Unusual Causes of Cough in Children

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Disclsure Statement

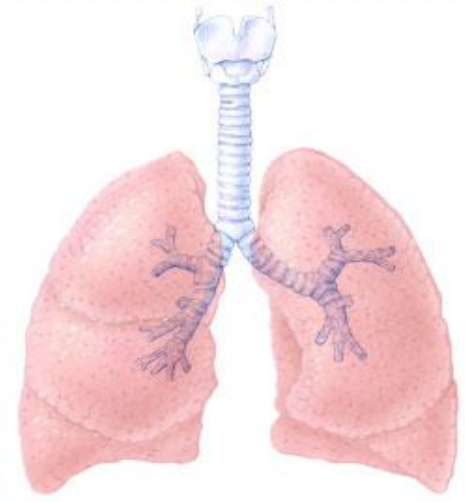
No relevant financial interest or other relationship with a commercial interest.

No discussion of unlabeled or investigational uses of medications.

Objectives

- Explain the pathophysiology of cough
- Develop a differential diagnosis for chronic cough
- Interpret diagnostic studies and apply to a patient's presentation
- Discuss medical therapies and goals of treatment
- Monitor outcomes of interventions

Cough - Physiology



- 3 Phases :
  - Inspiratory
  - Compressive
  - Expiratory
- Purpose is to clear the airways
  - Inhaled material
  - Mucus
  - Abnormal substances (pus, fluid)
- Effectiveness depends on respiratory muscles

Cough - Physiology

Inspiratory Phase

- Charactarized by inhalation of gas to near total lung capacity
- The greater the volume the greater the positive intrathoracic pressure
- Not a critical component
- Cough can be generated with small volumes

Cough - Physiology

Compressive Phase

- Glottis is closed and expiratory effort begins
- Glottic closure maintains lung volume while intrathoracic pressure increases
- High pressures transmitted to the CNS, mediastinum, and the CV, GI, GU, and MS systems

Cough - Physiology

Expiratory Phase

- Glottis opens releasing intrathoracic pressure
- Brief blast of turbulent air flow – 12 L/second
- Flow rate decreases, pulmonary pressures decrease, and lung volume falls
- Velocity dependent on degree of compression
- Velocity = Flow / Cross sectional Area

Cough – Function and Purpose

- Clear the airways
- Innate defense mechanism of protection for the lungs
  - Absence of cough can be harmful or fatal
- A warning sign of disease
- A detrimental symptom if persistent

Cough – Differential Diagnosis

- Common Cold
- Bronchiolitis
- Bronchitis
- Asthma
- COPD
- Allergic Rhinitis
- Sinusitis
- Pneumonia
- Inhalation Pneumonitis
- Aspiration
- Cystic Fibrosis
- Congestive Heart Failure
- Foreign Body
- GERD
- Croup
- Other infections

CASE ONE – Is it asthma?

CASE ONE

- 9 yr old boy referred to pulmonary clinic for evaluation of chronic cough
- Diagnosed with asthma by PCP and trialed on fluticasone/salmeterol and prn albuterol
- Neither medication helped so family stopped both
- Cough worse at night
- CXR normal
- PPD negative

CASE ONE

9 yr old boy with chronic cough

- Family history
- Birth history
  - Full term
  - Normal spontaneous vaginal delivery
  - No complications – routine care
- Social history
  - Lives with mom
  - No pets
  - Very active; on soccer team
  - 3rd grade

CASE ONE

9 yr old boy with chronic cough

Review of Systems

- General : Afebrile, no fatigue
- HEENT : No rhinitis, no recurrent ear infections
- Respiratory : Cough, no exercise intolerance, no wheezing
- Cardiac : No murmurs, palpitations or chest pain
- GI : Post tussive emesis, difficulty swallowing
- Skin: No eczema or other rashes
- Neuro : A/B student, no seizures

CASE ONE

9 yr old boy with chronic cough

- Vitals

Weight 23 kg, Height 132 cm, BMI <5%, Pulse ox 99%

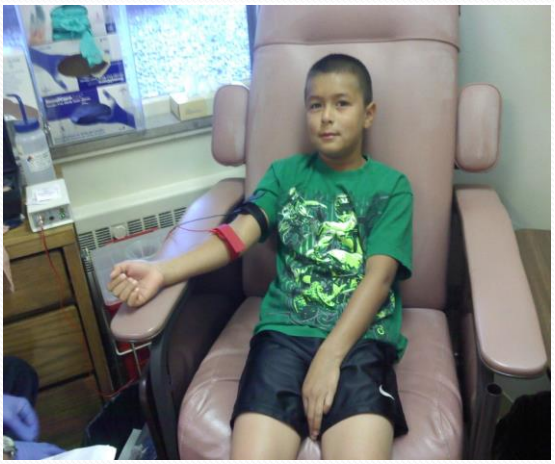
- Physical Exam
- Pulmonary Function Test

	Pre	Post
FVC	60	71
FEV1	59	59
Ratio	87	75
FEF25/75	50	43

CASE ONE

9 yr old boy with chronic cough

- Ordered sweat test
- Started lansoprazole
- Monitor bronchodilator use



CASE ONE

9 yr old boy with chronic cough

Follow up 7 months later

- Stopped lansoprazole
- Cough ongoing and worse at night
- No use of bronchodilator or steroids
- Sweat test results : 29 and 28

CASE ONE

9 yr old boy with chronic cough

- Weight 25 kg (23 kg previous visit); BMI 13
- Normal physical exam
- Pulmonary function test

	Pre	Post
FVC	101	89
FEV1	65	61
Ratio	59	62
FEF25/75	43	41

	Pre	Post
FVC	60	71
FEV1	59	59
Ratio	87	75
FEF25/75	50	43

Started beclomethasone MDI and fluticasone nasal spray; GI referral

CASE ONE

9 yr old boy with chronic cough

- 2 weeks later saw GI
- Poor weight gain
- Food getting stuck
- Scheduled for endoscopy the following month

CASE ONE

9 yr old boy with chronic cough

- Followed up 2 weeks later
- Taking beclomethasone
- Still coughing at night
- Weight 24.5 kg (25 kg previously)
- Bilateral expiratory wheezes
- Clubbing

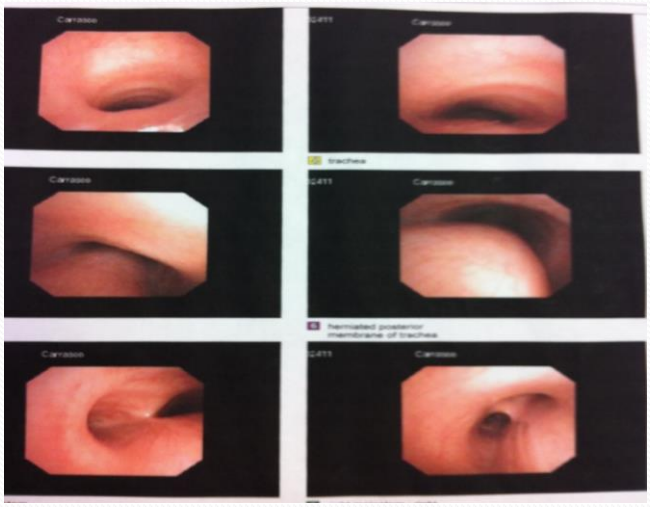
	Pre	Post
FVC	90	91
FEV1	43	47
Ratio	44	48
FEF25/75	21	27

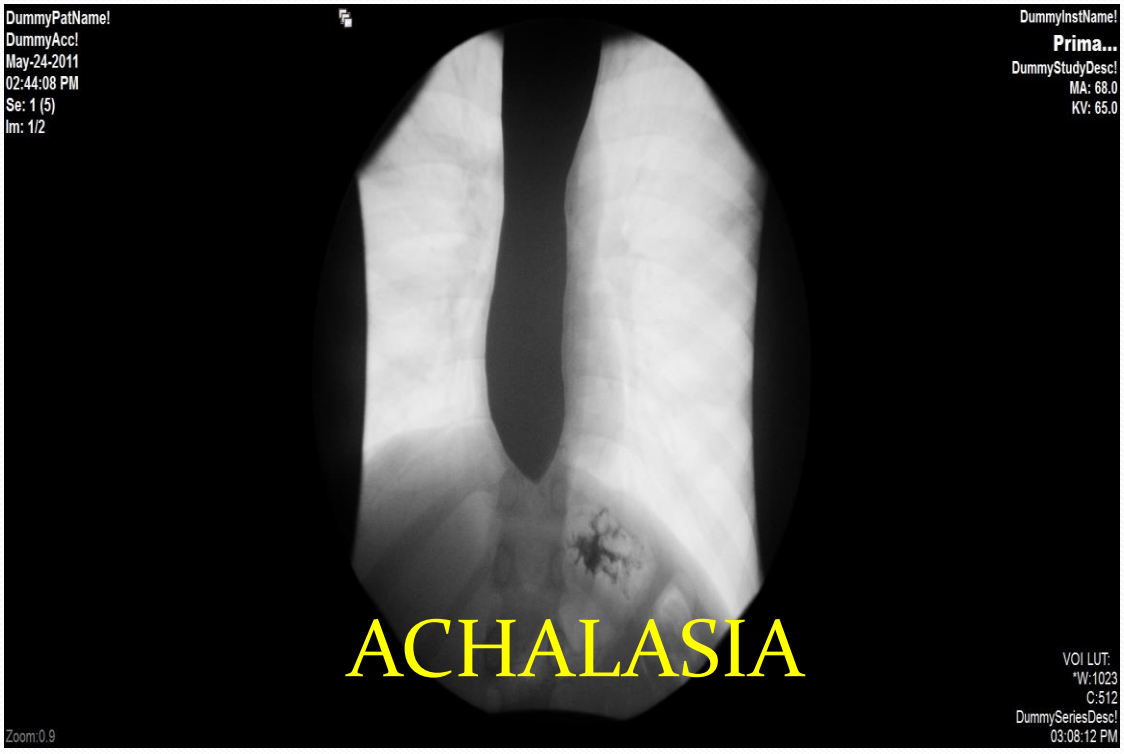
	Pre	Post
FVC	101	89
FEV1	65	61
Ratio	59	62
FEF25/75	43	41

CASE ONE

9 yr old boy with chronic cough

- Bronchoscopy and Endoscopy 2 weeks later

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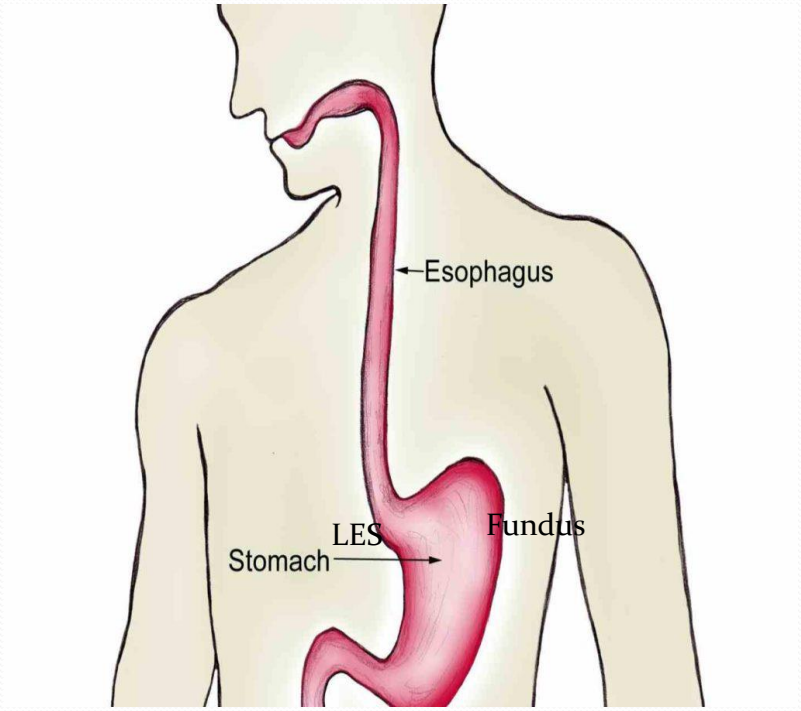

Esophagus
LES
Fundus
Stomach

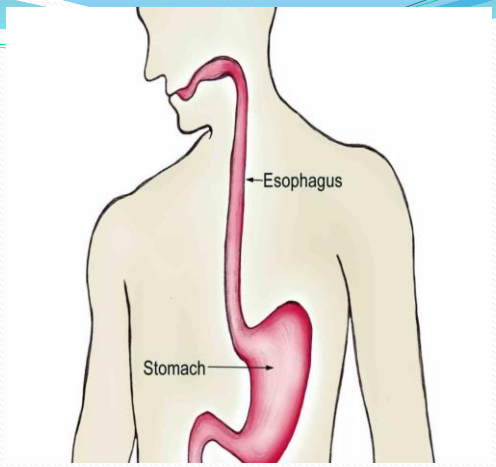
CASE ONE

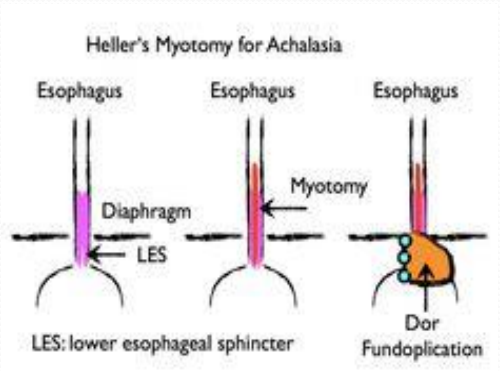
9 yr old boy with chronic cough

- Follow up 3 weeks later
- Using beclomethasone MDI
- Still coughing
- Weight 23.8 kg (24.5 kg previously)
- Pops and crackles on exam
- Digital clubbing
- Pulmonary Function Tests unchanged

CASE ONE

- Surgery 6 weeks later
- Heller myotomy
- Dor Fundoplication
- Follow up 6 weeks later
- Weight up to 28.1 kg





CASE ONE

9 yr old boy with chronic cough

- No medications
- Cough completely resolved
- Weight 29.5 kg
- Clubbing resolved
- Pulmonary Function Test

FVC	107
FEV1	103
Ratio	88
FEF25/75	97

	Pre	Post
FVC	90	91
FEV1	43	47
Ratio	44	48
FEF25/75	21	27

CASE ONE

9 yr old boy with chronic cough

- Now 19 years old
- No follow up visits
- Had ortho appointment in 2018 – weight 56.7 kg

CASE TWO – Is it just a virus?

CASE TWO

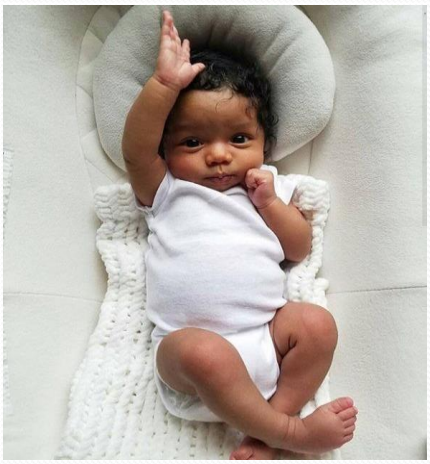
5 day old infant admitted to general pediatrics service for fever of 103 in May

- Mild cough
- No difficulty breathing, congestion, vomiting, or fussiness
- PMH : 39 wk GA, NSVD, no complications, breastfed
- Social : Lives with both parents and 2 siblings
- Physical Exam : No abnormal findings

CASE TWO

5 day old infant with cough

- Seen by PCP on day of admission and was febrile
- Admitted to general pediatrics service for fever to 103
- CBC : 6.79K WBCs with 21% bands
- CRP : 5.9
- Urinalysis and CMP normal
- No chest xray
- Cultures negative



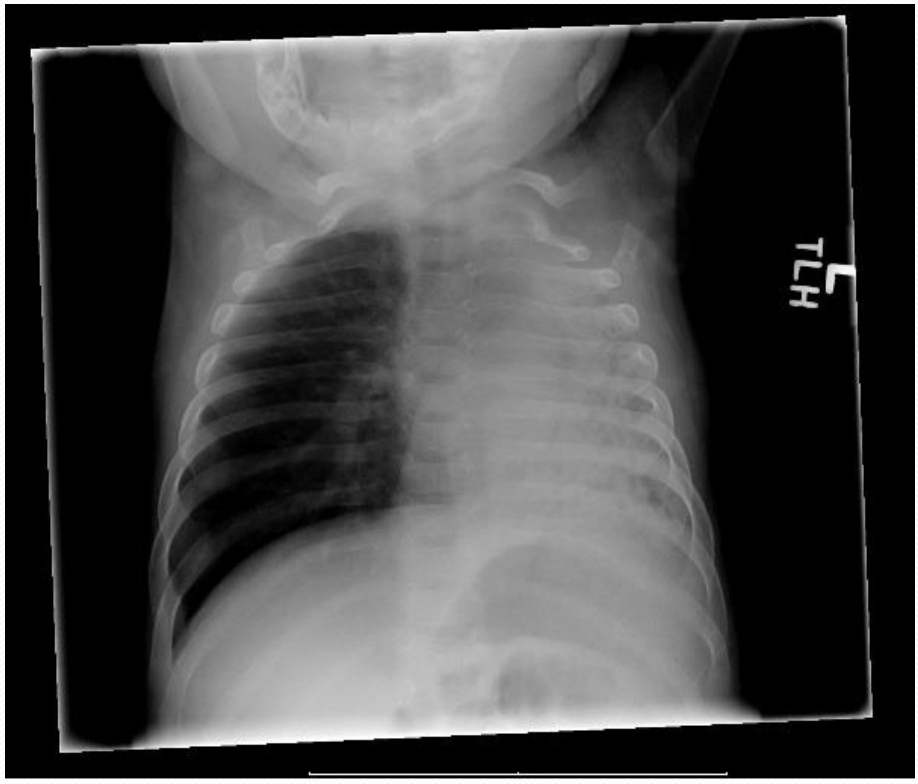
CASE TWO

- Continued to have daily cough
- Coughed more after eating
- Cough got worse and developed post-tussive emesis
- Tried sibling's albuterol without relief
- Seen by PCP at age 4 months old (September)
- Had coughing fit with a big mucus plug
- Sent to ER at Children's

CASE TWO

- WBC 22.30 (H)
- RBCS 4.25
- HGB 9.6
- HCT 29.9
- PLATELETs 526 (H)
-
- SEGS 59.9 (H)
- LYMPHOCYTE 34.1 (L)
- MONOCYTE 4.6
- EOSINOPHILS 0.5
- BASOPHIL 0.9

- CRP 17.1
- RSV negative
- CMP normal


L
TLH

CASE TWO

- **Final result**
- **Study Result**

- **INDICATION**: Persistent cough.
- **TECHNIQUE:** Frontal and lateral views of the chest are provided.
- **COMPARISON**: No prior studies are available for comparison.
- **FINDINGS**: There is focal consolidation of the left lobe, with associated volume loss. There appears to be mediastinal shift towards the left. Air bronchograms are present within the consolidated lung. The right lung appears hyperinflated. The trachea is midline, which is somewhat atypical in the setting of such significant atelectasis. The stomach appears to be below the left hemidiaphragm indicating no diaphragmatic defect is present. No focal consolidation involving the right lung is seen. Osseous structures are grossly unremarkable.
- **IMPRESSION**:
- Abnormal chest radiograph. There is focal consolidation of the entire left lung, with air bronchograms. There is an element of volume loss, as the heart is shifted towards the left. However, the trachea appears midline and there appears to be some possible compression of the left mainstem bronchus. This can be seen in the setting of tuberculosis, although the right lung appears normal. Cardiac anomalies such as an anomalous ascending aorta could produce a similar appearance. Echocardiogram or CT may be helpful for further evaluation.

CASE TWO

- **Final result**
- **Study Result**

- **INDICATION**: 3-month-old male with pneumonia. According to the electronic medical record, the patient has cough and congestion since 1 week of age.
-
- **TECHNIQUE**: Spiral scans were obtained thorough the chest following the administration of intravenous contrast material. The study was performed at 0003 hours.
-
- **FINDINGS**: There is diffuse opacification of the left lung with prominent air bronchograms present throughout. The left lung appears small in size, and there is ipsilateral shift of the heart and mediastinal structures. The left main stem bronchus is located inferiorly and appears to arise from the distal esophagus. Only a short, small, blind-ending bronchus is seen extending to the left side from the region of the carina. The right lung is clear. There are areas of adenopathy in the paratracheal, subcarinal and left hilar regions. The left pulmonary artery is very small in caliber. A few scans through the upper abdomen demonstrate abnormal orientation of the kidneys, suggesting horse shoe kidney formation.
-
- **IMPRESSION**:
-
- 1. Opacification of small left lung. The left main stem bronchus appears to arise from the distal esophagus and the left pulmonary artery is markedly small in caliber. Overall findings most likely represent a foregut malformation.
-
- 2. Paratracheal, subcarinal and left hilar adenopathy. This is likely reactive in nature, however, adenopathy related to TB or possibly malignancy cannot be completely excluded.

CASE TWO

Procedure Type
TTE Complete (Congenital) 2D Color Doppler and Spectral Doppler.

Position
Levocardia. Abdominal situs solitus. Atrial situs solitus. D Ventricular Loop. S Normal position great vessels.

Veins
Normal systemic venous drainage. **3 pulmonary veins seen entering LA. Left upper pulmonary vein not seen entering LA. Left lower pulmonary vein is hypoplastic.**

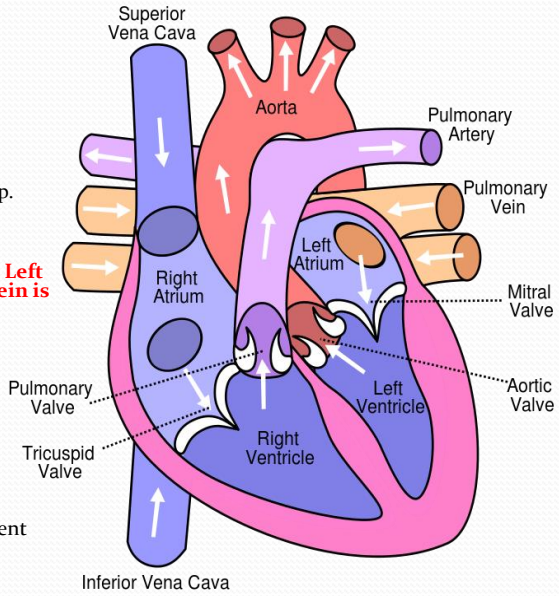
Atrium
Normal right atrial size. Normal left atrial size. Intact atrial septum.

AV Valves
Normal tricuspid valve. Normal mitral valve.

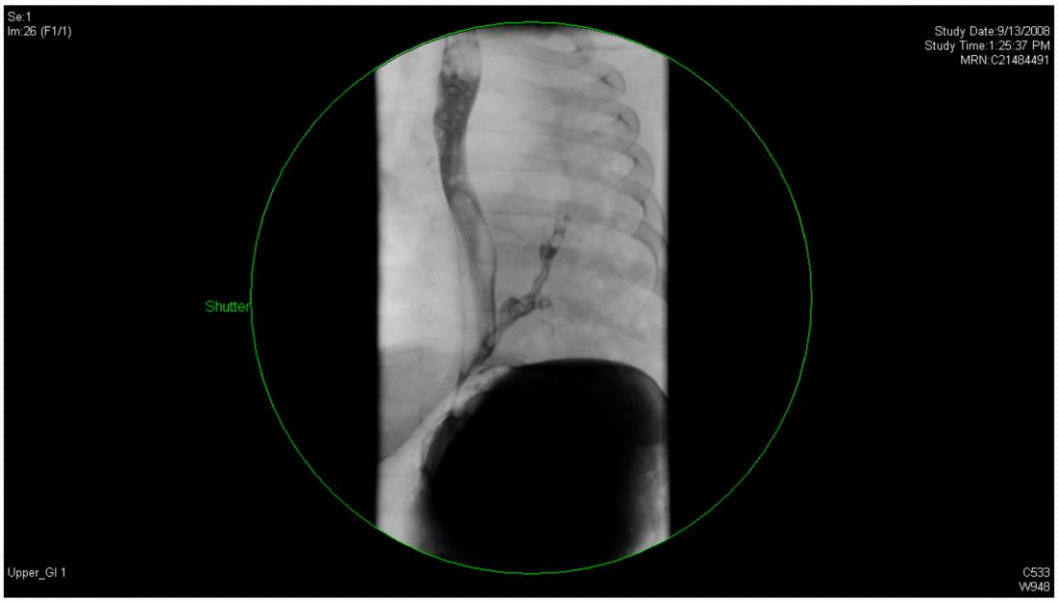
Ventricles
Normal right ventricle structure and size. Normal right ventricular systolic function. Normal left ventricle structure and size. Normal left ventricular systolic function. Intact ventricular septum. Normal septal motion consistent with normal right ventricular pr.

Semilunar
Normal pulmonic valve. Normal tricuspid aortic valve.

Vessels
No evidence of coarctation of the aorta. Normal left aortic arch. No patent ductus arteriosus. **The left pulmonary artery appears to be severely hypoplastic with reversal flow.** Normal right pulmonary artery. LPA = 3.2mm. RPA = 8.6mm.



CASE TWO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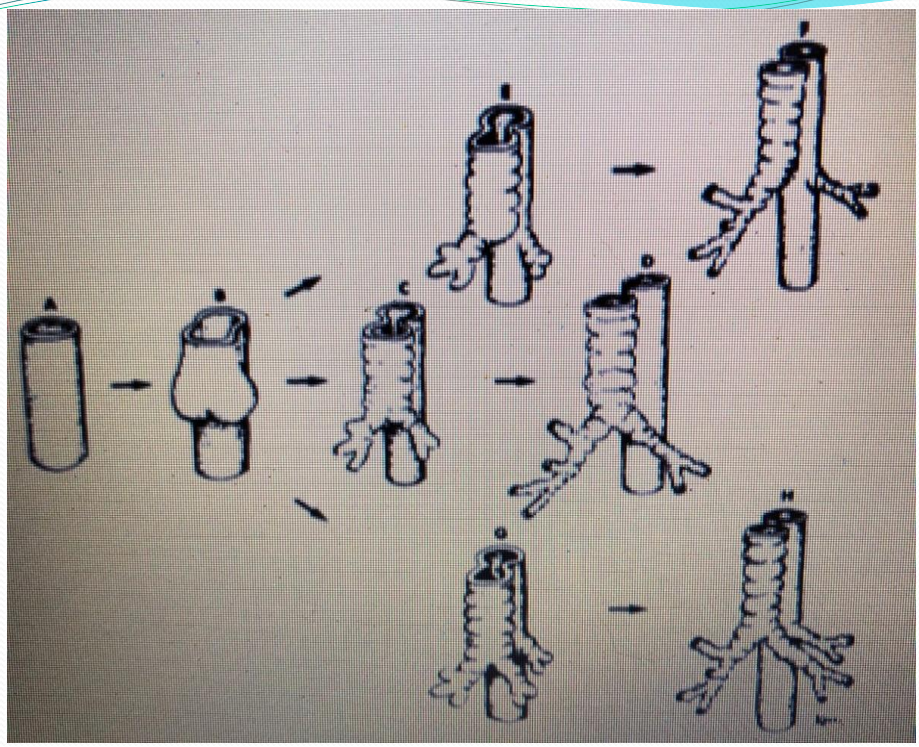
CASE TWO

Communicating bronchopulmonary foregut malformation

- Rare congenital anomaly
- Originate as developmental abnormalities of foregut budding of the bronchial tree or GI tract



CASE TWO

- Went to the OR later that month
- Thoracoscopic pneumectomy with transection of bronchoesophageal fistula

- Discharged home two week later
- Room air
- PO feeding

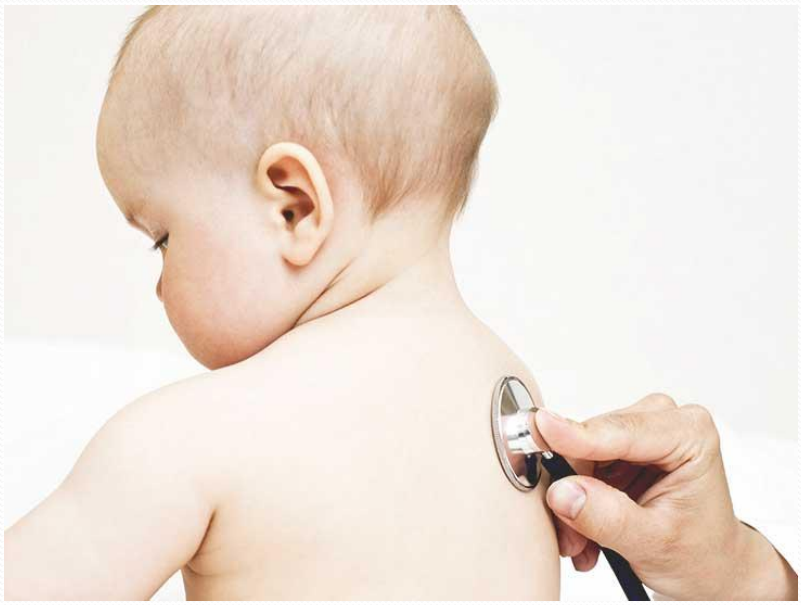
- At age 2 years had placement of tissue expander in left chest

CASE TWO

- Now 13 years old
- Active and playful
- Has asthma and takes beclomethasone MDI

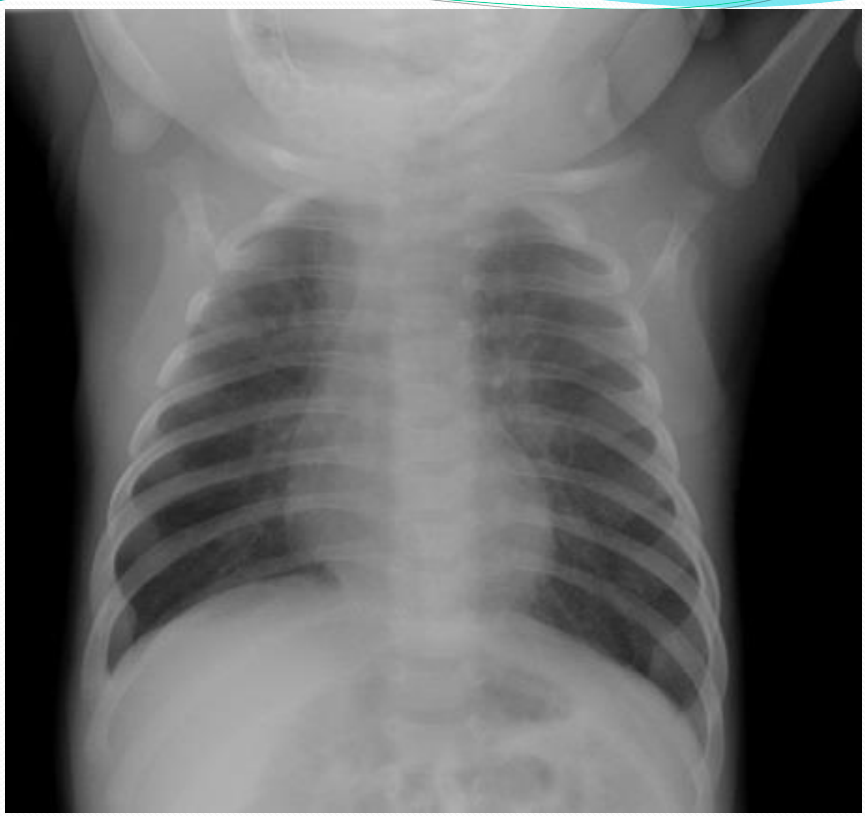
FVC Actual	1.74
FVC %	74%
FEV1	0.84
FEV1-%	41%
FEV1/FVC	49%
FEF25-75	20%

CASE THREE – Is it cystic fibrosis?



Case Three

- 2 month old infant presented to the ER on 6/23 with h/o nasal flaring since birth
- At age 2 weeks a CXR was normal
- Started on antibotics, budesonide, and PRN albuterol
- Pulse Ox 95%, RR 38
- Nasal flaring, SS/SC retractions, wheezing
- Echo, EKG, CBC and BMP normal
- CXR with hyperinflation
- Improved with suction and albuterol treatment



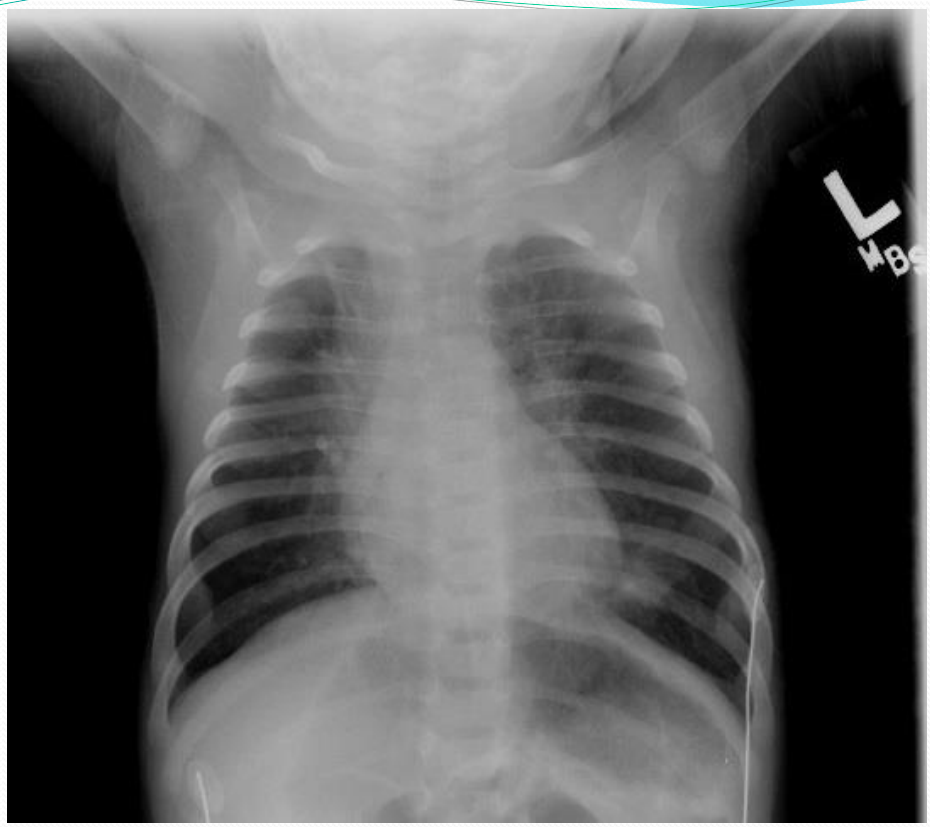
Case Three

- 2 month old infant returned to the ER 4 days later
- Worsening cough and wheezing
- Pulse ox 97%, RR 60, Temp 102.9
- Improved after suction, levalbuterol, and ipratropium bromide
- Discharged home

Case Three

2 month old returned to the ER 3 days later

- Had seen by PCP the previous day and started amoxicillin
- Pulse ox 100%, RR 40, Afebrile
- Wheezing with retractions
- Treated with 2 albuterol treatments, ipratropium bromide, and racemic epinephrine
- CXR with bilateral pneumonia
- Admitted to the general pediatrics service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Case Three

- 2 month old with chronic cough
- No hospital record

- Viral Panel : + parainfluenzae 3; pertussis negative

- Sweat chloride test : 5 in left arm, QNS in right arm

Case Three

- 2 month old infant with chronic cough
- Presented to pulmonary clinic for evaluation 2 weeks after hospitalization
- Family history : Uncle with asthma, sister with situs inversus, no asthma
- Social history : Lives with both parents, older sister. No pets, daycare, or smokers
- PMH : Born full term, no complications. Immunizations up to date

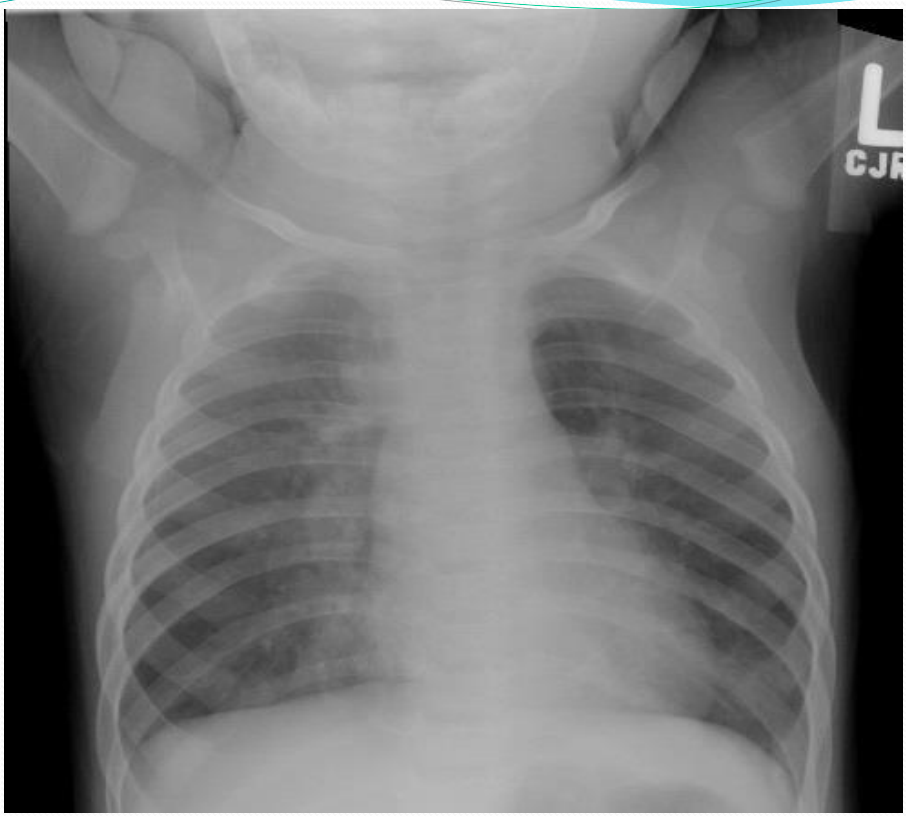
Case Three

- ROS : No otitis media, no choking or spitting up with feeds, no chronic rhinits, no foreign body, no hypotonia
- Normal vitals and physical exam
- Felt to be likely reactive airway disease
- Changed from budesonide to fluticasone MDI

Case three

- Pulmonary visit 9/14/06 – on amoxicillin for bronchitis; coughing and wheezing on exam; no changes

- ER visit 1/21/07 – Fever, cough, vomiting. Diagnosed with pneumonia and sent home with amoxicillin. Returned later the same day but able to go home



Case Three

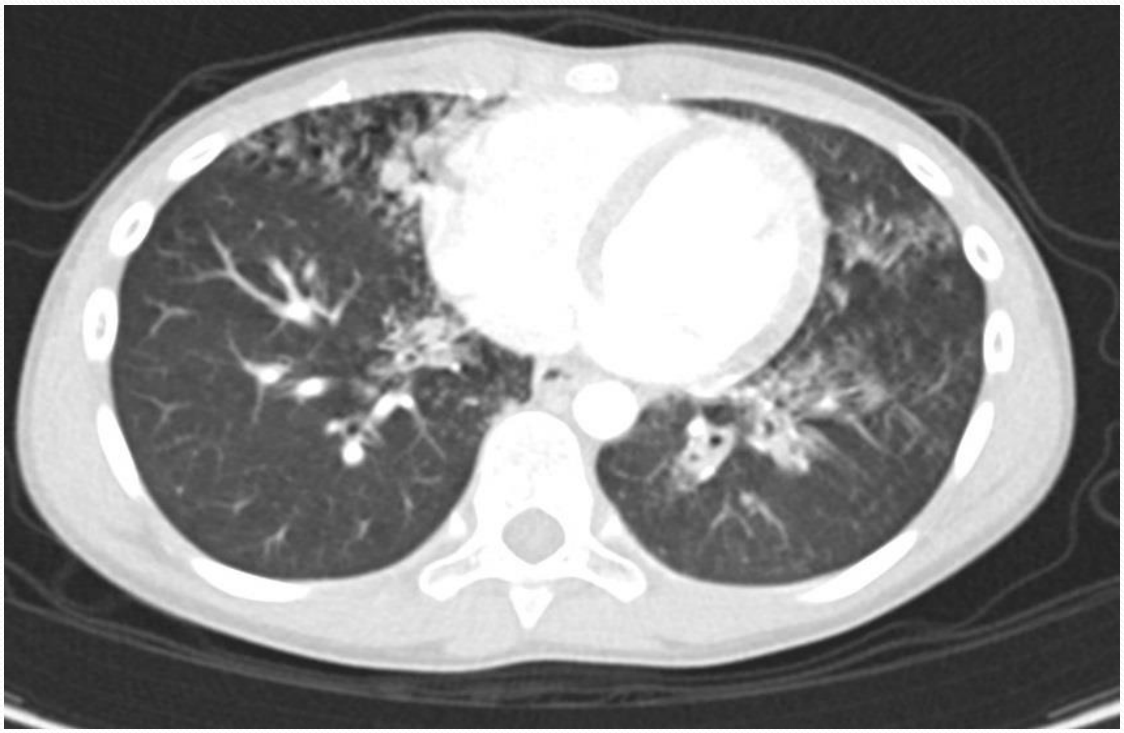
- Lost to follow up
- Pulmonary office visit on 1/11/16
  - Using albuterol once a month
  - Coughing up mucus everyday
  - Cough at night, but able to stay active
  - No daily medications
  - PE with coarse breath sounds
  - CXR with RML atelectasis, ? Bronchiectasis LLL

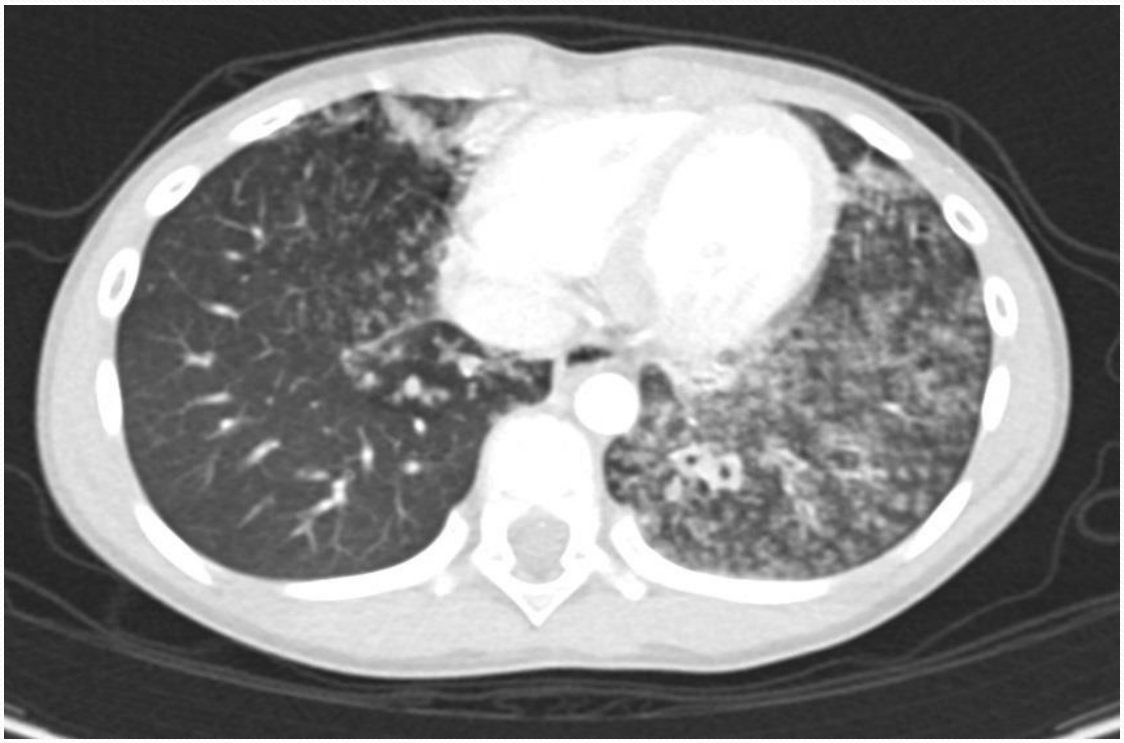
Case Three

- Pulmonary Function Testing
  - FVC 72% 79%
  - FEV1 60% 69%
  - Ratio 72% 76%
  - FEF25/75 35% 47%
- Started course of steroids and high dose combination mometasone/formoterol
- Ordered CT scan

Case Three

- Pulmonary visit 10/18/16 – did not get CT scan, PFTs unchanged, now having exercise symptoms – advised to get CT, allegry/immunology testing, and PCD genetics testing
- Five more office visits with no change and diagnostic studies not completed
- CT scan completed 12/20/17





Case Three

- Chest CT Results

Bilateral airspace disease in the right middle lobe and left lower lobe with some mild associated bronchiectasis in the left lower lobe. The pattern is indicative of small airway disease. There is no evidence of sequestration or CPAM. Differential considerations include aspiration, or atypical infection (fungal or mycobacterial).

Case Three

- Pulmonary visit 3/16/18
  - Discussed results of CT
  - Preliminary diagnosis of primary ciliary dyskinesia (PCD)
  - Started on airway clearance
  - Plan for bronchoscopy

Case Three

- Bronchoscopy done 2/21/19

Purulent secretions were coming out of medial takeoff of RML. The bronchoscope was then wedged in the RML. Two lavages of normal saline were instilled and then suctioned. Return was yellow and filled with mucus plugs and serosanguinous discharge . The bronchoscope was withdrawn to the level of the carina, and then wedged in the RML. Two lavages of normal saline were instilled and then suctioned, for a total of 40 mL instilled and 15 mL recovered. Return was yellow and filled with mucus plugs and serosanguinous discharge . A ciliary brush biopsy was performed in the trachea x 2.

Case Three

- Respiratory culture

Moderate growth Strep pneumoniae

Heavy growth Haemophilus influenzae beta lactamase negative

- Allergy testing negative
- Immunologic evaluation

Low IgA

Pneumococcal antibody titers non-protective

Case Three

- Ciliary biopsy

Specimen(s) Received:
1: Specimen for electron microscopy- CARINA BRUSHING

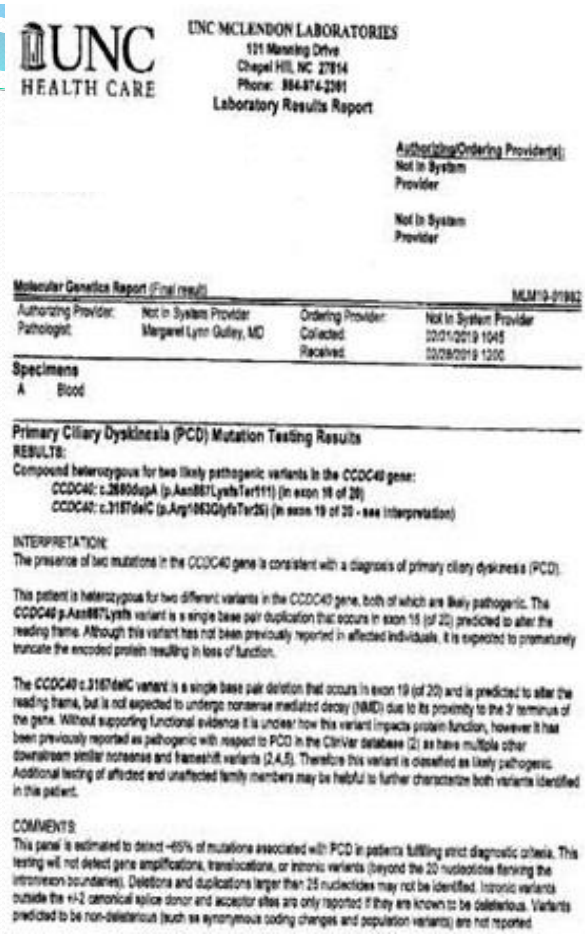
Final Diagnosis:
Right Carina Brushing:
Ciliary ultrastructural abnormalities present including
- **missing inner dynein arms**
- **transposition defects**
- **acentric central pairs**

Microscopic Description:
Electron Microscopy (19:EM106): Electron microscopic examination of this sampling of nasal respiratory epithelium reveals the specimen to be of acceptable technical quality and with an adequate number (>50) of favorably oriented cilia available for evaluation. **The observed transposition defects, acentric central pairs, and missing inner dynein arms may support a diagnosis of primary ciliary dyskinesia. This particular constellation of cilia abnormalities frequently reflects mutations of CCDC39 or CCDC40* resulting in inner dynein arm loss and microtubular disarray. Consideration might be given to securing a follow-up specimen, preferably from another site, for demonstration of the universality and permanence of this condition as the features described may also, independently, be seen in reactive/secondary changes which are also observed.**

Case Three

- PCD Genetics Testing

Heterozygous for two pathogenic variants in the CCDC40 gene consistent with primary ciliary dyskinesia



UNC HEALTH CARE

UNC MCLENDON LABORATORIES
101 Manning Drive
Chapel Hill, NC 27514
Phone: 984-974-2201
Laboratory Results Report

Authorizing/Ordering Provider(s):
Not In System Provider

Not In System Provider

Molecular Genetics Report (Final result) MLM19-01982

Authorizing Provider:	Not In System Provider	Ordering Provider:	Not In System Provider
Pathologist:	Margaret Lynn Gulley, MD	Collected:	02/01/2019 1045
		Received:	02/08/2019 1200

Specimens
A Blood

Primary Ciliary Dyskinesia (PCD) Mutation Testing Results
RESULTS:
Compound heterozygous for two likely pathogenic variants in the CCDC40 gene:
CCDC40: c.2690dupA (p.Asn897LysfsTer111) (in exon 18 of 20)
CCDC40: c.3187delC (p.Arg1063GlyfsTer25) (in exon 19 of 20 - see interpretation)

INTERPRETATION:
The presence of two mutations in the CCDC40 gene is consistent with a diagnosis of primary ciliary dyskinesia (PCD).

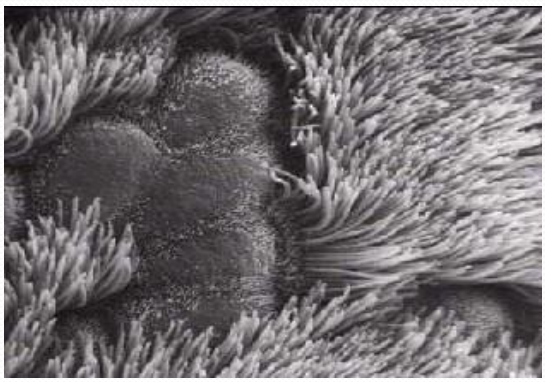
This patient is heterozygous for two different variants in the CCDC40 gene, both of which are likely pathogenic. The **CCDC40 p.Asn897Lysfs** variant is a single base pair duplication that occurs in exon 18 (of 20) predicted to alter the reading frame. Although this variant has not been previously reported in affected individuals, it is expected to prematurely truncate the encoded protein resulting in loss of function.

The **CCDC40 c.3187delC variant** is a single base pair deletion that occurs in exon 19 (of 20) and is predicted to alter the reading frame, but is not expected to undergo nonsense mediated decay (NMD) due to its proximity to the 3' terminus of the gene. Without supporting functional evidence it is unclear how this variant impacts protein function, however it has been previously reported as pathogenic with respect to PCD in the ClinVar database (2) as have multiple other downstream similar nonsense and frameshift variants (2,4,5). Therefore this variant is classified as likely pathogenic. Additional testing of affected and unaffected family members may be helpful to further characterize both variants identified in this patient.

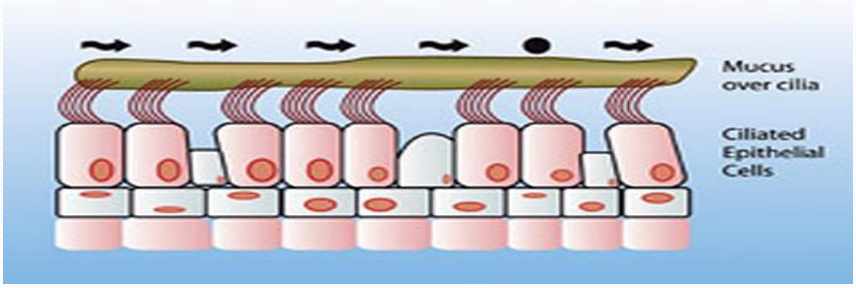
COMMENTS:
This panel is estimated to detect ~65% of mutations associated with PCD in patients fulfilling strict diagnostic criteria. This testing will not detect gene amplifications, translocations, or intronic variants (beyond the 20 nucleotides flanking the intron/exon boundaries). Deletions and duplications larger than 25 nucleotides may not be identified. Intronic variants outside the +/-2 canonical splice donor and acceptor sites are only reported if they are known to be deleterious. Variants predicted to be non-deleterious (such as synonymous coding changes and population variants) are not reported.

Primary ciliary dyskinesia (PCD)

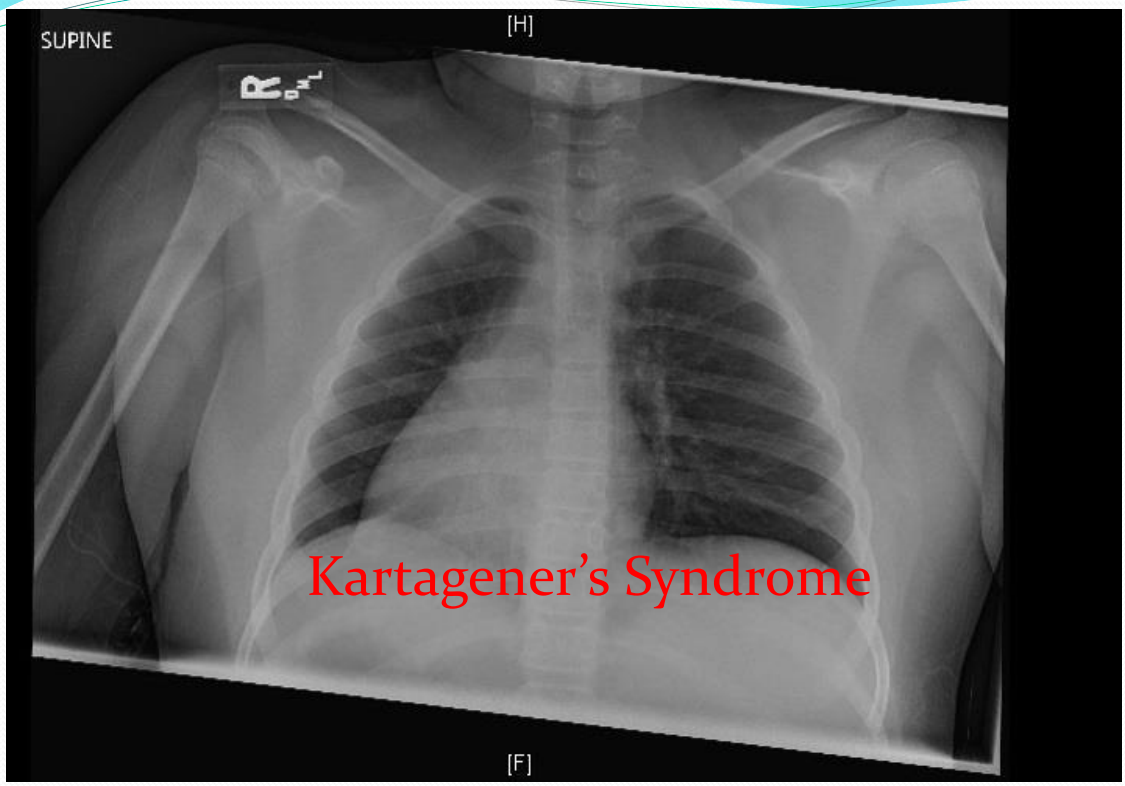
- Rare disorder inherited via autosomal recessive
- Variable Incidence estimated at 1:4000 to 1:50,000
- Defective movement of cilia in the respiratory tract



Primary ciliary dyskinesia



- Recurrent upper and lower respiratory tract infections
- Otitis media, sinusitis, chronic nasal congestion, pneumonia
- Conductive hearing loss
- Male infertility
- Situs inversus in 50% of patients with PCD



Kartagener's Syndrome

Diagnosing PCD

At least 2 of 4 of the following :

1. Unexplained neonatal respiratory distress in a term infant
2. Year round daily cough beginning before 6 months of age
3. Year round daily nasal congestion beginning before 6 months of age
4. Organ laterality defect

Diagnosing PCD

- Bronchoscopy with ciliary biopsy
- Electron microscopy evaluation of cilia
- Genetic test showing two mutations known to cause PCD
- Nasal nitric oxide
- High-speed videomicroscopy to assess ciliary beat pattern
- Rule out cystic fibrosis

Diagnosing CF

- Newborn Screening – Immunoreactive Trypsinogen (IRT)
- Sweat Chloride Test
- Genetic Testing

Treatment of PCD

- Chest physiotherapy
- Bronchodilators
- Mucolytics
- Hypertonic saline
- Anti-inflammatories
- Antibiotics

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