Interstitial Lung Disease in Children

ATS Fellows Track Symposium

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Children's Hospital of Philadelphia℠

Disclosures

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Off-label use and/or investigational use: General considerations will be discussed

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Objectives

- Recognize the presentations and impact of interstitial and developmental lung diseases in infants and children
- Describe an appropriate diagnostic evaluation plan for children with suspected interstitial lung disease (ILD)
- Identify opportunities for discovery and pathways to accelerate progress in ILD in children

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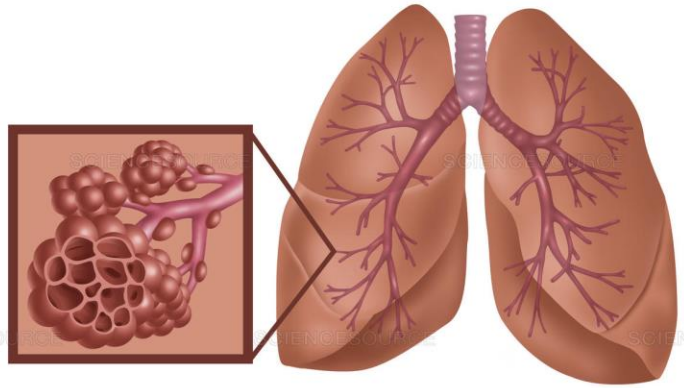
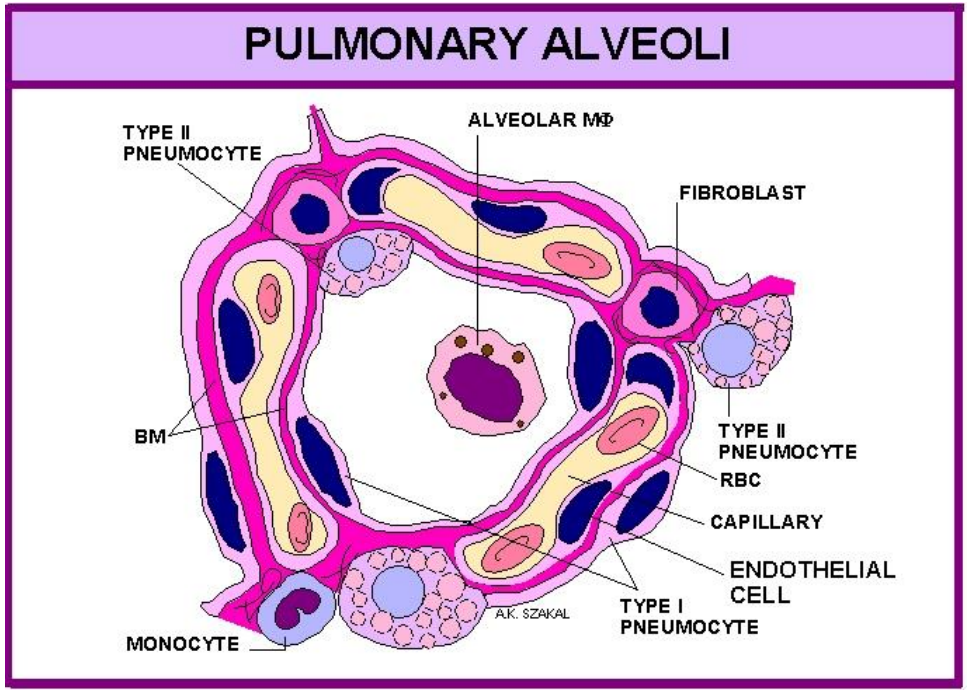
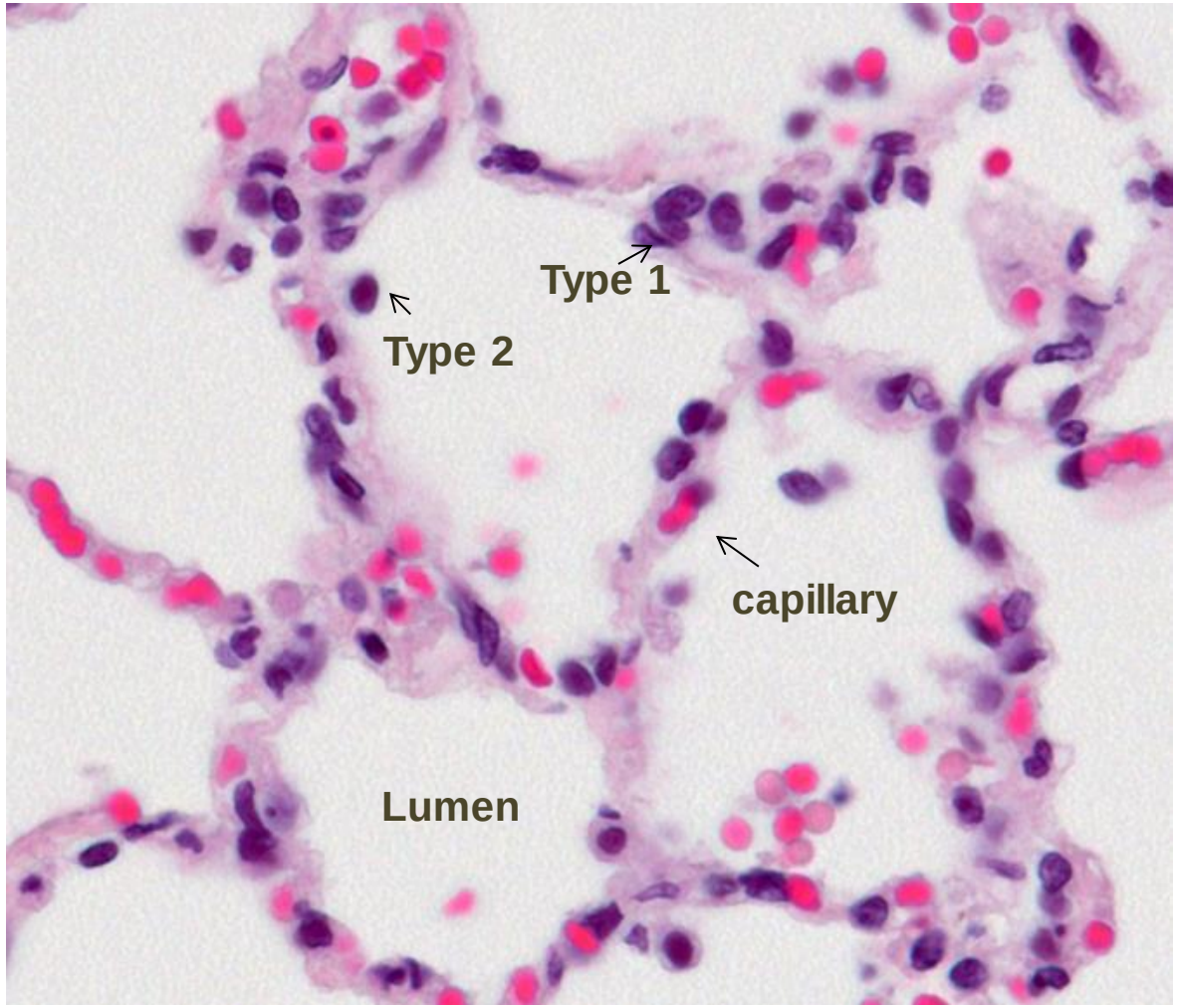
Interstitial = Alveolar-capillary membrane

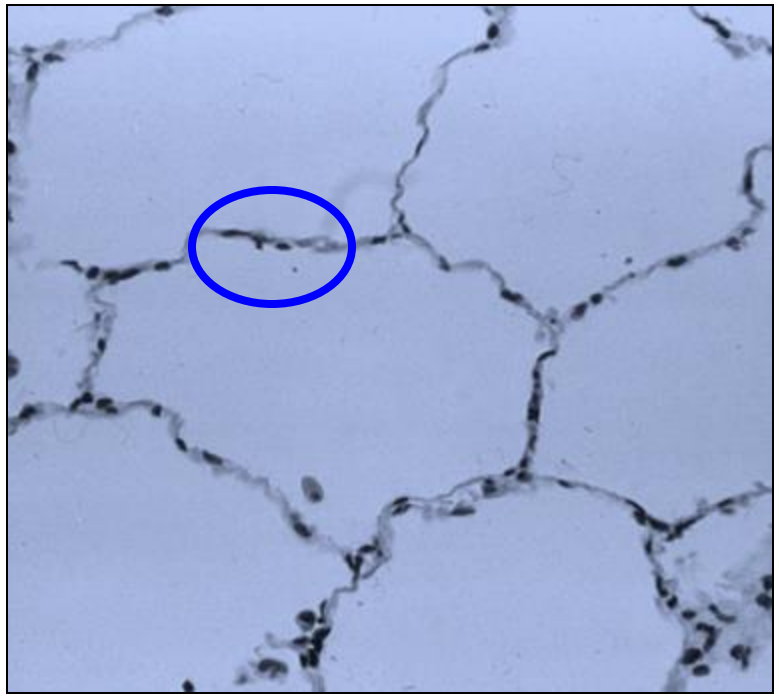




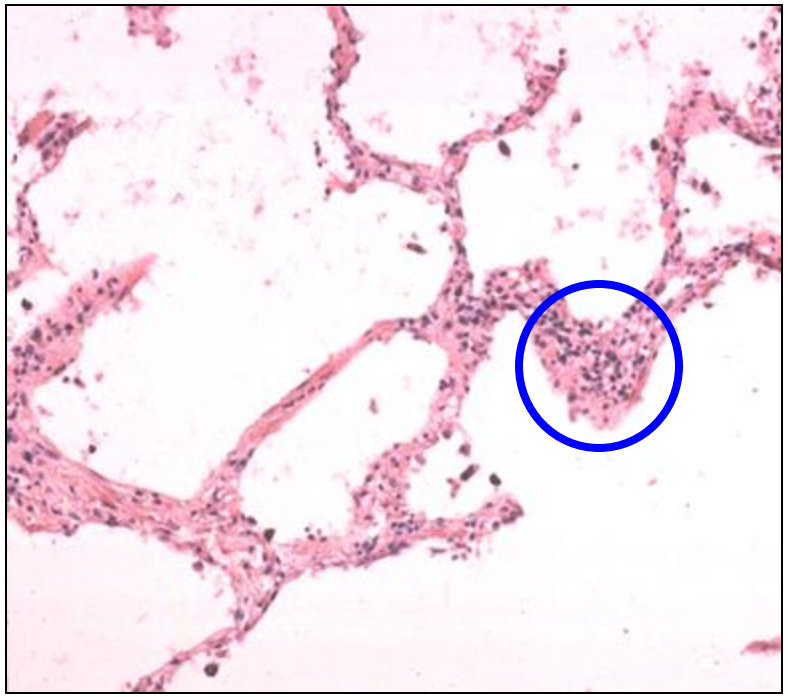


Courtesy of Gail Deutsch, MD

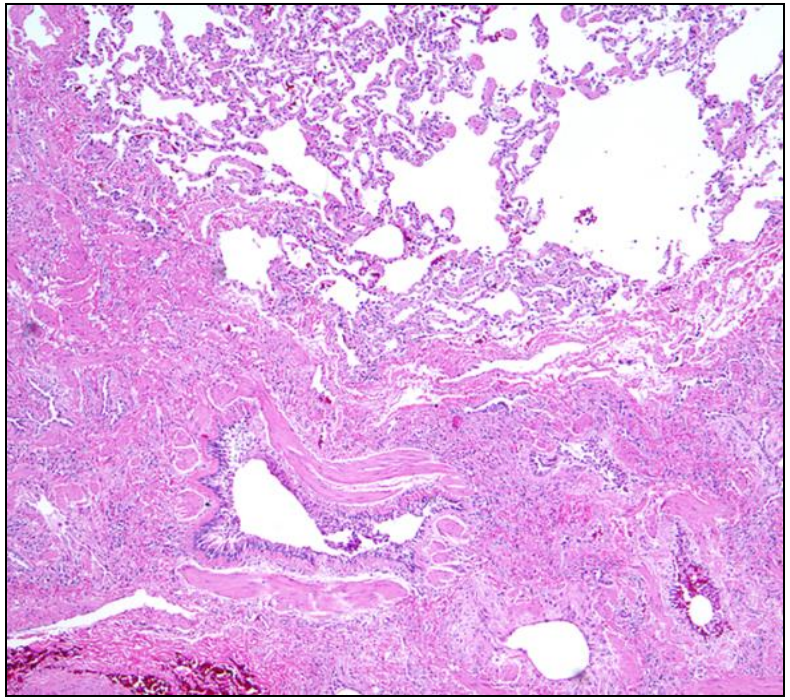
Interstitial Lung Disease (ILD) = Disruption of the interstitial space



Normal alveoli

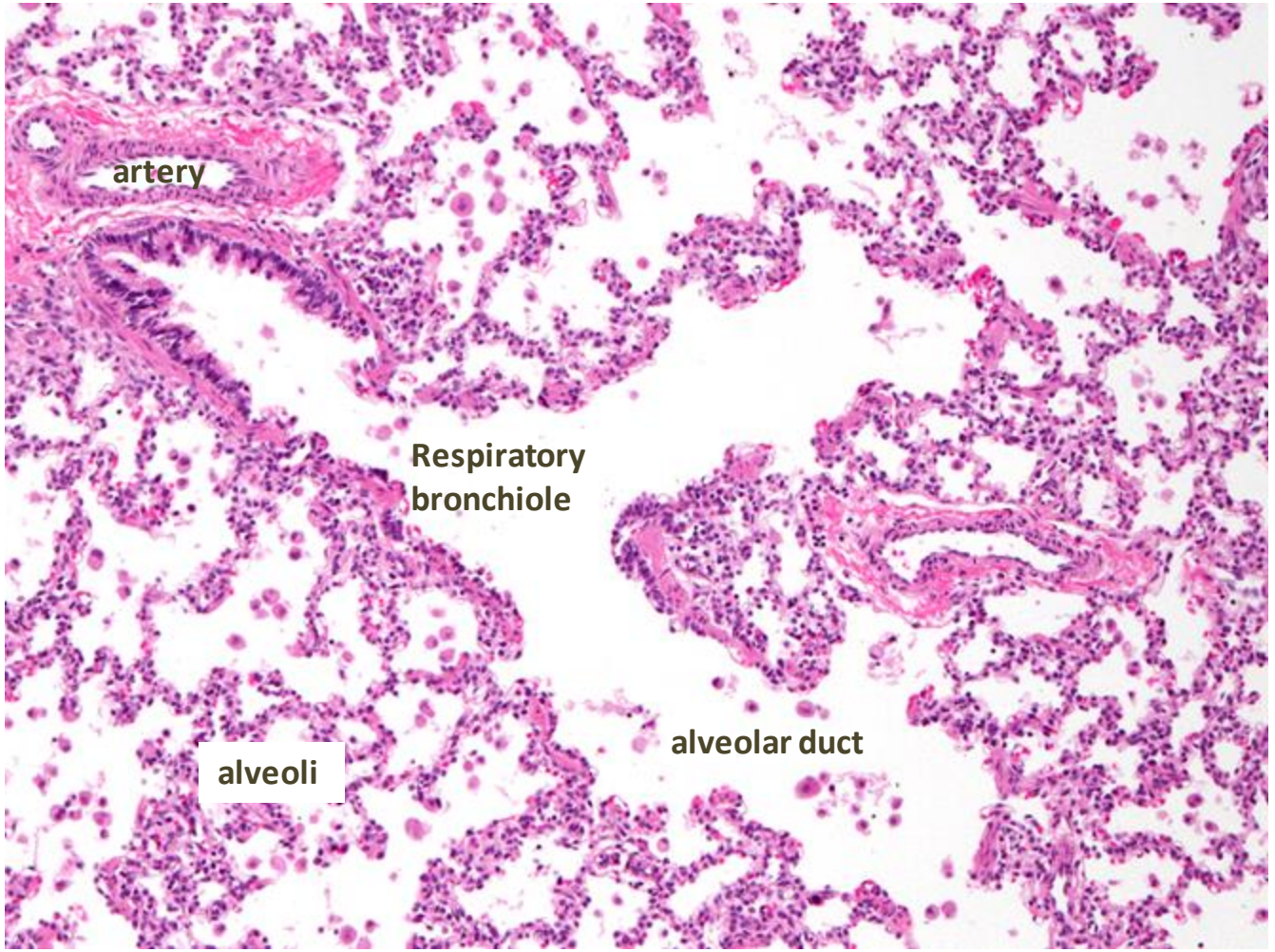


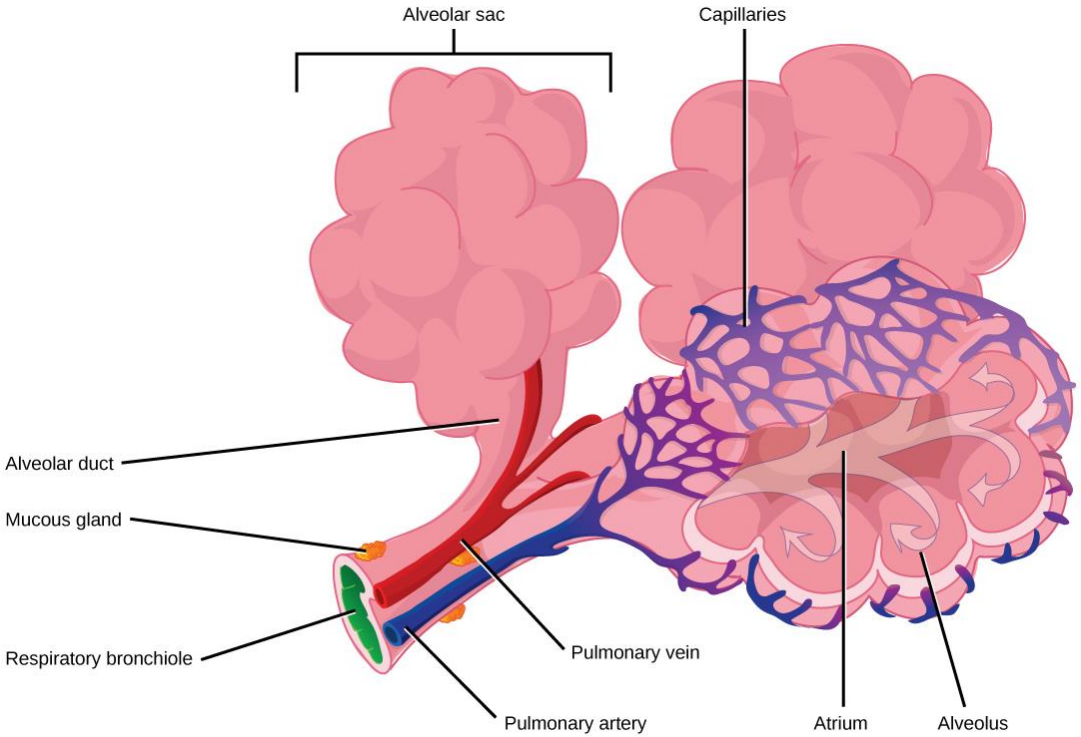
Mild-moderate ILD



Advanced fibrosis

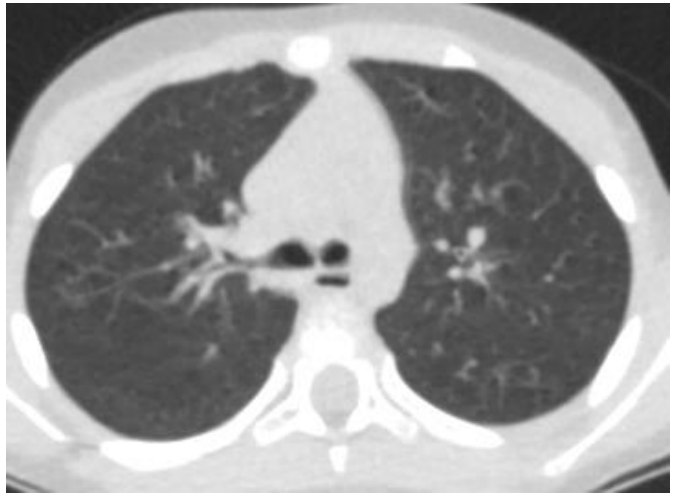
‘ILD’ also includes diseases impacting the terminal respiratory unit / acinus



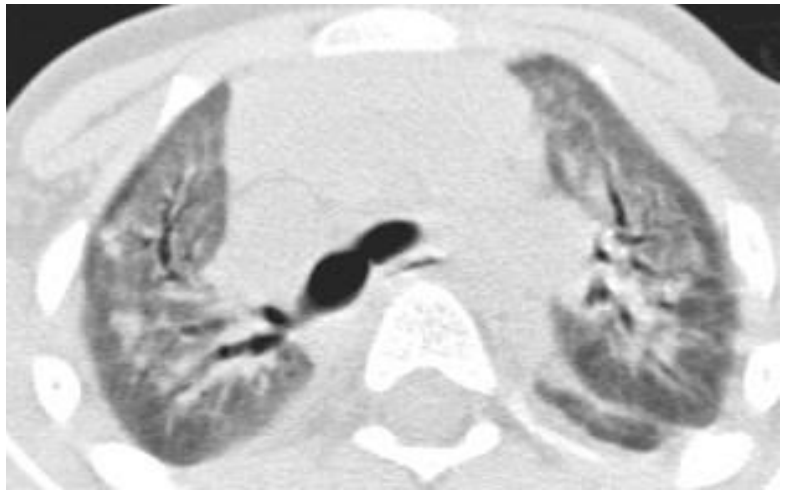


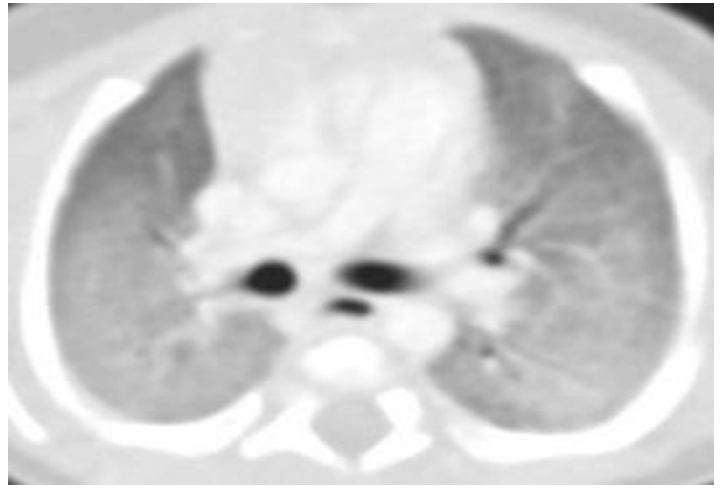
Courtesy of Gail Deutsch, MD

ILD: Think ‘Diffuse Lung Disease.’



Normal chest CT





ILD = diffuse lung disease

- Heterogeneous collection of rare diseases with overlapping clinical presentations
- Uncertain prevalence; difficult to diagnose
- Genetic and molecular mechanisms increasingly recognized
- High morbidity, though varying outcomes

Part of my early introduction to ILD

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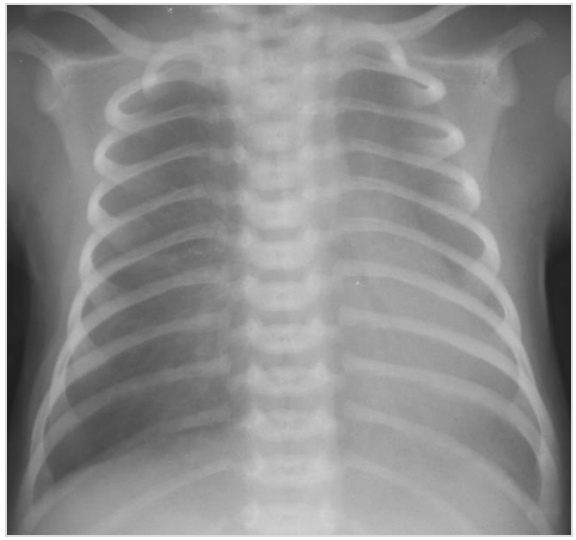
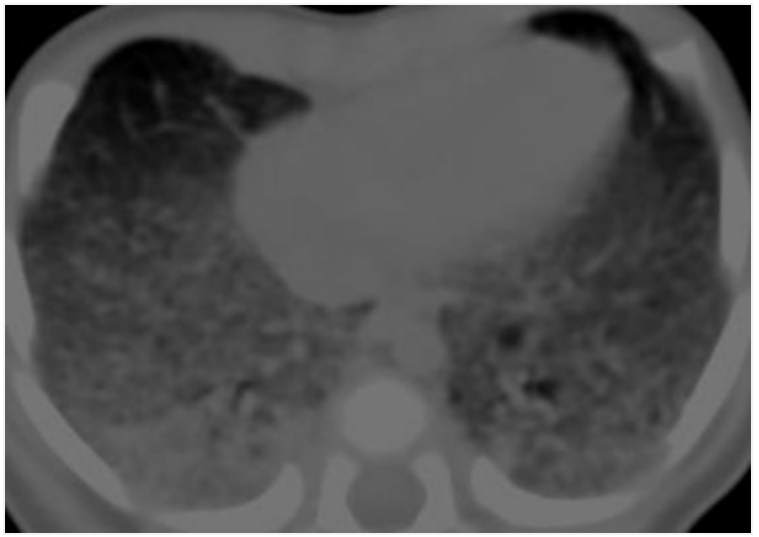
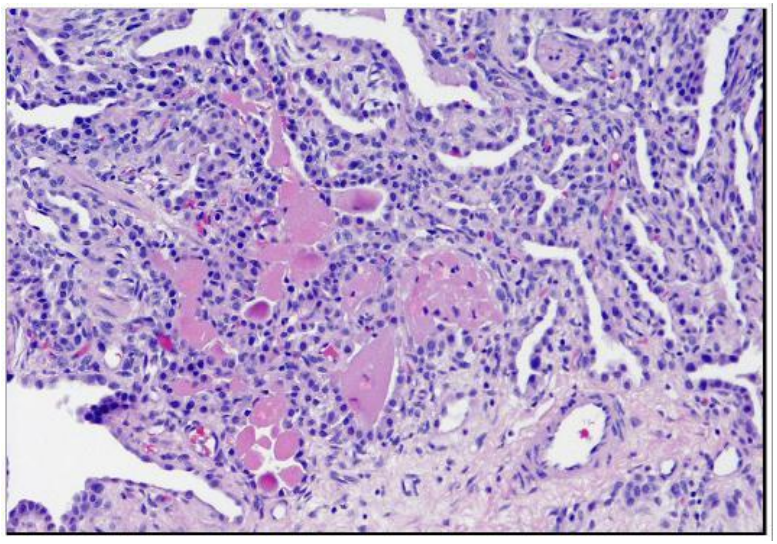
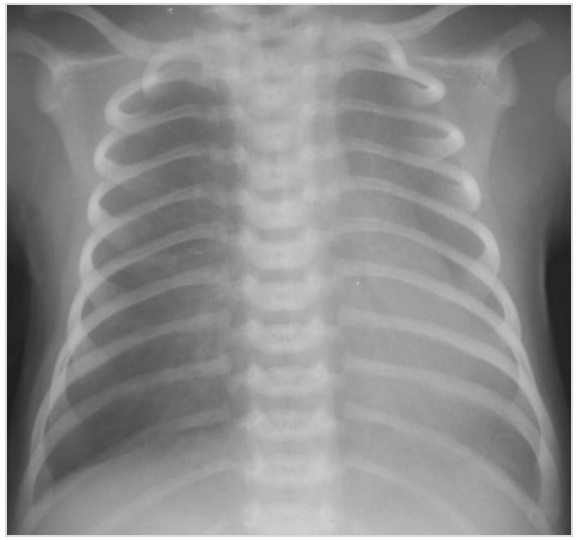


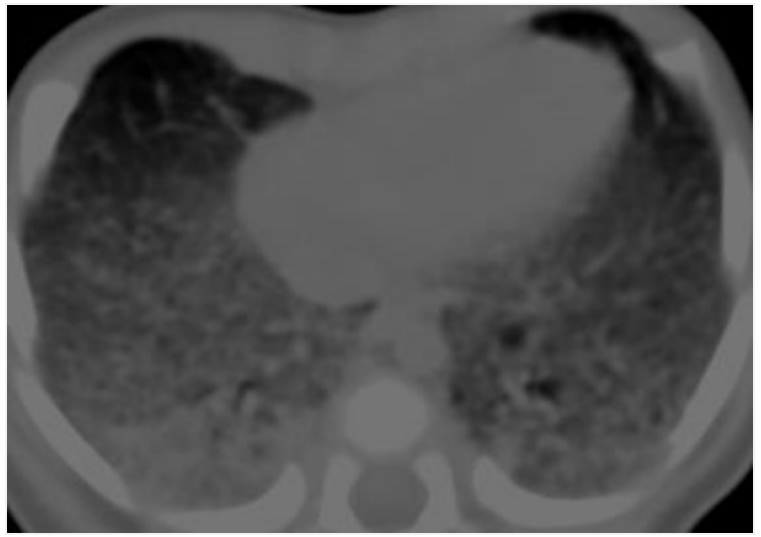


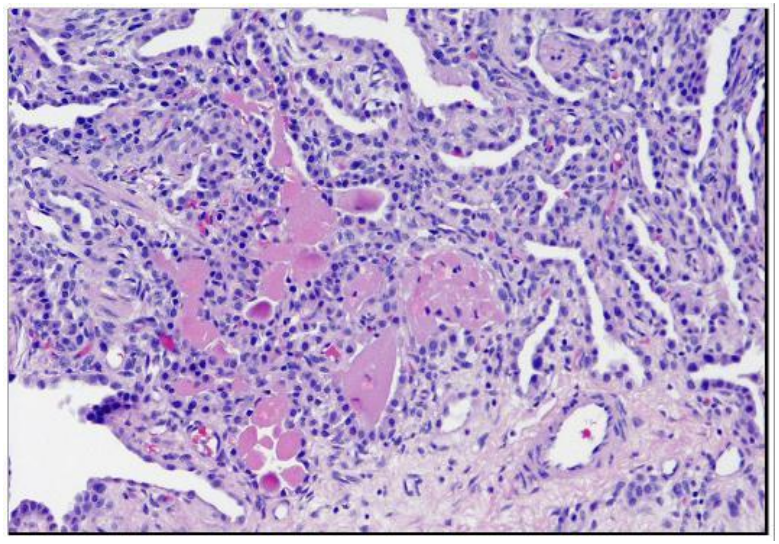


- 1994: Term infant with respiratory failure
- Remained oxygen dependent with ‘idiopathic ILD’
- 1999: Underwent bilateral lung transplant (age 5 yrs)

Part of my early introduction to ILD







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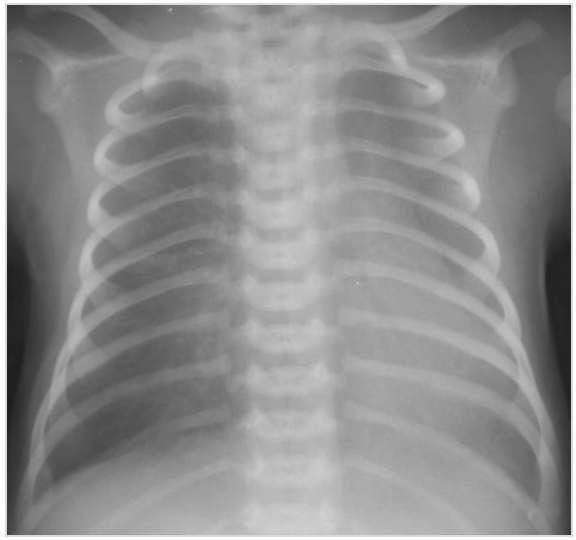
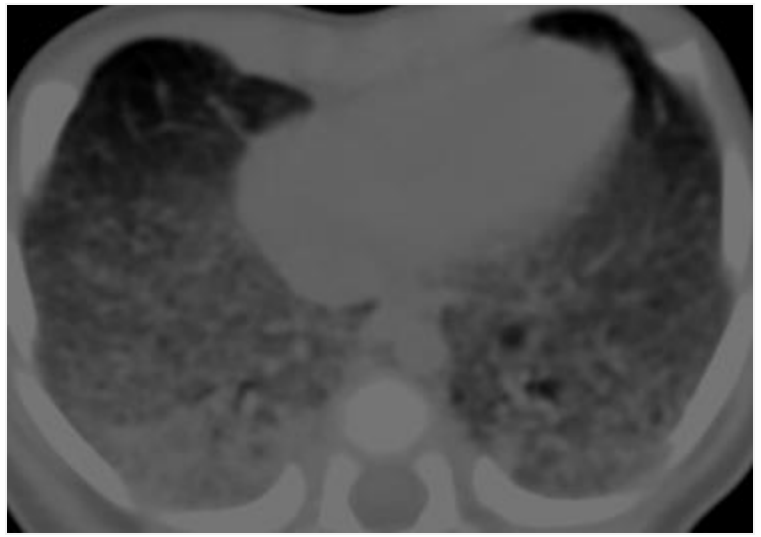
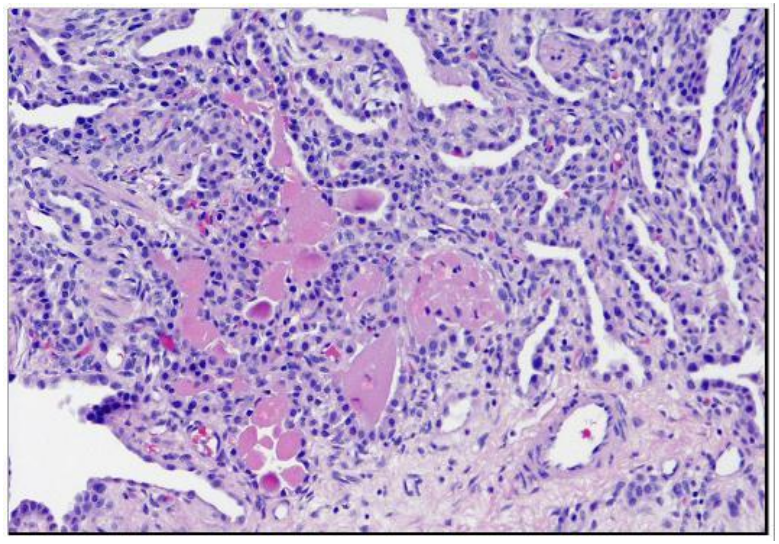






- 1994: Term infant with respiratory failure
- Remained oxygen dependent with ‘idiopathic ILD’
- 1999: Underwent bilateral lung transplant (age 5 yrs)
- 2002: Died of bronchiolitis obliterans syndrome
- 2004: Discovery of ABCA3 mutations as a cause of neonatal respiratory failure (Schulenin/Nogee, NEJM); diagnosis made retrospectively in this patient

Father becomes the founding president of the chILD Foundation

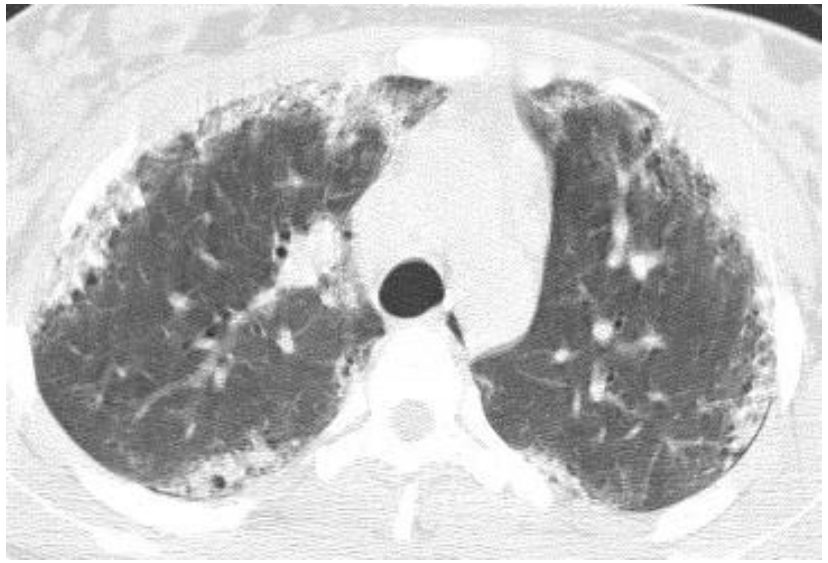
chILD

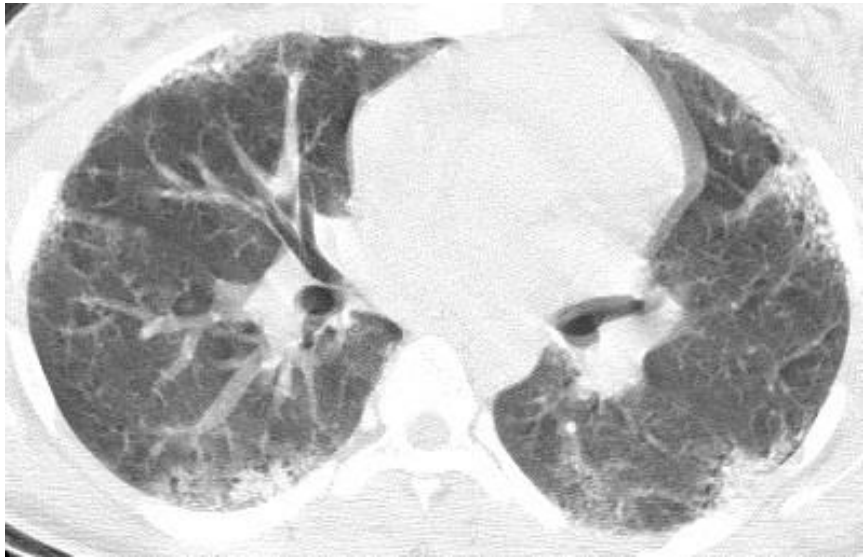
CHILDRENS INTERSTITIAL AND DIFFUSE LUNG DISEASE FOUNDATION

Synergy with other rare lung disease patient advocacy groups was essential to the establishment of the chILD Foundation.

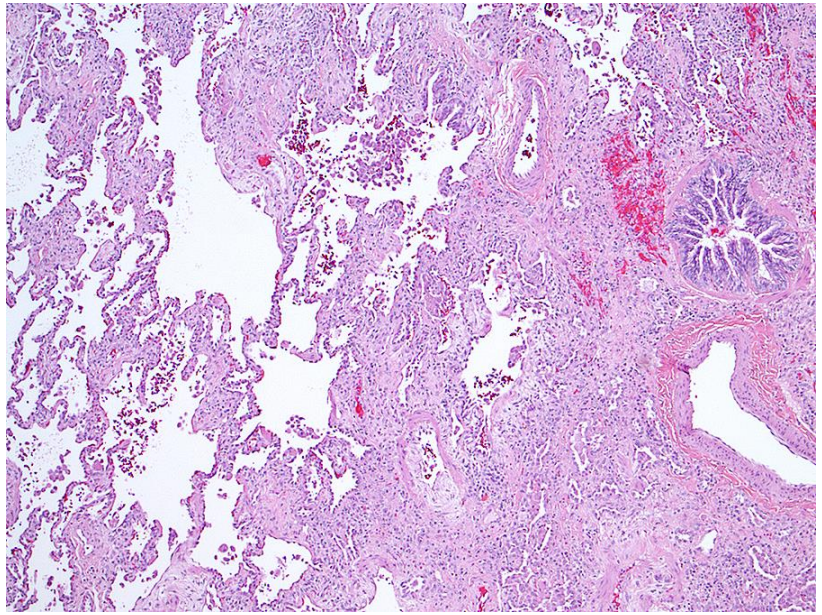
Another introduction to ILD: 15 yo with polymyositis

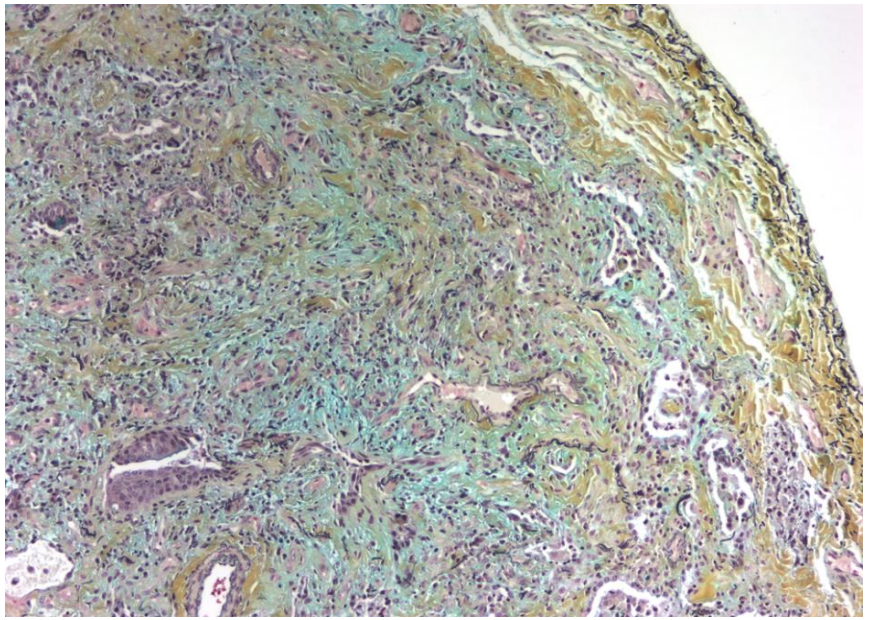
Subpleural predominant opacities





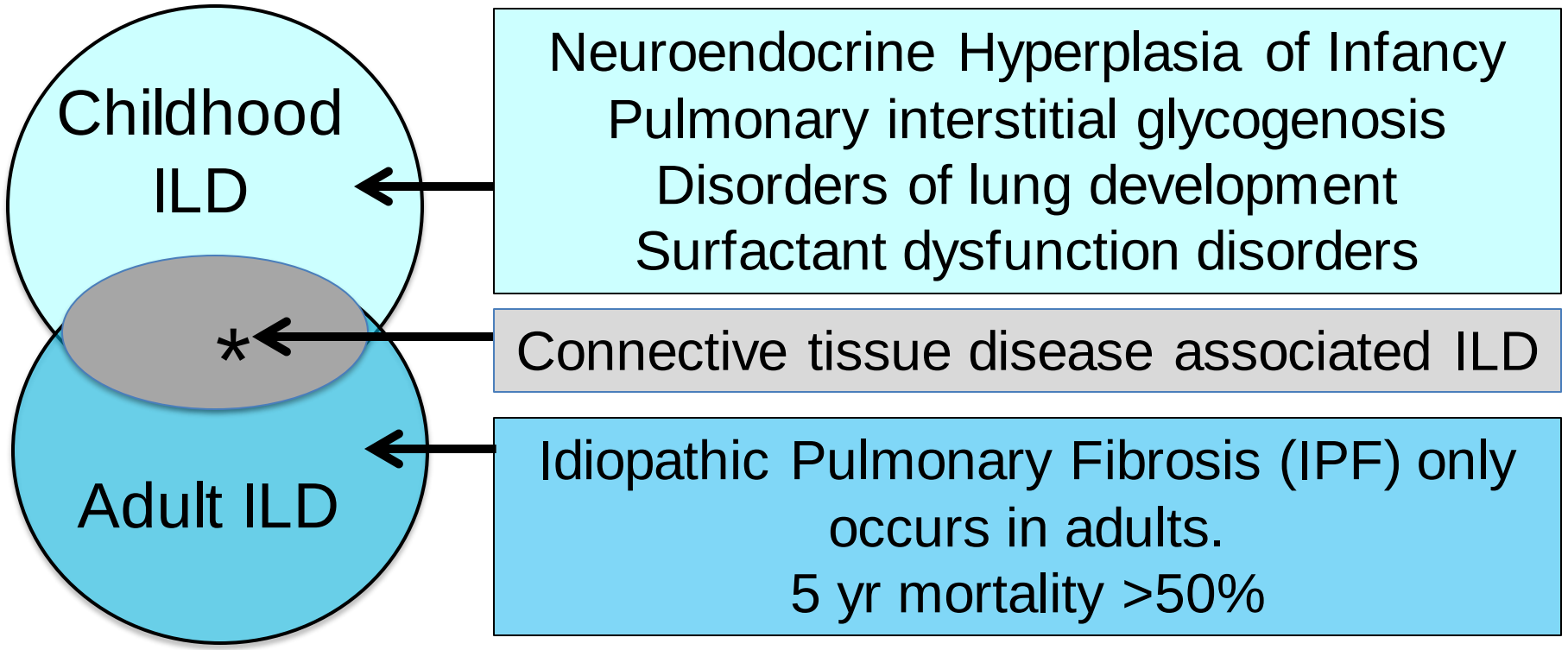
Dense fibrosis





Pentachrome stain

Early 2000s: Concerted efforts to distinguish ILD in children from that in adults



Recognizing ILD as an important part of pediatric lung disease

Leland Fan, MD

Spectrum of chronic ILD in children. 1992

Evaluation and therapy of chronic ILD in children. 1994

The safety and efficacy or thoracoscopic lung biopsy… 1996

Factors influencing survival in children with chronic ILD. 1997

Diagnostic value of transbronchial, thoracoscopic, and open lung biopsy… 1997

Evaluation of a diagnostic approach… 1998

Pediatric diffuse lung disease: diagnosis and classification using high-resolution CT. 1999

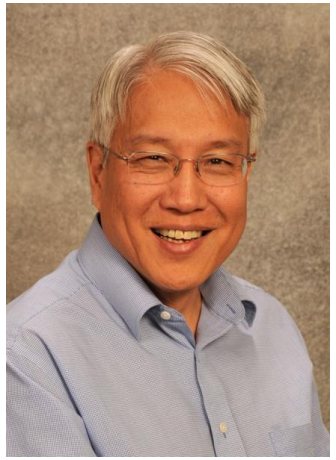
Pediatric ILD: children are not small adults. 2002

- Fan, AJRCCM 2002: Of reported pediatric cases of UIP/IPF, mortality occurred in only 4 of 99 cases. And, these cases lacked the histopathologic features of UIP.

Recognition of new forms of ILD in children

Larry Nogee

Robin Deterding



Leland Fan

Claire Langston

SFTPB 1993

SFTPC 2001

ABCA3 2004

NEHI: (2001) 2005

The Children's Interstitial Lung Disease (chILD) Research Network

- Established in 2004
- Initiated retrospective cohort studies to develop consensus terminology and diagnostic criteria
  - Reviewed all diagnostic lung biopsies performed for diffuse lung disease in:
    - Children ≤2 yrs of age (1999-2004); 11 centers: n=187*
    - Children 2-18 yrs of (2000-04); 12 centers: n=191**
- ATS Clinical Guideline published in 2013#
- Monthly conference calls and case presentations
- Educational and research conferences held annually

*Deutsch/Young et al, AJRCCM 2007
**Fan et al, Annals ATS 2015
#Kurland et al, AJRCCM 2013

Initial funding from NIH ORD/NCRR Rare Diseases Rare Lung Diseases Consortium grant (B Trapnell and F McCormack)

Development of the Classification System for childhood interstitial and diffuse lung diseases

Gail Deutsch

Diffuse Lung Disease in Young Children

Application of a Novel Classification Scheme

Gail H. Deutsch[1*], Lisa R. Young[2*], Robin R. Deterding[3], Leland L. Fan[4], Sharon D. Dell[5], Judy A. Bean[6], Alan S. Brody[7], Lawrence M. Nogee[8], Bruce C. Trapnell[9], Claire Langston[10], and the Pathology Cooperative Group: Eric A. Albright[11], Frederic B. Askin[12], Peter Baker[11], Pauline M. Chou[13], Carlyne M. Cool[14], Susan C. Coventry[15], Ernest Cutz[16], Mary M. Davis[17], Megan K. Dishop[10], Csaba Galambos[18], Kathleen Patterson[19], William D. Travis[20], Susan E. Wert[9], and Frances V. White[21]; on behalf of the ChILD Research Co-operative[†]

Divisions of [1]Pathology, [2]Pulmonary Medicine, [6]Epidemiology, and [9]Pulmonary Biology, and [7]Department of Radiology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; [3]Department of Pediatrics, Children's Hospital, Denver, Colorado; Departments of [4]Pediatrics and [10]Pathology, Texas Children's Hospital, Houston, Texas; Divisions of [5]Respiratory Medicine and [16]Pathology, The Hospital for Sick Children, Toronto, Ontario, Canada; Departments of [8]Pediatrics and [12]Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland; [11]Department of Anatomic Pathology, Children's Hospital, Columbus, Ohio; [13]Department of Pathology, Children's Memorial Hospital, Chicago, Illinois; [14]Department of Pathology, University of Colorado Health Science Center, Denver, Colorado; [15]Department of Pathology, Kosair Children's Hospital, Louisville, Kentucky; [17]Division of Pediatric Pathology, James Whitcomb Riley Hospital for Children, Indianapolis, Indiana; [18]Department of Pathology, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania; [19]Department of Laboratories, Children's Hospital and Regional Medical Center, Seattle, Washington; [20]Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, New York; and [21]Division of Surgical Pathology, Washington University School of Medicine, St. Louis, Missouri

AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 176 2007

2007 Clinical-Pathologic Classification of Diffuse Lung Disease in Childhood

Diffuse developmental disorders	Acinar dysplasia, congenital alveolar dysplasia, alveolar capillary dysplasia with misalignment of the pulmonary veins
Growth abnormalities	Pulmonary hypoplasia, chronic neonatal lung disease (BPD), related to chromosomal disorders, congenital heart disease
Specific conditions of unknown/poorly understood etiology (NEHI and PIG)	Neuroendocrine hyperplasia of infancy, pulmonary interstitial glycogenosis
Surfactant dysfunction disorders	*SP-B, SP-C, ABCA3,* congenital GMCSF receptor deficiency*, NKX 2.1 mutations,* other
Disorders of the normal host	Infectious and post-infectious processes, related to environmental agents (HSP), aspiration, eosinophilic pneumonia
Disorders related to systemic disease processes	Immune-mediated disorders (acquired PAP, pulmonary hemorrhage syndromes, collagen vascular disease), storage disease, Langerhans cell histiocytosis, malignant infiltrates
Disorders of the immunocompromised host	Congenital immunodeficiency or related to the solid organ, lung and bone marrow transplantation and rejection syndromes; opportunistic infections, related to therapeutic intervention
(Vascular) disorders masquerading as ILD	Arterial, venous, lymphatic disorders; congestive changes related to cardiac dysfunction
Unclassified	End-stage lung disease, inadequate biopsy

Langston and Dishop, Pathol Int 2004

Deutsch and Young et al, AJRCCM 2007

Eliminating 'Idiopathic' from Idiopathic Pulmonary Fibrosis (IPF)

- Positive family history is present for ~ 20% of cases of IPF.
  - Similar clinical course, imaging, and histopathologic findings in familial and sporadic cases
- Mutations in surfactant pathway genes are very rare causes of IPF; telomere-associated pathways predominate.
- Also role for common variants as risk alleles

Gene	% in adults with familial ILD
TERT	~ 8-15%
RTEL1	~ 5%
hTR	<1%
TINF2	<1%
DKC1	<1%
PARN	<1%
SFTPC	1-2%
SFTPA2	<1%
ABCA3	<1%
NKX2-1	<1%
Unknown	**~ 75%**

Modified from Kropski/Blackwell, ERJ 2015

There are numerous Pediatric Rare Lung Diseases.

Categories include:

Lung development

Surfactant system

Vascular biology

Lymphatics

Airway disorders

Systemic Diseases

Lung injury

NIH Workshop on Accelerating Scientific Progress for Pediatric Rare Lung Diseases;
***Annals ATS,* 2016**

Category and Subtypes	Specific Examples and Etiologies
Disorders of Lung Development	
Diffuse Developmental Disorders	Alveolar Capillary Dysplasia with Misalignment of Pulmonary Veins (ACDMPV); associated with disruption of *FOXF1* Acinar Dysplasia Congenital Alveolar Dysplasia
Lung Growth Abnormalities	Pulmonary Hypoplasia Bronchopulmonary Dysplasia
Pulmonary Interstitial Glycogenosis	Diffuse form or patchy form in conjunction with altered lung development
Congenital Malformations	Congenital pulmonary airway malformations Bronchogenic cysts Pulmonary sequestration Airway malformations Others
Genetic Disorders of Surfactant Metabolism	Associated with disruption of *SFTPB,SFTPC, ABCA3,* and *NKX2-1* Others, candidate genes/ gene variants not identified
Pulmonary Alveolar Proteinosis	GM-CSF autoantibodies Associated with disruption of *CSF2RA* and *CSF2RB* Lysinuric protein intolerance Other secondary PAP mechanisms
Neuroendocrine cell Hyperplasia of Infancy	Associated with *NKX2-1* mutation Others, etiology not identified
Cystic Fibrosis	Associated with disruption of *CFTR*
Primary Ciliary Dyskinesia	Associated with disruption of *DNAH5, DNAI1, DNAI2, CCDC114, ARMC4, LRRC6, HEATR2, SPAG1, DNAAF1, DNAAF2, CCDC39, CCDC40, RSPH4, RSPH9* and multiple other genes (>30) identified Others, candidate genes/ gene variants not identified
Pulmonary Vascular Disorders	
Pulmonary veno-occlusive disease	Associated with disruption of *EIF2AK4*
Pulmonary capillary hemangiomatosis Hereditary hemorrhagic telangiectasia	Associated with disruption of *ACVRL1*, *ENG*, and *SMAD4*
Congenital lesions (hemangiomas, others) Isolated pulmonary capillaritis Pulmonary Arterial Hypertension	Associated with disruption of *BMPR2;* multiple other genes identified Others, candidate genes/ gene variants not identified Associated with altered lung development, lung diseases, other systemic disorders, and other conditions or exposures
Lymphatic disorders	Pulmonary Lymphangiectasia Generalized lymphatic anomaly (Lymphangiomatosis) Kaposioform Lymphangiomatosis Others
Related to Systemic Diseases	
Connective Tissue (Rheumatologic) Disorders Metabolic or Lysosomal Storage Diseases Sarcoidosis	Niemann-Pick, Gaucher's disease, numerous others
Dyskeratosis Congenita Langerhans Cell Histiocytosis	*Associated with disruption of TERT, TERC, DKC1, TINF2,* and *RTEL1*
Associated with immunodeficiency syndromes Neurocutaneous Syndromes Hermansky-Pudlak Syndrome Sickle Cell Disease Others	Follicular bronchiolitis, lymphocytic interstitial pneumonia; multiple genetic etiologies Neurofibromatosis, Tuberous Sclerosis Complex, Ataxia-Telangiectasia, others Lung disease associated with disruption of *HPS1, AP3b1,* and *HPS4*
Other PRLDs	
Bronchiolitis Obliterans Hypersensitivity Pneumonitis Eosinophilic Pneumonia Radiation pneumonitis/fibrosis	Post-infectious or post-transplant/ pulmonary graft versus host disease
Pulmonary Alveolar Microlithiasis	Associated with disruption of *SLC34A2*
Plastic Bronchitis Others	Associated with cyanotic heart disease, sickle cell disease, lymphangiectasia, and others
Unclassified or Undefined	

What is the prevalence of childhood ILD?

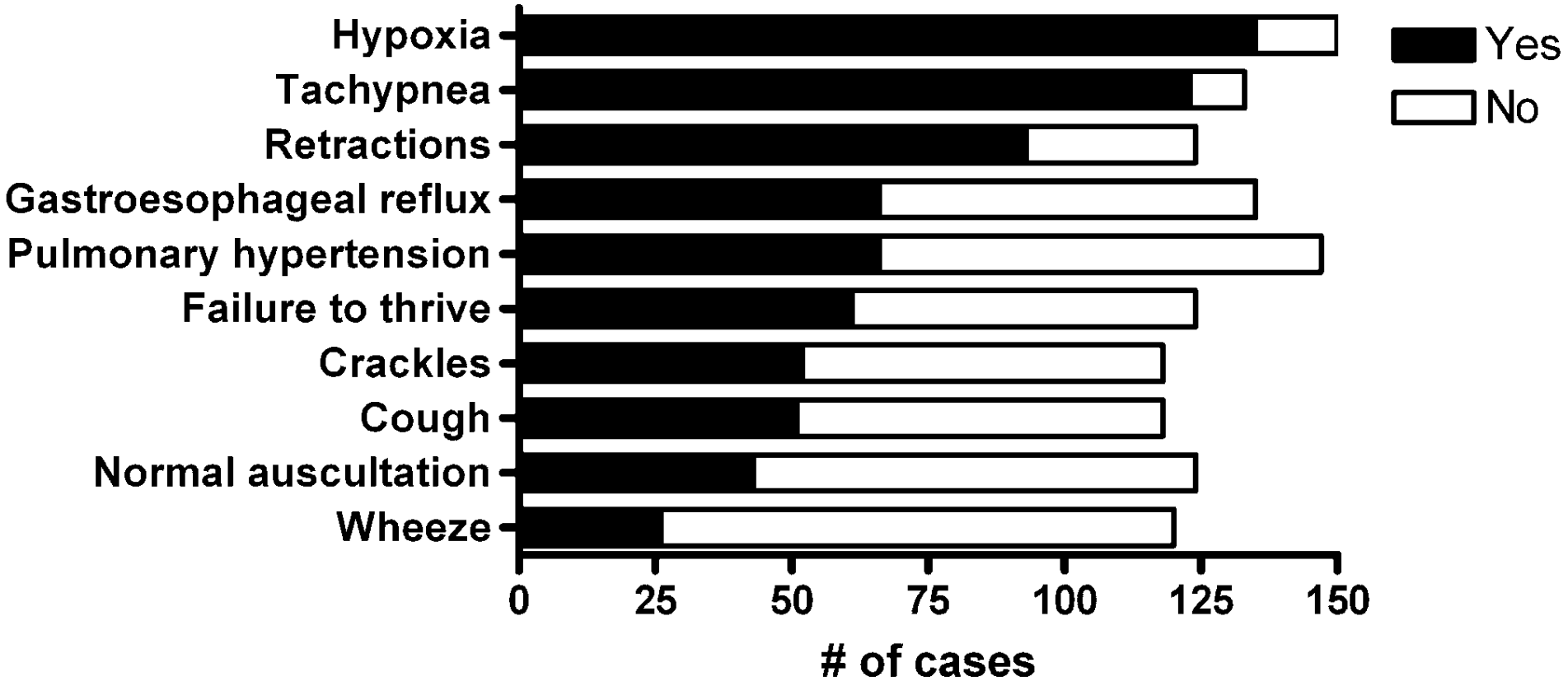
- Published reports range from 1 – 4 cases per million
- Data for those with identified genetic causes suggest these figures are vast underestimates.
  - ➢Surfactant protein B mutations (1 per million)
- Epidemiologic assessments are challenged by use of different case definitions and ascertainment methods.
  - Some studies required lung biopsy for inclusion
  - Some excluded children with immunodeficiency
- While rare, these cases probably exist everywhere.

J. Soares/ L Young; Pediatrics, 2013

Children with ILD initially present in a variety of clinical settings.

Primary Care Settings
Neonatal ICU
Cardiology / Cardiac ICU
Pediatric ICU
Emergency Department
Rheumatology
Allergy/Immunology
Hematology/Oncology
Gastroenterology
Endocrinology
Infectious Diseases
Genetics
Neurology
Nutritionist
Speech Pathologist

Diagnostic challenges: The clinical signs and symptoms of ILD overlap with many other more common disorders. *Think 'ILD Syndrome.'*



Deutsch GH and Young LR, for the Children's ILD Network, AJRCCM 2007

The first step in the diagnostic evaluation for possible ILD is to exclude other more common causes for these symptoms.

Evaluate and treat 'common' causes.

- Infection
- Structural heart disease (echocardiogram)
- Anatomic / large airway abnormalities or aspiration (bronchoscopy, swallow evaluation)
- Cystic Fibrosis (sweat chloride)
- Immunodeficiency

➢ Remember that sometimes you may identify a co-morbid diagnosis, not the underlying cause.

Kurland et al, An Official ATS Clinical Practice Guideline: Classification, Evaluation, and Management of Childhood Interstitial Lung Disease (chILD) in Infancy, AJRCCM 2013

Approach to possible ILD cases

- The clinical context informs the differential diagnosis and guides the diagnostic approach.
  - Age of onset of symptoms
  - Family history
  - Disease severity: Hypoxemia, nutritional status, pulm. hypertension
  - Clinical course: Progression, persistence, or improvement

- Considerations often include chest CT, genetic testing, and/or lung biopsy.
  - ➢ Technique and details are critical.

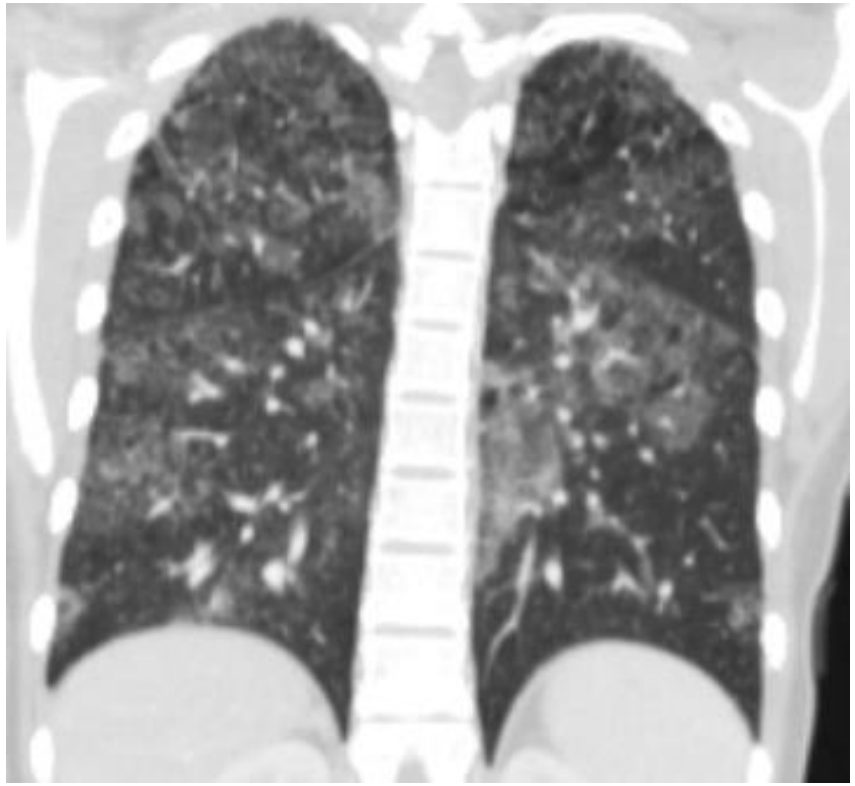
Kurland et al, AJRCCM 2013

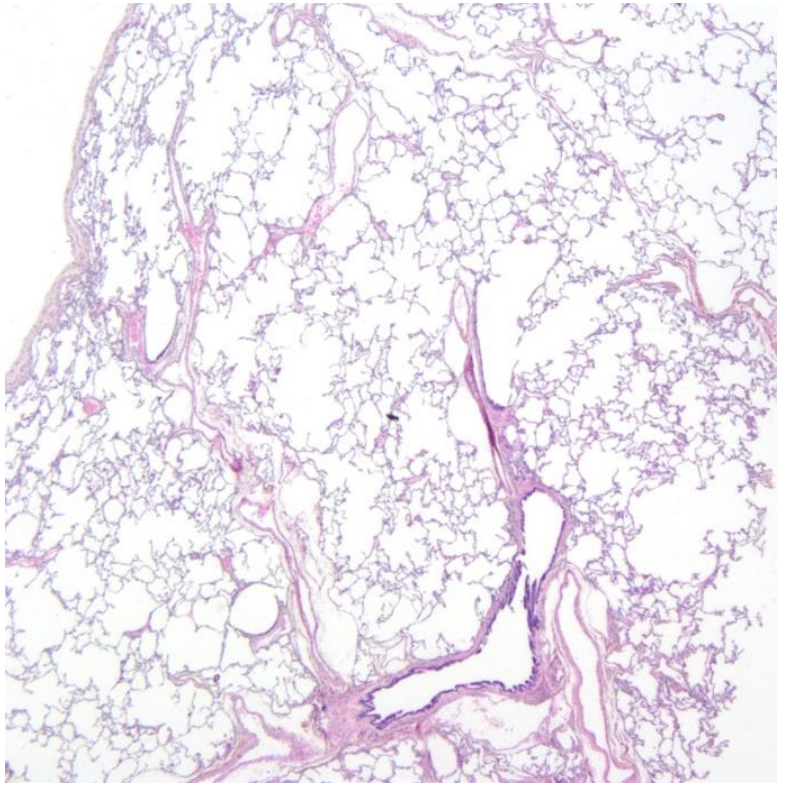
Role of Chest CT in ILD diagnosis

- Can accurately suggest a specific ILD diagnosis in some cases, altering treatment decisions and avoiding need for lung biopsy
- Talk with a radiologist in advance - technique is critical, especially in young children.
  - For a long time, the ILD field advocated for performing chest CT in infants and toddlers utilizing sedation/anesthesia, to avoid respiratory motion artifact and with raised volumes for inspiratory/expiratory images
    - Challenge of atelectasis
  - Practice shifting now with faster scanners at many centers and goals to minimize radiation dose
    - Expiratory imaging not always needed

When other studies fail to provide a specific diagnosis, and clinical urgency dictates, surgical lung biopsy, typically via VATS, should be considered.

Biopsy site is critical.



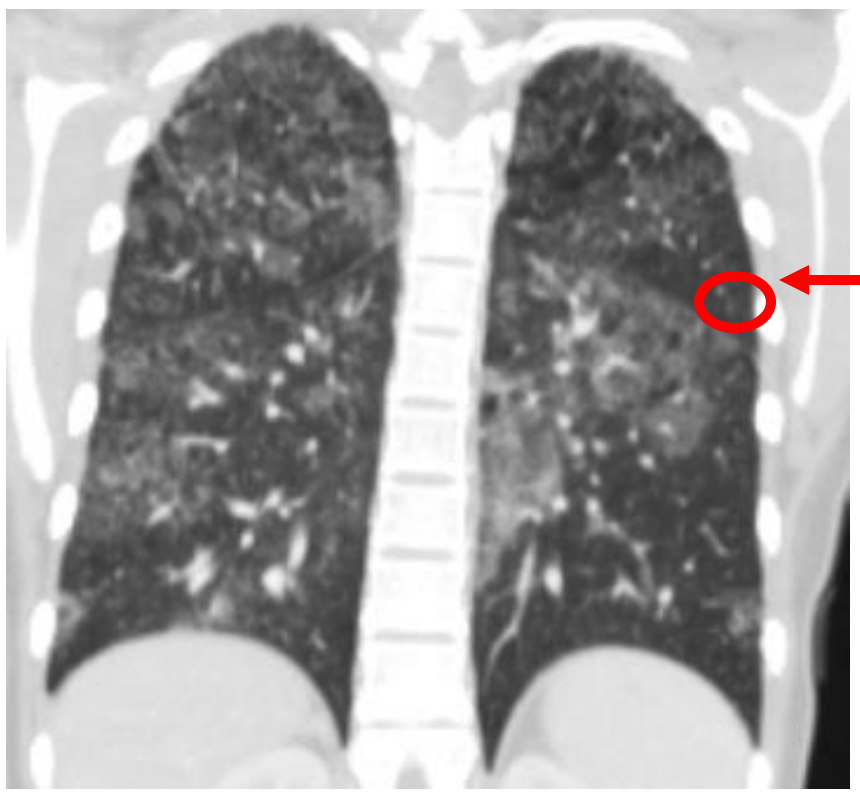


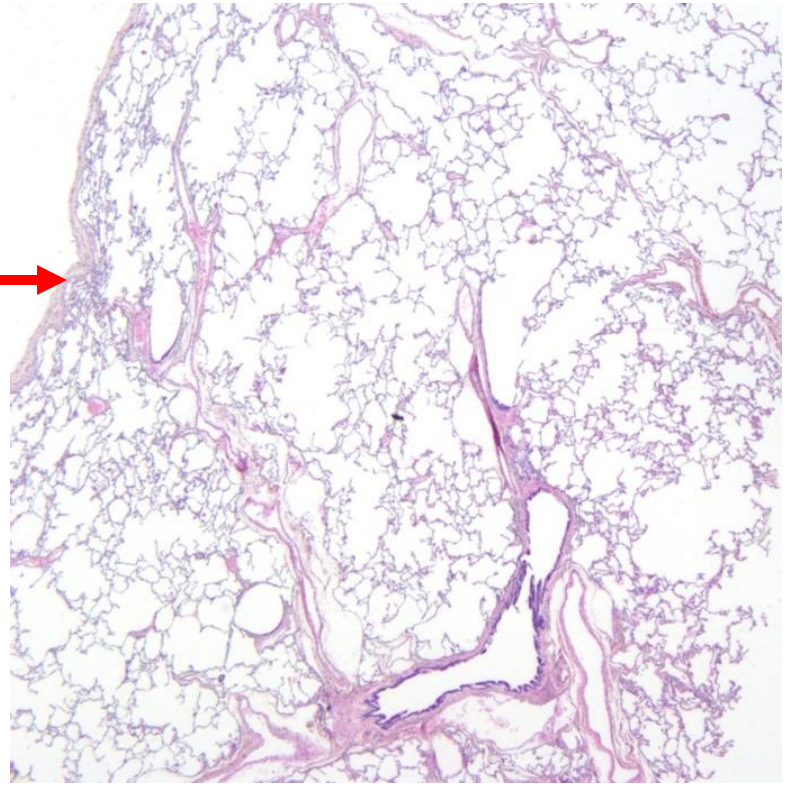
Diffuse ground glass opacities ⟷ Near normal lung biopsy

16 year old with exercise intolerance

PFTs: moderate restrictive defect and low DLCO

Biopsy site is critical.





Diffuse ground glass opacities ⟷ Near normal lung biopsy

- Biopsy from the tip of the lingula was non-diagnostic.

Tissue handling is critical for lung biopsies

Communication between clinician, radiologist, surgeon and pathologist essential to maximize tissue utilization

Site of biopsy

- Target region of involvement (not lingula or tip of right middle lobe)
- Preferable to have biopsies from **multiple** sites (patchy processes, hemorrhage, NEHI, bronchiolitis obliterans)
- Deep wedge resection required in all cases

Division of biopsy- received by pathologist unfixed, sterile

- Culture (viral, mycobacterial, fungal, bacterial)
- Snap frozen (PCR, molecular studies)
- Snap frozen in cryomatrix (immunofluorescence)
- Glutaraldehyde fixation for electron microscopy
- Light microscopy: Inflation fixed, sectioned perpendicular to deep surgical margin

Langston et al, PDP 2006

Growing role for genetic testing instead of lung biopsy in evaluation of ILD/DLD

- **Surfactant production**
  - *ABCA3*
  - *SFTPC*
  - *NKX2-1/TTF1*
  - *SFTPB*
  - *SFTPA1*
- **Surfactant catabolism**
  - *CSF2RA*
  - *CSF2RB*
  - *MARS*
  - *GATA2*
  - *OAS1*
  - *SCL7A7 (LPI)*
  - Others

- **Disorders of lung development**
  - *FOXF1*
  - *FLNA*
  - *TBX4*
- **NEHI**
  - *NKX2-1*
  - *FOXP1*
  - Others likely

- **Others**
  - *COPA*
  - *DKC*
  - Many immune-related

Reminders:

- ➢ Genetic counseling
- ➢ Timing of testing to avoid lung biopsy
- ➢ Limitations, Variants of unknown significance

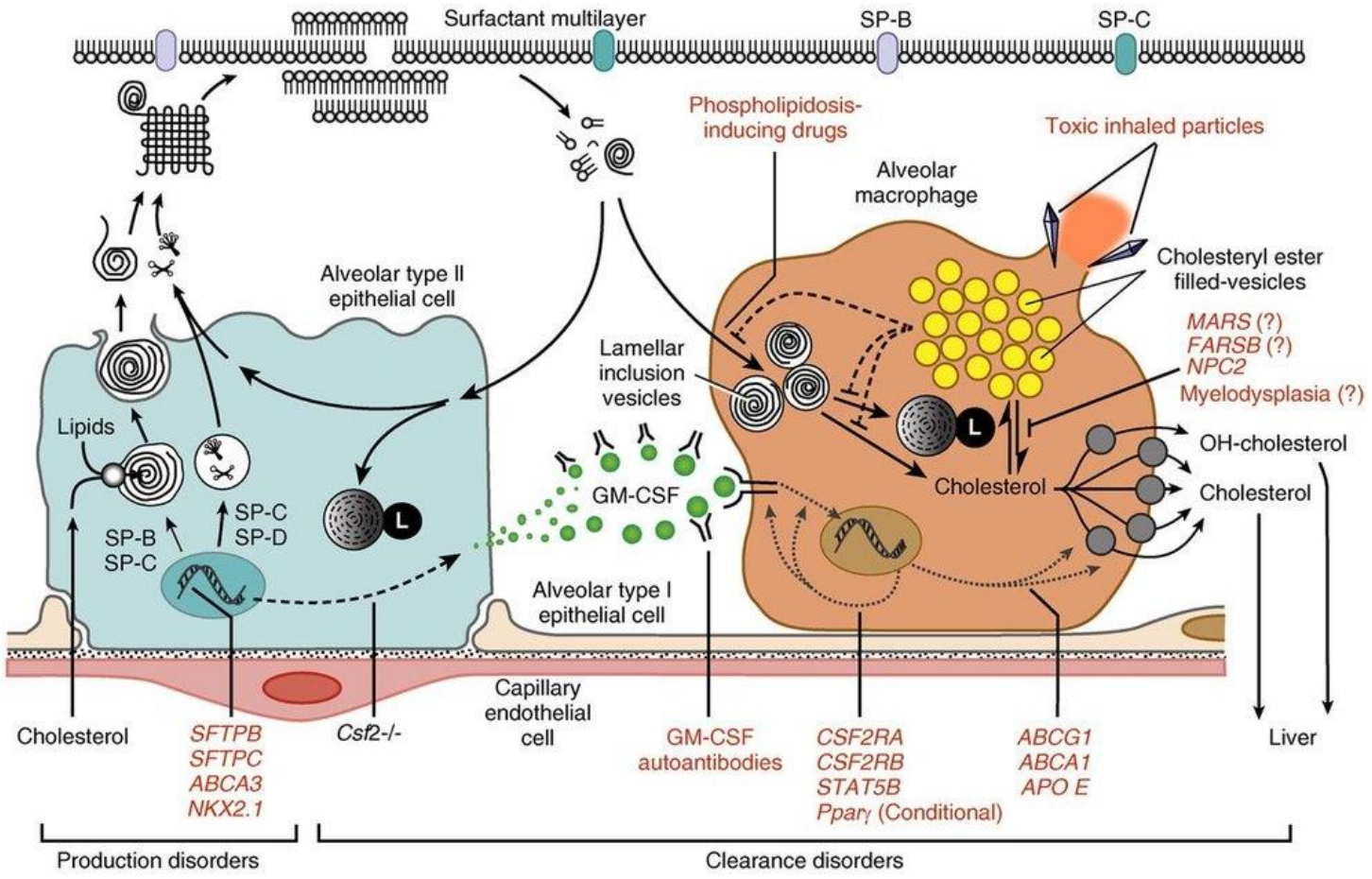
Disorders of Surfactant Production and Catabolism

- May present with neonatal respiratory failure or ILD in older children
- Cough, gastroesophageal reflux, and failure to thrive are common.
- Consider the clinical context and family history.
- Radiographic patterns may be suggestive.
- Most cases should be diagnosed by genetic testing (not lung biopsy).
  - Role for genetic counseling
  - Variants are not identified in a subset of cases with clinical, radiographic, or histologic patterns to suggest surfactant dysfunction.

Genetic Disorders of Surfactant Production and Catabolism

Type 2 cell: Surfactant Production

- *SFTPB*
- *STFPC*
- *ABCA3*
- *NKX2-1/TTF1*
- *Others?*



Macrophage: Surfactant Clearance

- *CSF2RA*
- *CSF2RB*
- *MARS*
- *GATA2*
- *STAT5B*
- *OAS1*
- *SCL7A7*
- Others

Genetic disorders surfactant production and catabolism have overlapping histopathologic findings

Genes

SFTPB

SFTPC

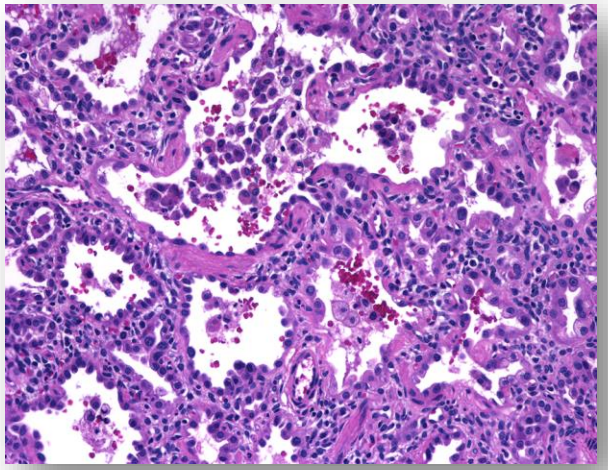
ABCA-3

NKX2.1

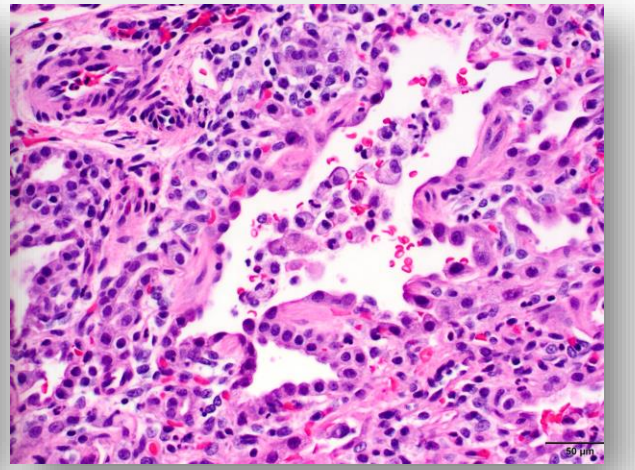
CSF2RA/B

Pathology

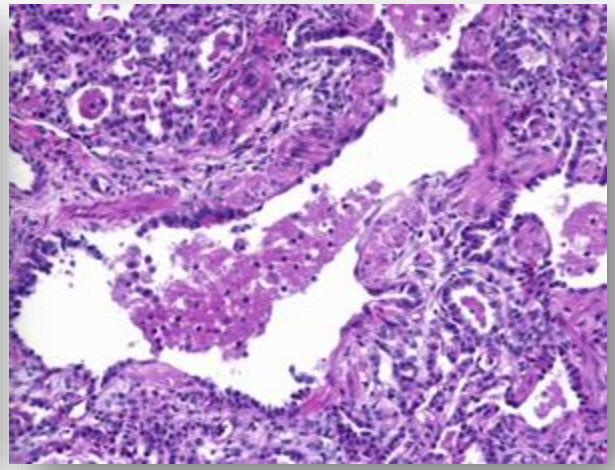
Pulmonary alveolar proteinosis (PAP)
Diffuse alveolar damage (DAD)
Chronic pneumonitis of infancy (CPI)
Desquamative interstitial pneumonitis (DIP)
Nonspecific interstitial pneumonitis (NSIP)
Deficient lung growth
Fibrotic lung disease /Usual interstitial pneumonia



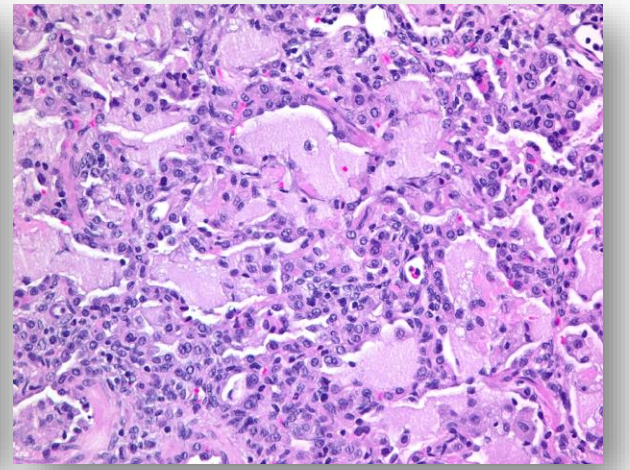
***SFTPC* / CPI**



***SFTPC* / DIP**



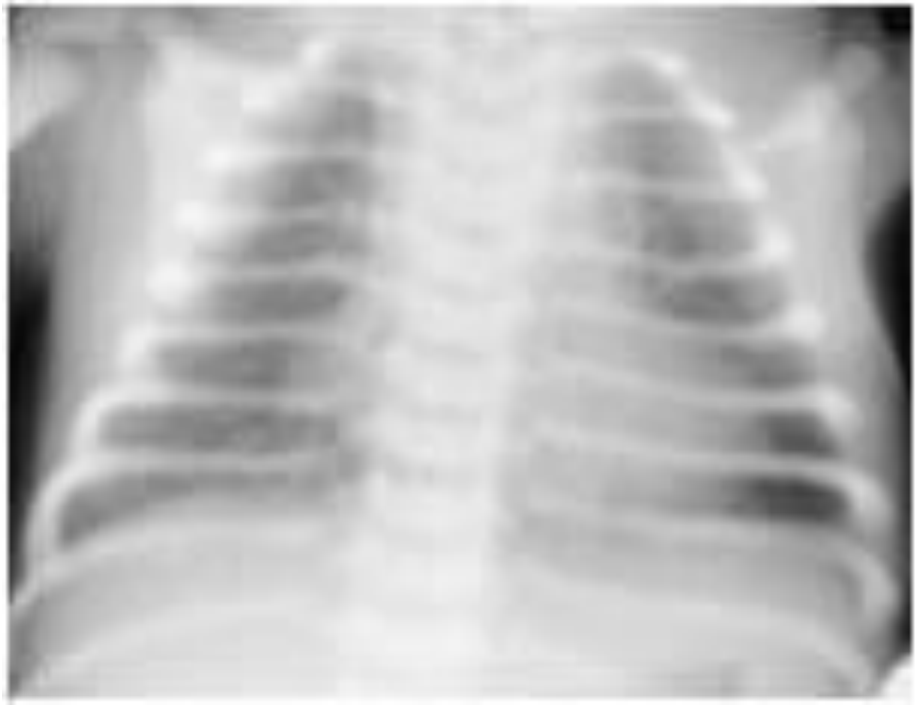
***ABCA-3* / PAP**

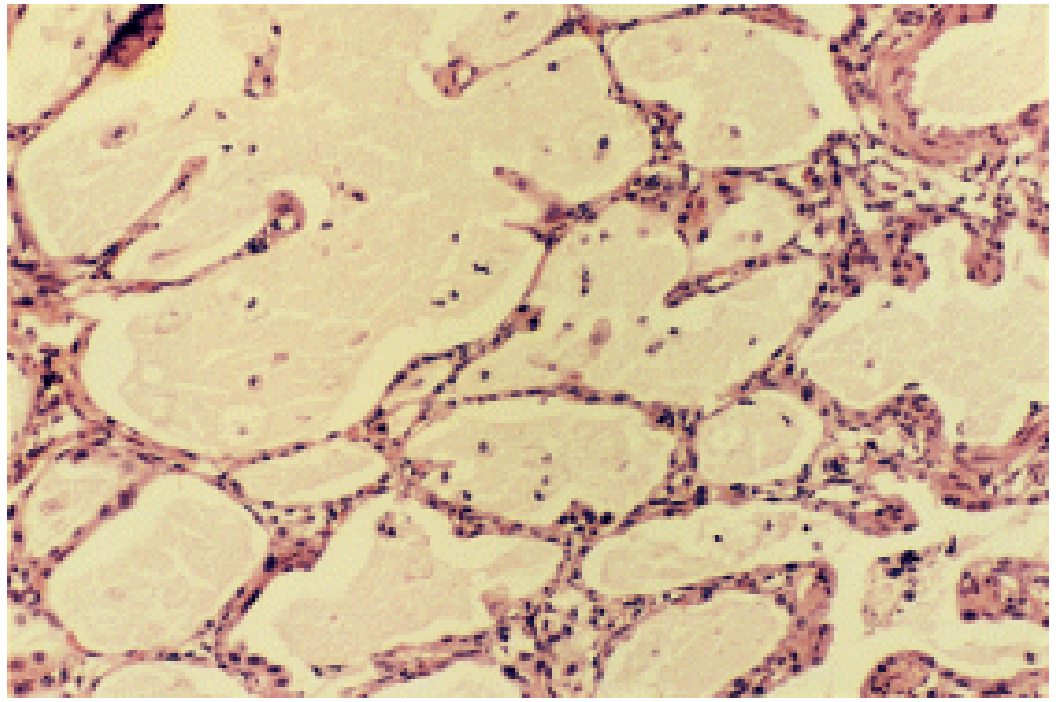


***SFTPB* / PAP**

SFTPB

- Recessive
- 1 per million
- Presents with neonatal RDS
- Most cases fatal without lung transplant

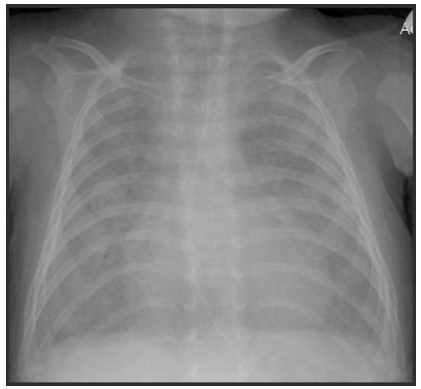


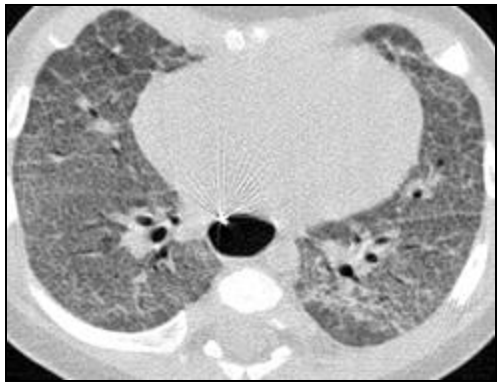


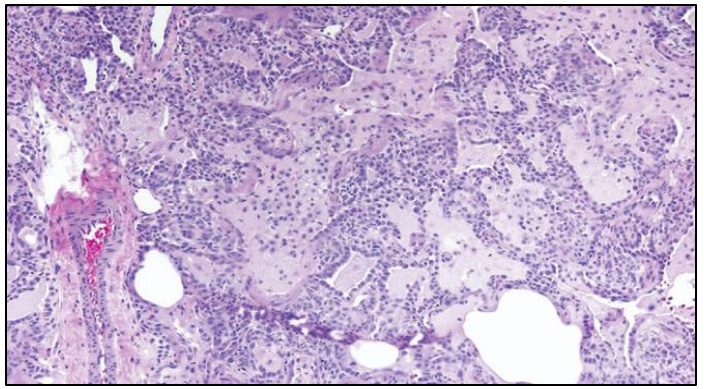
Williams/ Nogee, 1999

ATP-binding cassette member A-3 (*ABCA3*)

- Transmembrane protein on the limiting membrane of lamellar bodies
- Facilitates transport of lipids essential for surfactant production
- Recessive; 1 in 4,000 to 1 in 20,000
- Age-varying spectrum of radiologic and histologic findings







Neonate; died age 6 months
(Prestridge et al, J Peds 2006)

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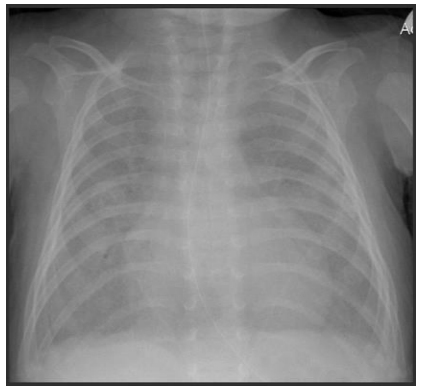
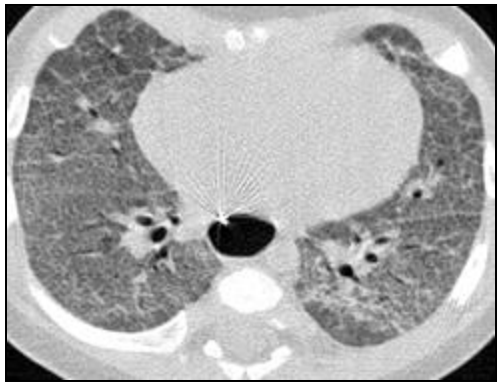
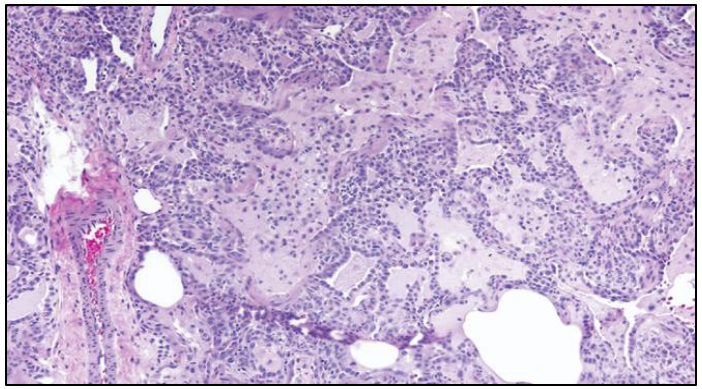

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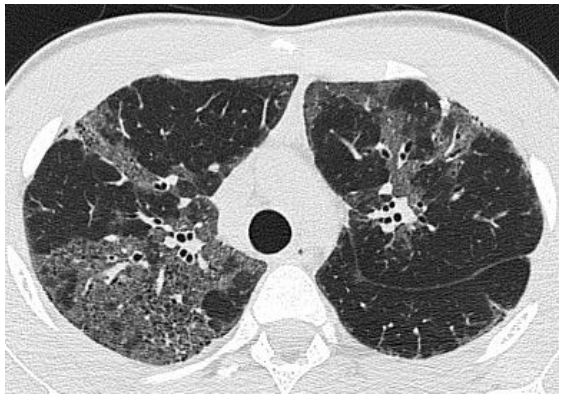
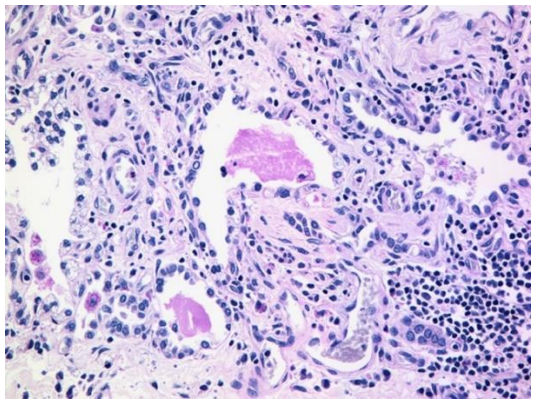
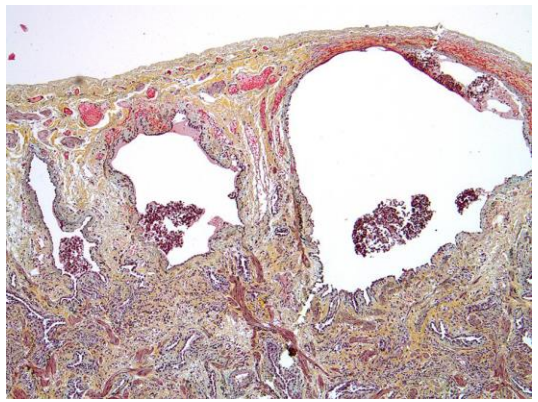
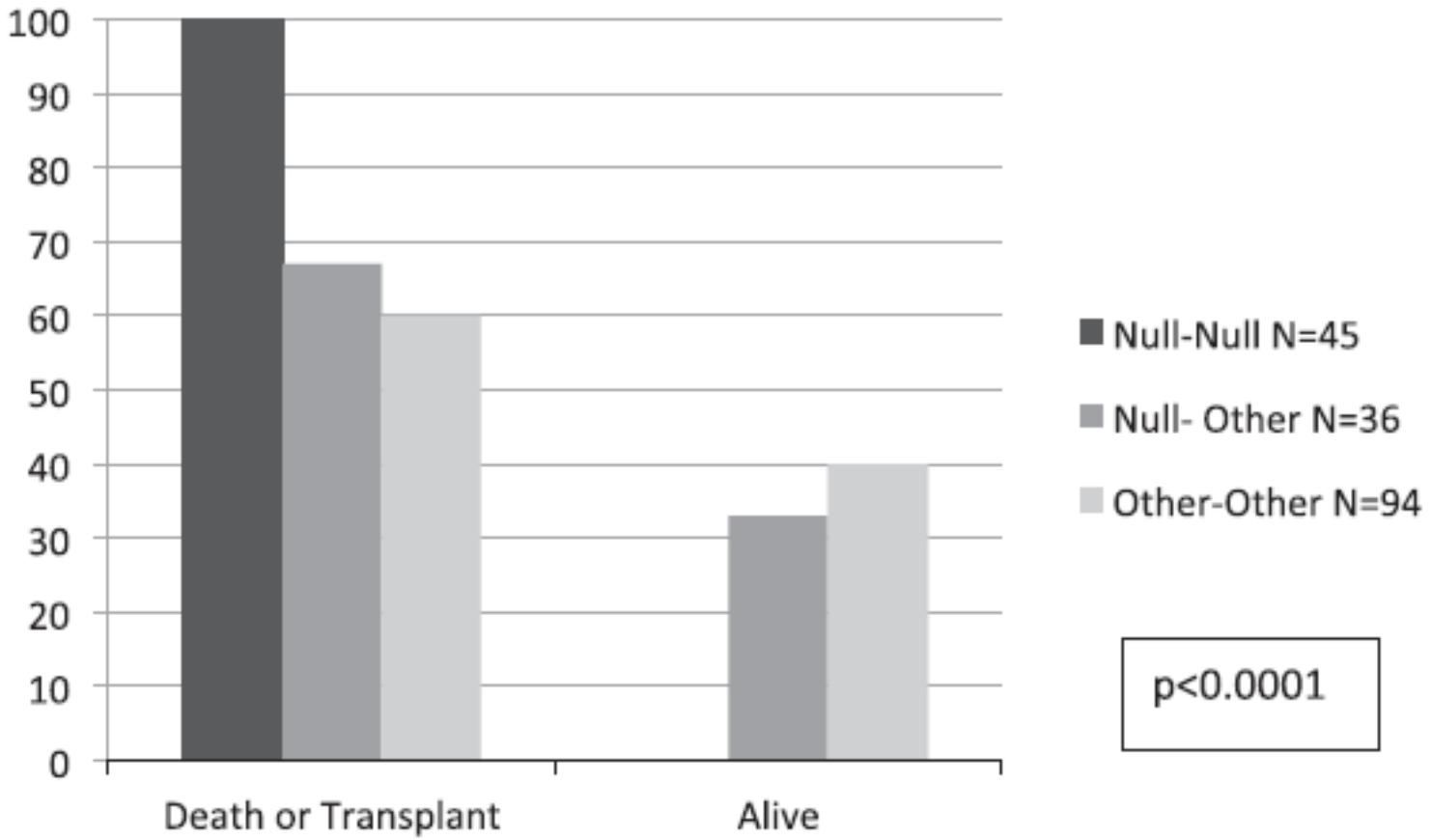




15 year-old; exercise intolerance; UIP pattern of fibrosis, FVC 93%, DLCO 76%
(Young et al, Chest 2008)

Genotype-phenotype correlations in ABCA3 associated lung disease



Prognosis of *ABCA3* mutations at 1 year of age

Wambach/Casey, AJRCCM 2014

Implications of single heterozygous *ABCA3* variants

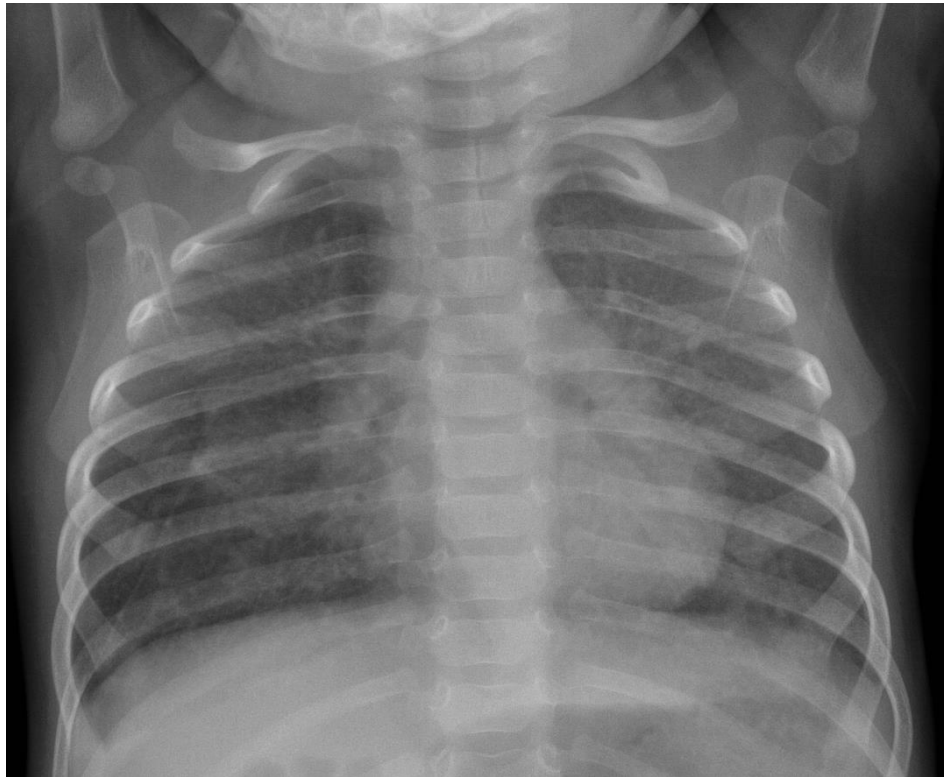
- Single *ABCA3* variants:
  - Are associated with respiratory distress syndrome (RDS)
  - A single ABCA3 mutation was found in 14.3% of RDS vs. 3.7% of non-RDS infants.

- From a rare disease to implications for a common one

Wambach et al, Pediatrics, 2012

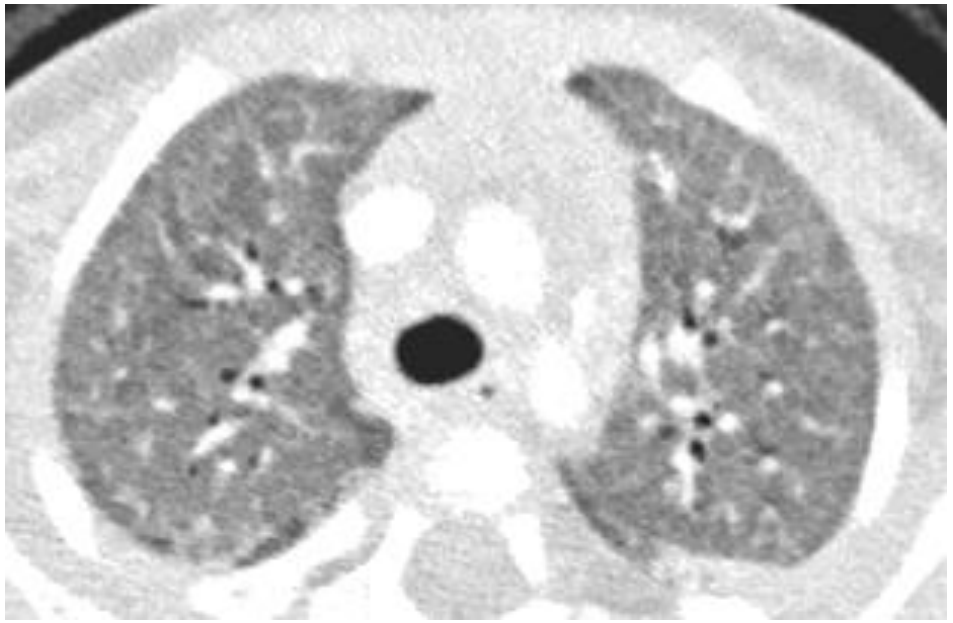
6 month old with RSV bronchiolitis, persistent oxygen requirement

- Healthy term infant
- Concerns prior to acute illness
  - ‘Chest congestion’
  - Grunting
  - Poor feeding
  - Decline in weight gain



Found to have a mutation in the gene encoding surfactant protein C *(SFTPC)*

- 50% cases are autosomal dominant with variable penetrance
- 50% sporadic disease caused by a de novo single mutation
- Population estimates not available, but likely <1/ 5000
- I73T (g.1286 T > C) is the most common mutation, accounting for approximately 30% of all cases reported



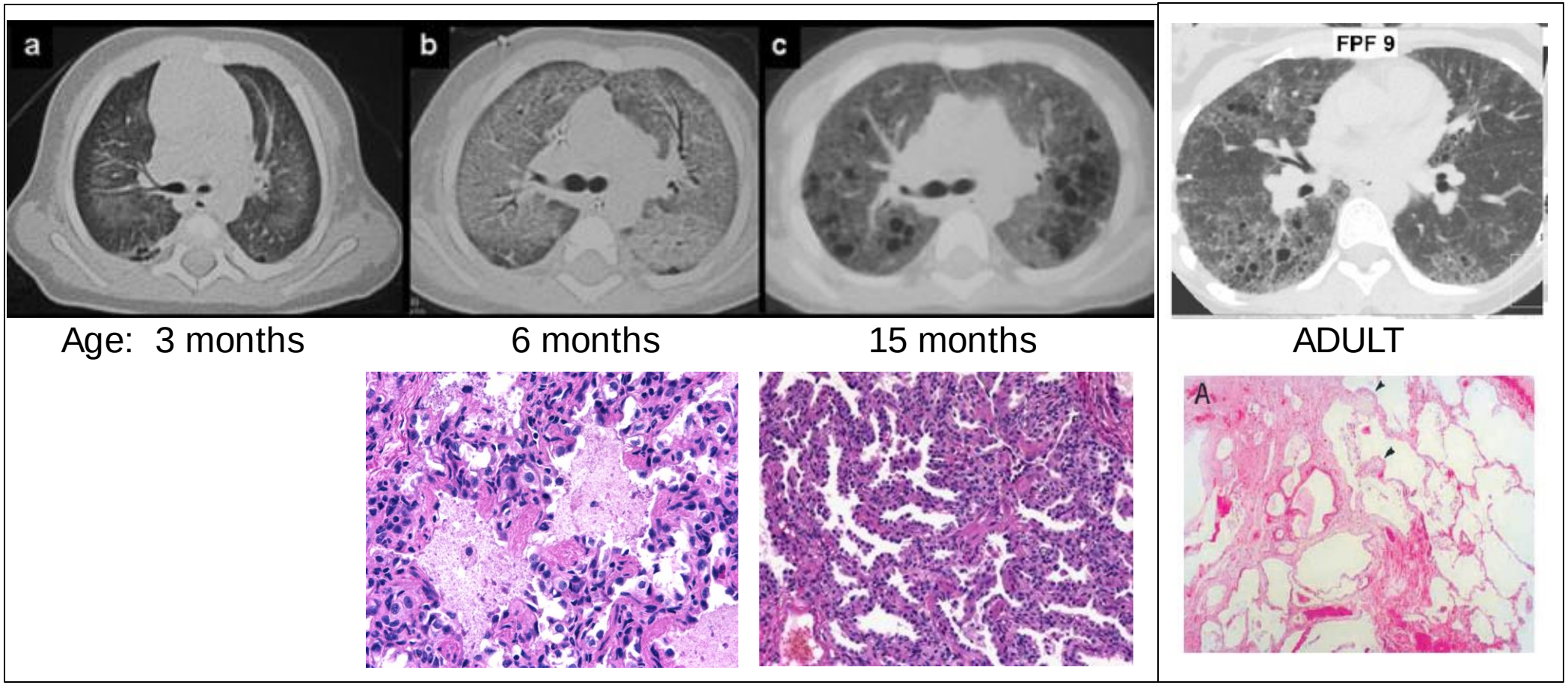
CT with diffuse ground glass opacity, mild reticulation

What happened in this case?
Not simply SP-C deficiency

- Toxic gain of function mechanism
- *SFTPC* encodes a 197 amino acid apoprotein which is cleaved into the mature protein
- Mutation causes:
  - incorrect folding,
  - impaired surfactant composition and function, and
  - accumulation resulting in endoplasmic reticulum stress, the unfolded protein response, and impaired autophagy.
- Results in inflammation and apoptosis of alveolar epithelial cells
- Strong evidence for interaction between viruses and mutant SP-C in alveolar epithelial cells

ILD due to surfactant protein C gene mutations shows evolution of findings from pediatric to adult disease.

- Variable severity, with a wide range of presentations: infants, children, adults, and also asymptomatic individuals

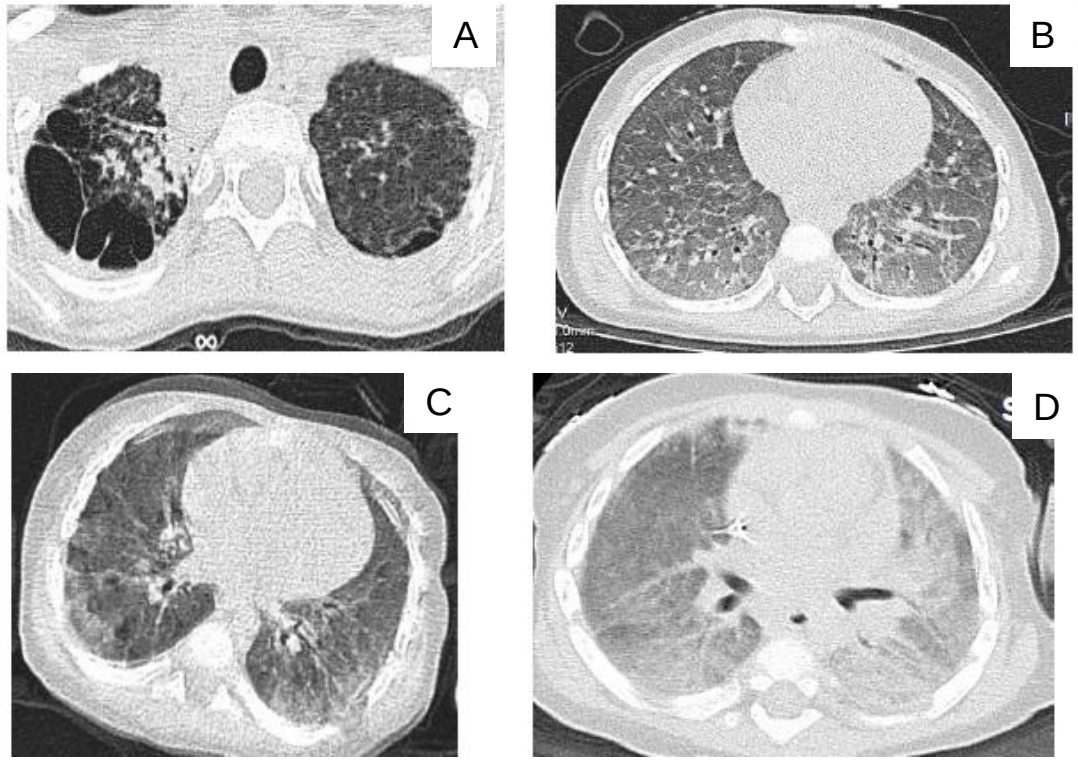


Histology provided by Gail Deutsch (Seattle)

Taam et al 2009; Van Moorsel et al 2010; Thomas et al 2002

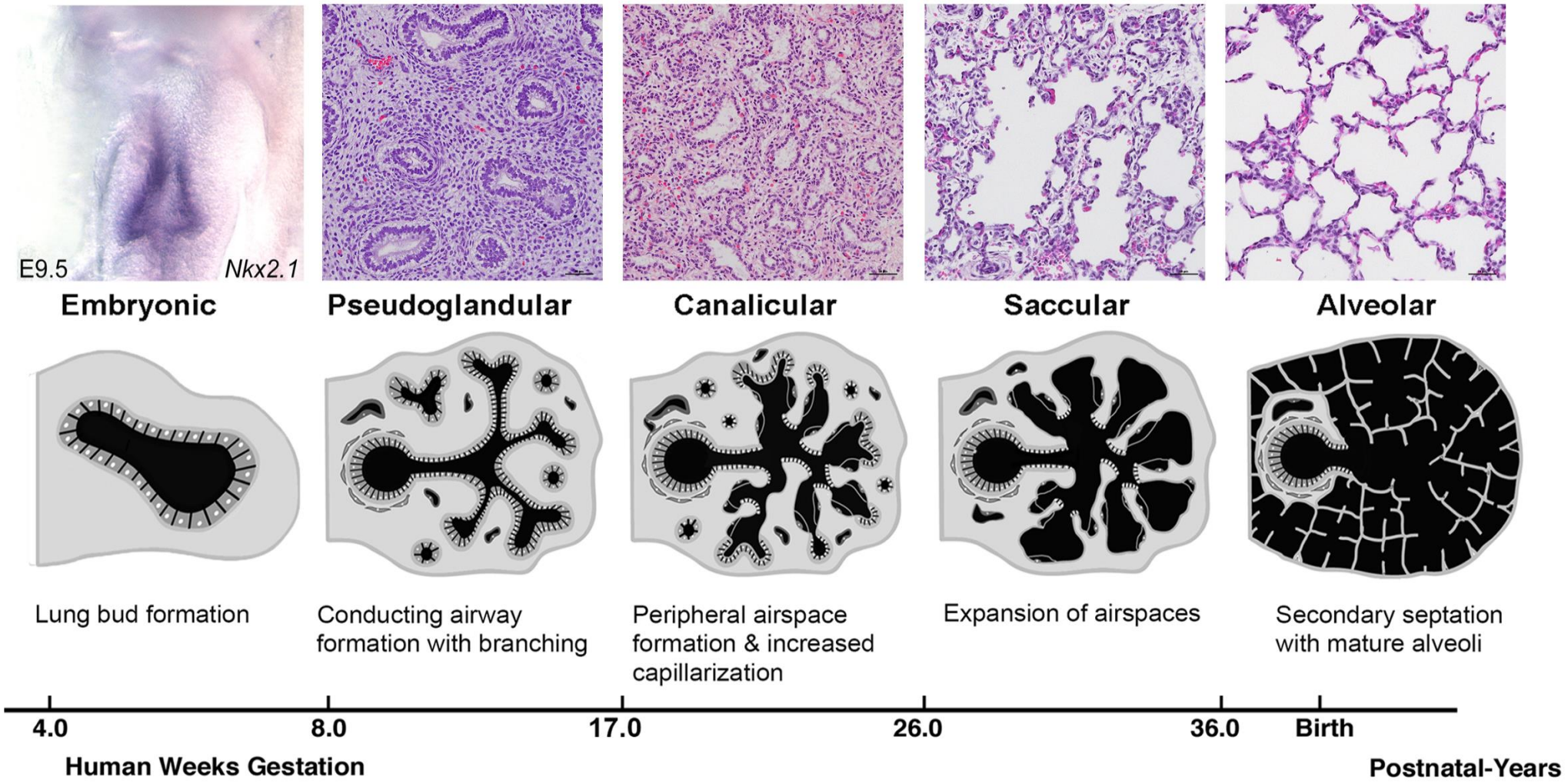
Spectrum of phenotypes with disruption of *NKX2.1/TTF1*

- Disease is due to loss-of-function variants or deletions of 1 allele.
- *NKX2.1* regulates expression of many genes (including *ABCA3*, *SFTPB*, and *SFTPC*)
- Causes “Brain-Thyroid-Lung Syndrome”
  - May include:
    - Congenital hypothyroidism
    - Chorea
    - Lung disease as the sole manifestation.
    - Recurrent infections as a prominent feature.
- Variable CT findings and histopathology
  - Can include alveolar simplification and/or surfactant accumulation



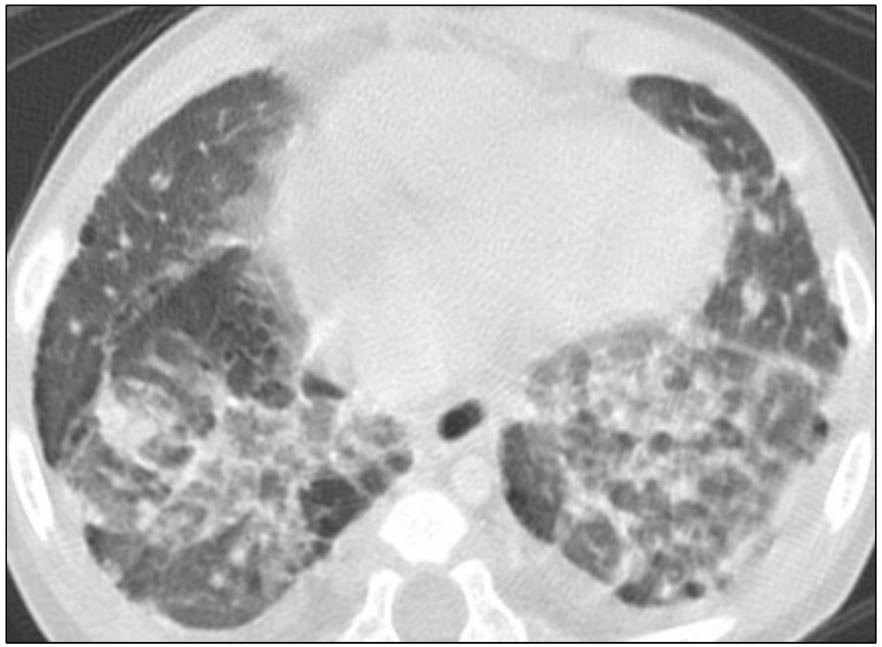
Hamvas et al, Chest 2013

Timeline of lung development

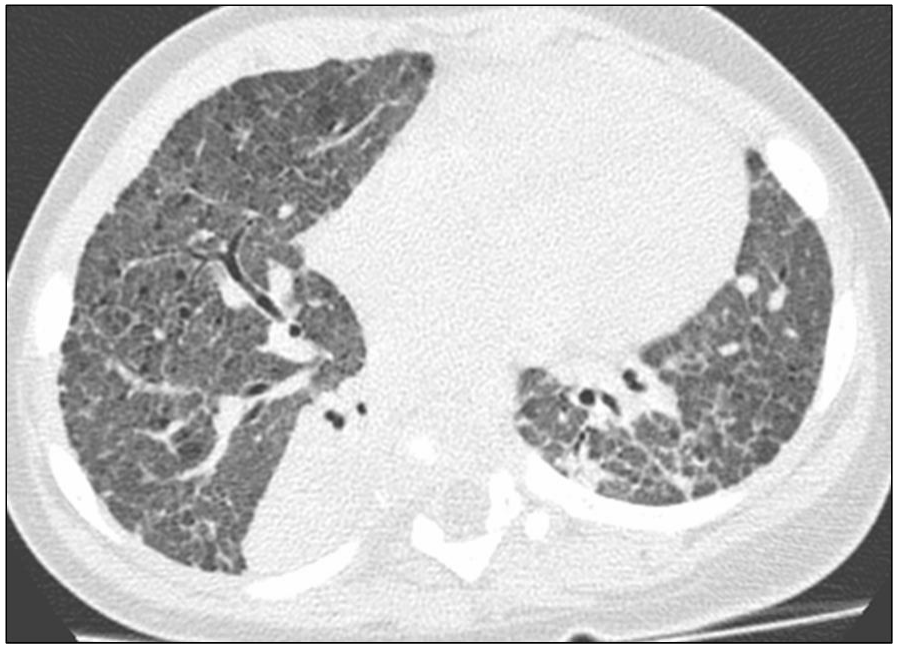


Alveolar Growth Abnormalities

- Variable clinical presentations and severity
- Imaging findings also variable, with irregular opacities, lobular hyperinflation, and cysts



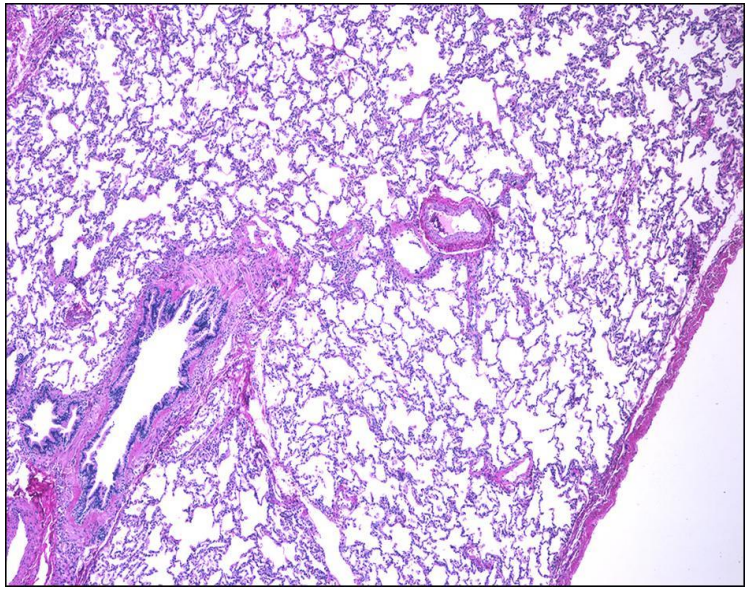
5 month-old, 32 week EGA infant
Trisomy 21 and an AV canal
Asymptomatic at age 3



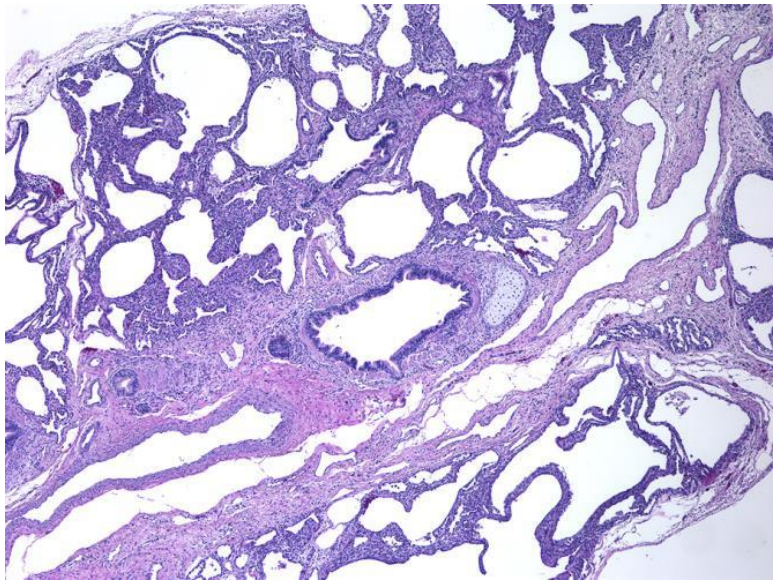
9 month-old, EGA 27 weeks, ASD;
Trach-vent dependent age 18 months

Alveolar Growth Abnormalities

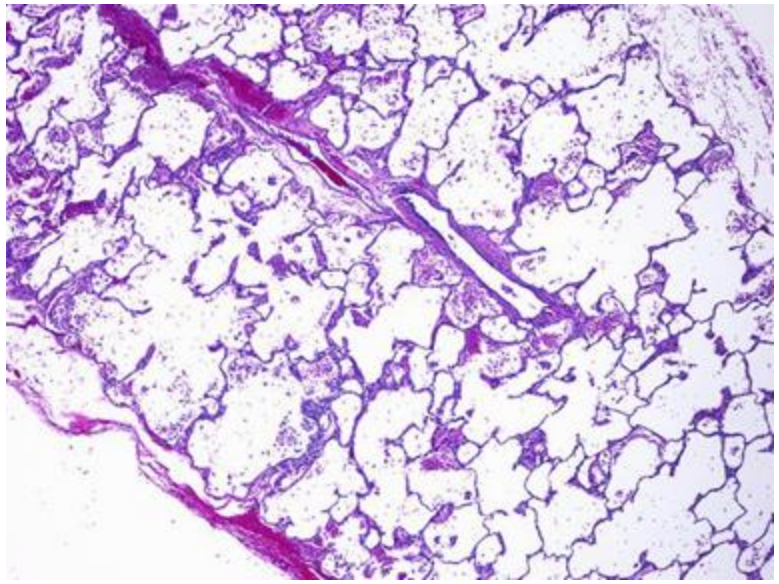
- Increased alveolar size
- Decreased complexity
- Difficult to quantitate clinically, in part, dependent on tissue inflation/ fixation



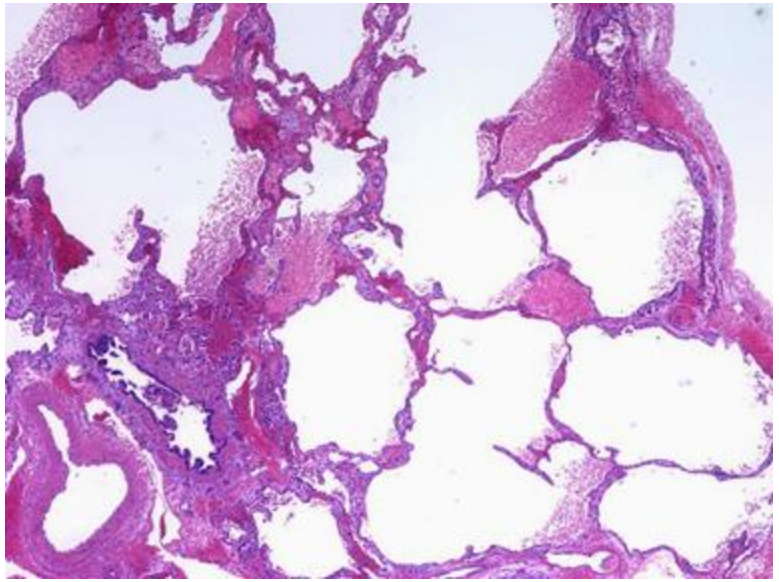
Normal Term



Oligohydramnios
Pulmonary hypoplasia



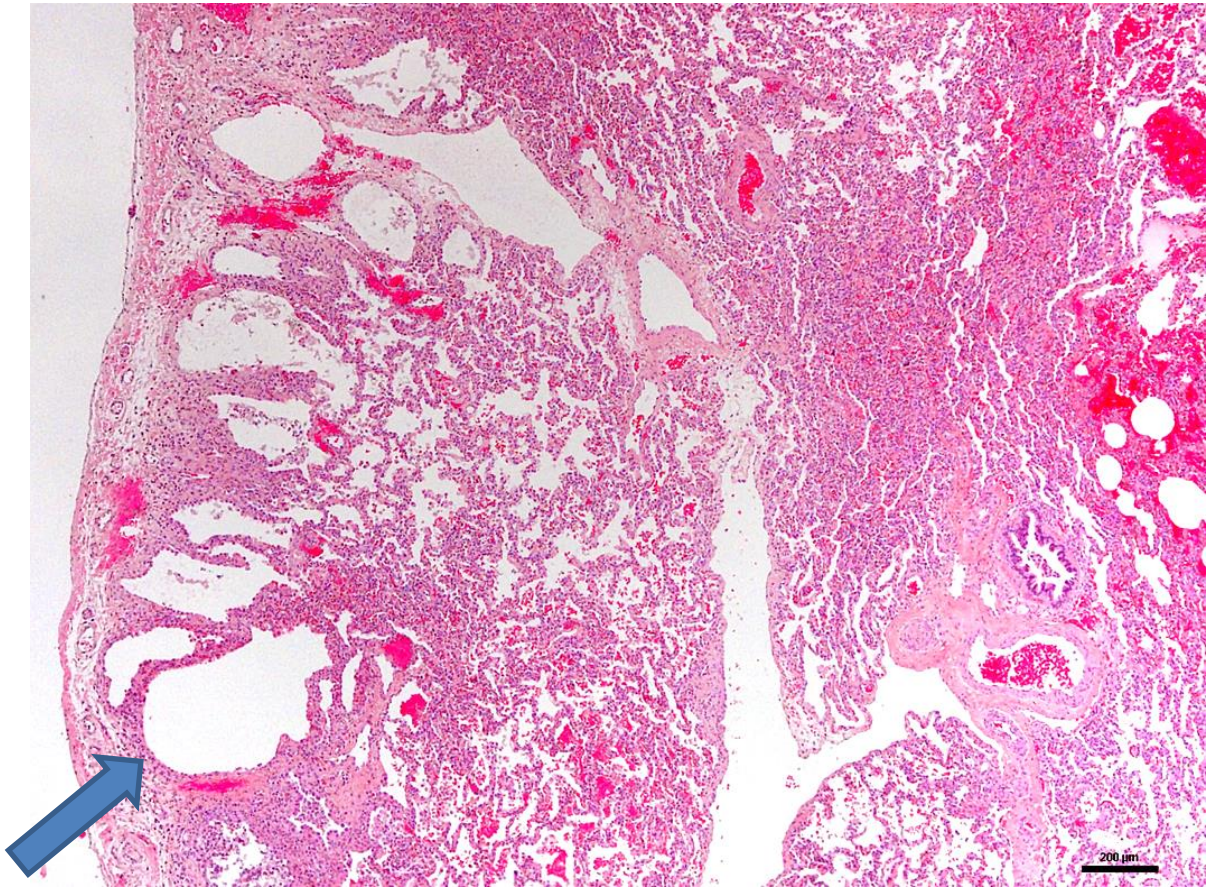
Preterm infant
Chronic neonatal lung disease



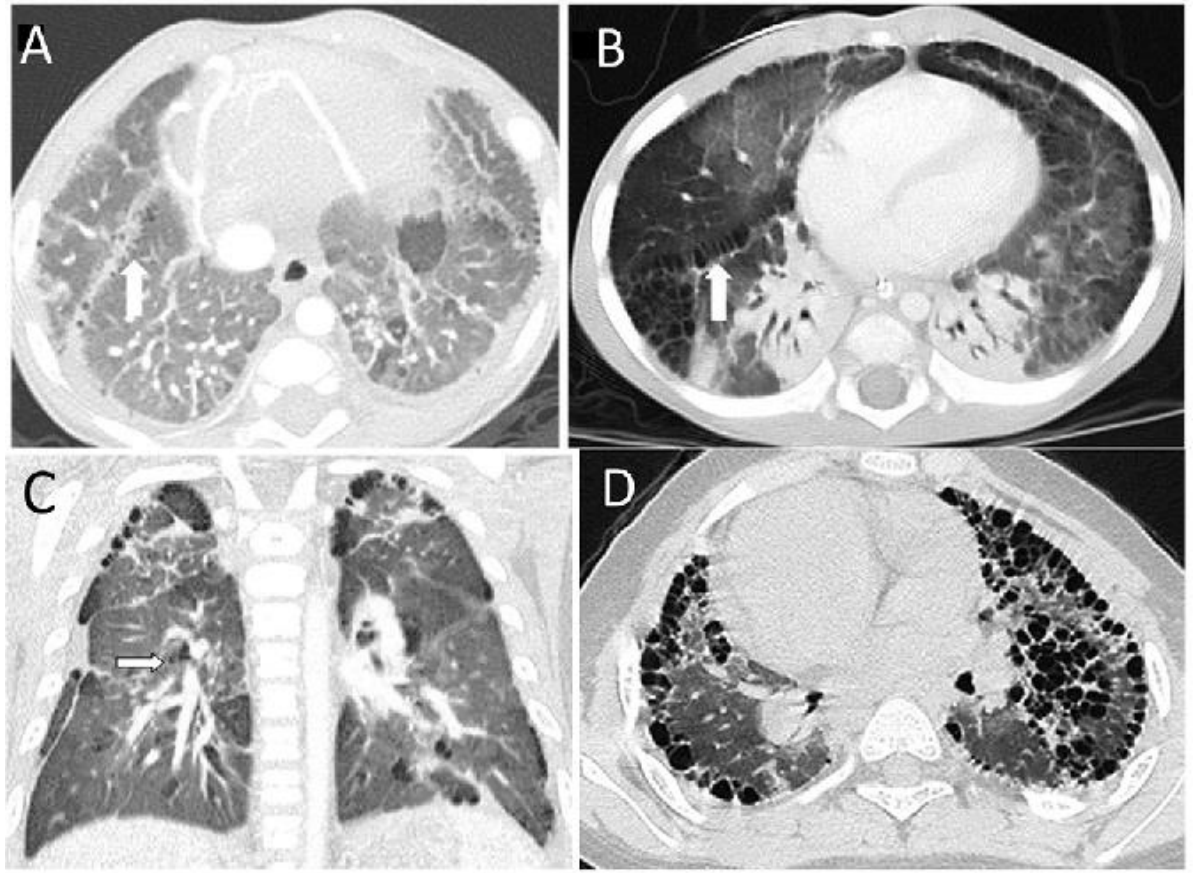
Term infant
Pulmonic stenosis-transplanted

Gail Deutsch

Alveolar Growth Abnormalities: Trisomy 21



8 months: Trisomy 21, pulmonary hypertension

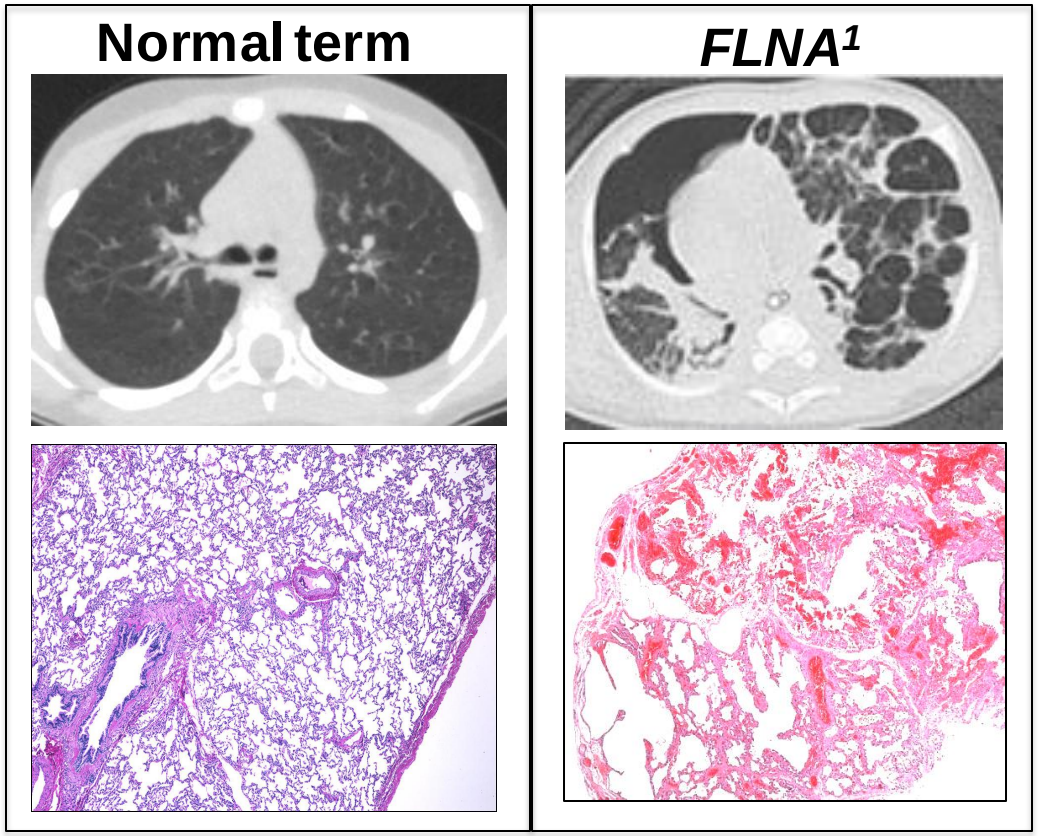


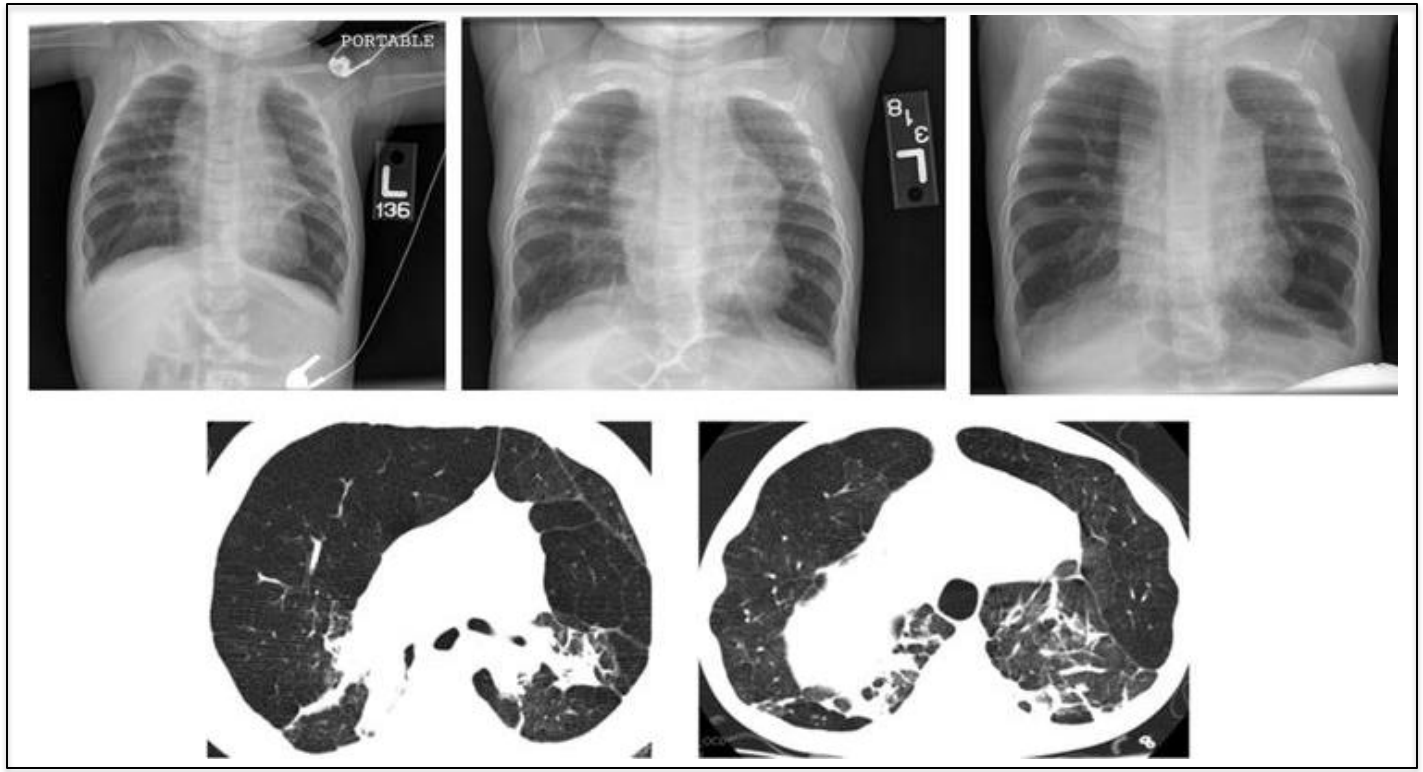
Subpleural cysts in children with trisomy 21

Lim et al., Annals Academy Medicine 2017

Filamin A (*FLNA*)

- Crosslinks actin filaments; anchoring of membrane proteins for the actin cytoskeleton
- X-linked, heterozygous loss of function pathogenic variants
- Associated with periventricular nodular heterotopia (PVNH) with or without epilepsy in females
- Severe pulmonary complications including respiratory failure
- Imaging: pulmonary hyperinflation and hyperlucency, dependent atelectasis
- Successful lung transplant reported



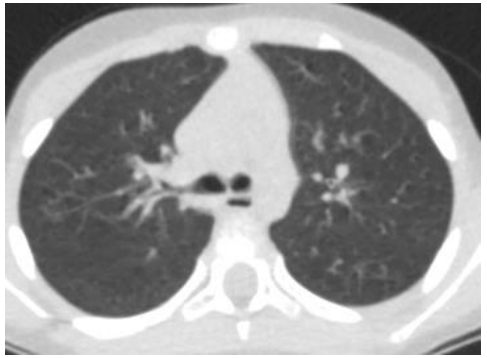


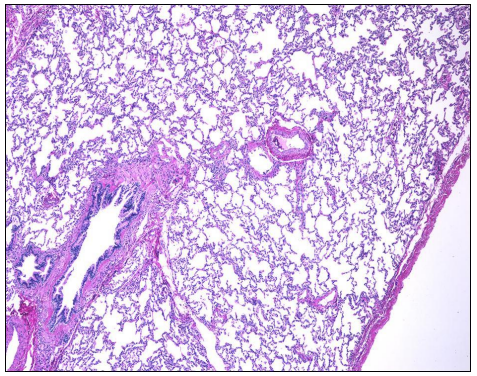
Shelmerdine et al, 2017; Burrage et al, J Peds 2017

Tbx4

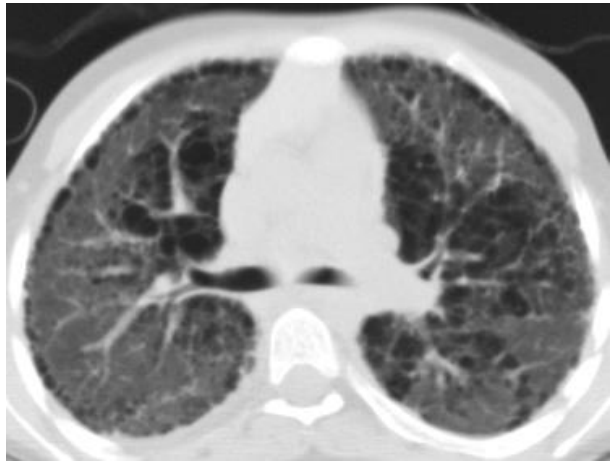
- T-box transcription factors critical for mesoderm differentiation and proliferation
- Expressed in lung mesenchyme, cardiac atrium, hind limbs and other
- Lung disease: acinar dysplasia, pulmonary hypertension
- Tbx4-FGF pathway disruption results in a phenotypic spectrum

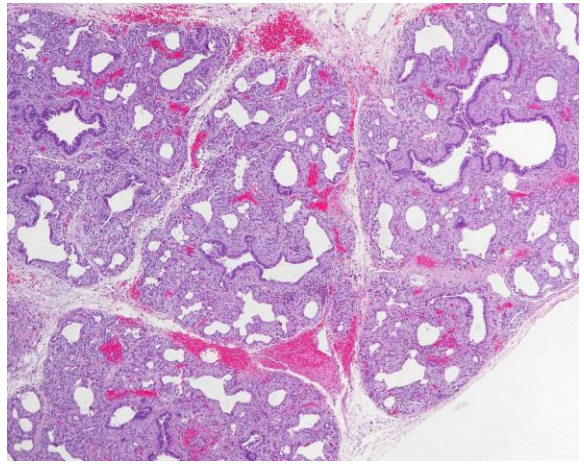
Normal term

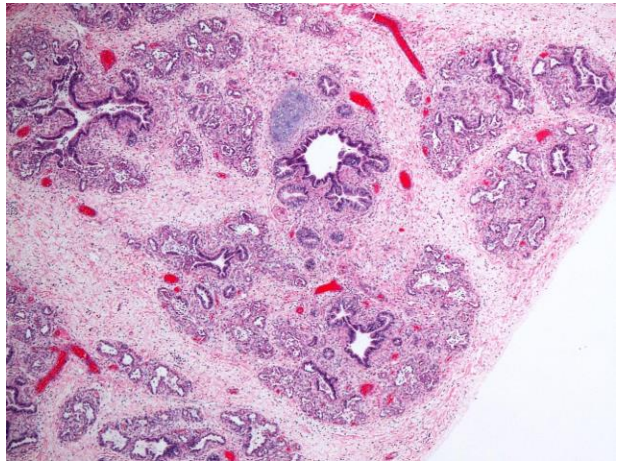




***TBX4* variant**







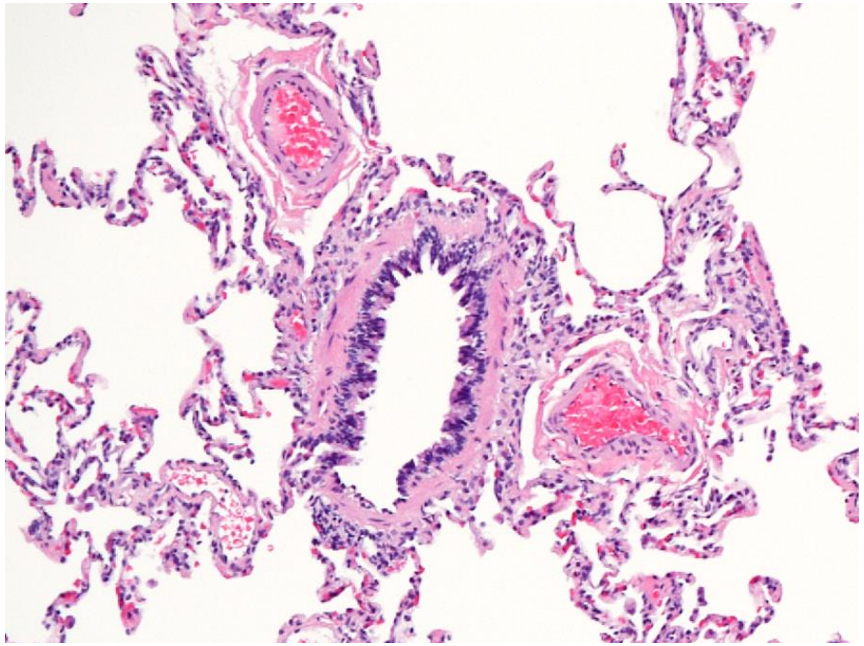
Spectrum of congenital alveolar dysplasia, acinar dysplasia, pulmonary hypoplasia

Suhrie et al. J Pediatr 2019; Karolak et al. Am J Hum Genet 2019; German et al. Am J Med Genet A. 2019

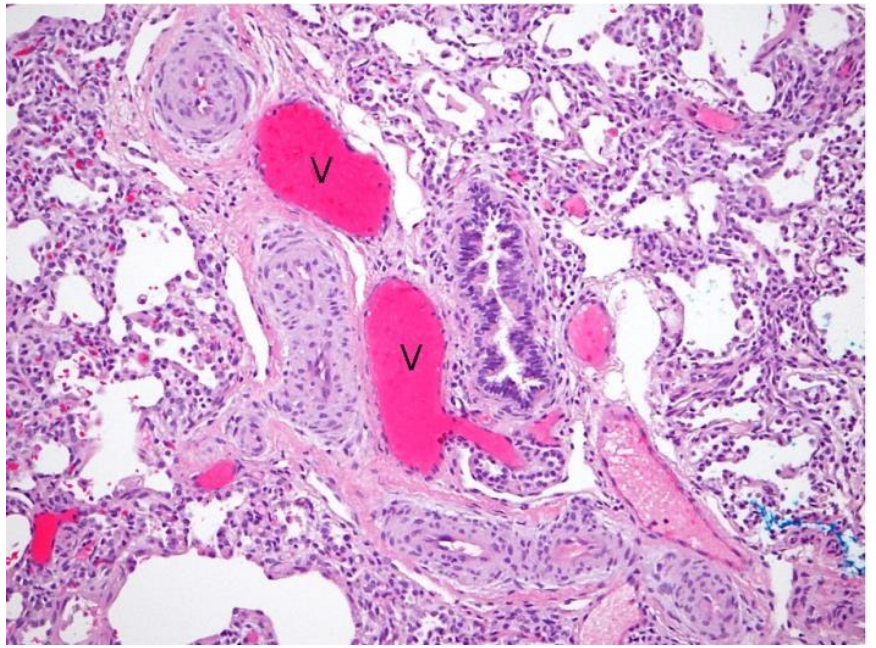
*CT courtesy of Eric Austin (Vanderbilt)

Alveolar Capillary Dysplasia with Misalignment of the Pulmonary Veins (ACDMPV)

- Neonatal respiratory failure and refractory pulmonary hypertension
- Majority of cases associated with heterozygous disruption of *FOXF1*
- Some cases with HLHS, intestinal malrotation, renal abnormalities
- *FOXF1* plays a critical role in mesoderm differentiation and development of the vasculature



Normal



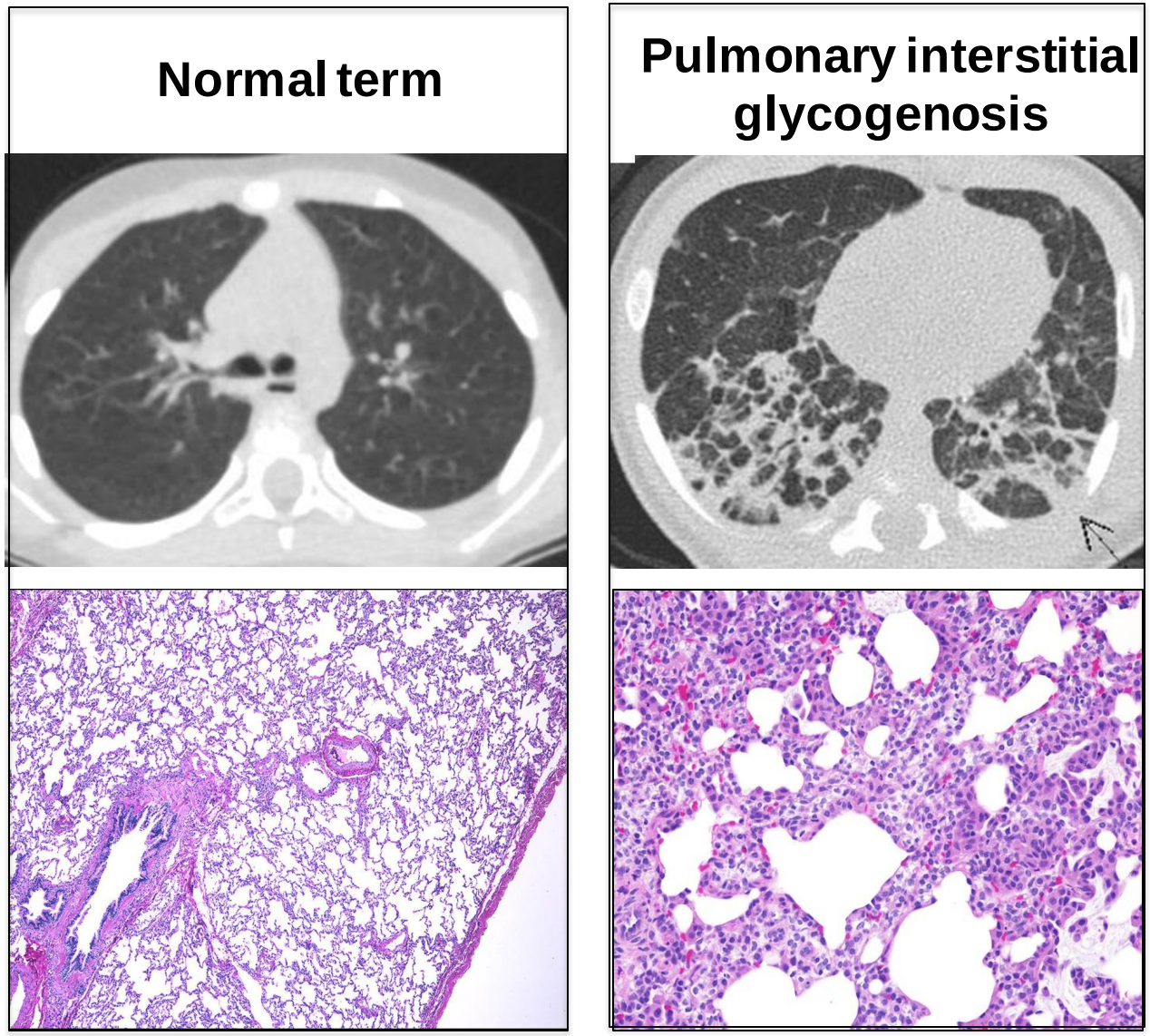
ACDMPV

Stankiewicz et al. Am J Human Genetics 2009; Szafranski et al. Human Genet 2016; Galambos, J Pediatr 2014;164:192-5

Gail Deutsch

Pulmonary Interstitial Glycogenosis (P.I.G.)

- Identified in young infants (<6 months) with tachypnea, hypoxemia, diffuse infiltrates, and pulmonary hypertension
- May be indistinguishable from lethal developmental disorders
- Patients often require mechanical ventilation and PH therapies

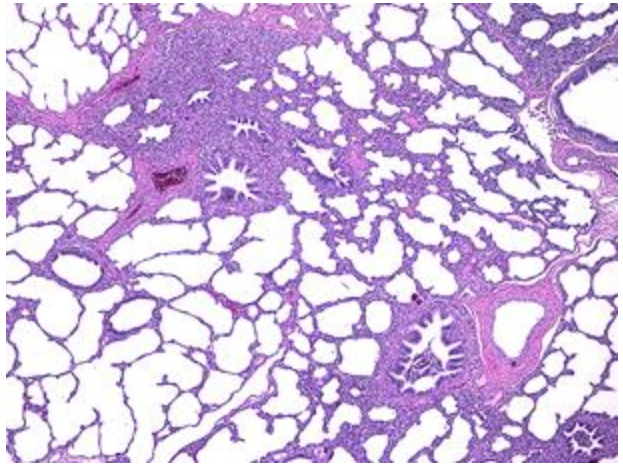


Deutsch and Young, 2010

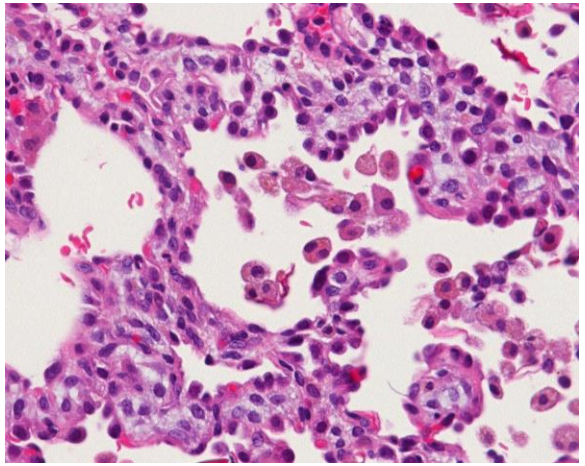
Schroeder et al., Chest 1992
Canakis et al., Am J Respir Crit Care Med 2002

A spectrum of Pulmonary Interstitial Glycogenosis is seen in a variety of settings

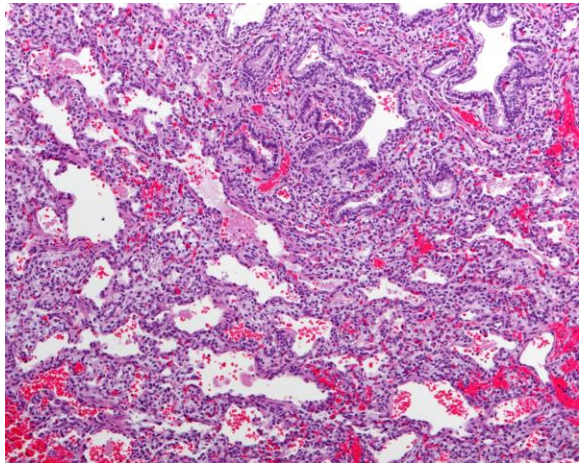
- Favored to be a reactive self-limited process in response to neonatal injury/hypoxia, in the context of lung development
- Prognosis is driven by co-morbidities
- Data suggest presence of lipofibroblast phenotype in P.I.G. *(Deutsch and Young, AJRCCM 2016)*



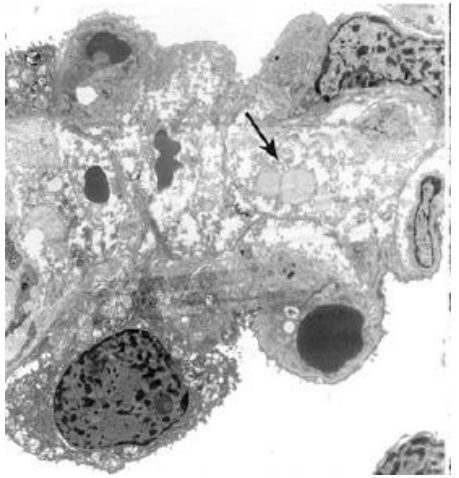
Growth abnormality + patchy P.I.G.



Meconium + P.I.G.



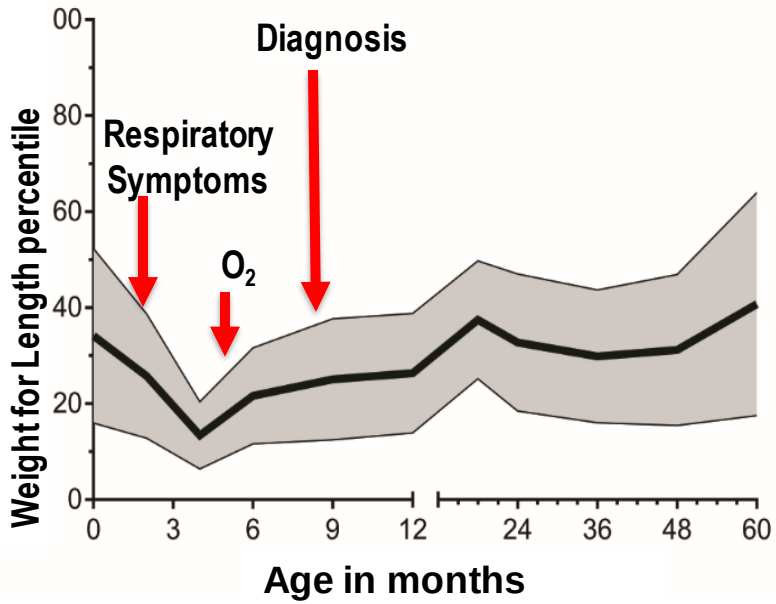
CPAM + P.I.G.



EM showing lipid bodies in P.I.G.

Neuroendocrine cell Hyperplasia of Infancy (NEHI)

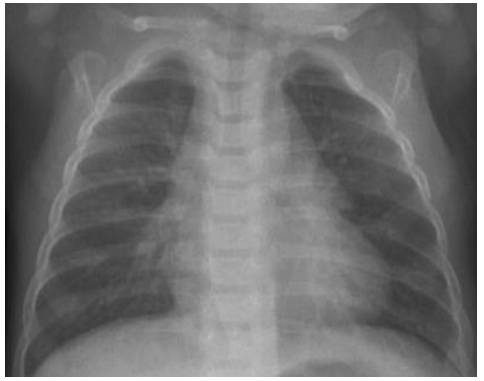
- Presents in the first year of life with chronic tachypnea, retractions, and hypoxemia
  - No significant symptoms at birth
- Crackles usually present, but not wheezing
- No sustained response to bronchodilators or corticosteroids
- Poor weight gain may precede pulmonary presentation
- Supplemental oxygen often needed for years, but gradual improvement occurs
- Persistence of respiratory impairment into adolescence and adulthood in some cases

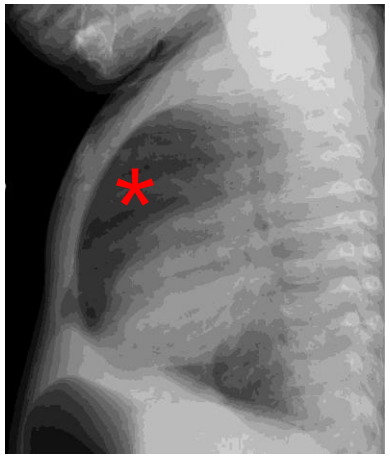


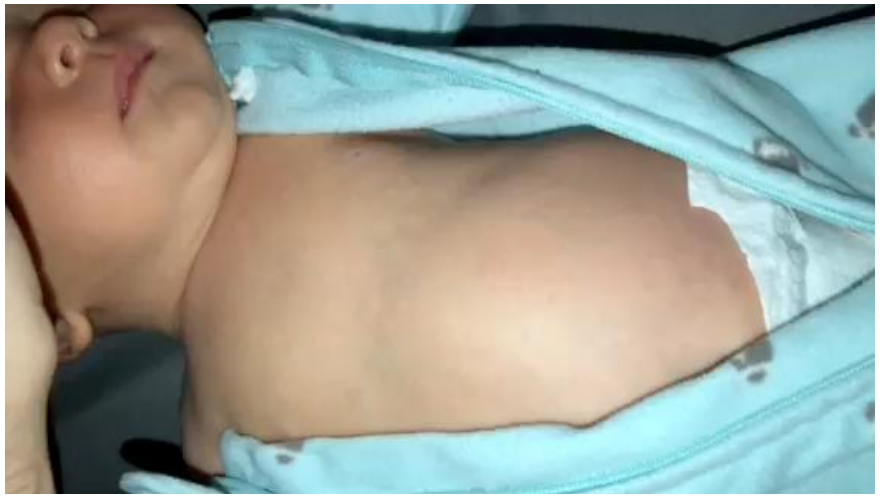
Deterding et al, 2006; Brody et al, 2011; Young et al, 2011; Soares/Young, 2013; Nevel/Young, 2018

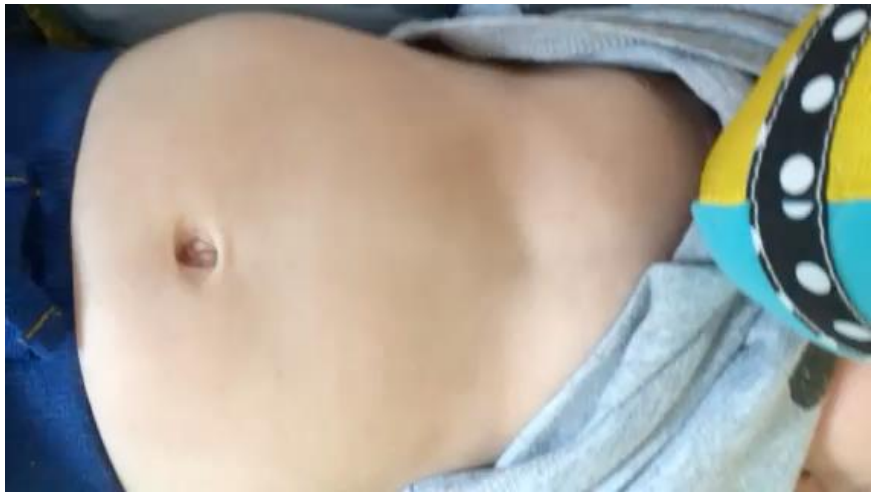
Chronic tachypnea in NEHI

- Respiratory rate often 60-80/min (or more)
- ‘Happy’ despite tachypnea and retractions
- Hypoxemia fluctuates
- May have barrel or bell shape to chest
- CXRs: perihilar infiltrates and hyperinflation
- May come to medical attention for superimposed viral illness… but ‘always breathes like this’

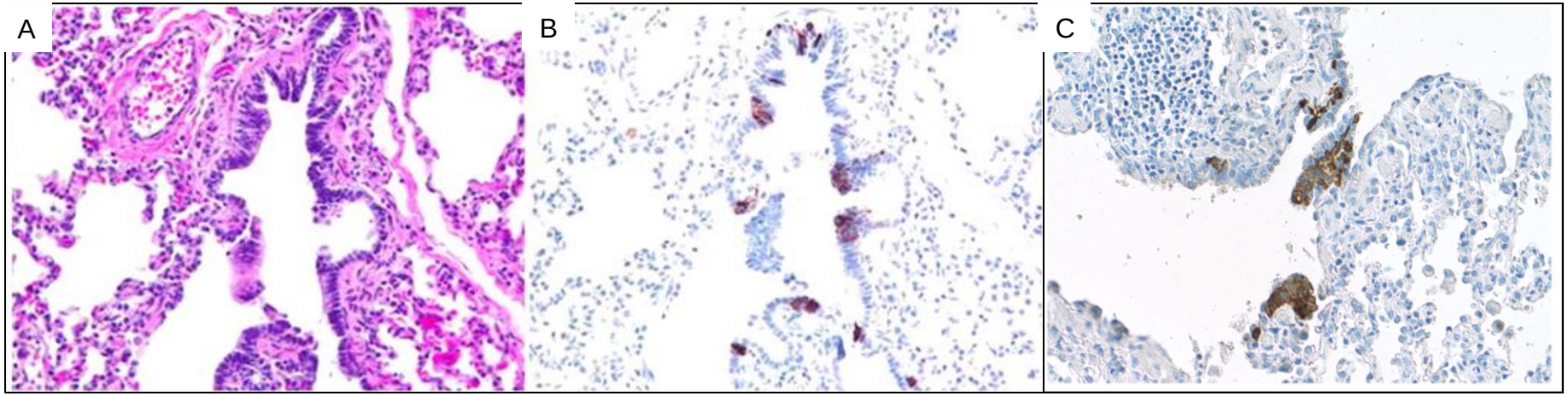








NEHI was named based on the presence of increased neuroendocrine cells amidst otherwise near-normal histology.



H&E

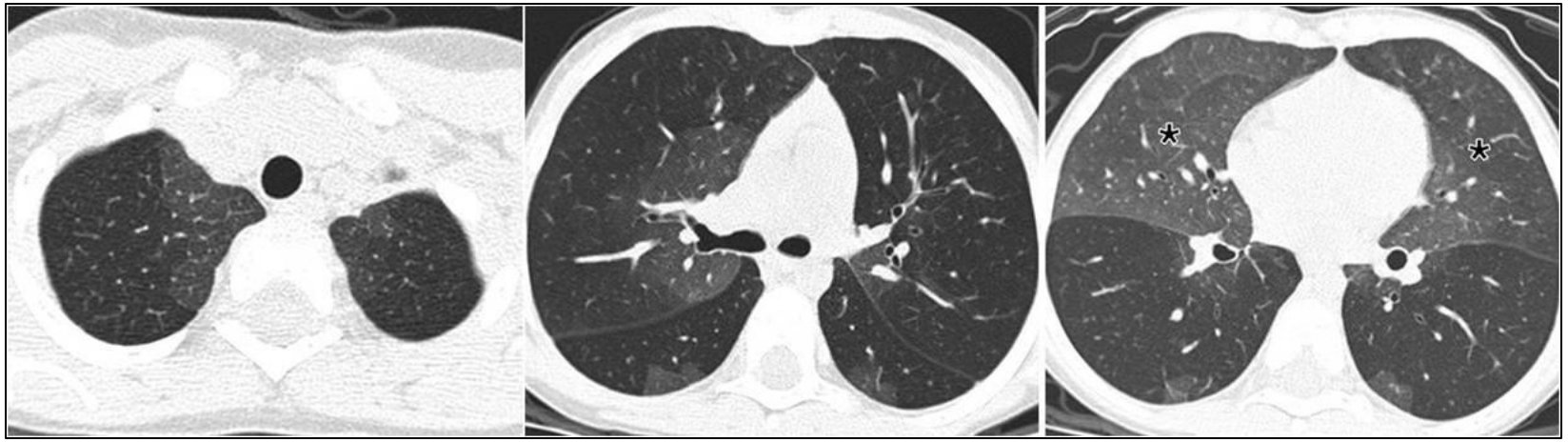
Bombesin: Pulmonary neuroendocrine cells (PNECs)

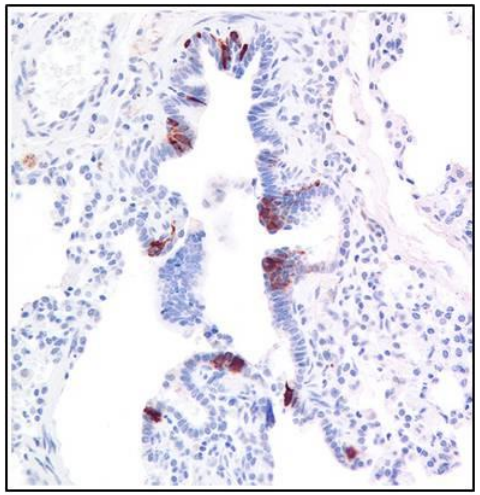
Bombesin: Neuroendocrine bodies (NEBs)

- Near-normal lung architecture, with mild increase in peri-bronchiolar smooth muscle
- Inflammation not prominent in lung biopsies or BAL cytology
- Increased solitary PNECs and NEBs, best identified by immunostaining for bombesin and serotonin

Deterding et al, Pediatr Pulmonol 2005; Popler/ Deterding Orphanet J Rare Dis 2013

Initially lung biopsy was required for diagnosis, but over time it has become apparent that there is a distinct chest CT pattern in NEHI.





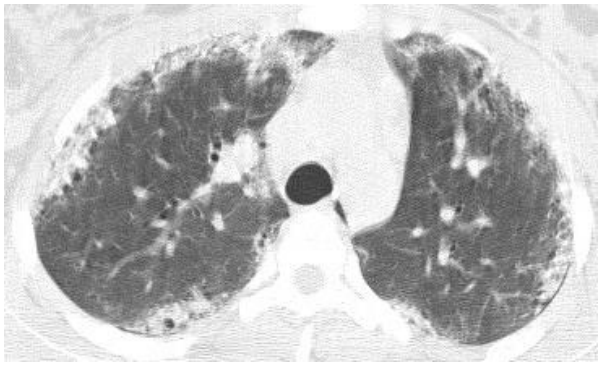
Clinical context + specific CT pattern = NEHI

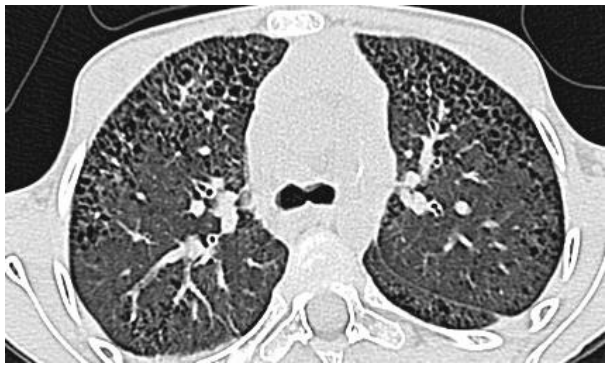
- Homogeneous ground-glass opacities centrally and in the RML & lingula
- Absence of other significant parenchymal abnormalities
- Air-trapping

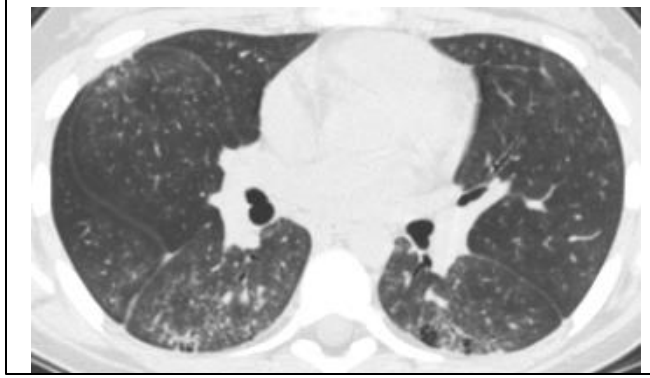
Brody et al, AJR 2010

ILD associated with connective tissue diseases

Reticulation and GGO; often subpleural predominant findings

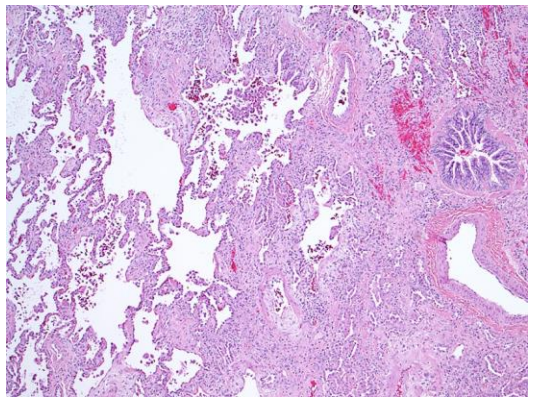


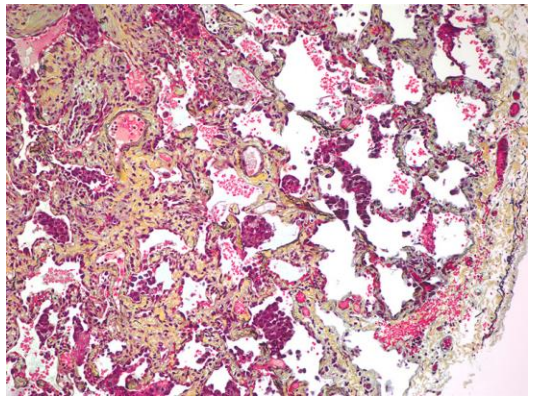




Histologic findings of multicompartment disease

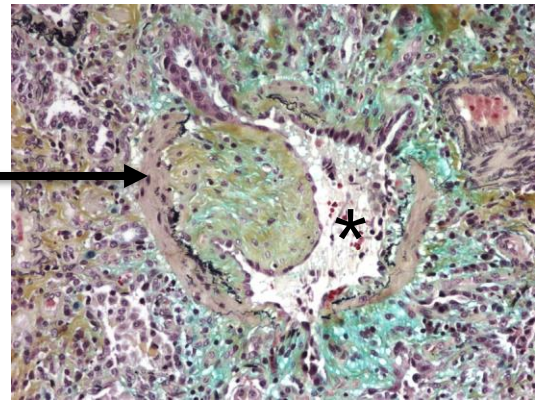
Areas of dense fibrosis and mixed inflammation

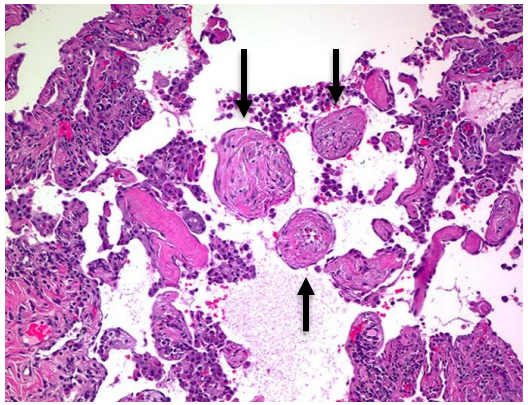




Pentachrome stain highlights collagen (fibrosis).

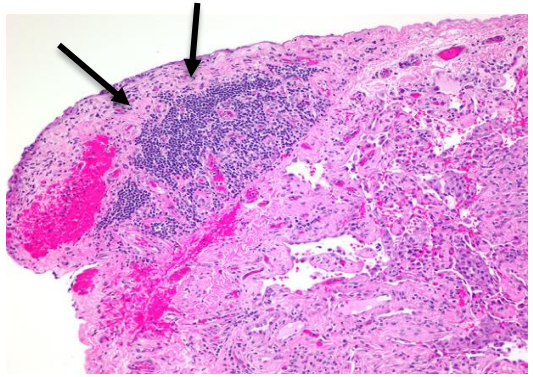
Airway Involvement (bronchiolitis obliterans)

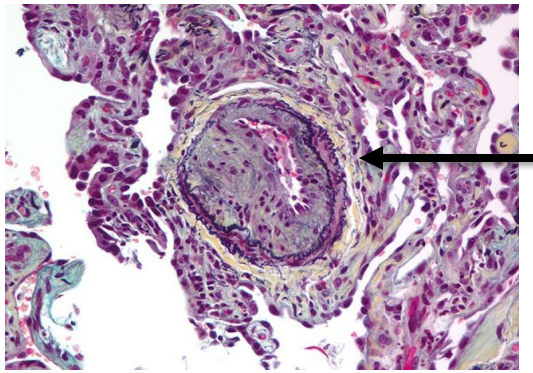




Foci of organizing pneumonia

Pleuritis



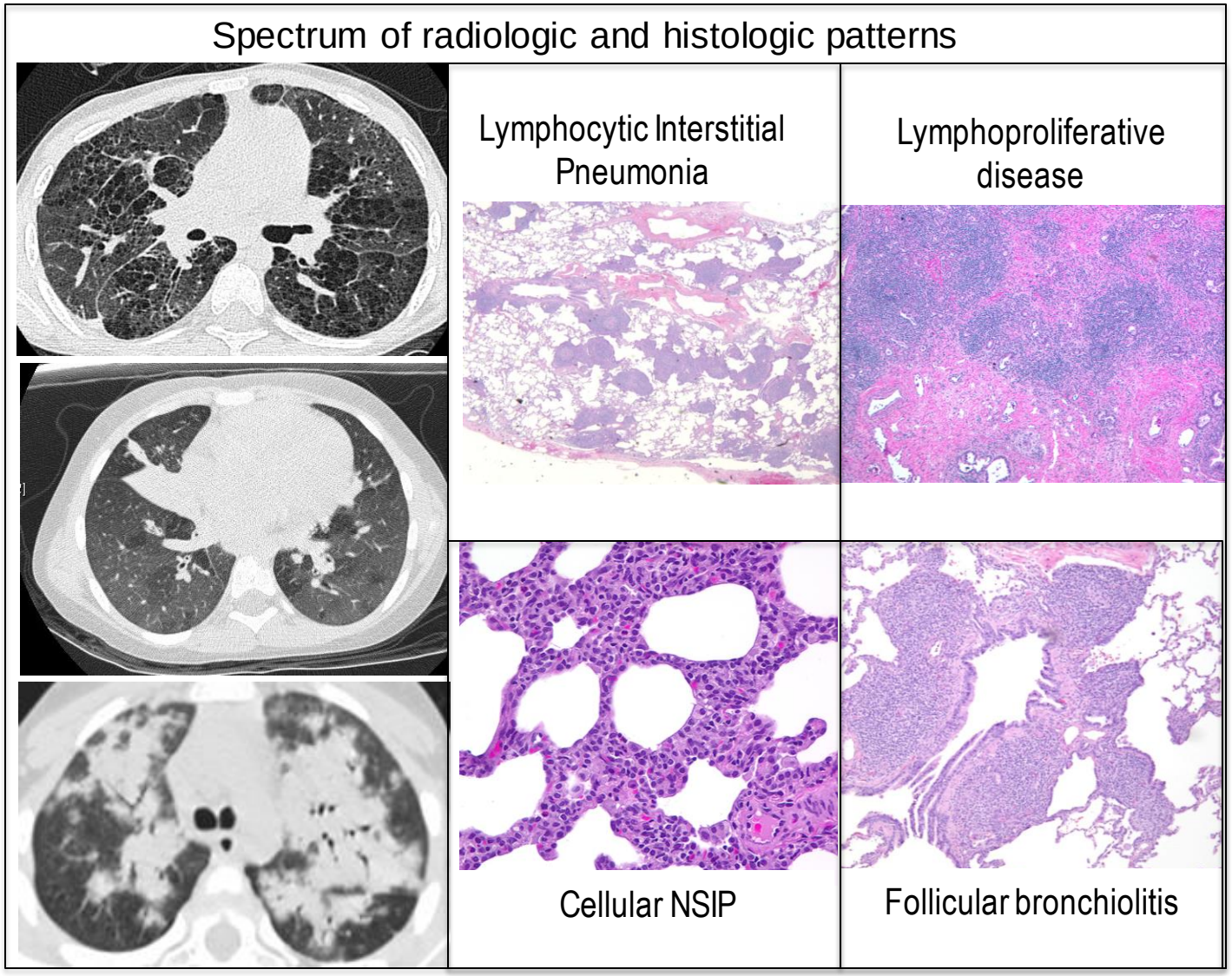


Pulmonary arteriopathy

Immunodeficiency associated ILD is another exciting area in which there is emerging genetic/molecular understanding.

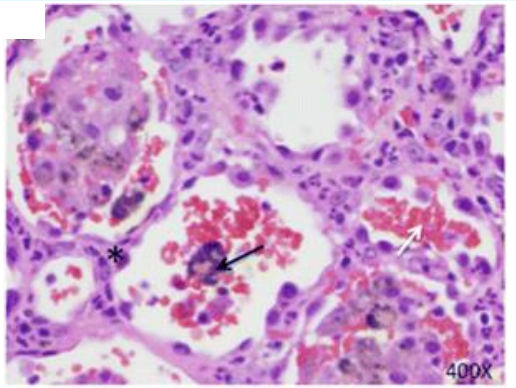
- Not just about infection
- Accounts for a large portion of lung biopsies
  - 22% in children 0-2 years*
  - 50% in children 3-18 years**
- Immune dysfunction may not be readily apparent.
- Numerous genetic mechanisms:
  - *XIAP/BIRC4, SH2D1A, GATA3, STAT3, COPA, TMEM173, and others*
- Potential for targeted immunomodulatory therapy

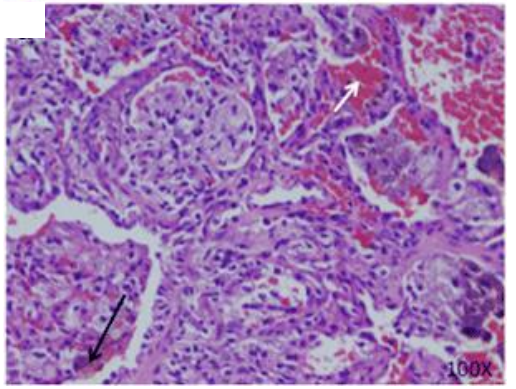
*Deutsch and Young et al, 2007; **Fan et al, 2015.

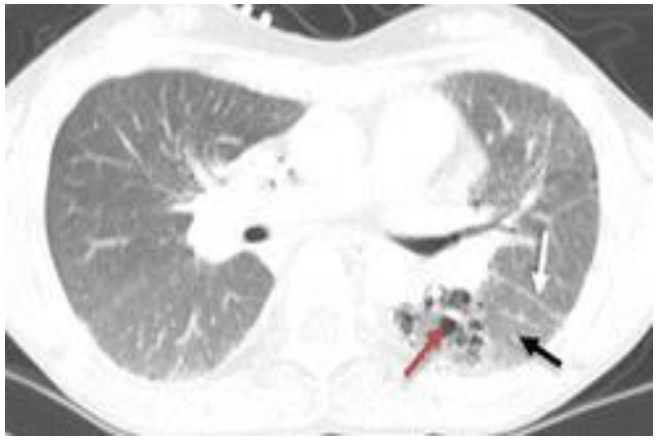


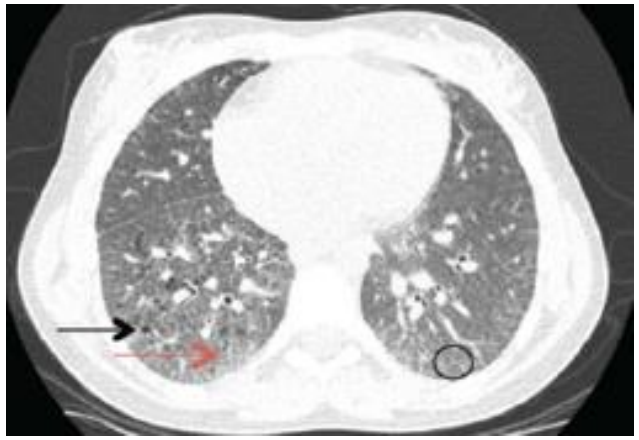
COP-A (Coatomer associated protein, α subunit)

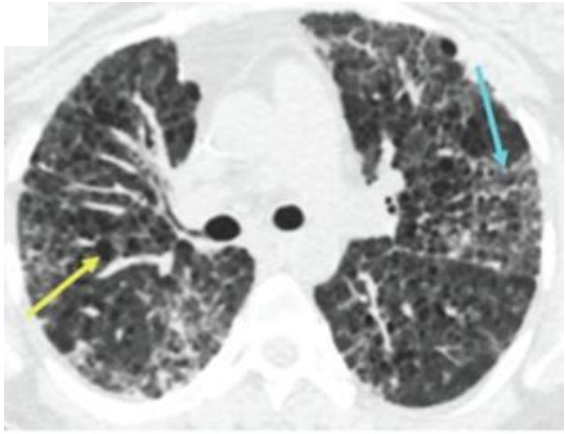
- Autosomal dominant, variable penetrance
- Manifestations include:
  - pulmonary hemorrhage or ILD
  - inflammatory arthritis, and
  - auto-antibodies
- Involved in trafficking retrograde Golgi -> ER
  - Mutations result in ER stress, UPR activation, defect in autophagy, and skewing towards Th17 phenotype

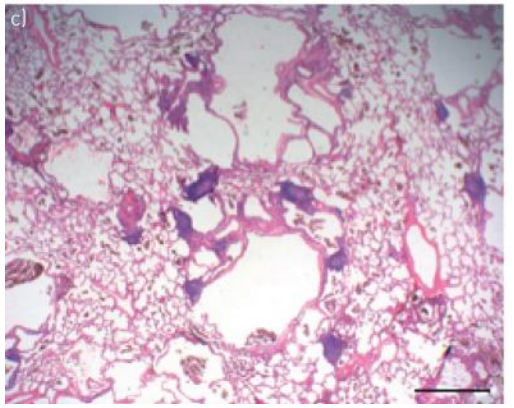








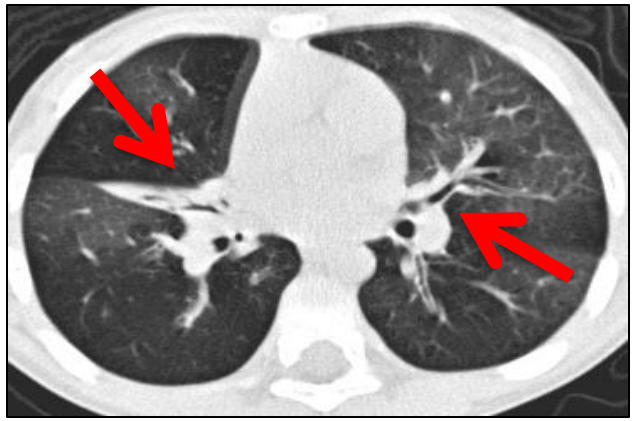




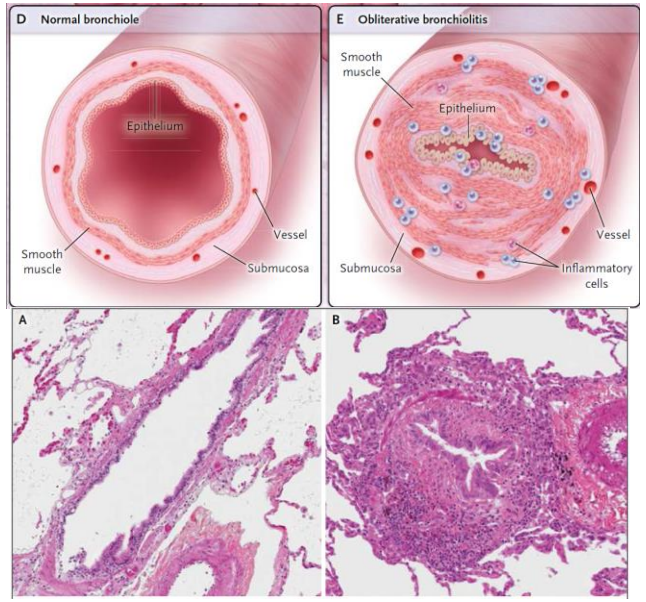
Watkin/Shum 2015; Vece et al 2016; Tsui/Shum 2018

ILD in other settings

Bronchiolitis Obliterans

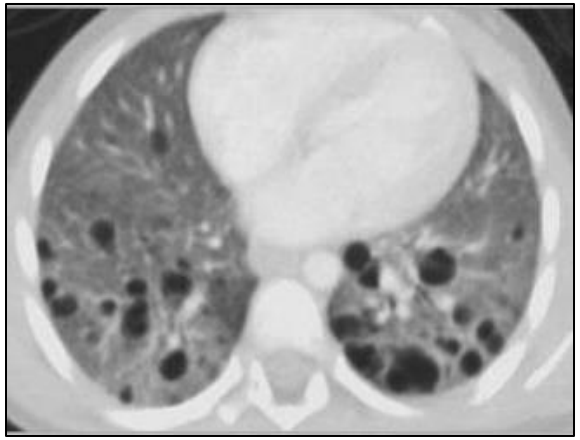


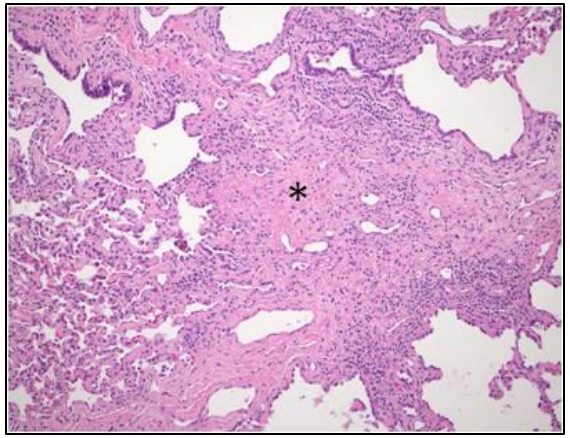
Normal Bronchiolitis obliterans



Barker AF et. al. NEJM, 2014

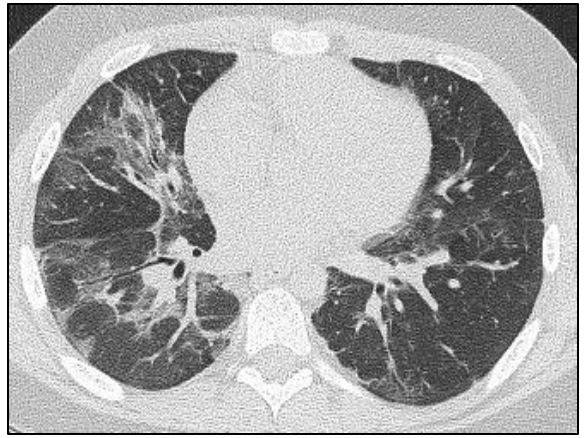
Radiation fibrosis

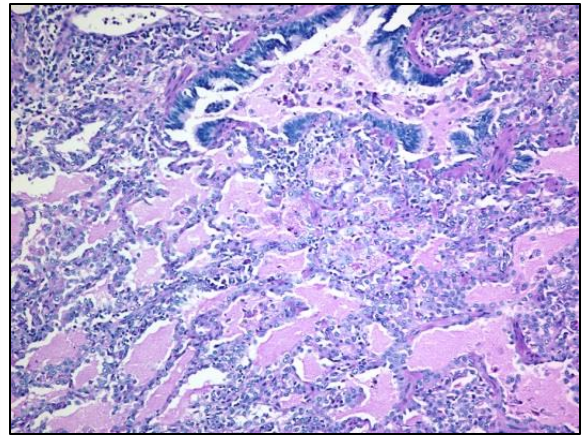




Wolf MS / Young LR,
Ped Radiol, 2015

ILD, unknown etiology





(TBD)

Common management themes

- Empiric therapies often include glucocorticoids and other immunomodulatory agents, but there have been no controlled trials.
- Monitoring and support of growth and nutrition
- Developmental screening and therapies
- Immunizations
- Avoidance of environmental tobacco smoke
- Treat potential comorbidities if present
- Screening for pulmonary hypertension
- Genetic counseling
- Family support

Considerations for long-term glucocorticoid therapy in children with ILD

- There have been no controlled trials.
- Treatment decisions should be made on a case-by-case basis, taking into account the severity of disease, rate of progression, prognosis without treatment, comorbidities, and family preferences.
- There is no evidence to inform the duration of corticosteroid therapy in children with ILD.
- Monitoring for side effects should include bone density scanning and assessment of growth and nutrition.

Other treatment considerations in ILD

- Steroid-sparing approaches
- Other immunomodulatory therapies
- Anti-fibrotic therapies – trials pending for children
- Lung transplant
- HSCT in some cases

U.S. National Registry for Childhood ILD

Registry Objectives

- To advance knowledge on the clinical features, management, and outcomes of children with ILD and other rare lung diseases
- To facilitate additional research in this field

Methods

- Longitudinal observational study
- Inclusion criteria:
  - Age 0-21 years and informed consent
  - Diagnosis or suspected diagnosis of ILD or diffuse lung disease
- Single IRB reliance agreement with CHOP as coordinating center; 20+ sites
- REDCAP database

Summary

- Think ILD = diffuse lung disease.
- Rule-out common causes of symptoms first, then work to make a specific diagnosis.
- There are many new genetic and molecular insights defining developmental and interstitial lung diseases.
- Treat comorbidities and provide supportive care.
- Protocol driven management and treatment trials are needed.
- Multicenter collaboration will continue to accelerate progress.

Thank You!

Question:
Variants or disruption of which of the following genes cause disease predominantly in an autosomal dominant or sporadic inheritance pattern?

- Surfactant Protein B (*SFTPB*)
- *ABCA3*
- *CSF2RA*
- Surfactant Protein C (*SFTPC*)
- *COPA*
- *NKX2.1*

Question:
Variants or disruption of which of the following genes cause disease predominantly in an autosomal dominant or sporadic inheritance pattern?

- Surfactant Protein B (*SFTPB*)
- *ABCA3*
- *CSF2RA*

} recessive

- Surfactant Protein C (*SFTPC*)
- *COPA*
- *NKX2.1*

} dominant or sproradic

Question:
Which of the following should NOT be on the differential of an infant in the NICU with neonatal respiratory failure?

- Surfactant Protein B (*SFTPB*)
- *ABCA3* deficiency
- Alveolar capillary dysplasia with misalignment of the pulmonary veins
- Neuroendocrine cell Hyperplasia of Infancy

Question:
Which of the following should NOT be on the differential of an infant in the NICU with neonatal respiratory failure?

- Surfactant Protein B deficiency
- *ABCA3* deficiency
- Alveolar capillary dysplasia with misalignment of the pulmonary veins
- **Neuroendocrine cell Hyperplasia of Infancy**