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Interstitial lung disease in newborns

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SUMMARY

The term ‘interstitial lung disease’ (ILD) refers to a group of disorders involving both the airspaces and tissue compartments of the lung, and these disorders are more accurately termed diffuse lung diseases. Although rare, they are associated with significant morbidity and mortality, with the prognosis depending upon the specific diagnosis. The major categories of ILD in children that present in the neonatal period include developmental disorders, growth disorders, surfactant dysfunction disorders, and specific conditions of unknown etiology unique to infancy. Whereas lung histopathology has been the gold standard for the diagnosis of ILD, as many of the disorders have a genetic basis, non-invasive diagnosis is feasible, and characteristic clinical and imaging features may allow for specific diagnosis in some circumstances. The underlying mechanisms, clinical, imaging, and lung pathology features and outcomes of ILD presenting in newborns are reviewed with an emphasis on genetic mechanisms and diagnosis.

Keywords

Lung development; Alveolar capillary dysplasia; Surfactant; Mutation; Genetic basis of disease; Neuroendocrine cell hyperplasia of infancy

1. Introduction

Interstitial lung disease (ILD) is a heterogeneous group of rare disorders of diverse and often unknown etiologies that cause acute or chronic respiratory signs and findings. Whereas the term ILD has become broadly accepted as a result of the pathologic changes observed in the pulmonary interstitium, these disorders often involve the airspaces, and the term ‘diffuse lung disease’ (DLD) may be more accurate. ILD/DLD has generally been classified in adults based upon the underlying histopathology, but the disorders seen in adults differ from those seen in children and even more so in neonates, and thus different approaches are needed. In the past ten years, collaborative efforts between clinicians, imagers, and pathologists have

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led to a classification system more appropriate for infants and children. Whereas this approach was based largely upon lung pathology, it is being increasingly recognized that many of the disorders affecting newborns and young infants have a genetic basis, which may allow for a specific diagnosis through non-invasive means. Recent advances in genetics based upon next-generation sequencing methods have allowed for more cost-effective genetic testing panels for known disorders and identification of new disorders through agnostic approaches using whole-exome or whole-genome sequencing. The approach to the diagnosis of ILD and understanding of the specific disorders is thus likely to continue to evolve rapidly. This review focuses on those disorders that typically present in the newborn period and which are likely to result in hypoxemic respiratory failure.

2. Classification of childhood interstitial lung disease (chILD)

A classification of ILD specific for infants aged <2 years was developed based upon review of clinical, imaging and lung biopsy data [1]. More than half (57%) needed supplemental oxygen at birth, and 21% had biopsies performed before age 2 months. Subsequent studies have utilized and expanded on this classification scheme, with the majority of included subjects having needed supplemental oxygen or respiratory support at birth, and disorders likely to present in the neonatal period have consistently accounted for more than half of cases (Fig. 1) [2–5]. Estimates of the prevalence of ILD in children have ranged from 0.13 to 16 cases per 100,000 children per year [6], but the overall incidence of ILD in newborns is unknown. ILD/DLD in newborns is associated with significant mortality, and children who succumbed early in infancy may not have been included in estimates that focused on older children. With improved recognition and ability to diagnose these disorders, more accurate estimates of their incidence and prevalence are likely to emerge.

2.1. Diffuse developmental disorders

Disorders that interrupt lung development result in diffuse lung disease in term newborns, characterized clinically by hypoxemic respiratory failure that is refractory to medical therapy. These conditions include acinar dysplasia, congenital alveolar dysplasia, and alveolar capillary dysplasia with misalignment of the pulmonary veins (ACDMPV) [3]. In acinar dysplasia (also referred to as type 0 congenital pulmonary airway malformation or CPAM), the pathology is consistent with an arrest of lung maturation at the pseudoglandular to canalicular phase of lung development, with no or few acinar structures and absent alveoli. These children are difficult to support even with maximal medical therapy and the diagnosis is usually made at autopsy. In congenital alveolar dysplasia the arrest of lung development is slightly later, at the late canalicular to saccular phase of lung development [3]. These infants also usually have severe lung disease and pulmonary hypertension but may be able to be supported and the diagnosis established by biopsy. There are few published studies on congenital alveolar dysplasia, which may overlap other lung developmental disorders, and no systematic evaluation of genetic causes has been performed. The incidence of developmental disorders is unknown. ACDMPV accounted for the majority of cases of irreversible lung dysplasia in one small series [7].

There are multiple reports of familial cases of acinar dysplasia strongly indicative of underlying genetic mechanisms, but no single candidate gene has been implicated. Isolated cases in association with other phenotypic findings have been associated with mutations in *FGFR2* and *TBX4* [8,9]. Pathologic features of acinar dysplasia were observed in children subsequently found to have *ABCA3* mutations, but other causative genes cannot be excluded [10,11].

2.2. Alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV)

This is an increasingly recognized form of diffuse lung disease resulting from abnormal lung development. Affected infants generally present with severe hypoxemic respiratory failure and pulmonary hypertension shortly after birth that is refractory to maximal medical management, including extracorporeal membrane oxygenation, leading to death in the neonatal period. Whereas this presentation and course is still the most frequently observed, relatively milder forms of the disease and later presentation have been recognized. Affected children frequently (50–75%) have abnormalities in other organ systems, including congenital heart disease, gastrointestinal, and genitourinary malformations. Recognition of familial cases suggested a genetic basis for the disorder, and deletions of and mutations in the *FOXF1* gene, which encodes a transcription factor important in vascular development, have been identified in the majority of infants with ACDMPV [12,13].

In addition to DNA sequence variants that alter or disrupt the *FOXF1* coding sequence, deletions involving part or all of the gene have accounted for a substantial portion of cases. Many of these deletions are located in the 5' untranslated region, which contains a lung-specific enhancer region and harbors two long non-coding RNAs (lncRNA) that are important for proper expression of the *FOXF1* gene; an additional enhancer is located in the intron [14,15]. This has important implications for diagnosis, as the absence of a mutation by sequence analysis does not exclude a deleterious *FOXF1* variant, and specifically designed or targeted microarray analysis may be needed to identify causative variants. As a *FOXF1* genetic variant cannot be identified in some infants with ACDMPV, other loci likely remain to be identified [15].

The majority of disease-causing *FOXF1* variants appear to be de novo and result in sporadic disease. However, well-documented familial cases indicate that there is variable expressivity of disease. This variability results from several mechanisms, including somatic mosaicism, and from the *FOXF1* locus being partially imprinted, such that manifestation of disease depends upon which parent transmitted the mutant allele and whether the mutation was in the coding region or involved deletion of the enhancer region [15–17].

Although rare, the diagnosis of ACDMPV should be suspected in a term infant with severe pulmonary hypertension of the newborn (PPHN), especially in the absence of risk factors for PPHN, such as sepsis, meconium aspiration, perinatal depression, or in-utero exposure to drugs that may cause premature closure of the ductus arteriosus. Relatively normal pulmonary compliance and the presence of extrapulmonary malformations increase suspicion for the disorder, although diffuse opacification may also be observed on chest radiographs [18]. The most expeditious route for establishing the diagnosis is by lung biopsy following established protocols [19]. Findings include a thickened interstitium with a poorly

developed capillary bed, abnormal lobulation, extension of arterial smooth muscle into intracinar blood vessels, and the presence of pulmonary veins running in the same bronchovascular bundle as the pulmonary arteries (the “misaligned veins”). Lymphangectasia is not rare. The identification of *FOXF1* as the predominant genetic cause of ACDMPV makes non-invasive diagnosis feasible, and clinical diagnostic testing is available through commercial diagnostic laboratories (<http://www.genetests.org>). Genetic testing allows a definitive diagnosis without having to perform a procedure on a critically ill, unstable child. However, the turnaround times for genetic testing may be unacceptably long in a critically ill child requiring maximal medical therapy. Additionally, such testing does not have 100% sensitivity, and genetic variants may be identified whose clinical significance is uncertain. Cardiac catheterization has also been proposed as a potential means for establishing the diagnosis [20].

2.3. Alveolar growth disorders

The largest diagnostic group (~25%) of infants aged <2 years evaluated by biopsy had what was termed an alveolar growth disorder, with pathology consistent with alveolar simplification [1]. Of this group, 43% were preterm infants and this pathology was consistent with bronchopulmonary dysplasia (BPD). Although not specifically indicated, these infants presumably underwent biopsy because the severity or persistence of their lung disease was sufficiently atypical that alternative diagnoses to BPD were considered. Neonatologists do not generally think of BPD as a form of ILD, but there is overlap in the clinical phenotypes of infants with BPD and those with other disorders discussed in this review. Abnormal growth was also observed in children with chromosomal disorders, especially trisomy 21, as well as in children with congenital heart disease, and term infants without apparent risk factors. That these conditions may be radiographically associated with diffuse lung disease is important to recognize in deciding whether to pursue additional diagnostic evaluation. Imaging abnormalities include hyperexpansion with hyperlucent areas and cysts on chest radiography, and chest computed tomography (CT) findings of linear and ground-glass opacities, as well as subpleural cysts [18].

A rare cause of growth disorders is deficiency of filamin A, a ubiquitously expressed actin-crosslinking cytoskeletal protein that is important for cellular migration. DLD resembling BPD has been recognized, with some affected infants being born prematurely and others at term [21]. Chest radiographs have generally shown markedly hyperexpanded, emphysematous-appearing lungs [18]. The gene is located on the X chromosome and mutations are inherited in a dominant fashion, with most affected infants being female, although affected male infants have been reported. CNS abnormalities, especially periventricular nodular heterotopias, are frequently observed in affected infants, along with cardiac, intestinal, skeletal, and dermal abnormalities.

The outcomes for children with growth disorders are variable, and long-term follow-up studies (excepting those focused on BPD) are not available. Mortality has ranged from 11% to 34%, and is likely related to the underlying condition [1,4].

3. Surfactant disorders

Mutations in genes encoding proteins needed for the production, function, and metabolism of pulmonary surfactant lipids and proteins account for ~20% of ChILD disorders and often present in the newborn period. The typical presentation is a term infant with DLD that clinically and radiographically resembles respiratory distress syndrome in prematurely born infants [22–27]. Disease onset in older infants and children without a history of neonatal lung disease also occurs [22,28–30]. Four genes have been identified to date in which mutations result in lung disease with overlapping clinical, imaging, and lung histopathologic features that are collectively called surfactant dysfunction disorders. These conditions are described in detail elsewhere in this issue, and key features are summarized in Table 1. Importantly, while imaging and lung histopathology findings may strongly support a diagnosis of surfactant dysfunction, determination of the responsible gene is important, as the inheritance patterns (and hence recurrence risk) and prognoses vary depending upon the causative gene.

4. Pulmonary alveolar proteinosis

An accumulation of proteinaceous material that fills distal air spaces may be a prominent finding in surfactant dysfunction disorders. The term pulmonary alveolar proteinosis (PAP) has been used because of the similarity in appearance to that observed in adults with a syndrome in which surfactant accumulates in distal airspaces and results in hypoxemia. However, PAP in adults is usually secondary to an auto-immune disorder, with neutralizing antibodies to granulocyte–macrophage colony-stimulating factor (GM-CSF) impairing macrophage function, resulting in defective clearance and catabolism of surfactant and its accumulation in the lung [31]. Mutations in the genes encoding the receptor for GM-CSF on alveolar macrophages may also result in a syndrome of PAP in children and adults, although such mutations have not been reported in newborn infants [32–34]. The underlying lung architecture in patients with auto-immune and inherited PAP from GM-CSF receptor mutations is usually well preserved in contrast to that observed in surfactant dysfunction disorders, where the interstitium is often markedly thickened, although eventually fibrosis may be seen in both sets of conditions. Characteristics of disorders which may result in the pathology of PAP, but occur in older children as opposed to newborns, are summarized in Table 2.

5. Specific conditions of unknown etiology unique to infancy

5.1. Neuroendocrine cell hyperplasia of infancy (NEHI; also known as persistent tachypnea of infancy, PTI)

This is a form of chILD that has accounted for ~8% of cases in retrospective studies, and is being increasingly recognized [1,3,5,35]. The characteristic presentation is that of chronic tachypnea in a young infant, often accompanied by a need for supplemental oxygen and failure to thrive. Chest radiographic findings are non-specific and include hyperexpansion and increased perihilar markings. CT findings may be characteristic with ground-glass opacities in non-dependent lobes, especially the right middle lobe and lingua [36]. On biopsy, the lung architecture is relatively normal in appearance, and the major finding is an

increased number of neuroendocrine cells that stain positively for bombesin, and a quantitative scoring system has been developed to aid in the diagnosis [37]. It is not clear whether the increased numbers of neuroendocrine cells directly contribute to the pathogenesis of the disorder or are secondary and a biomarker.

Whereas infants affected by NEHI generally present and are diagnosed in early infancy, the onset of signs may begin in the neonatal period [38]. Characteristic neonatal findings that might distinguish NEHI patients from those with transient disorders not been identified. The natural history of NEHI appears to be one of gradual improvement and mortality has not been reported, although affected children may need treatment with supplemental oxygen for years [35,38].

The incidence, prevalence, and etiology of NEHI are unknown. Familial cases are recognized, suggesting a genetic basis [39]. A mutation in *NKX2-1* was found in one family in which multiple members had a phenotype consistent with NEHI [40]. To date, this association has been confined to this single kindred, but these findings support the hypothesis that NEHI is a distinct disorder with a genetic basis. Identifying additional genetic mechanisms should aid in diagnosis, and potentially provide insights into the pathophysiology of the disorder.

5.2. Pulmonary interstitial glycogenosis (PIG)

This was described as a distinct entity in a small group of infants who had a chest radiographic appearance of hyperinflation and diffuse reticular infiltrates. Four of seven were premature and the only infant who died was born at 25 weeks of gestation [41]. The diagnosis of PIG is based upon biopsy findings, which include an interstitium widened by immature mesenchymal cells that contain glycogen (demonstrated by periodic acid–Schiff staining or on electron microscopy), with relatively little inflammation. Whereas PIG was present in ~5% of infants aged <12 months who underwent biopsy in several series, it likely represents an atypical form of lung injury or disordered metabolism in young infants rather than a specific disorder, as localized findings of PIG are also seen in biopsies from children with growth disorders and/or congenital heart disease and with NEHI [1,3,5,38,41]. It is unknown how often this finding occurs in infants who eventually recover from bronchopulmonary dysplasia and who never underwent biopsy, especially as infants with PIG may respond favorably to treatment with corticosteroids [41]. The etiology and mechanisms underlying PIG in the lung are unknown, as are its incidence and prevalence. Mortality has been observed in association with PIG, but is likely related to the underlying condition [41–43].

6. Primary ciliary dyskinesia

Primary ciliary dyskinesia (PCD) is a disorder resulting from absent or abnormal ciliary function in the respiratory epithelia leading to poor mucous clearance with secondary complications of chronic sino-pulmonary disease. Almost half of affected subjects have situs inversus (Kartagener's syndrome) or other laterality defects. The disorder results from mutations in genes needed for normal ciliary development or function and is inherited in an autosomal recessive fashion. Mutations in more than 30 genes have been reported to date,

with the number increasing rapidly with advances in genetic discovery. As cilia contain more than 200 proteins it is likely that many more genetic mechanisms remain to be discovered [44].

Primary ciliary dyskinesia is not a form of interstitial lung disease, but the majority (>80%) of affected children present with neonatal respiratory distress and are admitted to neonatal intensive care units [44–46]. A finding of situs inversus or other laterality defect in a term newborn with respiratory distress should thus raise suspicion for PCD. However, >50% of PCD subjects will have normal situs, and the diagnosis may thus not be considered in the newborn period. The reported median age of diagnosis for PCD was 4.3 years, indicating that an opportunity for earlier diagnosis exists [46]. Recent studies have helped to characterize features of the neonatal lung disease associated with PCD by comparing features of neonatal lung disease in term infants eventually diagnosed with PCD compared to those with neonatal respiratory distress from other causes [46]. PCD subjects presented later (median 12 h compared to 1 h) and had a longer duration of needing supplemental oxygen. Lobar collapse or consolidation was widespread (70%) in PCD subjects but not observed in controls. The combination of need for supplemental oxygen for >2 days and lobar collapse or consolidation had a sensitivity of 83% and specificity of 96% for predicting PCD. The diagnosis of PCD may be established by electron microscopic analysis of ciliary ultrastructure in a respiratory epithelial sample, which can be obtained by nasal scraping. However, normal ciliary ultrastructure may be seen in PCD with some genetic defects [44]. Genetic testing with next-generation sequencing panels is also available. Nasal nitric oxide measurement may be a useful biomarker in older children but is not applicable to newborn infants. Characteristic clinical features of PCD in infants include early-onset, year-round nasal congestion and wet cough, and the development of these findings in an infant with a history of unexplained neonatal respiratory distress should prompt referral and evaluation for PCD [45].

7. Other genetic causes of ILD in older children

With advances in DNA sequencing methods, genetic causes of disease are being identified at an increasing rate, including many involving the lungs. Examples include COPA syndrome, which involves mutations in a gene encoding a protein involved in intracellular retrograde transport from the Golgi apparatus to the endoplasmic reticulum, and stimulator of interferon genes (STING)-associated vasculopathy of infantile-onset (SAVI), secondary to mutations in an endoplasmic reticulum transmembrane protein [47,48]. Both disorders result in abnormal immune function and are associated with inflammatory interstitial lung disease in infants. Whereas the presenting pulmonary findings associated with these disorders have mainly been observed in patients after the neonatal period, neonatal tachypnea was noted in some subjects with SAVI. As testing for these disorders becomes incorporated into diagnostic panels, it is possible that neonatal presentations will be recognized. The discovery of these disorders also serves to emphasize the role of genetic mechanisms in ILD/DLD in infants and newborns and the power of newer genetic approaches to uncover new disorders and disease mechanisms.

8. Diagnostic approach to ILD in newborns

Approaches to the diagnosis of chILD have been outlined [49,50]. It is important to first exclude known causes of lung disease – including structural heart disease and pulmonary hypertension – by echocardiography. In older infants, cystic fibrosis and immunodeficiency should be excluded. Evaluation should generally include high-resolution CT, and bronchoscopy may be helpful to exclude anatomical issues, infection, and aspiration. In newborns, strong consideration should be given to early genetic testing. The availability of next-generation sequencing panels allowing for simultaneous analysis of multiple genes is rapidly supplanting the need to decide which gene(s) to prioritize in terms of testing [50]. The drawback of such panels is that variants may be identified in multiple genes, some of which will be of unknown significance. Lung biopsy should be considered when the time for obtaining genetic results will delay diagnostic decisions needed to influence management (including redirection of care) or if genetic testing is ambiguous or unrevealing (Figure 2).

9. Conclusion

ChILD disorders frequently present in the neonatal period and are associated with significant morbidity and mortality. Clinical presentations range from intractable hypoxemic respiratory failure to milder respiratory signs and findings that persist after discharge. An underlying genetic basis occurs frequently in chILD, and newer genetic methodologies are uncovering the basis for previously cryptogenic disorders. Genetic discoveries and testing allow for non-invasive diagnosis and the results are important for predicting prognosis and counseling families regarding recurrent risk. A classification for chILD has been developed, and, although based upon lung pathology findings, with recognition of specific clinical and imaging patterns along with genetic testing, diagnosis is likely to become less reliant on biopsy. Timely diagnosis can allow for appropriate decisions with respect to management and follow-up.

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Practice points

- Interstitial lung disease refers to a group of disorders involving both the airspaces and tissue compartments of the lung.
- The major categories of ILD in children that present in the neonatal period include developmental disorders, growth disorders, surfactant dysfunction disorders, and specific conditions of unknown etiology unique to infancy.
- Many of the disorders have a genetic basis; non-invasive diagnosis is feasible, and characteristic clinical and imaging features may allow for specific diagnosis in some circumstances.

Research directions

- Determination of the incidence, prevalence and natural history of chILD disorders.
- Improved understanding of specific cellular mechanisms and pathophysiology.
- Development and validation of biomarkers to aid in diagnosis, response to therapy, and prognosis for specific chILD disorders.
- Identification of additional genes responsible for chILD disorders, including NEHI.
- Development of effective therapies for chILD disorders.

Fig. 1.

Distribution of diagnoses of interstitial lung disease in infants aged <2 years. The chart indicates the percentage of cases in each diagnostic category collated from retrospective studies [1,3–5,35]. Disorders and diagnoses in bold type are those more likely to present in the newborn period. BPD, bronchopulmonary dysplasia; NEHI, neuroendocrine cell hyperplasia of infancy; PIG, pulmonary interstitial glycogenosis; PAP, pulmonary alveolar proteinosis.

Fig. 2.

Evaluation of newborn with diffuse lung disease' (DLD) and hypoxemic respiratory failure of unclear etiology. Known disorders that can cause diffuse lung disease (such as pneumonia) should first be excluded. High-resolution chest tomography (HRCT), genetic testing, and lung biopsy are all important components of the evaluation, but the sequences of evaluations is influenced by the clinical history, the severity and trajectory of the child's lung disease, and the family history. For children whose disease is rapidly progressing, lung biopsy is likely to yield a diagnosis in the least time; as many of the conditions that result in such severe disorders have known genetic causes, genetic testing should also be pursued. Genetic testing should be prioritized in children with a positive family history of a childhood interstitial lung disease (chILD) disorder. For children with clinical features associated with growth disorders, supportive findings on HRCT may be sufficient for presumptive diagnosis, although lung biopsy is definitive. Genetic testing in these children may also be helpful primarily by excluding other known (single-gene) disorders. Next-generation sequencing panels are more cost- and time-effective than sequential single-gene panels, unless there is a family history of a known disorder. DLD, diffuse lung disease; GA, gestational age; ECMO, extracorporeal membrane oxygenation; PPHN, persistent pulmonary hypertension of the newborn.

Table 1

Summary of surfactant dysfunction disorders.

Gene	<i>SFTPB</i>	<i>SFTPC</i>	<i>ABCA3</i>	<i>NKX2-1</i>
OMIM locus	*178640 #265120	*178620 #610913	*601615 #610921	*600635 #610978
Phenotype	SMDP1	SMDP2	SMDP3	
Chromosomal location	2p11.2	8p21.3	16p13.3	14q13.3
Protein	SP-B	SP-C	ABCA3	TTF-1
Protein function	Enhances spreading and absorption of surfactant lipids; organizes lamellar body structure	Enhances spreading and absorption of surfactant lipids	Imports surfactant lipids into lamellarbodies; sequesters cholesterol	Transcription factor important for expression of SP-B, SP-C, ABCA3, SP-A, and many other genes
Inheritance	Recessive	Dominant; sporadic	Recessive	Sporadic; dominant
Phenotypic features	RDS	chILD > aILD > RDS	RDS > chILD >> aILD	RDS, chILD, aILD, recurrent infection; hypothyroidism; CNS (movement disorders, hypotonia, developmental delay)
Mechanism	Loss-of-function	Toxic gain-of-function; abnormal routing; dominant-negative	Loss-of-function	Haploinsufficiency
Histology	Macrophages and proteinaceous material in airspaces ± cholesterol clefts. AEC2 hyperplasia, interstitial thickening with mesenchymal cells > fibrosis.			
Prominent histologic diagnoses	PAP, CPI	CPI, NSIP, DIP, PF, UIP	PAP, DIP, NSIP, PF, UIP	Deficient alveolarization; lobular remodeling; DIP, PAP, NSIP
Electron microscopy	Disorganized lamellar bodies	Normal to variable LBs	Small, “fried-egg” lamellar bodies	Variable
Outcome	Fatal	Variable	May be fatal in early infancy; variable	Variable

OMIM, Online Mendelian Inheritance in Man; SMDP, surfactant metabolic dysfunction, pulmonary; SP-, surfactant protein; ABCA3, member A3 of ATP binding cassette family; TTF1, thyroid transcription factor 1; RDS, respiratory distress syndrome; chILD, childhood interstitial lung disease; aILD, adult-onset interstitial lung disease; AEC2, alveolar type 2 cell; PAP, pulmonary alveolar proteinosis; CPI, chronic pneumonitis of infancy; NSIP, non-specific interstitial pneumonitis; DIP, desquamative interstitial pneumonitis; PF, pulmonary fibrosis; UIP, usual interstitial pneumonitis.

Table 2

Characteristics of disorders which may result in the pathology of pulmonary alveolar proteinosis (PAP), but occur in older children as opposed to newborns

Gene	Protein/function	Chromosomal location	Inheritance pattern	Age of onset	Pulmonary phenotype	Extrapulmonary involvement	OMIM
<i>FOXP1</i>	Transcription factor	16q24.1	Sporadic, dominant	Birth	PPHN	Frequent, cardiac, GI, GU	*601089 #265380
<i>FLNA</i>	Actin binding protein	Xq28	Dominant	Neonatal to older	“BPD” hyperinflation	CNS; seizures (periventricular heterotopias), multi-organ	*300017 #300049
<i>CSF2RA</i>	GM-CSF receptor α-chain	Xp22.33 Yp11.2	Recessive	Childhood	PAP	None	*306250 #300770 (SMDP5)
<i>CSF2RB</i>	GM-CSF receptor β-chain	22q12.3	Recessive	Childhood, adult	PAP	None	*138981 #614370 (SMDP5)
<i>SLC7A7</i> (lysine protein intolerance)	Solute carrier	14q11.2	Recessive	Infancy, childhood	PAP	GI (vomiting), failure to thrive	*603593 #222700
<i>MARS</i>	Methionyl tRNA synthetase component	12q13.3	Recessive	Infancy to adult	PAP	Liver disease, anemia, hypothyroidism, Charcot-Marie- Tooth	*156560 #615486 #616280
<i>GATA2</i>	Transcription factor	3q21.3	Dominant	Childhood	PAP	Immunodeficiency, myelodysplasia	*137925 #614172
<i>COPA</i>	Intracellular Transport protein	1q23.2	Dominant	Infancy > adult, asymptomatic	ILD, hemorrhage	Arthritis, immune	*601924 #616414
<i>TMEM173</i> (SAVI, STING- associated vasculopathy, infantile- onset)	STING	5q31.2	Sporadic, dominant	Infancy; may have symptoms (tachypnea) in perinatal period	ILD	Autoimmune, vasculopathy skin	*612374 #615934

OMIM, Online Mendelian Inheritance in Man; PPHN, persistent pulmonary hypertension of the newborn; BPD, bronchopulmonary dysplasia; GI, gastrointestinal; GU, genitourinary; CNS, central nervous system; GM-CSF, granulocyte-macrophage colony-stimulating factor; STING, STimulator of INterferon Genes.