Primary Ciliary Dyskinesia: Overview and Update

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University of North Carolina at Chapel Hill

Genetic Diseases of Mucociliary Clearance Consortium

In

Funded by:

NIH
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Rare Clinical Research Network
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PCD Foundation
Primary Ciliary Dyskinesia

Turning Discovery Into Health
Financial Disclosures

• Vertex Pharmaceuticals, INC
  – Research grant

• Parion Sciences, INC
  – Research grant

• Circassia Pharmaceuticals, INC
  – Research grant

Reference to unlabeled/unapproved use of drugs:
• None
Primary Ciliary Dyskinesia is a Rare Disease

NIH Office of Rare Diseases: affects <200,000 in US
~7,000 rare diseases affect 25-30 million in US
Primary Ciliary Dyskinesia is a Rare Disease

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Rare Lung Diseases

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<tbody>
<tr>
<td>Cystic fibrosis (CF)</td>
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**Common Lung Disease**

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<tr>
<th>Disease</th>
<th># in US</th>
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<tbody>
<tr>
<td>Asthma</td>
<td>22,000,000</td>
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</table>
Primary Ciliary Dyskinesia Timeline: Advances with New Technology

Kartagener triad
- situs inversus
- chronic sinusitis
- bronchiectasis

Primary Ciliary Dyskinesia
- chronic oto-sino-pulmonary disease
- situs inversus totalis in ~ 50%
- male infertility (defective sperm motility)
- usually autosomal recessive

more recent observations:
- neonatal respiratory distress in ~85%
- heterotaxy (or situs ambiguus) in at least 10%
  - congenital heart disease in at least 5%

1st Case Report
1904

Kartagener Triad
1933

Immotile Cilia Syndrome
1976

Primary Ciliary Dyskinesia
1981

Low nNO in PCD
1994

1st gene defect identified
1999

>40 known PCD genes
2020
Audience Response Question 1

You are counseling parents whose child has just been diagnosed with primary ciliary dyskinesia (PCD). What is the typical mode of inheritance for PCD?

A. Autosomal dominant  
B. X-linked  
C. Autosomal recessive  
D. Polygenic disorder (mutations in multiple different genes)  
E. Chromosomal disorder
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Airway Host Defense: Mucociliary and Cough Clearance

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<th>CF</th>
<th>PCD</th>
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<tr>
<td>MCC</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CC</td>
<td>+</td>
<td>-</td>
<td>++</td>
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Graph showing clearance of radiotope over time with different conditions: Normal, CF, PCD, and Controlled coughs.
# Phenotypic Clinical Features in PCD

<table>
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<tr>
<th>Clinical feature</th>
<th>Pediatric (n=31, 8 mo-18 yr)</th>
<th>Adult (n=47, 19-73 yr)</th>
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<tbody>
<tr>
<td>Chronic cough</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Chronic rhinitis/sinusitis</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Chronic otitis media</td>
<td>100%</td>
<td>92%</td>
</tr>
<tr>
<td>Neonatal resp. distress</td>
<td>87%</td>
<td>65%</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>61%</td>
<td>98%</td>
</tr>
<tr>
<td>Situs inversus</td>
<td>68%</td>
<td>46%</td>
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GDMCC:
Genetic Disorders of Mucociliary Clearance Consortium
PI: M Knowles (initiated 2004)

Specific Aims:
• Develop a clinical research network to study rare diseases of the airways, focusing on PCD
• Test for disease-causing mutations in PCD to develop genetic diagnostic approach
• Perform a longitudinal study in infants and children with PCD to define the clinical pathogenesis of airways disease by serial tracking of:
  – Standardized clinical history, respiratory cultures, pulmonary function tests and chest CT scans.

http://rarediseasesnetwork.epi.usf.edu/
Participants Evaluated by GDMCC (2004-2018)

- UNC (n=519)
- Seattle (n=58)
- Denver (n=187)
- Toronto (n=110)
- St. Louis (n=117)
- NIH (n=120)
- Stanford (n=57)
- Indiana (n=28)
- McGill (n=50)
- Chicago (n=24)
- Total (n=1,270)
Criteria-defined clinical features in PCD

Participants <18 yo referred to GDMCC:

**Confirmed PCD (n=205)**
- Age (yr)  7.8 +/- 5.4
- nNO (nl/min) 20.9 +/- 21.8

**Other/Undefined (n=187)**
- Age (yr)  7.0 +/- 4.5
- nNO (nl/min) 258.3 +/- 146.9

### Participants (<18 years of age) Fulfilling Criterion

<table>
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<tr>
<th>Criteria-defined clinical features</th>
<th>PCD (n=204)</th>
<th>Other disease or Undefined (n=185)</th>
<th>Adjusted Odds Ratio (95% Confidence intervals)*</th>
<th>P-value</th>
</tr>
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<tr>
<td>Unexplained neonatal respiratory distress (#1)</td>
<td>116 (57%)</td>
<td>21 (11%)</td>
<td>6.6 (3.5,12.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Early onset, year-round wet cough (#2)</td>
<td>128 (62%)</td>
<td>48 (26)</td>
<td>3.1 (1.7,5.5)</td>
<td>0.0001</td>
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<tr>
<td>Early onset nasal congestion (#3)</td>
<td>151 (74%)</td>
<td>74 (40%)</td>
<td>3.4 (1.9,6.3)</td>
<td>&lt;0.0001</td>
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<td>Laterality defect (#4)</td>
<td>109 (53%)</td>
<td>28 (15%)</td>
<td>7.7 (4.0,14.9)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Multiple ear infections in first 2 years of life (#5)</td>
<td>89 (43%)</td>
<td>66 (35%)</td>
<td>1.0 (0.6,1.8)</td>
<td>0.981</td>
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* after adjusting for age at enrollment

Number of PCD clinical features: Sensitivity and specificity

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<tr>
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<th>Sensitivity</th>
<th>Specificity</th>
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<tr>
<td>Number of general clinical features</td>
<td></td>
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<tr>
<td>4</td>
<td>0.37</td>
<td>0.97</td>
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<tr>
<td>3</td>
<td>0.84</td>
<td>0.74</td>
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<tr>
<td>2</td>
<td>0.99</td>
<td>0.22</td>
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<tr>
<td>1</td>
<td>1.00</td>
<td>0.04</td>
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<td>0.96</td>
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<tr>
<td>2</td>
<td>0.80</td>
<td>0.72</td>
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<tr>
<td>1</td>
<td>0.96</td>
<td>0.41</td>
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<td>0</td>
<td>1.00</td>
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Audience Response Question 2

Which of the following patients is MOST LIKELY to have primary ciliary dyskinesia?

A. 8 year old child with situs inversus totalis but no chronic respiratory symptoms.
B. 17 year old girl who developed chronic cough at 15 years of age and now has bronchiectasis on chest CT.
C. 3 year old child with year-round wet cough, year-round nasal congestion and history of neonatal respiratory distress despite term gestation.
D. 14 year old with history of chronic intermittent asthma and allergic rhinitis with recent sinus CT showing mucosal thickening of the right maxillary sinus.
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What is the best way to diagnose PCD?

Panel of tests

• Clinical criteria
• Nasal nitric oxide measurement
• Ciliary biopsy for electron microscopy
• Genetic testing for mutations PCD genes
• Other testing
  • Ciliary biopsy w/ high speed videomicroscopy
  • Immunoflourescent analysis of ciliary biopsy
  • Mucociliary clearance studies

Nasal Nitric Oxide Measurement

- Direct measurement of NO in gas phase
- On line detection of chemiluminescence by photomultiplier tube
- Sensitive (parts per trillion)
- Maneuvers to eliminate contamination with alveolar gases
  - Blowing against resistor
Nasal NO Plateau Tracings in Healthy Control and PCD
Nasal Nitric Oxide (nNO) is Low in PCD

Cut-off 77 nl/min

Leigh MW et al, Ann ATS 2013:10:574-81
Nasal Nitric Oxide (nNO) is Low in PCD
Exception: RSPH1

Knowles MR et al, AJRCCM 2014;189:707
Leigh MW et al, Ann ATS 2013:10:574-81
Examination of Ciliary Structure and Function

- Visualize turbinate with surgical otoscope
- Brush inferior surface of lower turbinate with biopsy brush or scrape with curette
- Immediately place sample in culture media to examine motility by high-speed videomicroscopy
- Process for electron microscopy to examine ciliary ultrastructure
PCD: Ciliary Ultrastructural Defects

Dynein Arms Defects
• Absence/shortening ODA, alone
• Absence/shortening ODA+IDA
• Absent IDA+Microtubular Disorganization (MTD)
• Absence /shortening IDA, alone (?non-specific)
PCD: Ciliary Ultrastructural Defects

Central Complex Defects
(up to 90% appear normal)
• Absence of radial spoke (RS) or spoke head
• Absence of central pair with transposition of outer doublet to the center
• Associated genes: *RSPH9, RSPH4A, RSPH1*

Daniels, ML, Human Mutat 2013
High-speed videomicroscopy: Ciliary beat patterns

Normal
Planar motion w/ forward power stroke and backward recovery stroke
CBF 12.8 Hz
Immotility 0%

Stiff/dyskinetic
ODA defect
CBF 2.3 Hz
Immotility 55.0%

Virtually immotile
ODA+IDA defect
CBF 0.8 Hz
Immotility 79.8%

Circular
Absence of central pair
CBF 10.7 Hz
Immotility 0%

Chilvers, Am J Respir Crit Care Med. 2004;169:634-7
Genetic Testing for PCD is Complex
Multiple PCD genes; multiple pathogenic mutations for each PCD gene

Genes with Mutations

Altered Proteins

Altered Structure/function

Disease
PCD Molecular Genetic Testing

Challenging: Extensive genetic heterogeneity; 43 genes (911 coding exons); account for ~70% of PCD patients.
### PCD Genotype - EM Phenotype

#### “Hallmark” EM Defects

**ODA alone defects**
- DNAH5**
- DNAI1*
- DNAI2
- DNAL1
- NME8 (TXNDC3)
- ARMC4
- CCDC103
- CCDC114
- CCDC151
- TTC25

**ODA+IDA defects**
- CCDC103
- CFAP300 (C11orf70)
- DNAAF2 (KTU)
- DNAAF4 (DYX1C1)
- LRRCC6
- PIH1D3 [x-linked]
- SPAG1
- ZMYND10

**IDA alone defect**
- TTC12

### Other Defects

#### Oligocilia
- CCNO
- MCIDAS
- FOXJ1 [aut dominant]

#### EM defect not defined
- DNAH1
- DNAH8

### Normal/Near Normal EM

**ODA structural protein**
- DNAH11*
- DNAH9

**Central pair protein**
- HYDIN
- CFAP221
- STK36
- SPEF2

**Nexin-link proteins**
- CCDC164 (DRC1)
- GAS8 (DRC4)
- CCDC65 (DRC2)

**Radial spoke proteins**
- RSPH1
- RSPH3
- RSPH4A
- RSPH9
- DNAJB13

**Basal body**
- GAS2L2
- IFT protein
- LRRCC56

**Protein kinase**
- NEK10

**PCD + other syndrome**
- Retinitis pigmentosa
- RPGR [x-linked]
- Oro-facial-digital Syndrome
- OFD1 [x-linked]

Most prevalent genes
* in 4-10% of PCD patients
** in >15% of PCD patients
PCD Diagnostic Approach

Clinical Features

Access to nNO testing (with chemiluminescence device and standardized protocol) at specialty center AND Cooperative patient ≥ 3 years old, capable of performing nNO testing maneuver.

Yes to both (preferred pathway):

Nasal nitric oxide measurement

Low nNO level

Diagnosis of PCD if CF is excluded:
- Advise repeat nNO to verify low value

Unlikely PCD diagnosis
- Pursue genetic testing if strong clinical features

Pursue additional corroborative PCD testing

No to either:

Extended genetic testing panel

Biallelic pathogenic variants in PCD-associated gene

Single pathogenic variant in PCD-associated gene

No pathogenic variants in PCD-associated genes

Diagnosis of PCD

Electron microscopy of ciliary ultrastructure

Recognized ciliary ultrastructural defect

Normal ciliary ultrastructure

Inadequate sample or indeterminate analysis

Diagnosis of PCD

PCD Still Possible

Unknown

Primary Ciliary Dyskinesia

Natural History of Lung Disease during Childhood
Respiratory Pathogens in PCD children: Cross-sectional plot by age category

Participants ≤ 18 yrs at entry
- 137 with confirmed PCD
- 49% male; 82% Caucasian
- Age at enrollment 7.8 ± 4.6 yr
- Baseline plus 5 annual visits

Respiratory cultures
- at 728 of 732 visits
- 70.3% expectorated sputum
- 29.7% deep pharyngeal

Pseudomonas aeruginosa
- In 40/137 participants
- Mucoid in 4 participants
- Persistent in 13 participants

Davis SD et al. Am J Respir Crit Care Med 199:190-198, 2019
PCD: Longitudinal change in lung function: Wide range in severity and progression of lung disease

FEV$_1$ (% pred)  FVC (% pred)

Linear regression of f/u years from 1$^{st}$ measured lung function

Marthin: AJRCCM 181:1262, 2010
PCD in Childhood: Lung Function vs Age: Cross-sectional Analysis

[Diagram showing FEV₁ vs Age with different markers for Outer dynein arm defect and Microtubular disorganization, with defined genetic defects listed]

Davis SD: Am J Respir Crit Care Med 191:316-24, 2015
PCD in Childhood: Lung Function vs Age
Longitudinal Analysis by Ultrastructural Phenotype

Mean annual change in ppFEV1 for whole cohort is $-0.57\%$ (SE $0.25; p=0.03$)

Davis SD et al. Am J Respir Crit Care Med 199:190-198, 2019
PCD Genotype - Lung Disease Severity

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<td>MCIDAS</td>
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Most prevalent genes
* in 4-10% of PCD patients
** in >15% of PCD patients

Milder lung dz
Role of Cilia in Directing Orientation of Organs:
More than Situs Inversus
Situs Inversus Totalis is Random in PCD: Identical twins with PCD

- Identical (monozygotic) twins with discordant organ sidedness:
  - situs solitus
  - situs inversus totalis
- Supports hypothesis that situs inversus is a random event in PCD

Nodal Cilia and Left-right Asymmetry

Nodal Cilia and Left-right Asymmetry

Congenital Heart Disease and Heterotaxy in PCD

• Background
  – 1982-2005: 3 case reports of PCD with heterotaxy 1-3
• 2007: International retrospective study of prevalence of heterotaxic defects in PCD4
  – 337 PCD patients from 4 countries on 3 continents
    • USA (n=147)
    • Germany (n=128)
    • Canada (n=36)
    • Australia (n=26)

2. Engesath VG et al. Pediat Pulmon 16: 9-12, 1993
3. Schmura K et al. Respiration 72: 427-430, 2005
Congenital Heart Disease and Heterotaxy in PCD

PCD Patients n=337

- Situs Solitus n=155 (46%)
- Heterotaxy n=21 (6.3%)
- Situs Inversus Totalis n=161 (47.7%)

- Vascular Anomalies n=4 (1.2%)
- Complex Congenital Heart Disease n=8 (2.4%)
- No cardiac or Vascular anomalies n=9 (2.7%)

- Retrospective review of clinical data and imaging
- Combined data from Chapel Hill, NC (147), Toronto, Canada (36), New South Wales, Australia (26), Freiburg, Darmstadt & Cologne, Germany (128)

Features Associated with Heterotaxy

**Cardiovascular**
- Atrioventricular discordance
- Transposition of great arter.
- Left atrial isomerism
- Right atrial isomerism
- Double outlet right ventricle
- Pulmonary stenosis/atresia
- Single ventricle
- L. vent. outflow obstruction
- Septal defects
- Total/partial anomalous pulmonary venous return
- Interrupted IVC
- Bilateral SVC
- Conduction system defects

**Non-cardiovascular**
- Asplenia
- Polysplenia
- Two bi-lobed (left) lungs
- Two tri-lobed (right) lungs
- Biliary atresia
- Abdominal situs inversus
- Thoracic situs inversus
- Intestinal malrotation

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<td>CCDC40*</td>
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<td>DNAH9</td>
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<td>DNAH8</td>
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- ** in 4-10% of PCD patients
- ** in >15% of PCD patients

**Most prevalent genes**

PCD + other syndrome
- Retinitis pigmentosa +PCD
- RPGR (x-linked)
- Oro-facial-digital Syn +PCD
- OFD1 (x-linked)
Management of PCD Lung Disease

• No published clinical trials to direct evidence-based therapy
• Management based on the “experience” of specialist with chronic lung disease
  – Few centers follow more than handful of patients with PCD
Management of PCD Lung Disease: General principles

- Enhance airway clearance
- Prevent respiratory infections
- Monitor respiratory cultures and respiratory function
- Treat respiratory infections appropriately
- Avoid exposure to airway irritants
- Maintain healthy lifestyle

Audience Response Question 3

You are caring for a 7 year old with Primary Ciliary Dyskinesia (PCD). This child’s parents inquire about specific therapies for PCD. Which of the following therapies has been tested in randomized, placebo-controlled trials in PCD patients and demonstrated to have clinical benefit?

A. Recombinant DNase
B. Hypertonic saline
C. Suppressive antibiotic therapy with azithromycin
D. None of the above
You are caring for a 7 year old with Primary Ciliary Dyskinesia (PCD). This child’s parents inquire about specific therapies for PCD. Which of the following therapies has been tested in randomized, placebo-controlled trials in PCD patients and demonstrated to have clinical benefit?

A. Recombinant DNase
B. Hypertonic saline
C. Suppressive antibiotic therapy with azithromycin
D. None of the above
Priorities for PCD Clinical Care and Clinical Research Centers

- Create network of PCD Centers of Excellence and Clinical Practice Guidelines
- Make accurate and early diagnosis of PCD
  - Clinical clues / access to diagnostic testing
- Create centralized patient registry
  - Define true prevalence / incidence of PCD
  - Track longitudinal data on large # of PCD patients
  - Identify clinical features linked with prognosis / progression
- Assess outcome measures for clinical trials
  - Lung function/chest CT/ microbiology
  - Health-related Quality of Life Tool for PCD
- Perform clinical trials
PCD Research Teams

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NIH ORD/NCATS/NHLBI
PCD patients and families