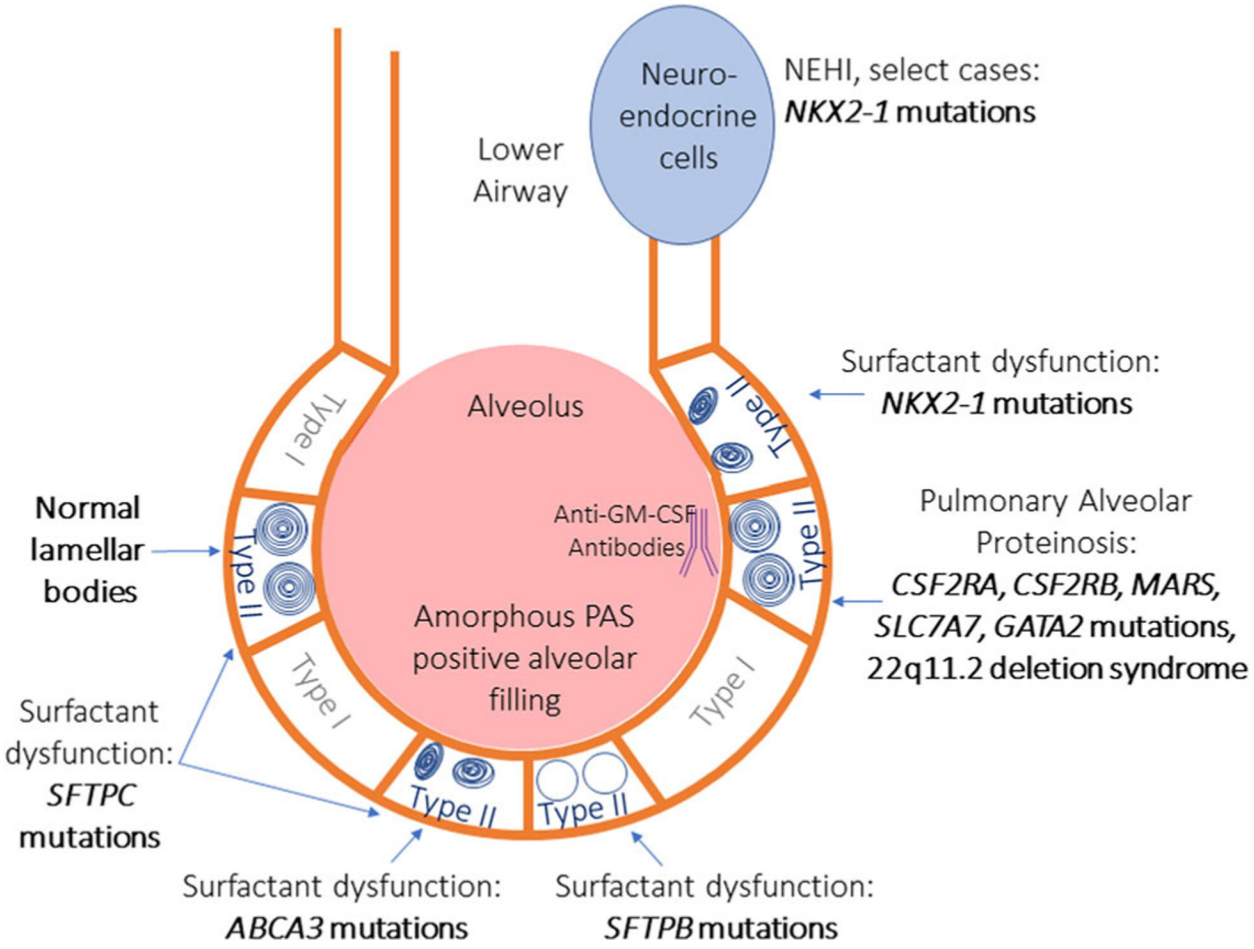

FIGURE 1.

Cartoon overview of disorders of surfactant dysfunction. The lower airway and alveolus are represented. Type I and type II alveolar cells line the airway. Type II cells contain lamellar bodies that are responsible for generating surfactant. Normal type II alveolar cells have a circumferential organized appearance. SFTPC mutations cause milder surfactant dysfunction and may have normal or disorganized lamellar bodies. ABCA3 and NKX2–1 mutations can also have a range of severity of surfactant dysfunction and both have small disorganized lamellar bodies. Of note, neuroendocrine hyperplasia of infancy has also been reported in association with NKX2–1 mutations, which affects the lower airways rather than the alveolus. Mutations in SFTPB cause the most severe surfactant dysfunction, often lethal in the newborn period, and lamellar bodies are often decreased or absent. Mutations causing pulmonary alveolar proteinosis have normal lamellar bodies and normal surfactant secretions, rather, antibodies are generated to disrupt mechanisms of surfactant homeostasis. GM-CSF, granulocyte-macrophage colony-stimulating factor; PAS, periodic acid-Schiff

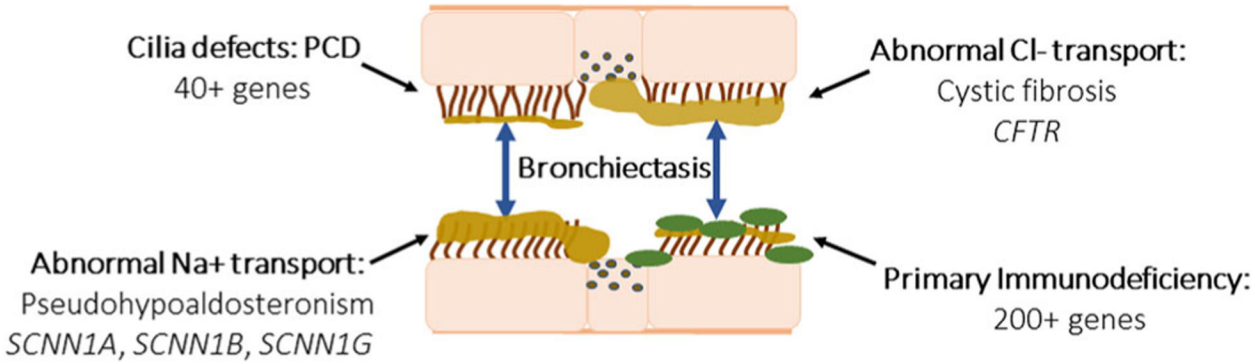

FIGURE 2.

This cartoon represents the four main genetic categories of bronchiectasis, or dilation of the airway: (1) ciliary abnormalities, such as primary ciliary dyskinesia, which is caused by mutations in over 40 genes affecting cilia function or structure (2) abnormal epithelial Chloride (Cl^{-}) transport, characteristic of cystic fibrosis, and mutations in CFTR, resulting build-up of thick tenacious airway secretions. (3) Abnormal sodium (Na^{+}) transport as seen in pseudohypoaldosteronism due to mutations in SCNN1A, SCNN1B, and SCNN1G, which also cause thickened dehydrated airway secretions. (4) Primary immunodeficiencies, which comprise over 200 genetic conditions that cause impaired immune responses to infection, triggering increased mucus production and impaired airway clearance. CFTR, cystic fibrosis transmembrane conductance regulator; PCD, primary ciliary dyskinesia

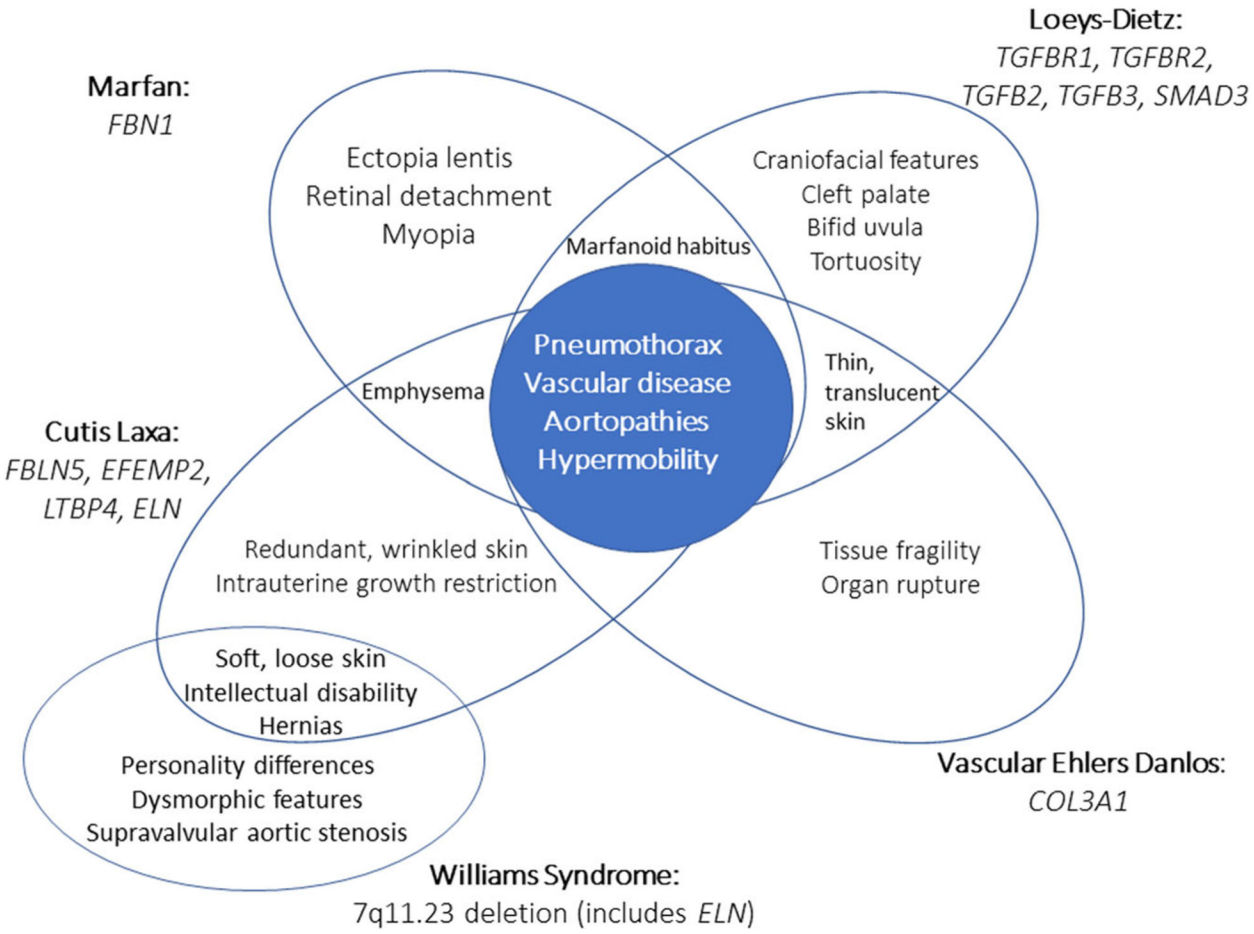

FIGURE 3.

This Venn diagram illustrates the phenotypic overlap of connective tissue disorders associated with pneumothorax, Marfan syndrome (FBN1), Loeys-Dietz (TGFBR1 and TGFBR2), vascular Ehlers-Danlos syndrome (COL3A1), cutis laxa (FBLN5, EFEMP2, LTBP4, and ELN), and Williams syndrome (7q11.23 deletion, which includes ELN). Central features of these diseases, however, include pneumothorax, joint hypermobility, and vascular disease, including aortopathies

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TABLE 1

Overview of genetic pulmonary diseases presenting in childhood

Condition	Associated genes	Inheritance pattern	Pulmonary features	Additional clinical features
Alveolar capillary dysplasia with misalignment of pulmonary veins	FOXF1	AD	RDS, ACD, PH	Cardiovascular, gastrointestinal, and genitourinary malformations
Autosomal recessive pseudohypoaldosteronism-type 1	*SCNN1A, SCNN1B, SCNN1G*	AR	BE, Rl	Salt wasting, failure to thrive, and muscle weakness
BHD syndrome	*FLCN*	AD	PX, C	Cutaneous hamartomas, renal cysts, and renal cancers
Brain-lung-thyroid syndrome	*NKX2–1*	AD	RDS, ILD, PF, NEHI	Chorea, other neurological symptoms, hypothyroidism
Congenital central hypoventilation syndrome	*PHOX2B*	AD	CH	Hirschprung's disease, neural crest-derived tumors, autonomic dysfunction
Cutis laxa	*FBLN5, EFEMP2, LTBP4, ELN*	AR, AD	PX, E, PH	Loose, saggy, inelastic skin, hernias, visceral diverticula, joint hypermobility
Cystic fibrosis	*CFTR*	AR	BE, Rl, PX	Pancreatic insufficiency and male infertility
Hereditary hemorrhagic telangiectasia	*ACVRL1, ENG, GDF2, SMAD4*	AD	AVMs, PAH	Telangiectasias, hepatic and cerebral AVMs, juvenile polyposis syndrome (SMAD4)
FLNA-Associated periventricular heterotopia	*FLNA*	XL	E, ILD, PAH, PX	Intellectual disability, seizures, and cardiac valvular anomalies
Heritable pulmonary arterial hypertension	*BMPR2, ACVRL1, BMPR1B, CAV1, CBLN2, EIF2AK4, ENG, KCNA5, KCNK3, SMAD9*	AD	PAH	
Hermansky-Pudlak syndrome	*AP3B1, AP3D1, BLOC1S3, BLOC1S6, DTNBP1, HPS1, HPS3, HPS4, HPS5, HPS6*	AR	PF, RLD	Oculocutaneous albinism, bleeding diathesis, common in Puerto Rico
Immune deficiencies	Over 200 genes	AR, AD, XL	BE, ILD, PAP, Rl	Various additional features depending on underlying defect
Loeys-Dietz syndrome	*TGFBR1, TGFBR2*	AD	PX, C, RLD	Aortic dilation, skeletal deformities, bifid uvula, velvety, translucent skin
Marfan syndrome	*FBN1*	AD	PX, E, BE, PF	Tall stature, joint laxity, aortic dilation, arachnodactyly, and ocular findings
Primary ciliary dyskinesia	*ARMC4, C21orf59, CCDC39, CCDC40, CCDC65, CCDC103, CCDC114, CCDC151, CCDC164, CCNO, CFAP298, DNAAF1, DNAAF2, DNAAF3, DNAAF4, DNAAF5, DNAH1, DNAH5, DNAH8, DNAH11, DNAI1, DNAI2, DNAJB13, DNAL1, DRC1, HEATR2, HYDIN, GAS8, LRRC6, MCIDAS, NME8, OFD1, PIH1D3, RPGR, RSPH1, RSPH3, RSPH4A, RSPH9, SPAG1, TTC25, TXNDC3, ZMYND10*	AR, XL	BE, RDS, Rl	Laterality defects, recurrent infections, and male infertility

Condition	Associated genes	Inheritance pattern	Pulmonary features	Additional clinical features
Pulmonary alveolar proteinosis	*CSF2RA, CSF2RB, MARS, SLC7A7, GATA2*, 22qll.2 deletion	AR	PAP	MARS, *SLC7A7, NPC2, GATA2*, and 22qll.2 are syndromic conditions
Short telomere syndromes	TERC, *TERT, DKC1, TINF2, RTEL1, ACD, CTC1, NOP10, NHP2, PARN, USB1, WRAP53*	AD, AR, XL	PF, RLD, AVMs	Nail and skin abnormalities, oral leukoplakia, short stature, premature graying, genitourinary abnormalities, brain abnormalities, bone marrow failure syndromes, and cirrhosis
Surfactant deficiencies	*ABCA3, SFTPB, SFTPC*	AD, AR	RDS, ILD, PAP, PF	Failure to thrive
Vascular Ehlers-Danlos syndrome	*COL3A1*	AD	PX, C	Easy bruising, thin and translucent skin, and tissue fragility

Abbreviations: ACD, alveolar capillary dysplasia; AVMs, arteriovenous malformations; BE, bronchiectasis; BHD, Birt-Hogg-Dubé; C, lung cysts; CCHS, congenital central hypoventilation syndrome; CH, central hypoventilation; E, emphysema; ILD, interstitial lung disease; LDS, Loeys-Dietz syndrome; NEHI, neuroendocrine cell hyperplasia of infancy; PAH, pulmonary arterial hypertension; PAP, pulmonary alveolar proteinosis; PF, pulmonary fibrosis; PH, pulmonary hypertension; PX, pneumothorax; RDS, respiratory distress syndrome; RI, recurrent infections; RLD, restrictive lung disease.