When immune dysregulation strikes the lungs

Cross Canada Rounds

Heidi Schaballie
Hospital for Sick Children, Toronto

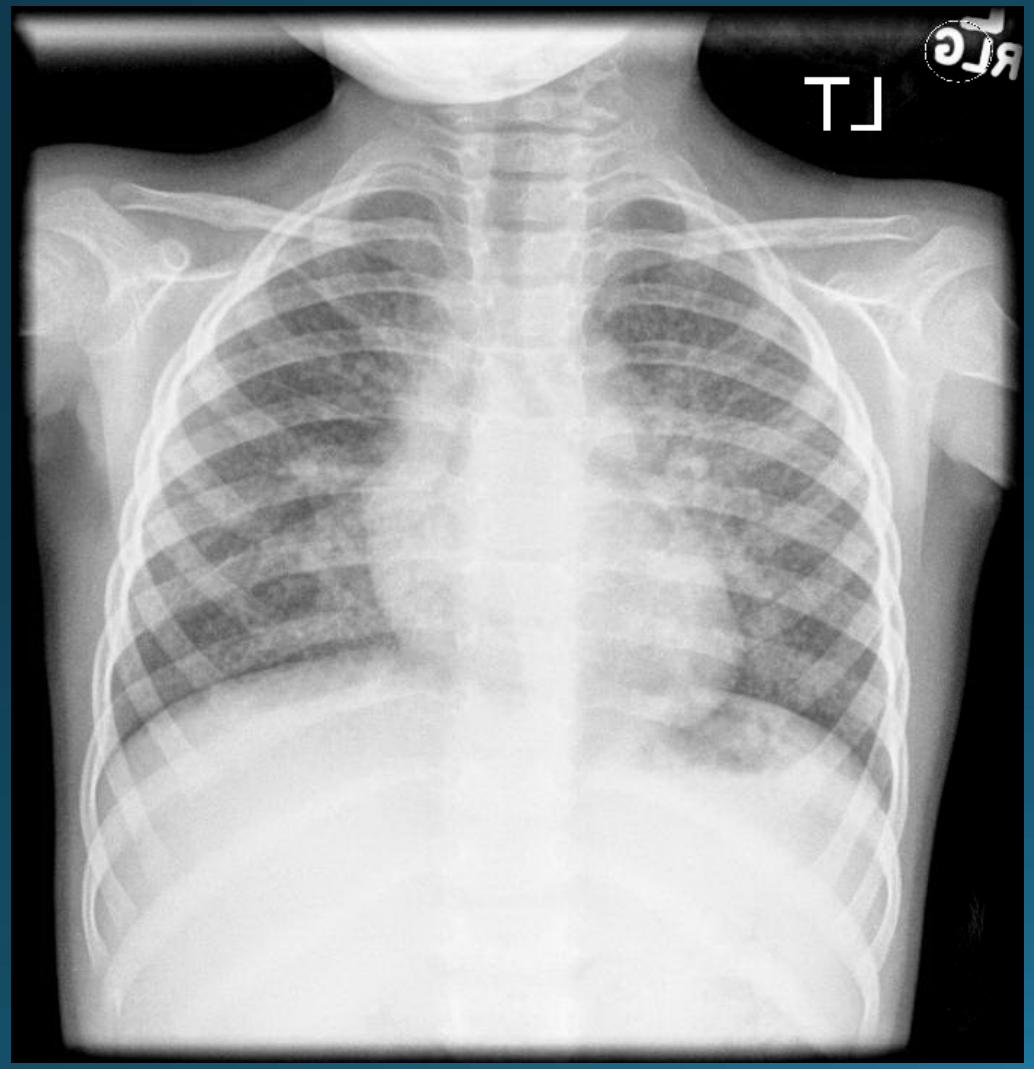
January 18, 2018

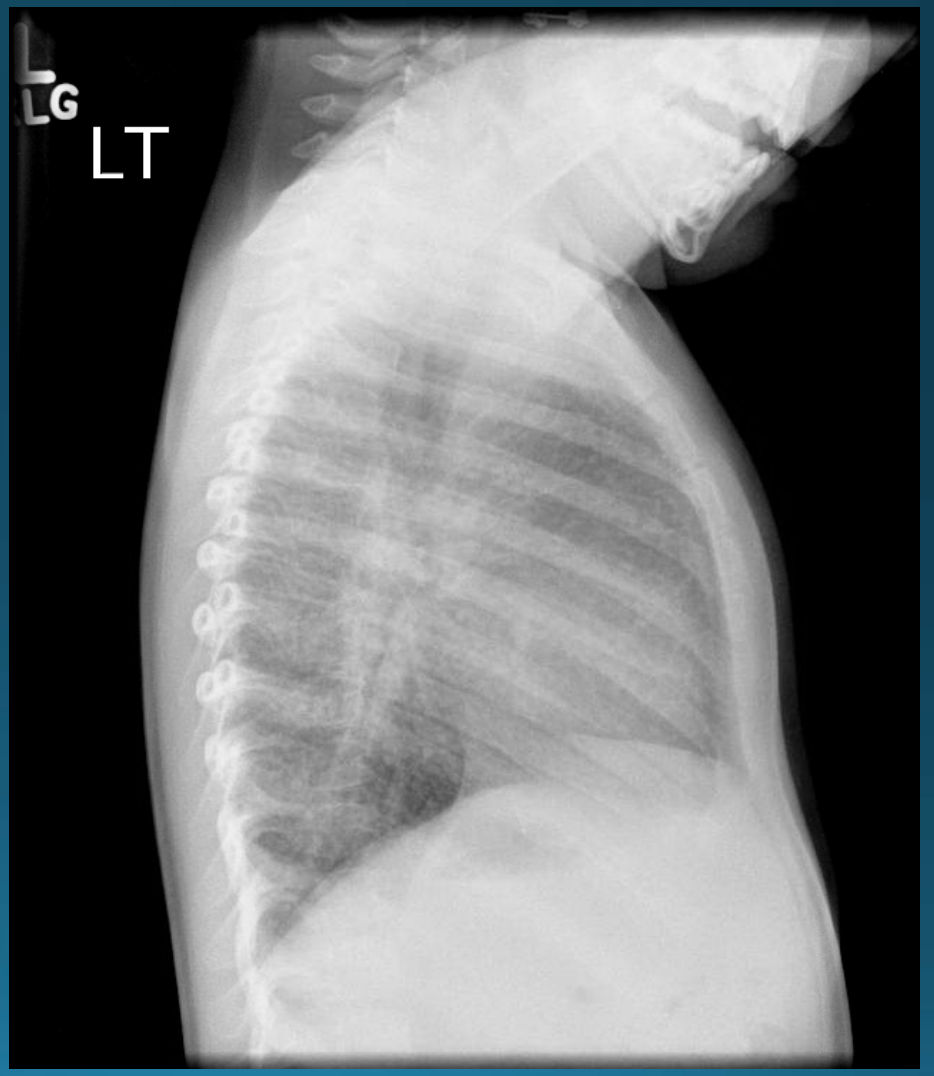
Objectives

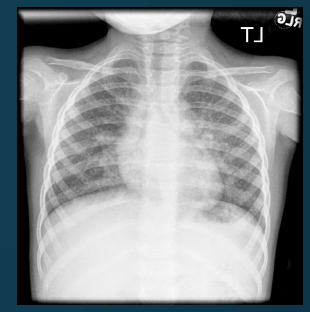
Differential diagnosis and diagnostic approach for diffuse lung disease (DLD) associated with systemic inflammation

2.5 yo girl with abnormal Chest X-ray

?





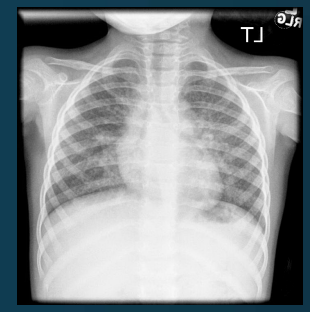


History of Presenting Illness

Presentation Rheumatology Oct 2010:

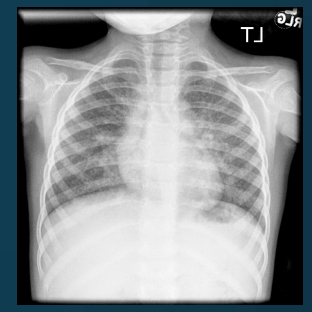
- One month history of joint pain progressively involving both wrists, left knee, both hips
- Associated with morning stiffness for two to three hours
- Not improving with NSAIDS (Naprosyn) BID
- No rash, no fever, no weight loss
- Decreased appetite for more than one month
- Heavy breathing when tired or after crying since birth

Current medications: Naprosyn 100 mg BID, Tylenol PRN



Past medical history

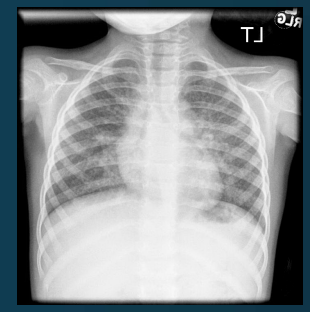
- Born preterm at 34 weeks, SVD, birth weight 2.1 kg, no significant complications pre- or postnatally
- Was switched from cows milk to soy milk as a baby for ‘respiratory symptoms’ considered as cows milk allergy
- A few ear infections which needed antibiotics for 7 days
- Normal neuro development
- No admissions or surgery
- Vaccinations up to date



Family history

- Father (29 yrs): TB cervical lymph node in 2003, fully treated and recovered
- Mother (31 yrs): pauci-immune glomerulonephritis and pulmonary fibrosis, now end-stage lung disease and oxygen dependent
- 4 yo brother: healthy
- No consanguinity

Travel history: Dominican Republic 3 months prior to symptoms



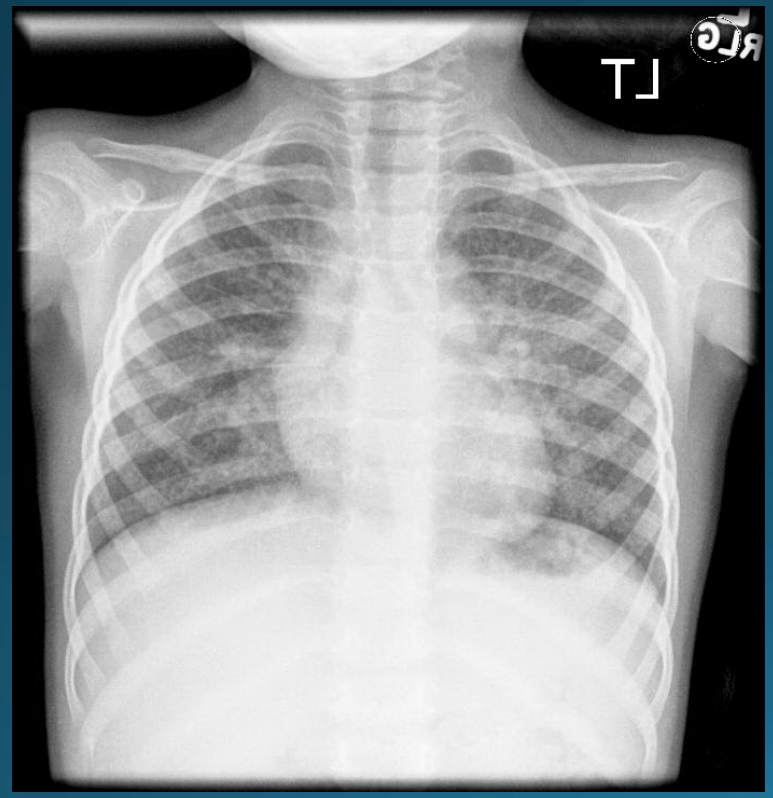
Physical examination

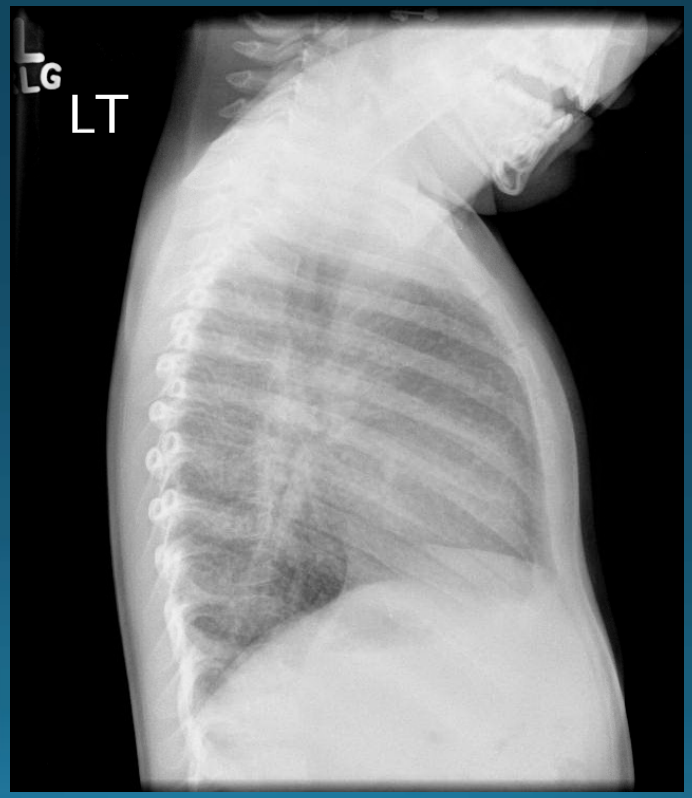
- Height 50-75th percentile, **weight just below 3rd percentile**
- Generally well
- Normal skin.
- CVS: well perfused, normal pulsations, heart sounds normal, no murmurs
- Resp: **resting resp rate of 42/min**, mild intercostal indrawing in the lung bases, good breath sounds bilaterally, no adventitious sounds, no finger clubbing
- Abdomen: soft, non-tender, no hepato/splenomegaly
- ENT: mild nasal congestion, ears and throat normal.
- 3 cervical lymph nodes of about 1 cm diameter, 1 right axillary lymph node of 0.3 cm diameter
- **Multiple joint pain and swelling** of the fingers, knees, ankles, subtalar joints and MTP joints of both feet and right wrist, mild decreased range of motion of both hips

Investigations?

?

- 2,5 yo girl with failure to thrive, multiple arthritis and diffuse lung disease





Diffuse Lung Disease (DLD) in children

- Heterogeneous group of rare conditions
- Formerly called Interstitial Lung Disease (ILD)
- High morbidity and mortality
- Prevalence 0,13 - 16,2/100.000 (but under recognized)
- DLD in children <2 years very distinct from ILD in adults
- DLD in older children show greater overlap with ILD in adults

Vece et al. Chest 2016, Kurland et al. Am J Resp Crit Care Med 2013

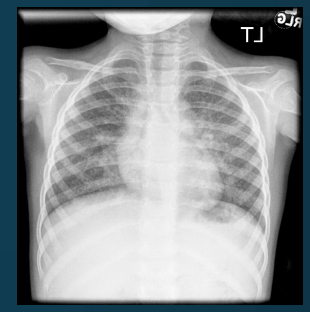
Diagnostic steps in DLD in children

Adapted from ATS guidelines for chILD in children <2 years old

- Laboratory evaluation (CBC and differential, ESR, auto-antibodies, complement, immunoglobulins, serology for infections, coagulation)
- Echocardiography
- High resolution, controlled ventilation chest CT scan
- (infant) PFT
- Bronchoscopy with BAL: exclude infection, detect airway abnormalities, alveolar hemorrhage
- Lung biopsy if non-invasive diagnostic work-up does not yield result or if there is clinical urgency to identify the underlying disease
- Genetic testing depending on clinical presentation, urgency and familial history

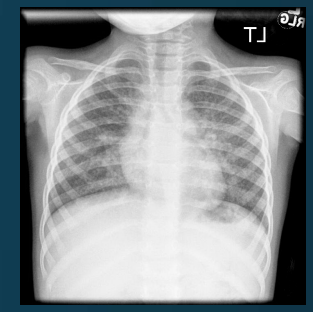
Vece et al. Chest 2016, Kurland et al. Am J Resp Crit Care Med 2013

CASE: Laboratory investigations



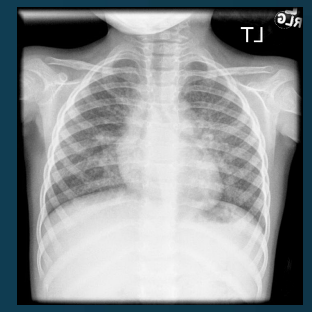
- WBC count normal, HGB 125 g/l and platelets 415x10^9/l
- Serology: HIV -, aspergillus -, blastomycosis -, coccidiomycosis -, histoplasmosis -
- Normal coagulation, liver function, kidney function, albumin, TSH, ferritin 17.7 ug/l
- Immune work-up:
  - **IgG, IgA and IgM elevated**
  - VZV IgG positive, measles IgG positive, mumps IgG positive, rubella IgG positive
  - EBV VCA and EBNA positive
  - **Double negative T cells 2.76%**, otherwise normal lymphocyte immunophenotyping
  - Normal C3 and C4
  - **ESR 58 mm/hr, CRP 6,7 mg/l**
  - **ANA 1/640, RF negative**

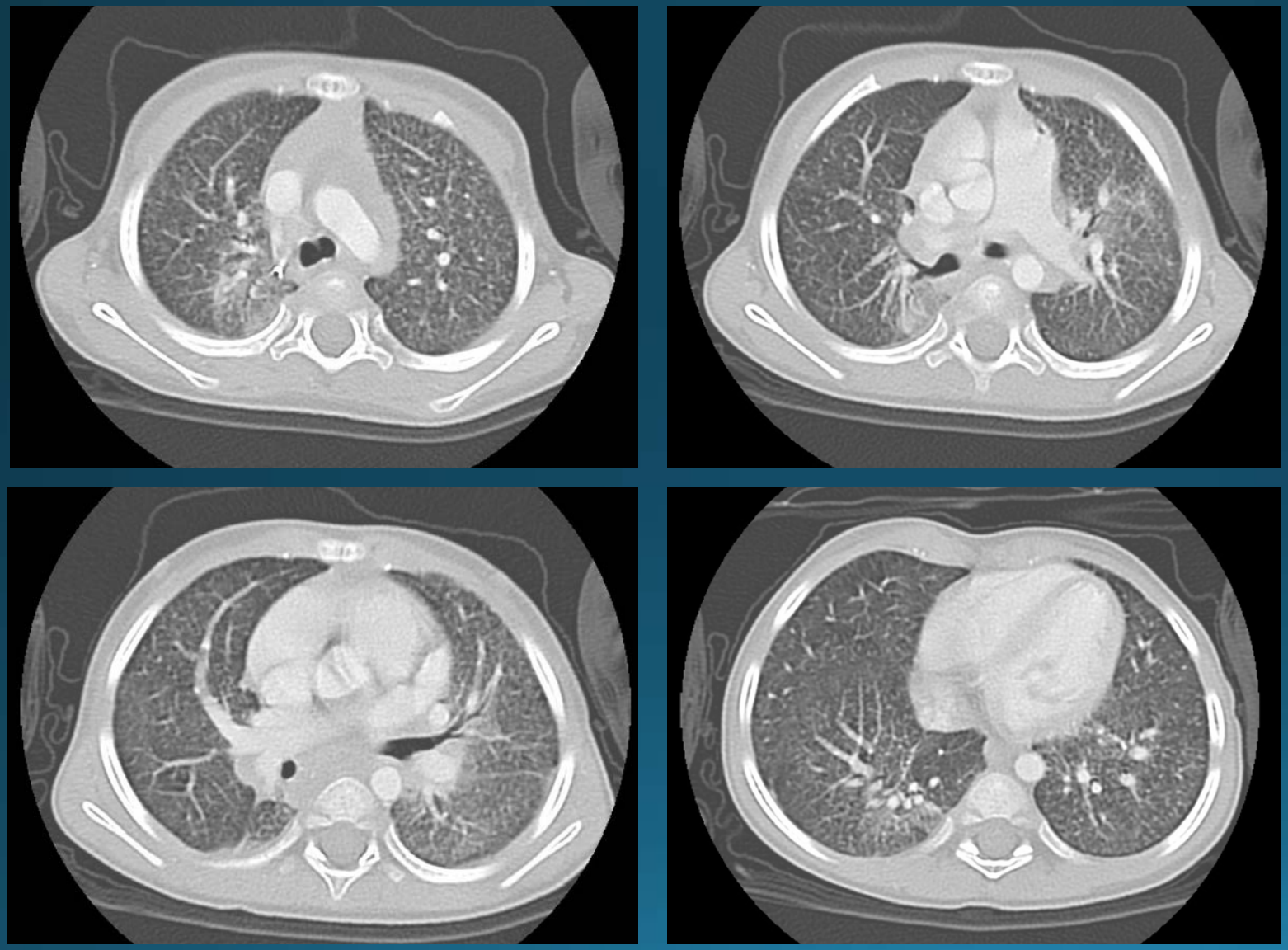
CASE: other investigations



- **X-ray wrist and hips bilat:** Metaphyseal lucent band distal radius which can be seen with systemic illness such as juvenile idiopathic arthritis or leukemia. Clinical correlation recommended. No abnormality of the visualized bones otherwise evident.
- Bone marrow: normal
- Abdominal ultrasound: no lymphadenopathies, no organomegaly
- Tuberculin skin test: negative
- Spot urine VMA and HVA: mildly elevated (no acid preservative)
- Echocardiography: uncooperative child but non-suggestive of pulmonary hypertension

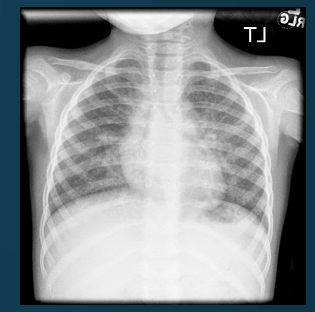
CASE: Chest CT scan





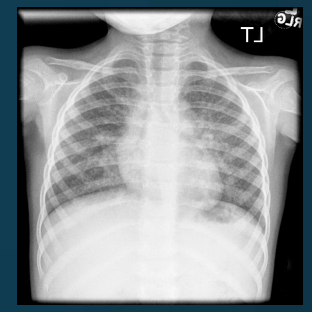
Diffuse nodular pattern
Patchy infiltrates
Some tree in bud
Slightly enlarged lymph nodes

CASE: bronchoscopy



- BAL: 25% lymphocytes, majority are mature T cells, 65% macrophages, small number of hemosiderophages with variable iron content
- PCR: M pneumoniae -, C. pneumoniae -, C, psitacci -, HSV -, CMV - and EBV -, adeno -, RSV-, hMPV –
- Microscopy: pneumocystis –, no acid fast bacilli seen
- Culture: no mycobacteria cultured at 7 weeks, conventional culture gram pos cocci, no fungus isolated
- M.TB molecular testing negative

CASE: lung biopsy (right lower lobe)



- No viruses in cell culture
- PCR: m. pneumoniae -, c. pneumoniae -, c. psittaci -, adeno -, EBV positive
- No pneumocystis seen
- Culture negative for fungus, bacteria and mycobacteria
- Pathology:
  - Microscopy: large aggregates of lymphoid tissue at peribronchiolar regions, some with active germinal centers. Lymphocytes are predominantly B cells and CD4 T cells = follicular bronchiolitis
  - EM: swelling of endothelial cell cytoplasm, tubulo-reticular inclusions, some alveolar capillaries contain aggregates of platelets

Lung biopsy of mother reviewed: follicular bronchiolitis at 3 years, diffuse alveolar hemorrhage at 7 years

CONCLUSION

?

2,5 yo girl with severe, poly-articular arthritis, ILD with pathological diagnosis of follicular bronchiolitis, systemic inflammation and elevated ANA

What is your differential diagnosis at this point?

Differential diagnosis of DLD in children

Langston - ATS classification

Birth - infancy	**Disorders more common in infancy (50% of DLD)** • **Developmental disorders** • **Growth abnormality disorders** • **Specific conditions of unknown etiology** • **Surfactant dysfunction mutations**	• Alveolar capillar dysplasia with misalignement of pulmonary veins (ACDMPV) • BPD, related to chromosomal disorders, associated with congenital heart disease • Neuroendocrine Cell hyperplasia of Infancy (NEHI), pulmonary interstitial glycogenosis (PIG) • Surfactant deficiencies (*SFTPB*, *SFTPC*, *ABCA3*, *NKX2.1*), pulmonary alveolar proteinosis
Child - adolescent	**Disorders related to systemic disease**	Sarcoidosis, immune mediated collagen vascular disease, storage disease, langerhans cell histiocytosis, GPA
Infant - adolescent	**Disorders of the normal host/ environmental exposure**	Infectious/post-infectious, hypersensitivity pneumonitis, aspiration, eosinophilic pneumonia
Infant - adolescent	**Disorders of the immunocompromised host**	Opportunistic infections, related to transplantation and rejection, related to therapeutic interventions
Birth - adolescent	**Disorders masquerading as interstitial lung disease**	Pulmonary hypertension, cardiac dysfunction, veno-occlusive disease, lymphatic disorders
	Unknown	Biopsy tissue cannot be classified

Langston Pediatr Dev Pathol 2006, Kurland Am J Resp Crit Care Med 2013

Diffuse Lung Disease in Biopsied Children 2 to 18 Years of Age

Application of the chILD Classification Scheme

Leland L. Fan[1], Megan K. Dishop[2], Csaba Galambos[2], Frederic B. Askin[3], Frances V. White[4], Claire Langston[5],

Aim:

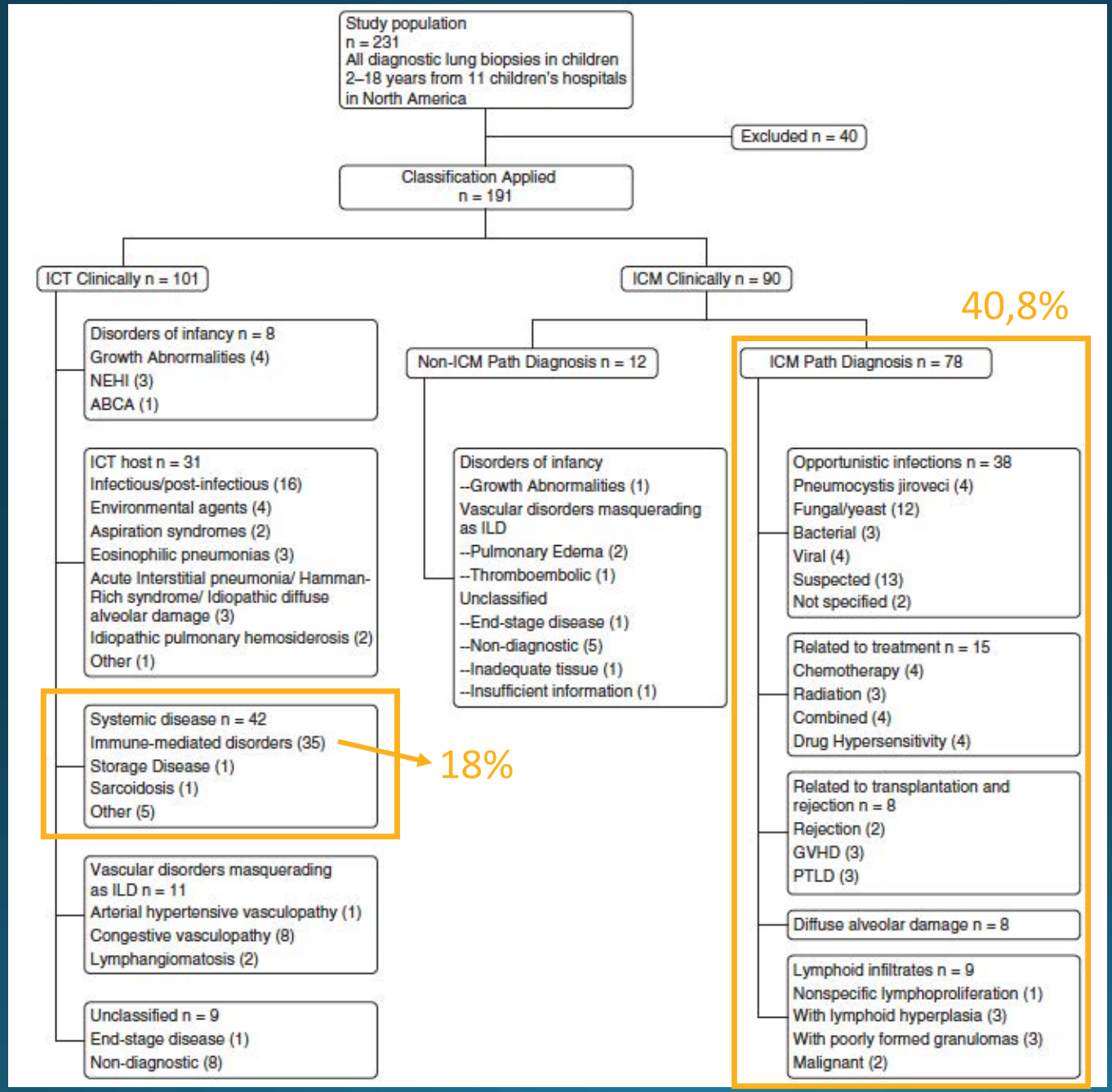
- Describe the spectrum of **biopsy-proven** DLD in North America
- Apply the Langston – ATS classification scheme in children **2-18 years old**

Methods:

Patients 2-18 year old who underwent lung biopsy for DLD from 12 North American institutions were included

Results:

191 cases included for final analysis


Study population
n = 231
All diagnostic lung biopsies in children 2–18 years from 11 children's hospitals in North America
Excluded n = 40
Classification Applied
n = 191
ICT Clinically n = 101
ICM Clinically n = 90
40,8%
Disorders of infancy n = 8
Growth Abnormalities (4)
NEHI (3)
ABCA (1)
ICT host n = 31
Infectious/post-infectious (16)
Environmental agents (4)
Aspiration syndromes (2)
Eosinophilic pneumonias (3)
Acute Interstitial pneumonia/ Hamman-Rich syndrome/ Idiopathic diffuse alveolar damage (3)
Idiopathic pulmonary hemosiderosis (2)
Other (1)
Systemic disease n = 42
Immune-mediated disorders (35)
Storage Disease (1)
Sarcoidosis (1)
Other (5)
18%
Vascular disorders masquerading as ILD n = 11
Arterial hypertensive vasculopathy (1)
Congestive vasculopathy (8)
Lymphangiomatosis (2)
Unclassified n = 9
End-stage disease (1)
Non-diagnostic (8)
Non-ICM Path Diagnosis n = 12
Disorders of infancy
--Growth Abnormalities (1)
Vascular disorders masquerading as ILD
--Pulmonary Edema (2)
--Thromboembolic (1)
Unclassified
--End-stage disease (1)
--Non-diagnostic (5)
--Inadequate tissue (1)
--Insufficient information (1)
ICM Path Diagnosis n = 78
Opportunistic infections n = 38
Pneumocystis jiroveci (4)
Fungal/yeast (12)
Bacterial (3)
Viral (4)
Suspected (13)
Not specified (2)
Related to treatment n = 15
Chemotherapy (4)
Radiation (3)
Combined (4)
Drug Hypersensitivity (4)
Related to transplantation and rejection n = 8
Rejection (2)
GVHD (3)
PTLD (3)
Diffuse alveolar damage n = 8
Lymphoid infiltrates n = 9
Nonspecific lymphoproliferation (1)
With lymphoid hyperplasia (3)
With poorly formed granulomas (3)
Malignant (2)

Diffuse Lung Disease in Biopsied Children 2 to 18 Years of Age

Application of the chILD Classification Scheme

Leland L. Fan[1], Megan K. Dishop[2], Csaba Galambos[2], Frederic B. Askin[3], Frances V. White[4], Claire Langston[5],

Results:

- 4,7% were categorized as disorders of infancy
- 40,8% as disorders of the immunocompromised host
- 18% as immune-mediated disorders in systemic disease
- Mortality was 52,8% in immunocompromised patients (median FU 1 yr) and 20% in systemic disease (median FU 2 yrs)
- Original classification provided a useful template but expansion of the categories was necessary to make it applicable to older children

Conclusion:

Large proportion of diffuse lung disease in older children occurs in association with immunodeficiency and autoimmune disease

This was associated with poor outcome

Disorders more common in infancy (50% of DLD) • **Developmental disorders** • **Growth abnormality disorders** • **Specific conditions of unknown etiology** • **Surfactant dysfunction mutations**	• Alveolar capillar dysplasia with misalignement of pulmonary veins (ACDMPV) • BPD, related to chromosomal disorders, associated with congenital heart disease • Neuroendocrine Cell hyperplasia of Infancy (NEHI), pulmonary interstitial glycogenosis (PIG) • Surfactant deficiencies (*SFTPB*, *SFTPC*, *ABCA3*, *NKX2.1*), pulmonary alveolar proteinosis
1. **Disorders related to systemic disease**	Sarcoidosis, immune mediated collagen vascular disease, storage disease, langerhans cell histiocytosis, GPA
Disorders of the normal host/ environmental exposure	Infectious/post-infectious, hypersensitivity pneumonitis, aspiration, eosinophilic pneumonia
2. **Disorders of the immunocompromised host**	Opportunistic infections, related to transplantation and rejection, related to therapeutic interventions, **primary immunodeficiencies**
Disorders masquerading as interstitial lung disease	Pulmonary hypertension, cardiac dysfunction, veno-occlusive disease, lymphatic disorders
Unknown	Biopsy tissue cannot be classified

1. DLD related to systemic inflammatory disease

Pulmonary manifestations of systemic inflammatory disease in childhood

DLD

	JIA	SLE	JDM	SSC	MCTD	Sarcoidosis	WG	MPA
Frequency at initial presentation[a]	+	++	+	+++	+	+++	+++	+
Frequency during disease course[b]	+	+++	+	+++	+++	+++	+++	++
Chest wall/diaphragm[c]	+	+	+++	+	+	–	–	–
Pleural disease[d]	++	+++	–	+	++	+	+	–
Large airway lesions[e]	–	–	–	–	–	++	++	–
Bronchiectasis	+	+	–	+	–	+	+	–
Acute pneumonitis[f]	+	++	+	–	–	–	–	–
Interstitial lung disease (ILD)[g]	+	+	+	+++	++	+	–	–
Pulmonary granulomas	–	–	–	–	–	+++	+++	–
Vasculitis/DAH	+	+	–	+	+	–	++	+++
Pulmonary hypertension	–	+	+	++	++	–	–	+
Thrombosis	–	++	–	–	–	–	+	–

Kendig and Chernick's. Disorders of the Respiratory Tract in Children. Chapter 57.

Juvenile idiopathic arthritis (JIA)

- Most common rheumatological disorder in childhood: 150/100.000
- Heterogeneous group of diseases characterized by arthritis with onset <16 years, persists at least 6 weeks and for which no specific cause can be found
- Pulmonary complications are rare (4-8%)
  - Commonest: pleuritis
  - Increasing frequency: Pulmonary hypertension, ILD, alveolar proteinosis
- Most JIA patients with biopsy proven pulmonary disease are RF positive
- Treatment:
  - NSAIDs and corticosteroids
  - MTX
  - Biologicals

Kendig and Chernick's. Disorders of the Respiratory Tract in Children. Richardson et al. Arch Dis Childhood 2016.

Systemic lupus erythematosus (SLE)

- Relatively rare in children: 10-20/100.000
- Presents <18 years in 15-20%
- Characterized by the presence of a variety of autoantibodies, resulting in multisystem inflammation and organ damage
- Most common presenting features in pediatric patients: arthritis, malar rash, nephritis and CNS disease
- Pulmonary involvement in 18-40% within first year of diagnosis
  - Pleuritis, acute pneumonitis (rare), alveolar hemorrhage, **chronic interstitial disease (extremely rare)**, thrombosis, pulmonary hypertension
- Treatment: First exclude infection/thromboembolism/drug toxicity or secondary to impact of renal/cardiac disease
  - Corticosteroids = mainstay
  - Hydroxychloroquine (majority of patients)
  - MMF and azathioprine as steroid-sparing agents
  - (MTX and cyclosporine)

Kendig and Chernick's. Disorders of the Respiratory Tract in Children. Richardson et al. Arch Dis Childhood 2016.

Systemic scleroderma (SSc)

- Rare in children: 0,05/100.000, F>M
- 10% of adults with SSc have onset in childhood
- ‘Diffuse’ vs. ‘limited’ form, in childhood 90% is diffuse
- Diffuse SSc is an autoimmune vasculopathy that causes inflammation and excessive fibrosis affecting the skin and multiple other organs
- 80% ANA positive
- Pulmonary involvement in 50% (minor diagnostic criteria for SSc)
  - DLD (most common) or pulmonary hypertension (4-9%)
  - Often asymptomatic
- Treatment:
  - Cyclophosphamide, MMF, azathioprine, rituximab
  - Lung transplant if limited other organ involvement
  - HSCT

Kendig and Chernick’s. Disorders of the Respiratory Tract in Children. Richardson et al. Arch Dis Childhood 2016.

Juvenile dermatomyositis (JDM)

- Rare in children: 0,2-0,4/100.000
- Commonest inflammatory myopathy in children
- Capillary vasculopathy causes characteristic cutaneous and muscle manifestations (proximal muscle weakness and elevated skeletal muscle enzymes)
- Symptomatic pulmonary involvement (DLD) is very rare in children (<1%) (vs. adults up to 70%)
- Treatment:
  - Corticosteroids and MTX
  - Cyclosporine (effective in JDM-associated DLD)
  - Other in selected cases: High dose IVIG, Rituximab, cyclophosphamide

Kendig and Chernick's. Disorders of the Respiratory Tract in Children. Richardson et al. Arch Dis Childhood 2016.

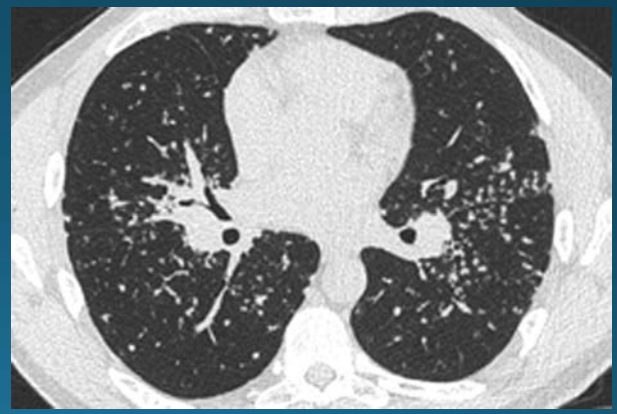
Mixed connective tissue disease (MCTD)

- Rare in children
- Characterized by the presence of high titer anti-RNP antibodies in combination with clinical features of SLE, SSc and/or dermatomyositis
- Three criteria must be met for diagnosis:
  1. Raynaud's phenomenon
  2. Positive anti-RNP antibodies
  3. At least one abnormal sign or symptom from either SLE, SSc or dermatomyositis
- Pulmonary involvement in 75% of adults, probably similar for children
  - Pulmonary fibrosis, pleural effusions and pulmonary hypertension are most common pulmonary findings
- Treatment: conventional therapies used for SLE, SSc and dermatomyositis

Kendig and Chernick's. Disorders of the Respiratory Tract in Children. Richardson et al. Arch Dis Childhood 2016.

Sarcoidosis

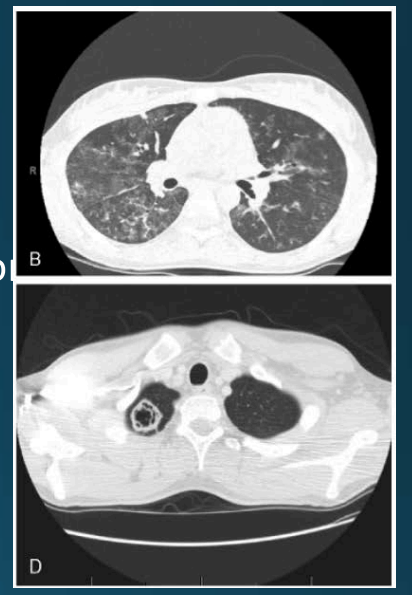
- Mostly young adults, rare in children
- Chronic inflammatory multisystem disease of unknown etiology
- Characterized by epithelioid cell granulomatous lesions that are non-caseating
- Classical sarcoidosis presents >8 years of age
- Pulmonary involvement in >90%, affecting thoracic lymph nodes and pulmonary parenchyma
- Most disease will resolve spontaneously within 2 years
- Chance of spontaneous remission can be predicted from CXR abnormalities
- Treatment dependent of stage of disease:
  - No treatment
  - Corticosteroids
  - MTX
  - Hydroxychloroquine
  - Lung transplantation



Kendig and Chernick's. Disorders of the Respiratory Tract in Children. Richardson et al. Arch Dis Childhood 2016.

ANCA-associated vasculitides

- Necrotizing vasculitis of small vessels with pauci-immune deposits in the blood vessel walls
- ’Pulmonary-renal syndrome’
- Granulomatosis and polyangiitis (GP, Wegener’s granulomatosis)
  - 65% of pediatric ANCA-vasculitis is GP
  - Anti-MPO and anti-PR-3 ANCA
  - Typical triad of upper airway, lower respiratory tract and renal disease, associated with constitutio symptoms but also other organ involvement
  - Pulmonary involvement in 80%
  - Treatment: plasmapheresis, corticosteroids and cyclophosphamide (acute), MTZ and azathioprine (maintenance),
    Rituximab
- Microscopic polyangiitis (MPA)
  - Involving skin, joints, kidneys and lungs
  - High anti-MPO-ANCA, no anti-PR-3 ANCA
  - No granulomatous inflammation
  - Pulmonary hemorraghe in 10-30%
  - Treatment: similar to GP



Kendig and Chernick’s. Disorders of the Respiratory Tract in Children.

Drug-induced pulmonary complications in rheumatological diseases

Drug	Indication	Pulmonary complication[1 58]
Methotrexate	JIA, JDM, JSLE, SSc, vasculitis, sarcoidosis	Pulmonary toxicity (methotrexate lung)
Azathioprine	JIA, vasculitis	Interstitial pneumonitis, bronchiolitis and diffuse alveolar damage
Cytokine modulators (etanercept, infliximab, rituximab)	JIA	Interstitial pneumonitis
Sulfasalazine	JIA	Fibrosing alveolitis, interstitial pneumonitis
Cyclophosphamide	Arthritis	Interstitial pneumonitis
Leflunomide	Arthritis	Interstitial pneumonitis

JDM, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; JSLE, juvenile systemic lupus erythematosus; SSc, systemic sclerosis.

Hypersensitivity pneumonitis, pulmonary fibrosis, organizing pneumonia, acute lung injury and reactive airway disease

INFECTION

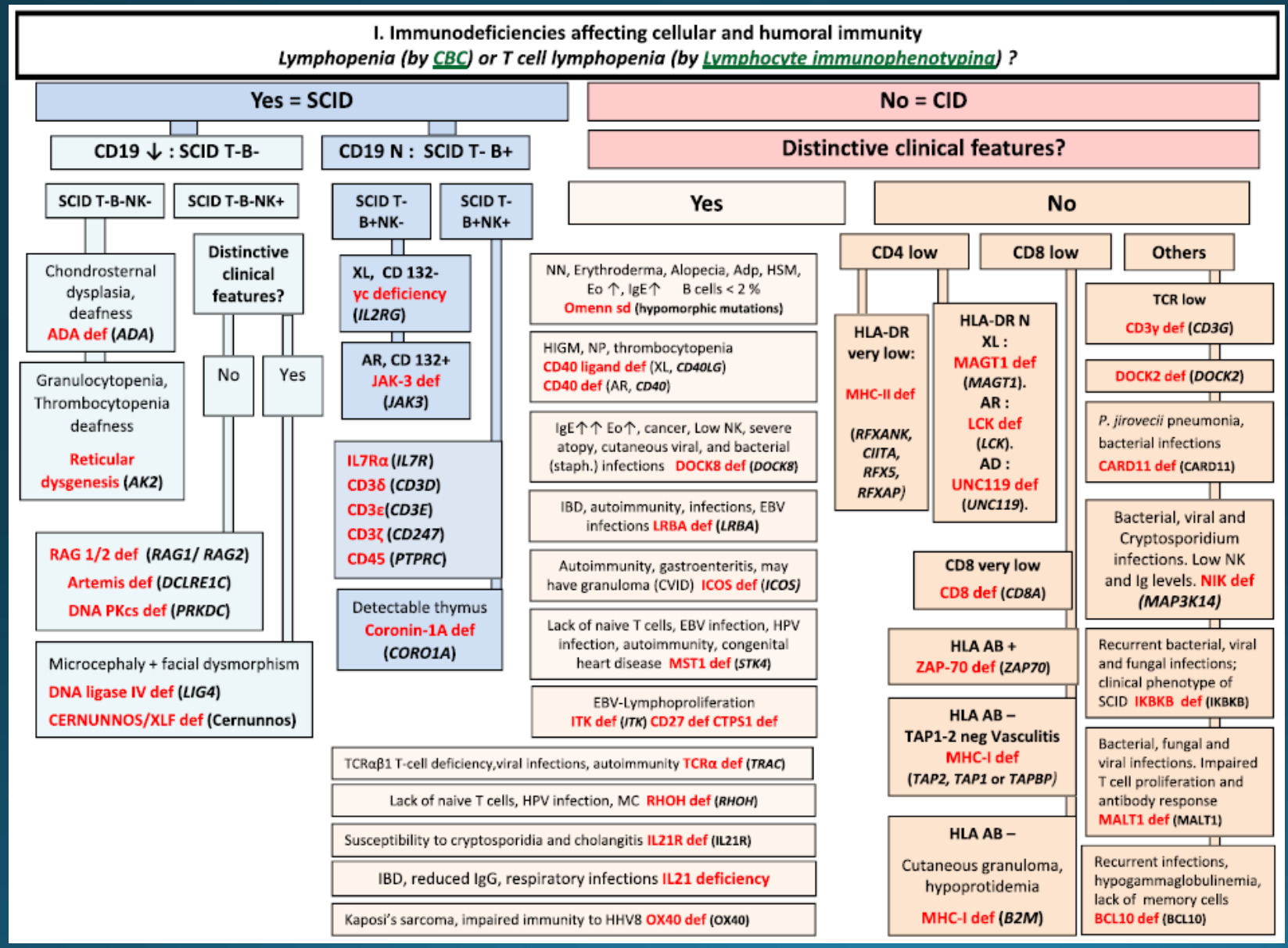
Richardson et al. Arch Dis Childhood 2016

Disorders more common in infancy (50% of DLD) • **Developmental disorders** • **Growth abnormality disorders** • **Specific conditions of unknown etiology** • **Surfactant dysfunction mutations**	• Alveolar capillar dysplasia with misalignement of pulmonary veins (ACDMPV) • BPD, related to chromosomal disorders, associated with congenital heart disease • Neuroendocrine Cell hyperplasia of Infancy (NEHI), pulmonary interstitial glycogenosis (PIG) • Surfactant deficiencies (*SFTPB*, *SFTPC*, *ABCA3*, *NKX2.1*), pulmonary alveolar proteinosis
1. **Disorders related to systemic disease**	Sarcoidosis, immune mediated collagen vascular disease, storage disease, langerhans cell histiocytosis, GPA
Disorders of the normal host/ environmental exposure	Infectious/post-infectious, hypersensitivity pneumonitis, aspiration, eosinophilic pneumonia
2. **Disorders of the immunocompromised host**	Opportunistic infections, related to transplantation and rejection, related to therapeutic interventions, **primary immunodeficiencies**
Disorders masquerading as interstitial lung disease	Pulmonary hypertension, cardiac dysfunction, veno-occlusive disease, lymphatic disorders
Unknown	Biopsy tissue cannot be classified

2. DLD related to Primary Immunodeficiency

- Primary immunodeficiencies (PID) = genetic errors of immunity
- Variety of phenotype in at least 1 of 5 categories:
  - Infection
  - Auto-immunity
  - Auto-inflammation
  - Allergy
  - Tumors
- Exponential increase in identified PIDs since the application of whole exome sequencing
- Classification by the International Union of Immunological Societies (IUIS) Expert Committee for Primary Immunodeficiencies
- In 2015 almost 300 single-gene inborn errors of immunity identified, 34 more than in the 2013 classification

The 2015 IUIS Phenotypic Classification for Primary Immunodeficiencies

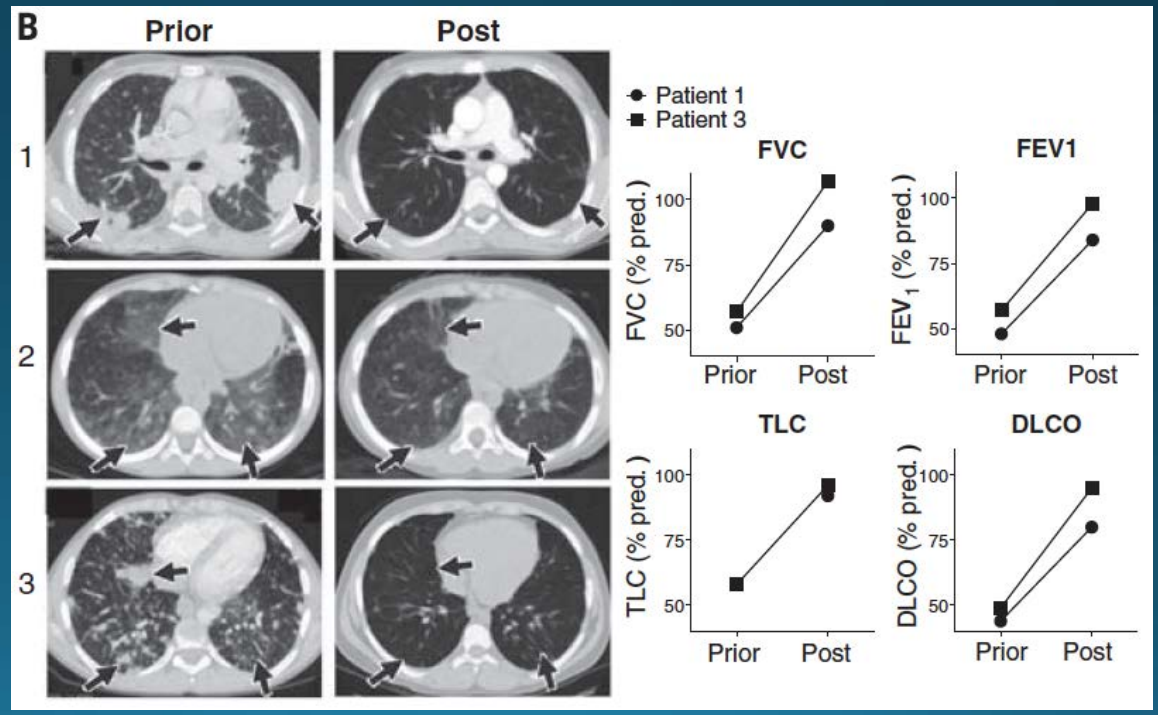


Boushifa et al. J Clin Immunol 2015

LRBA deficiency

- LRBA deficiency is an autosomal recessive disease characterized by hypogammaglobulinemia, infections, auto-immunity and lymphoproliferation
- Previously categorized as Common Variable Immunodeficiency Disorder (CVID)
- Caused by mutations in lipopolysaccharide-responsive vesicle trafficking, beach and anchor containing (*LRBA*) gene, encoding a protein needed for normal autophagy and involved in the control of regulatory T cells

Prior and post treatment with abatacept (CTLA4-Ig fusion protein)



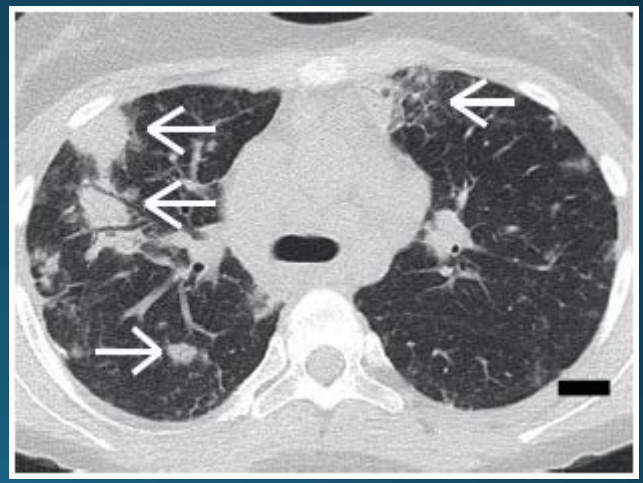
Lo et al. Science 2015, Lopez-Herrera et al. Am J Human Genet 2012

CTLA4 deficiency

- Very similar clinical presentation as LRBA deficiency: hypogammaglobulinemia, infections, auto-immunity and lymphoproliferation
- Autosomal dominant inheritance with incomplete penetration (haploinsufficiency)
- 66% of patients had granulomatous-lymphocytic interstitial lung disease

Table 1 Clinical phenotype of patients with *CTLA4* mutations

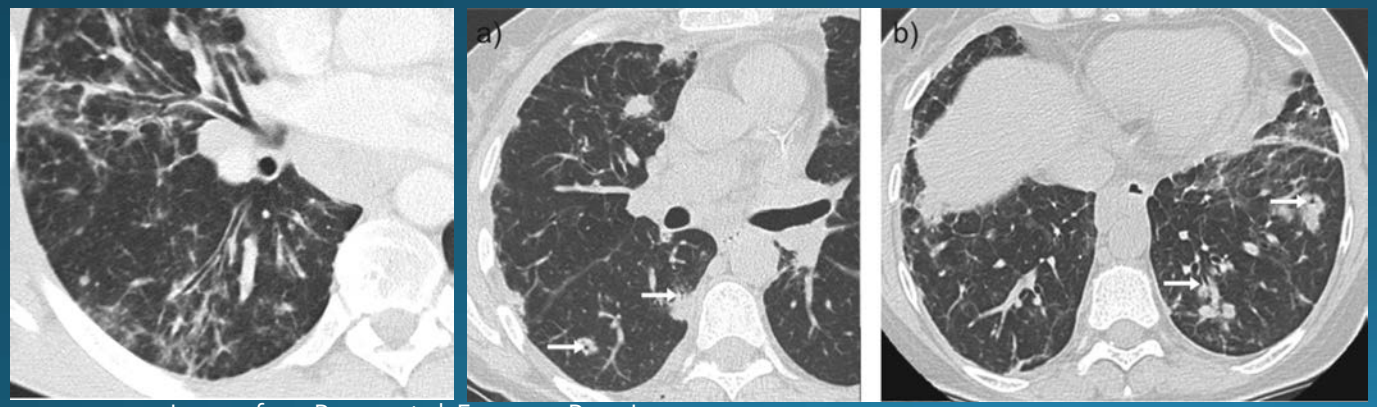
Clinical manifestations	Patients	Frequency
Diarrhea/enteropathy	A.II.5, A.II.8, A.II.9, A.III.1, A.III.3, B.II.1, B.II.2, B.II.4, C.II.4, E.II.3, F.II.2	11/14 (78%)
Hypogammaglobulinemia	A.II.5, A.II.8, A.II.9, A.III.1, A.III.3, C.II.3, B.III.2, D.II.1, E.II.3, F.II.2	10/13 (76%)
Granulomatous lymphocytic interstitial lung disease	A.II.8, A.II.9, A.III.3, B.II.4, B.III.2, C.II.3, D.II.1, E.II.3	8/12 (66%)
Respiratory infections[a]	A.II.5, A.II.8, A.II.9, B.II.4, B.III.2, C.II.3, E.II.3, F.II.2	8/14 (57%)
Organ infiltration (bone marrow, kidney, brain, liver)	A.II.9, A.III.1, A.III.3, B.II.2, B.II.4, C.II.3, D.II.1	7/14 (50%)
Splenomegaly	A.II.5, A.II.9, A.III.3, C.II.3, D.II.1, E.II.3	6/12 (50%)
Autoimmune thrombocytopenia	A.III.1, A.III.3, C.II.3, E.II.3, F.II.2	5/14 (35%)
Autoimmune hemolytic anemia	C.II.3, D.II.1, E.II.3, F.II.2	4/14 (28%)
Lymphadenopathy	A.III.3, C.II.3, D.II.1, E.II.3	4/14 (28%)
Psoriasis and other skin diseases[b]	A.III.1, B.II.1, B.II.2	3/14 (21%)
Autoimmune thyroiditis	A.II.5, D.II.1	2/13 (15%)
Autoimmune arthritis	A.II.5, A.III.1	2/14 (14%)
Solid cancer	B.II.4	1/14 (7%)



Schubert et al. Nature Medicine 2014

Common Variable Immunodeficiency Disorders (CVID)

- Primary antibody deficiency characterized by hypogammaglobulinaemia, impaired production of specific antibodies after immunization and increased susceptibility to infections
- Phenotypical and genetic heterogeneity
- More rare in children
- Monogenic forms probably count for only 2-10% of patients with CVID
- Many diseases previously classified as CVID are now regarded as distinct PID (eg LRBA deficiency, CTLA4 deficiency, hypomorphic *RAG1*/*RAG2* mutations)
- 8-20% of patients with CVID develop 'granulomatous-lymphocytic interstitial lung disease' (GLILD)



Images from Bouvry et al. European Resp J 2013

Hurst et al. J Allergy Clin Immunol Pract 2017

STAT3 gain-of-function mutations

- Early onset lymphoproliferation and auto-immunity
- Autosomal dominant
- Increased STAT3 transcriptional activity leads to impaired cytokine signaling and diminished regulatory T cell compartment

Table 1. Patient characteristics

Patient	Age at onset, sex	Current age	STAT3 variant*	Autoimmunity				Lymphoproliferation		Postnatal short stature†
				Hematologic	Endocrine	GI	Other	LAD	Other	
1	4y, M	10y	p.G421R	AIHA	No	Hepatitis	Scleroderma, polyarthritis	Yes	HSM	Yes
2	7y, M	31y	p.T663I	AIHA, AITP	No	No	No	Yes	HSM	No
3	3y, M	25y	p. R152W	AIHA, AITP	IDDM	No	Alopecia, lung nodules	Yes	HSM	No
4	13y, M	32y	p.V353F	AIHA, AITP, AIN	No	No	Inflammatory lung disease	Yes	No	No
5	3y, F	5y	p.Q344H	AIHA	No	Enteropathy	LIP	Yes	HSM	Yes
6	5y, F	9y	p.E415K	none	IDDM	Enteropathy, achalasia	Atopic dermatitis	Yes	HSM	Yes
7	<1y, F	23y	p.T716M	AIHA, AITP, AIN	Hypothyroid	Enteropathy	No	No	No	Yes
8	3y, F	Dec 11y	p.N420K	AIHA, AITP, AIN	No	No	Polyarthritis	Yes	No	No
Family 1										
9, Proband	<1y, F	26y	p.A703T	AIHA, AITP, AIN	No	Small bowel thickening	LIP, atopic dermatitis, alopecia	Yes	HSM	Yes
10, Father	15y, M	Dec 28y	p.A703T	AIHA, AIN	No	No	LIP	Yes	HSM	n/a
11, Sibling	12y, F	24y	p.A703T	AITP, AIN	No	No	No	Yes	HSM	n/a
Family 2										
12, Proband	<1y, M	4y	p.T716M	none	No	Enteropathy	No	No	No	Yes
13, Father	EO, M	32y	p.T716M	AITP	No	Enteropathy	No	No	Hodgkin lymphoma	Yes‡

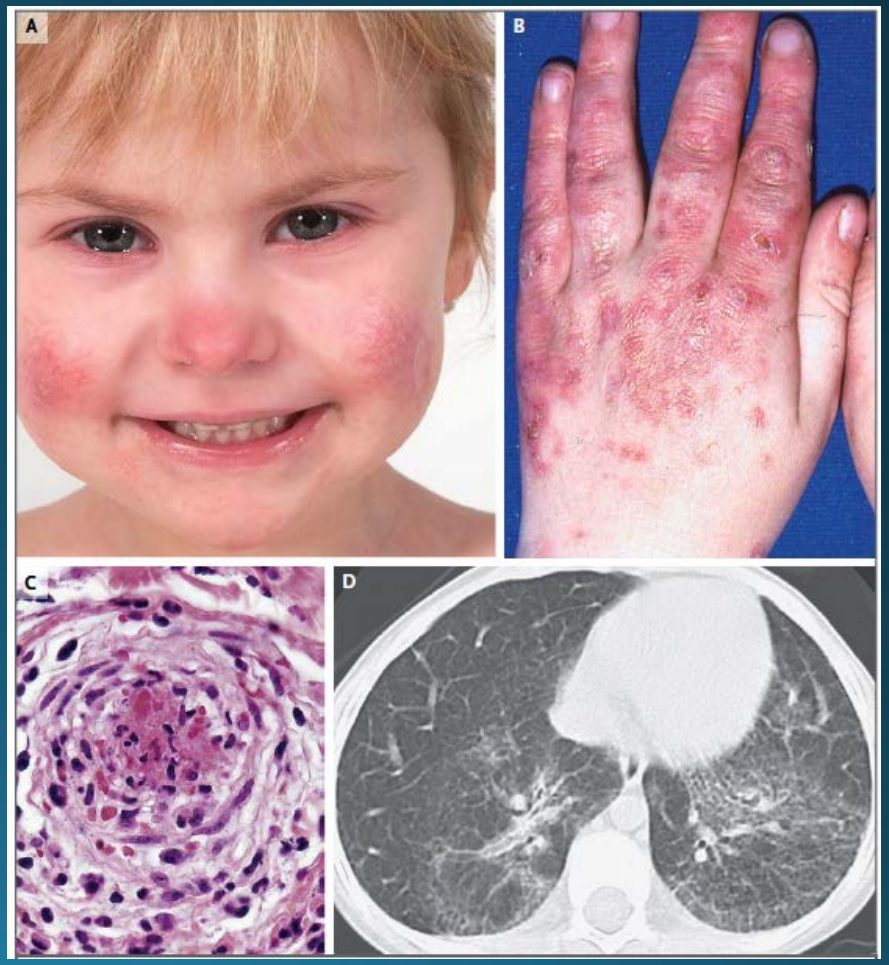
Milner et al. Blood 2015

STING-associated vasculopathy with onset in infancy (SAVI)

- Caused by gain-of-function mutations in TMEM173
- TMEM173 encodes STING = stimulator of interferon genes
- Chronic activation of STING-interferon pathway

- Clinical manifestations:
  - Systemic inflammation (fever, elevated ESR)
  - Peripheral vascular inflammation ‘chill blains’
  - Interstitial lung disease (90% of patients)

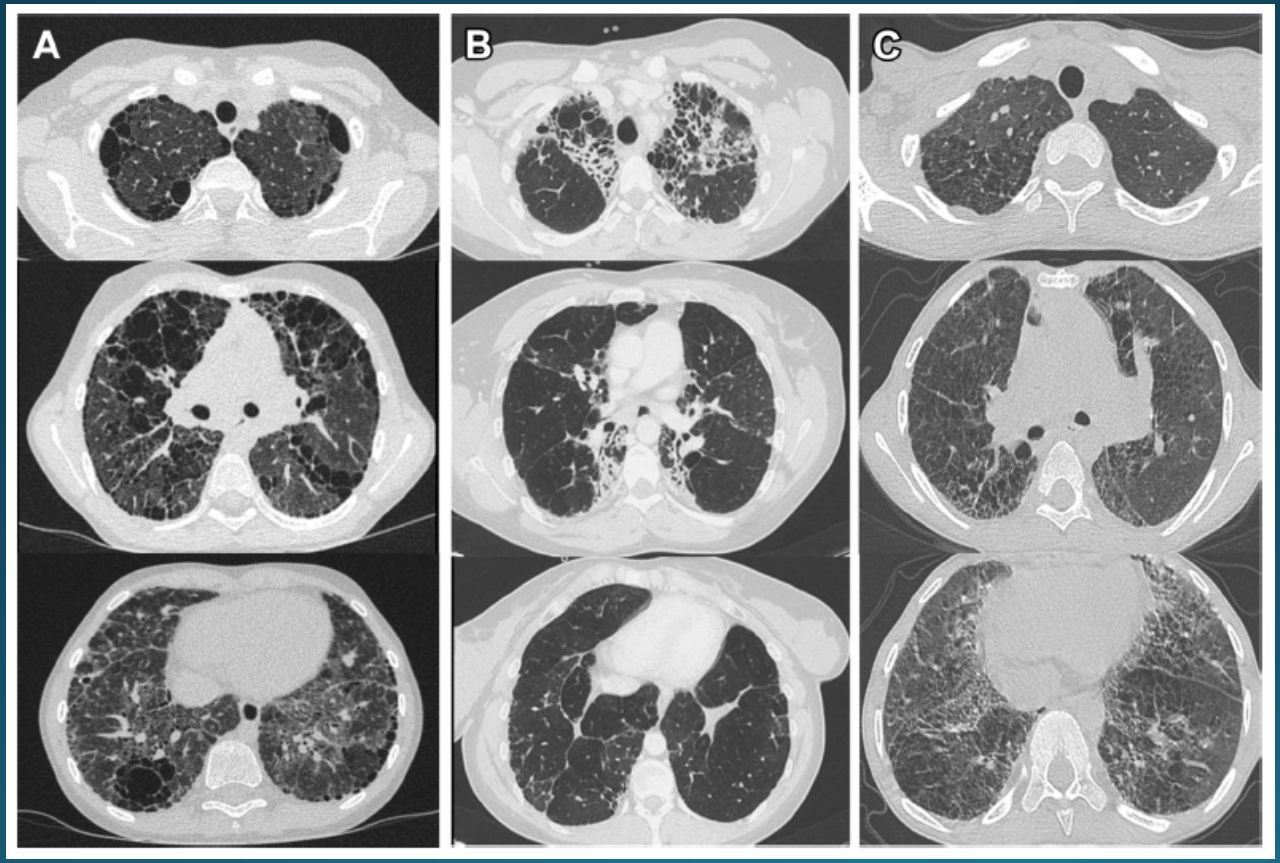
- Diagnosis allows targeted therapy e.g. JAK inhibitors



Liu et al. NEJM 2014

‘Severe pulmonary fibrosis as the first manifestation of interferonopathy (TMEM173)’ – Picard et al. Chest 2016

TMEM173 mutations found by WES in 2 children (12 yo and 5 mo) and 1 adult who presented with ILD



?

2,5 yo girl with severe, poly-articular arthritis, ILD with pathological diagnosis of follicular bronchiolitis, systemic inflammation and elevated ANA

Mother has a very similar phenotype thus apparent autosomal dominant inheritance

How would you proceed?

COPA mutations impair ER-Golgi transport and cause hereditary autoimmune-mediated lung disease and arthritis

Levi B Watkin[1,2,16], Birthe Jessen[3,16], Wojciech Wiszniewski[4,16], Timothy J Vece[1], Max Jan[3], Youbao Sha[5],

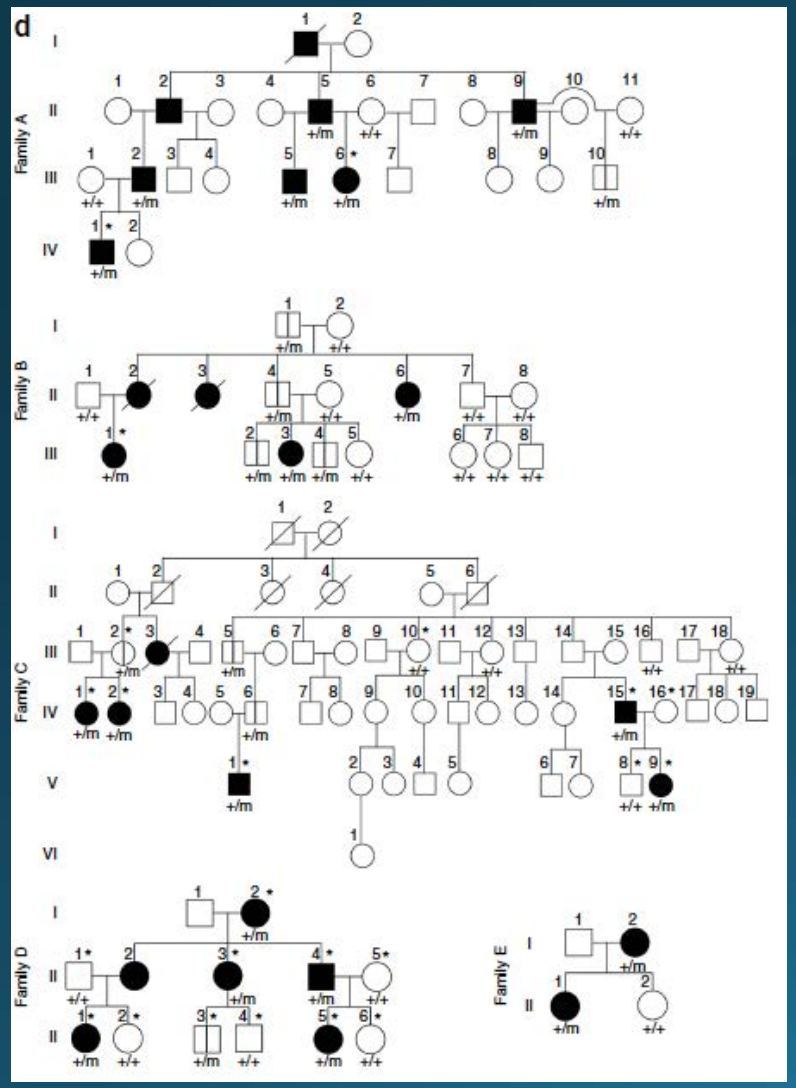
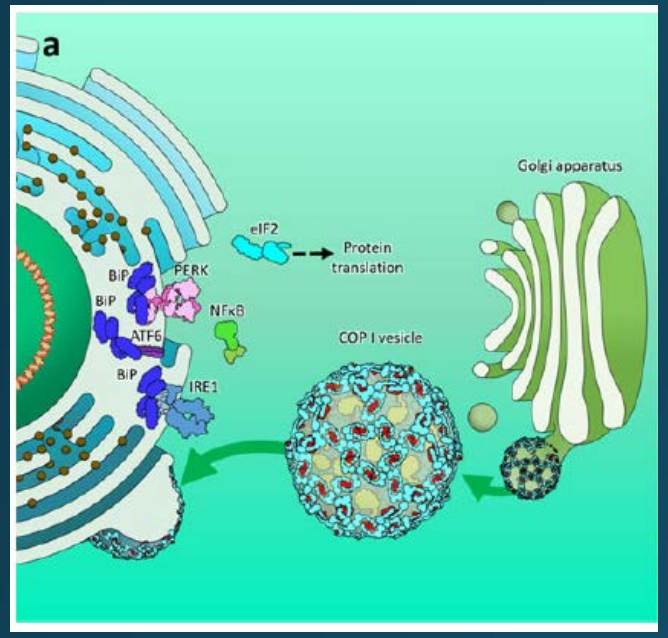


Table 1 Demographic and clinical characteristics of affected individuals with *COPA* mutations

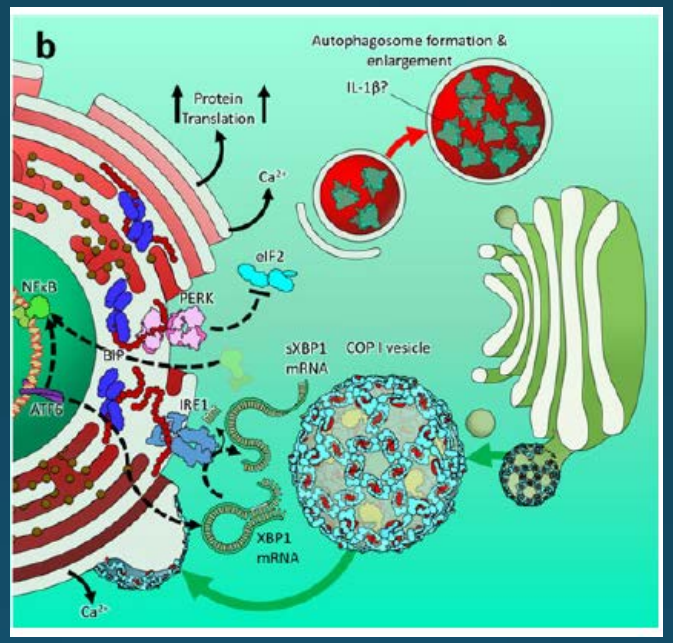
Demographic and clinical characteristics	Patients *n* (%)
Total	21
Age at presentation <5 years	16 (76)
Sex	
Male	8 (38)
Female	13 (62)
Symptom at initial presentation	
Tachypnea, cough, hemoptysis	14 (67)
Joint pain	5 (24)
Arthritis	20 (95)
Pulmonary manifestations	
Hemorrhage or interstitial lung disease	21 (100)
Autoantibodies	18 (86)
ANAs	14 (67)
ANCAs	15 (71)
RF	9 (43)
Response to immunosuppression	21 (100)

Nature Genetics 2015

Potential pathobiological mechanism



Healthy



COPA mutation:

decreased binding capacity of COPa for protein cargo
-> deficit in proteins that are usually recycled leads to increased ER stress
-> activation of proinflammatory transcriptional programs
-> autophagosome formation and enlargement
-> antibody production and increased Th17 cells

Vece et al. J Clin Immunol 2016

Treatment of COPA Syndrome

- Exacerbations:
  - Cyclophosphamide or Rituximab
  - Often also steroids
- Maintenance:
  - Methotrexate or Azathioprine
  - Etanercept
  - Hydroxychloroquine
  - IVIG at immunomodulatory dose
- Lung transplantation
- Unsure whether HSCT would improve outcome
- Mechanistic approach:
  - mTOR inhibitor (sirolimus) given that ER stress leads to increased mTOR activity
  - Hydroxychloroquine prevents autophagy

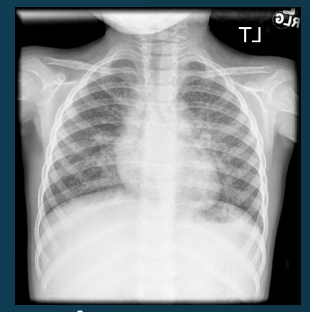
Immune-mediated pulmonary hemorrhage syndromes

Table 1 Clinical Features of COPA Syndrome and Other Immune-mediated Pulmonary Hemorrhage Related Syndromes

	Associated Gene	Inheritance pattern	Pulmonary Hemorrhage	Renal Disease	Arthritis	GGO on chest CT	Cysts on chest CT	Other ILD	Skin Disease
Copa Syndrome	*COPA*	AD	+++	++++	+++	+++	+++	++	+
ANCA-associated vasculitis	NA	NA	++++	+++	+	++++	–	–	+
SLE	NA	NA	+	++++	++++	+++	–	++++	+++
SAVI-syndrome	*TMEM173*	AD	–	+	–	+++	–	+++	++++

Copa cotamer associated protein a, *ANCA* anti-neutrophil cytoplasmic antibody, *SLE* systemic lupus erythematosis, *SAVI* Stimulator of interferon genes–associated vasculopathy with onset in infancy, *AD* autosomal dominant, *NA* not applicable, *ILD* interstitial lung disease, *GGO* ground glass opacities

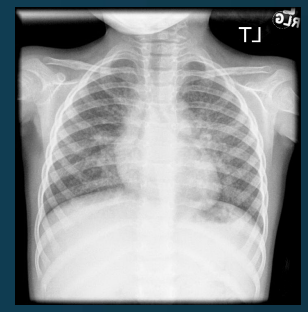
Vece et al. J Clin Immunol 2016

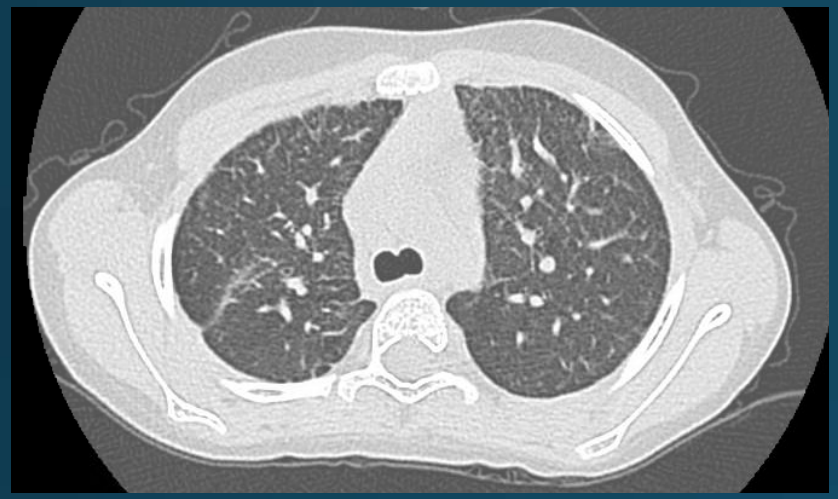


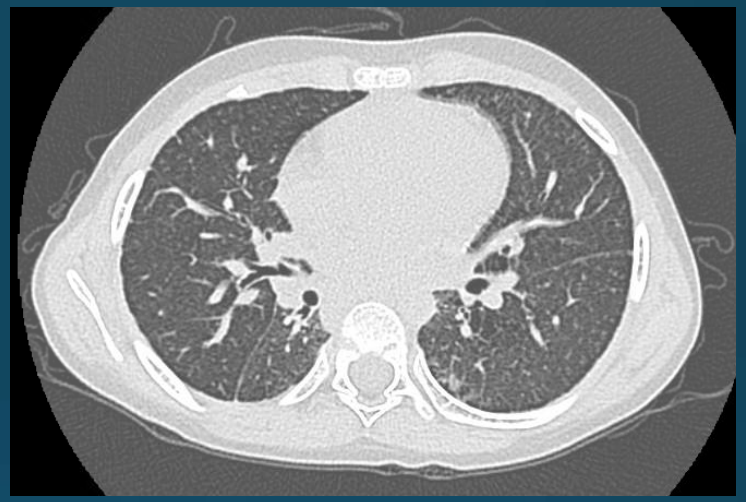
CASE: Treatment

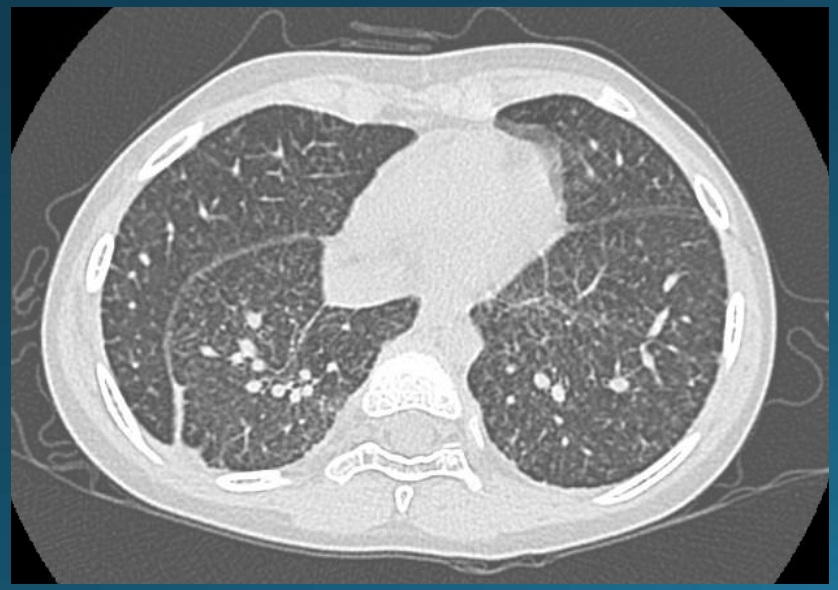
- Received two doses of Rituximab April 2011 given two weeks apart: improved for one month then relapse of arthritis and tenosynovitis (21 joints involved)
- June 2011: started on prednisone 2 mg/kg/d + hydroxychloroquine (Plaquenil®) + azathioprine (Imuran®)
- Starting August 2011 prednisone weaned to 1 mg/kg and Imuran increased to 2.5 mg/kg/d
- Sept 2011: resting resp rate 40 -> 32/', sat 98%. Improvement of chest X-ray.
- Dec 2012: Azathioprine switched to mycophenolate mofetil (Cellcept®)
- August 2012: CT chest shows decrease of the number of centrilobular nodules, significant improvement of ground-glass opacities
- August 2013 started on monthly Rituximab infusion for steroid-sparing (+ IVIG), MMF discontinued
- February 2014 stop Rituximab for GI intolerance, MMF restarted
- Very slow continuous weaning of prednisone to stop February 2017

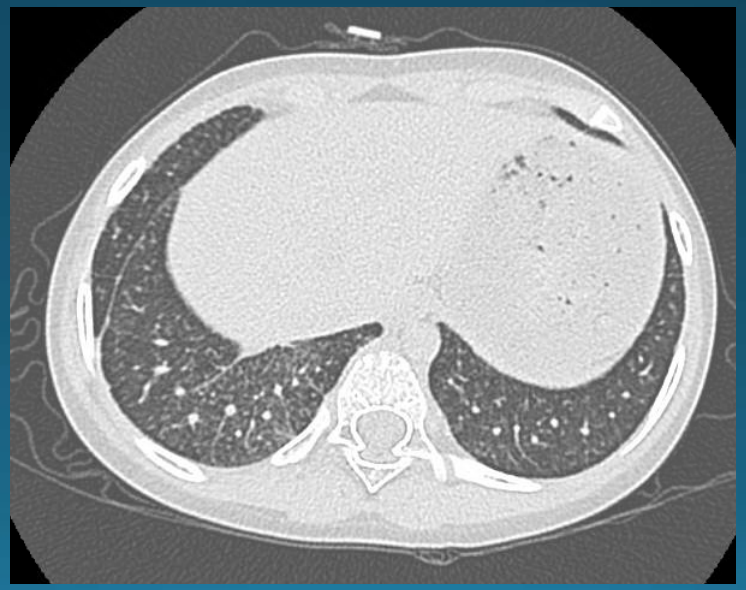
CASE: CT Chest Dec 2016





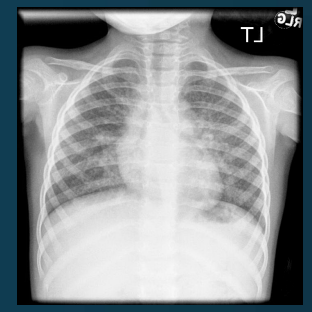






Diffuse centrilobular nodularity
Septal thickening and lung volume loss

CASE: Recent evolution



- Heterozygous COPA mutation identified in both mother and patient
- Current treatment hydroxychloroquine + MMF + substitution IVIG
- Only symptom is some cough with activity, stable, no shortness of breath
- Normal 6-minute walking test (480 m, sat pre 100%, post 100%)
- Sleep study February 2016: overnight tachypnea (38/') but no hypoxia or hypoventilation
- LFT 11/2017: FVC 46% - FEV1 44%, Severe restrictive pattern, unchanged from previous

Take home messages

- DLD contains a heterogeneous group of underlying disorders
- >50% of DLD >2 years of age is caused by immune-mediated disorder or immunodeficiency (primary or secondary)
- Respiratory symptoms may sometimes be the predominant or only feature of systemic inflammatory disease or immunodeficiency at initial presentation
- Always consider pulmonary disease secondary to other organ involvement or secondary to treatment in systemic diseases
- Diagnosis of the underlying systemic disease or immunodeficiency is important to direct treatment
- Growing role of genetic testing in the evaluation of DLD

References

- Kendig and Chernick's. Disorders of the respiratory tract in children. 8th edition. Elsevier Saunders Philadelphia 2012.
- Picard C, Al-Herz W, Bousfiha A, Casanova JL, Chatila T, Conley ME, Cunningham-Rundles C et al. Primary Immunodeficiency Diseases: an Update on the Classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency 2015. J Clin Immunol. 2015 Nov;35(8):696-726.
- Bousfiha A, Jeddane L, Al-Herz W, Ailal F, Casanova JL, Chatila T, Conley ME et al. The 2015 IUIS Phenotypic Classification for Primary Immunodeficiencies. J Clin Immunol. 2015 Nov;35(8):727-38.
- Bogaert DJ, Dullaers M, Lambrecht BN, Vermaelen KY, De Baere E, Haerynck F. Genes associated with common variable immunodeficiency: one diagnosis to rule them al? J Med Genet. 2016 Sep;53(9):575-90.
- Hurst JR, Verma N, Lowe D, Baxendale HE, Jolles S, Kelleher P, Longhurst HJ et al. British Lung Foundation/United Kingdom Primary Immunodeficiency Network Consensus Statement on the Definition, Diagnosis, and Management of Granulomatous-Lymphocytic Interstitial Lung Disease in Common Variable Immunodeficiency Disorders. J Allergy Clin Immunol Pract. 2017 Jul - Aug;5(4):938-945.
- Picard C, Thouvenin G, Kannengiesser C, Dubus JC, Jeremiah N, Rieux-Laucat F, Crestani B et al. Severe Pulmonary Fibrosis as the First Manifestation of Interferonopathy (TMEM173 Mutation). Chest. 2016 Sep;150(3):e65-71.
- Liu Y, Jesus AA, Marrero B, Yang D, Ramsey SE, Sanchez GAM, Tenbrock K et al. Activated STING in a vascular and pulmonary syndrome. N Engl J Med. 2014 Aug 7;371(6):507-518.
- Schubert D, Bode C, Kenefeck R, Hou TZ, Wing JB, Kennedy A et al. Autosomal dominant immune dysregulation syndrome in humans with CTLA4 mutations. Nat Med. 2014 Dec;20(12):1410-1416.
- Lo B, Zhang K, Lu W, Zheng L, Zhang Q, Kanellopoulou C, Zhang Y et al. Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy. Science. 2015 Jul 24;349(6246):436-40.
- Vece TJ, Young LR. Update on Diffuse Lung Disease in Children. Chest. 2016 Mar;149(3):836-45.
- Kurland G, Deterding RR, Hagood JS, Young LR, Brody AS, Castile RG, Dell S et al. American Thoracic Society Committee on Childhood Interstitial Lung Disease (chILD) and the chILD Research Network. An official American Thoracic Society clinical practice guideline: classification, evaluation, and management of childhood interstitial lung disease in infancy. Am J Respir Crit Care Med. 2013 Aug 1;188(3):376-94.
- Fan LL, Dishop MK, Galambos C, Askin FB, White FV, Langston C, Liptzin DR et al. Diffuse Lung Disease in Biopsied Children 2 to 18 Years of Age. Application of the chILD Classification Scheme. Ann Am Thorac Soc. 2015 Oct;12(10):1498-505.
- Lopez-Herrera G, Tampella G, Pan-Hammarström Q, Herholz P, Trujillo-Vargas CM, Phadwal K, Simon AK et al. Deleterious mutations in LRBA are associated with a syndrome of immune deficiency and autoimmunity. Am J Hum Genet. 2012 Jun 8;90(6):986-1001.
- Schubert D, Bode C, Kenefeck R, Hou TZ, Wing JB, Kennedy A, Bulashevska A et al. Autosomal dominant immune dysregulation syndrome in humans with CTLA4 mutations. Nat Med. 2014 Dec;20(12):1410-1416.
- Milner JD, Vogel TP, Forbes L, Ma CA, Stray-Pedersen A, Niemela JE, Lyons JJ et al. Early-onset lymphoproliferation and autoimmunity caused by germline STAT3 gain-of-function mutations. Blood. 2015 Jan 22;125(4):591-9.
- Richardson AE, Warrier K, Vyas H.Respiratory complications of the rheumatological diseases in childhood. Arch Dis Child. 2016 Aug;101(8):752-8.