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Genetic Basis of Children's Interstitial Lung Disease

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Specific genetic causes for children's interstitial lung disease (chILD) have been identified within the past decade. These include deletions of or mutations in genes encoding proteins important in surfactant production and function (SP-B, SP-C, and ABCA3), surfactant catabolism (GM-CSF receptor), as well as transcription factors important for surfactant production (TTF1) or lung development (Fox F1), with heterozygous deletions or loss-of-function mutations of the latter resulting in alveolar capillary dysplasia (ACD) with misalignment of the pulmonary veins. Familial pulmonary fibrosis in adults may result from mutations in genes encoding components of telomerase and SP-A2. While not yet reported in children, the expression of these genes in alveolar type II epithelial cells supports a key role for the disruption of normal homeostasis in this cell type in the pathogenesis of interstitial lung disease. The identification of specific genetic causes for chILD now allows for the possibility of non-invasive diagnosis, and provides insight into basic cellular mechanisms that may allow the development of novel therapies.

Introduction

Significant advances have been made in the past decade in understanding the underlying causes for children's interstitial lung disease (chILD). The observations that lung disease often had its onset in early infancy and was progressive despite maximal medical treatment and that chILD was often familial suggested that genetic mechanisms were likely to be important in causing chILD.[1,2] While historically this heterogeneous group of disorders was classified using schema modeled after adult disorders and based upon the appearance of the lung pathology, specific molecular causes have been identified such that these disorders are often no longer idiopathic in nature. The recognition that specific genetic mechanisms cause some forms of chILD can allow for specific noninvasive diagnostic testing, counseling families concerning recurrence risks, prediction of natural history, and for a classification based upon underlying mechanisms of disease. These disorders also provide insight into normal lung metabolism, and the underlying mechanisms have implications for the pathogenesis of some forms of adult ILD and pulmonary fibrosis. The majority of single gene disorders identified to date encode proteins important in the function and metabolism of pulmonary surfactant, but it seems likely that the number of direct genetic causes or contributors to chILD will continue to expand and involve other pathways.

Overview of Pulmonary Surfactant Components and Metabolism

Pulmonary surfactant is the mixture of lipids and proteins needed to reduce alveolar surface tension and prevent end-expiratory atelectasis.[3] Inadequate production of pulmonary surfactant is the main cause of the respiratory distress syndrome (RDS) in prematurely born infants.[4] Genetic mechanisms disrupting surfactant production and function can cause diffuse lung disease in full-term infants that clinically and radiographically resembles RDS in premature infants, although it does not resolve or respond to exogenous surfactant replacement.

Surfactant is produced in alveolar type II cells (AEC2s), where it is packaged into lysosomally derived organelles called lamellar bodies, which are secreted by exocytosis.[5] The secreted surfactant complex must adsorb to the air–liquid interface and then spread efficiently in order to effectively reduce surface tension. The principal lipid in surfactant responsible for its surface tension lowering properties is disaturated phosphatidylcholine (DSPC). DSPC, however, adsorbs very slowly to an air–liquid interface, and the presence of 2 extremely hydrophobic proteins, surfactant proteins B (SP-B) and C (SP-C), confers important properties upon surfactant lipids to allow for proper surface tension lowering.[6] Pulmonary surfactant also contains 2 other more hydrophilic, structurally related proteins, SP-A and SP-D,

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which are part of the collectin family and have important roles in innate immunity.[7,8] Surfactant is both recycled back into type II cells by incompletely characterized mechanisms, as well as catabolized by alveolar macrophages. Maturation of the alveolar macrophages is dependent upon signaling by granulocyte–macrophage colony-stimulating factor (GM-CSF) through binding to a specific receptor on the surface of the macrophages.[9,10] Reduction in the functional amount of GM-CSF due to autoantibodies results in defective macrophage clearance of surfactant components from the airspaces and the syndrome of alveolar proteinosis in older children and adults.[11–13]

Surfactant Metabolic Dysfunction Disorders

Mutations in genes encoding 3 different proteins with important roles in surfactant function and metabolism, SP-B, SP-C, and member A3 of the ATP-binding cassette family of transporters (ABCA3), result in lung disease with overlapping clinical, radiographic, and lung histopathological features. SP-B is a 79-amino acid extremely hydrophobic protein that is encoded by a single gene on chromosome 2 (*SFTPB*) that directs the production of a larger proprotein from which the mature SP-B peptide found in the airspaces is generated by post-translational proteolytic processing at both the N- and C-termini. SP-C is a 35-amino acid extremely hydrophobic protein that is encoded by a small gene on chromosome 8 (*SFTPC*). Like SP-B, mature SP-C is generated by post-translational proteolytic processing at both the N- and C-termini of a larger precursor protein (proSP-C).[14] Both SP-B and SP-C are found in mammalian-derived surfactants used for replacement therapy in newborns with RDS, and are critical for the effectiveness of these products.[15] ABCA3 is a member of a family of transporters that hydrolyze ATP to move substances across biological membranes.[16] The 1,704-amino acid protein contains 2 membrane-spanning and 2 nucleotide-binding domains, and is encoded by a large gene on chromosome 16 (*ABCA3*).[17,18] ABCA3 is expressed in a number of tissues, but most highly in the lung, where it is localized to the limiting membrane of lamellar bodies within the alveolar type II cells.[19–21] Other members of the ABCA subfamily transport lipids, and given its localization, it is likely that ABCA3 facilitates the transport of lipids essential for surfactant function, in particular DSPC into lamellar bodies, a hypothesis that is supported by data derived from observations in humans and experimental animals.[22,23] Reduced surface tension-lowering ability and amounts of surfactant phospholipids, particularly PC, DSPC, and phosphatidylglycerol (PG), were demonstrated in lung fluid obtained from ABCA3-deficient infants.[24] AEC2s of ABCA3-deficient infants and mice contain small organelles with densely packed membranes and eccentrically placed electron-dense cores instead of normally formed lamellar bodies, consistent with a role for ABCA3 in lamellar body biogenesis.[25–27]

Human lung disease due to an inability to produce SP-B was the first recognized genetic cause of surfactant dysfunction.[28] Affected infants are generally full-term and develop symptoms and signs of lung disease within hours of birth, and radiographically have diffuse lung disease that resembles RDS in prematurely born infants.[29–31] The lung disease is usually relentlessly progressive, and the majority of affected infants die within 3 months of birth despite maximal medical therapy, including surfactant replacement and extracorporeal membrane oxygenation. The disease is inherited in an autosomal recessive fashion, and the diagnosis can be established by the identification of disease-causing mutations on both alleles. A frameshift mutation resulting in a net insertion of 2 bases into codon 121 and termed 121ins2 is the most frequently found *SFTPB* mutation, has accounted for about two-third of the mutant alleles identified to date, and its occurrence in unrelated subjects is due to a common ancestral origin.[29,32,33] Currently, lung transplantation is the only effective therapy for severely affected infants completely unable to produce SP-B.[34,35] Rare infants have been reported who have exhibited a relatively milder course, and survived for months to years, and who usually have mutations that allow for some SP-B production.[36,37]

SFTPC mutations were recognized a cause of interstitial lung disease in 2001.[38] The age-of-onset and severity of symptoms of individuals with *SFTPC* mutations vary greatly, from severe RDS in neonates to apparent idiopathic pulmonary fibrosis in the sixth decade, and adults with mutations associated with disease in other family members may be asymptomatic.[39–44] Young infants typically present with hypoxemia in room air, failure to thrive, and diffuse infiltrates on chest radiograph. Multiple *SFTPC* mutations have been identified and one mutation (c.218T>C, p.I73T) has been found in multiple unrelated families and accounted for 25%–35% of the mutant *SFTPC* alleles identified to date.[39–41,43–48] Apparent *de novo SFTPC* mutations resulting in sporadic lung disease have accounted for about half of reported cases of *SFTPC*-related lung disease. All mutations identified to date are predicted to alter the amino acid sequence of the SP-C proprotein. Disease is believed to result from a toxic gain-of-function mechanism whereby mutations cause misfolding of proSP-C, protein aggregation, and exposure of hydrophobic epitopes in the endoplasmic reticulum (ER). These events elicit the unfolded protein response and result in ER stress, with eventual alveolar type II cell apoptosis and inflammation.[49–55]

The optimal therapies of individuals with *SFTPC* mutations are unknown. Therapeutic lung lavage in infancy, corticosteroids, and hydroxychloroquine have been reported to improve the clinical status in case reports, but the highly variable natural history of the disease makes interpretation of these uncontrolled observations difficult.[43,45,56] No randomized, placebo-controlled nor cross-over studies of these treatments have been reported. Lung transplantation has been performed in individuals with progressive deterioration in lung function.[57]

ABCA3 deficiency is the most recently recognized cause of surfactant dysfunction but may be the most common.[25,30,58] The phenotype of the initial population of infants studied was similar to that of SP-B deficiency with severe and generally fatal RDS. However, the clinical course of patients with ABCA3 deficiency is much more variable than that of SP-B deficiency, and prolonged survival is being increasingly recognized.[24,30,44,59–68] While many affected infants had symptoms of lung disease in the immediate neonatal period, onset of respiratory symptoms later in childhood has been recognized.[59,64,66] There is extensive allelic heterogeneity, with mutations throughout the gene having been identified. Several mutations have been studied in *in vitro* systems, and a classification proposed based upon mutations that

either preclude ABCA3 production or intracellular transport (type I), or impair the ability of protein to bind and/or hydrolyze ATP or transport phospholipids across membranes (type II).[69–72] One specific mutation, the substitution of valine for glutamic acid in codon 292 (p.E292V or c.875A>T) has been identified in multiple unrelated children with generally milder disease and the phenotype of chILD. *In vitro* studies indicate that this mutation results in less impairment in ABCA3 function than other type II mutations.[72] These findings support the hypotheses that retained function may attenuate disease severity, and that genotype may thus be able to predict phenotype to some extent and even a small boost in ABCA3 production or function could improve the clinical status of such patients. The finding that corticosteroids increased ABCA3 expression *in vitro* provide a rationale for such treatment, although clinical data beyond anecdotal reports supporting the efficacy of steroids (or other treatments) for individuals with proven ABCA3 deficiency are lacking.[73]

Thyroid Transcription Factor 1 Haploinsufficiency

Thyroid transcription factor 1 (TTF1), also known as *Nkx2.1* or TITF1, is a member of the homeobox family of transcription factors that is critically important for the expression of multiple genes important in surfactant production and function, including those for SP-A, SP-B, SP-C, and ABCA3. The gene is located on the long arm of chromosome 14 (14q13.3), and TTF1 is also expressed in the thyroid gland, where it is critical for thyroid development, as well as in the central nervous system, particularly in the basal ganglia.

A role for TTF1 in human lung disease was initially recognized in full- or near-term neonates with RDS and hypothyroidism who had complete deletions of one copy of the Nkx2.1 locus.[74,75] Subsequently, complete loss-of-function mutations on one allele (haploinsufficiency) were recognized in individuals with a phenotype of hypothyroidism, neurological manifestations, particularly choreoathetoid movements, and pulmonary disease ranging from neonatal RDS to chronic respiratory symptoms in childhood.[75–77] TTF1 mutations were also reported as the cause of benign familial chorea, in which the affected individuals were not recognized to have pulmonary symptoms.[78–80] The term "brain–thyroid–lung" syndrome has been used to describe the phenotype, although the extent of symptoms related to each organ involvement is highly variable, such that patients may have normal or borderline thyroid function and normal pulmonary function by history, although many of the patients have not been formally evaluated for lung disease.[81–84] Fatal lung disease has been reported, and reported lung histopathology findings are consistent with surfactant dysfunction. Whether TTF1 mutations can result in a phenotype with only pulmonary manifestations is unknown. However as thyroid function may be normal, and the initial neurological symptoms may be non-specific (hypotonia, developmental delay) with chorea developing later, it is possible that this mechanism is not considered in young infants with chILD. The mechanisms for lung disease due to TTF1 haploinsufficiency presumably relate to decreased production of surfactant components, in particular SP-B, SP-C, and ABCA3, but this has not been rigorously examined.

Alveolar Capillary Dysplasia with Misalignment of the Pulmonary Veins

ACD is a disorder of lung development involving inadequate development of the pulmonary capillary bed and with pulmonary veins found in the same bronchovascular bundles as pulmonary arteries rather than associated with pulmonary lymphatics.[85–87] Affected infants typically present with severe pulmonary hypertension in the neonatal period that is unresponsive to medical management and ultimately fatal. Rarely, somewhat milder cases with later-onset presentation and more prolonged survival have been reported.[88–92] The diagnosis is made primarily through histological examination of lung tissue, although cardiac catheterization may also be helpful. The incidence is unknown, but ACD accounted for the majority of cases of lung developmental disorders as determined by biopsy in one series[93] and for 5 of 9 cases of fatal neonatal lung disease in a series from the UK.[94] Extrapulmonary-associated anomalies have been observed in 50%–75% of cases, and the occurrence of familial cases supports a genetic mechanism.[95]

Recently microdeletions in 16q24.1 were found in a group of children with lung pathology findings of ACD along with other anomalies, including cardiac, gastrointestinal, and genitourinary anomalies.[96] This region includes the genes for several members of the forkhead box (Fox) family of transcription factors, and sequence analysis revealed heterozygous loss-of-function FoxF1 mutations in 4 of 18 patients with ACD examined, supporting the role of this transcription factor in the pathogenesis of the pulmonary phenotype, although the mechanism remains unknown.

The FoxF1 mutations and 16q24.1 microdeletions were apparent *de novo* events, and did not account for all of the cases of ACD examined. An autosomal recessive pattern of inheritance has been implicated in some familial cases of ACD, and thus there are almost certainly other genes that can result in this phenotype.[95] However, these observations provide the means for a non-invasive diagnosis in some cases, and confirm one genetic basis for this disorder.

GM-CSF Receptor Deficiency

One of the histological features of surfactant dysfunction is an accumulation of granular, eosinophilic material in the distal airspaces, a finding that resembles what is seen in pulmonary alveolar proteinosis (PAP) in adults. The onset of symptoms in PAP is usually more insidious and slowly progressive, and while the airspaces are filled with proteinaceous material the underlying lung architecture is generally well preserved without the AEC2 hyperplasia, mesenchymal thickening, and fibrosis observed with surfactant dysfunction disorders. Moreover, the molecular basis for PAP is due to the presence of neutralizing antibodies to GM-CSF, leading to impairment of alveolar macrophage development and failure of the macrophages to properly catabolize surfactant.[97] PAP is thus a distinct entity clinically, pathologically, and mechanistically, and the term congenital alveolar proteinosis to describe newborns with surfactant dysfunction is best avoided.

GM-CSF acts through binding to a specific receptor that has 2 components, a specific α chain and a β chain that is also shared by the receptors for IL-3 and IL-5. Ablation of the β chain in mice resulted in the phenotype of PAP in

homozygous null animals.[98,99] Functional deficiency of β chain was reported in 1997 in children with infantile onset of PAP, but the early phenotype of these children was not consistent with that of PAP, and no convincing defect in the gene encoding the β chain (*CSF2RB*) was identified or has yet been reported.[100] Clear genetic defects in the gene encoding the α chain (*CSF2RA*), which is located in the pseudoautosomal region of the X chromosome, were recently reported as a cause for PAP in children.[101,102] These reports convincingly establish that genetic mechanisms can disrupt GM-CSF signaling and result in PAP in childhood. The incidence and prevalence of this disorder are unknown, as are the extent of variability in the age of onset due to mutations in this pathway. While there may be clinical overlap with chILD, the lung pathology is likely to remain distinct from that of surfactant dysfunction and other forms of chILD.

Lung disease with features of PAP can also be seen in children with lysinuric protein intolerance (LPI), a disorder of cationic amino acid transport caused by mutations in the solute carrier gene, *SLC7A7*.[103,104] Children affected by this autosomal recessive disorder may have episodes of hyperammonemia, recurrent vomiting, and failure to thrive, but can present with pulmonary symptoms in infancy.[105–107] While the basic defect for LPI has been elucidated, the mechanisms for PAP resulting from this disorder are unknown. The recurrence of pulmonary disease in an infant following heart–lung transplantation suggests that correcting the metabolic defect in pulmonary epithelial cells did not resolve the underlying pathophysiology.[108]

Surfactant Protein A2 and Telomerase Mutations in Adults with Familial Pulmonary Fibrosis

Mutations in the genes encoding the components of telomerase (*TERT, TERC*) have been reported as a cause of familial pulmonary fibrosis in adults, and recently mutations in one of the genes encoding surfactant protein A, *SFTPA2*, have been reported in association with the phenotype of familial pulmonary fibrosis and pulmonary adenocarcinoma.[109–112] In addition to synthesizing surfactant components including SP-A, AEC2s are the progenitor cells for type I cells following lung cell injury, and telomerase is necessary for the maintenance of a dividing cell population. While mutations in these genes have not yet been reported as a cause of chILD, these observations further support a key role for injury to the AEC2 in the pathogenesis of ILD and pulmonary fibrosis.

Pathology

The lung pathology findings associated with surfactant dysfunction are discussed elsewhere in this issue. The findings at the level of light microscopy are not specific for a given disorder, although electron microscopy can be helpful in distinguishing SP-B and ABCA3 deficiencies from other causes of surfactant dysfunction. Genetic testing, which is now available for many of these disorders in clinical diagnostic labs, is needed to provide a specific diagnosis, although there are children with lung pathology findings of surfactant dysfunction in whom testing for mutations in all known genes has proved negative. These observations suggest that either genetic variants in regions of the genes not examined, such as untranslated regions, or mutations in other genes not yet established as having a role in surfactant metabolism and dysfunction are also a cause of this phenotype.

Genetic Approach to Diagnosis

Specific features of each chILD disorder with known genetic etiologies are summarized in Table 1. The identification of specific genetic causes of chILD provides a means for establishing a diagnosis non-invasively. Timely diagnosis will allow for accurate counseling regarding prognosis, avoiding unnecessary therapies, and referral for specific therapies such as lung transplantation if indicated. However, clinical genetic testing is expensive, not all disorders have a known genetic cause, and not all mutations in a gene are detected by current approaches. Interpretation of results of genetic testing may not be straightforward. Determination of whether novel missense mutations or ones close to splice junctions cause lung pathology or are simply rare yet benign polymorphisms may not be possible. There is also no easy way to distinguish whether a child heterozygous for only one *SFTPB* or *ABCA3* disease-causing mutation is affected or simply a carrier with a different underlying mechanism for disease. Rapidly progressive disease may preclude waiting for the results of genetic testing. Lung biopsy thus remains important for diagnosis in some patients.

Newborns with hypoxemic respiratory failure and diffuse disease radiographically due to surfactant dysfunction or ACD are not distinguishable on clinical criteria from those with reversible causes of lung disease. A positive family history of lung disease, lack of clinical risk factors associated with severe lung disease in full-term infants, and failure to improve in the expected timeframe should prompt consideration of one of these disorders. Extrapulmonary organ involvement, including cardiac, gastrointestinal, or genitourinary tract anomalies suggests the possibility of ACD and FoxF1 haploinsufficiency, and hypothyroidism or CNS abnormalities suggests TTF1 haploinsufficiency. As deletions in the regions involving the loci responsible for both conditions have been reported, a comparative genomic hybridization assay should be considered, along with targeted mutational testing for FoxF1 and TTF1, respectively. If the disease solely involves the lungs, mutational analysis for ABCA3 and SP-B deficiencies should be considered. *SFTPC* testing in critically ill neonates should be performed if prior testing for ABCA3 and SP-B is negative and a strong index of suspicion for surfactant dysfunction persists (Fig. 1). Lung biopsy still may be needed in some cases.

As prolonged survival is unusual in children with SP-B deficiency or ACD, testing for *SFTPB* mutations or FoxF1 mutations and deletions is likely to have very low yield in older children with diffuse lung disease. Genetic testing for *SFTPC* and *ABCA3* mutations should be considered in older children who present with hypoxemia, failure-to-thrive, and/or diffuse lung disease by imaging studies when no clear diagnosis has been established. The onset of symptoms in the neonatal period favors *ABCA3* deficiency as the mechanism, whereas later onset of symptoms is more typical of *SFTPC* mutations, but there is sufficient overlap in the age-of-onset of symptoms that analyzing both genes is often necessary, and heterozygosity for an *ABCA3* mutation may influence the course of patients with *SFTPC* mutations. Neurological symptoms, particularly choreoathetoid

Table 1. Known Genetic Causes of ChILD Syndrome

	Alveolar capillary dysplasia	*SP-B deficiency*	*ABCA3 deficiency*	*SP-C dysfunction*	*Brain–thyroid–lung syndrome*	*GM-CSF receptor deficiency, α chain*	*Lysinuric protein intolerance*
OMIM	#265380	#265120 SMDP1	#610921 SMDP3	#610913 SMDP2	#610978	#300770 SMDP4	#222700
Locus	FoxF1	SFTPB	ABCA3	SFTPC	TTF1 (Nkx2.1)	CSF2RA	SLC7A7
Chromosomal location	16q24.1	2p12-p11.2	16p13.3	8p21	14q13.3	Xp22.32, Yp11.3	14q11.2
Inheritance	AD, sporadic	AR	AR	AD, sporadic	AD, sporadic	AR	AR
Mechanism	Haplo insufficiency	Loss of function	Loss of function	Toxic gain of function	Haplo insufficiency	Loss of function	Loss of function
Onset of pulmonary symptoms	Neonate	Neonate	Neonate, infancy, childhood	Neonate < infancy to adult	Newborn, infancy	Childhood	Infancy to childhood
Principal histology	ACD/MPV	SDM	SDM	SDM	SDM	PAP	PAP
Other findings	Cardiac, GI, or GU malformations				Hypothyroidism Neurological		Hyperammonemia Vomiting Failure to thrive
Course	Severe, fatal	Severe, fatal	Variable	Variable	Variable		Progressive

Abbreviations: OMIM, Online Mendelian Inheritance in Man; SMDP, surfactant metabolism dysfunction, pulmonary; AD, autosomal dominant; AR, autosomal recessive; ACD/MPV, alveolar capillary dysplasia with misalignment of the pulmonary veins; SDM, surfactant dysfunction, metabolic; PAP, pulmonary alveolar proteinosis; GI, gastrointestinal; GU, genitourinary; GM-CSF, granulocyte–macrophage colony-stimulating factor; SP-B, surfactant protein B; SP-C, surfactant protein C; ABCA3, surfactant protein ABCA3; TTF1, thyroid transcription factor 1.

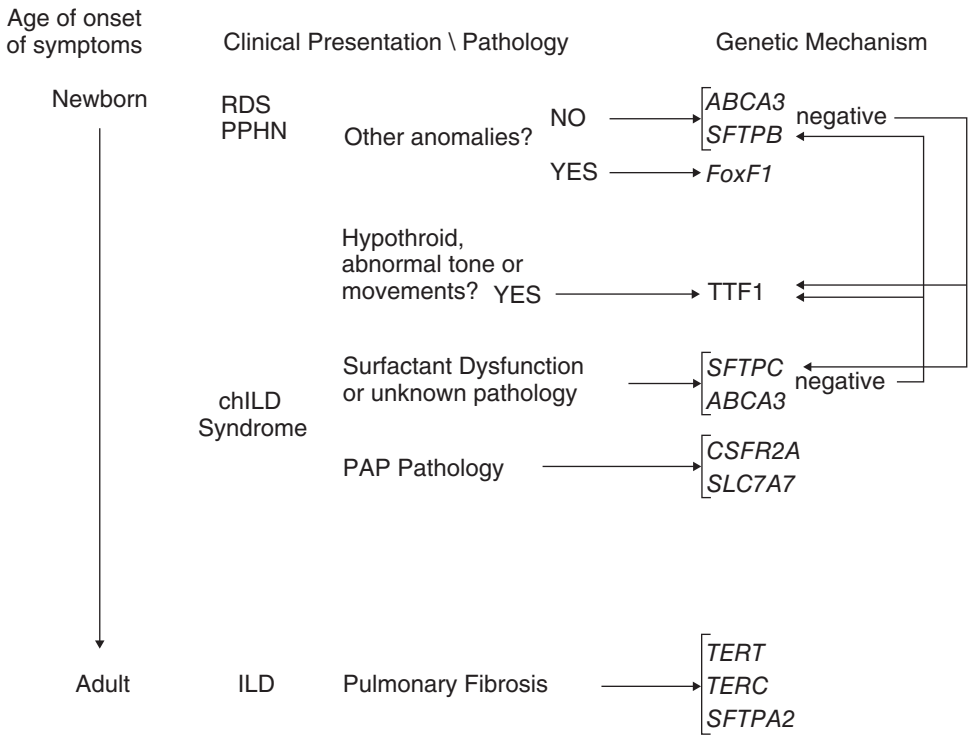

FIG. 1. Approach to genetic diagnosis of children's interstitial lung disease (chILD). Potential genetic mechanisms based upon age of the patient (neonatal to adult, from top to bottom) and phenotypic characteristics (middle) are listed on the right. Arrows point to primary genes to be analyzed; if results of initial studies are negative, arrows on right indicate secondary genetic studies to be considered. Abbreviations: RDS, Respiratory distress syndrome; PPHN, persistent pulmonary hypertension of the newborn; PAP, pulmonary alveolar proteinosis. See text and Table 1 for details on genetic loci.

movements, and/or chemical hypothyroidism and elevated levels of thyroid-stimulating hormone should prompt evaluation for deletions and mutations in TTF1. Children whose clinical and bronchoalveolar lavage or lung biopsy findings are more consistent with PAP should be evaluated for *CSF2RA* defects and the diagnosis of LPI considered. The figure outlines which genes should be considered for analysis based upon age of the patient and phenotype.

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