



## Primary Ciliary Dyskinesia

Synonyms: Immotile Cilia Syndrome, Kartagener Syndrome

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### Summary

The purpose of this overview is to increase the awareness of clinicians regarding primary ciliary dyskinesia and its genetic causes and management. The following are the goals of this overview.

#### Goal 1

Describe the clinical characteristics of primary ciliary dyskinesia.

#### Goal 2

Review the genetic causes of primary ciliary dyskinesia.

#### Goal 3

Provide an evaluation strategy to identify the genetic cause of primary ciliary dyskinesia in a proband.

#### Goal 4

Inform genetic counseling of family members of an individual with primary ciliary dyskinesia.

#### Goal 5

Review management of primary ciliary dyskinesia.

## 1. Clinical Characteristics of Primary Ciliary Dyskinesia

Primary ciliary dyskinesia (PCD) is associated with:

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- Abnormal ciliary structure and function and biogenesis defects that result in retention of mucus and bacteria in the respiratory tract and lead to chronic otosinopulmonary disease;
- Abnormal flagellar structure resulting in abnormal sperm motility.

## Clinical Manifestations of Primary Ciliary Dyskinesia

### Pulmonary Disease

The progression and severity of lung disease varies among individuals. More than 75% of full-term neonates with PCD have "neonatal respiratory distress" requiring supplemental oxygen for days to weeks despite term gestation; however, few are diagnosed with PCD at this age [Mullowney et al 2014].

Chronic airway infection is apparent in early childhood. Most children have chronic year-round wet cough, sputum production, and chronic wheezing. Lung function test results are consistent with obstructive lung disease. Sputum cultures typically yield oropharyngeal flora, *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Staphylococcus aureus* beginning in early childhood, after which *Pseudomonas aeruginosa* (first smooth and then mucoid) becomes more prevalent. While rare in childhood, infection with non-tuberculous mycobacteria occurs in more than 10% of adults [Noone et al 2004, Knowles et al 2013].

Chronic airway infection results in bronchiectasis that may be apparent in some young children and is almost uniformly present in adulthood on chest CT examination [Knowles et al 2013, Davis et al 2015]. Digital clubbing is typically associated with bronchiectasis.

A subset of adults with chronic airway infection have calcium deposition in the lung and, as a result, expectorate small calcium stones (lithoptysis) [Kennedy et al 2006]. Some develop end-stage lung disease in mid-adulthood and several have undergone lung transplantation. Progression of lung disease can be slowed with appropriate therapy.

### Nasal Congestion and Sinus Infections

Chronic sinusitis and nasal congestion (frequently with mucostasis and prominent nasal drainage) begin in the first months of life, often at birth. Sinus infections persist through adulthood [Leigh et al 2009].

### Chronic/Recurrent Ear Infection

Apparent in most young children with PCD, chronic/recurrent ear infection becomes less apparent by school age. In many infants and young children, chronic otitis media is associated with transient hearing loss that may affect speech development. If untreated, infections of the middle ear may result in irreversible hearing loss [Majithia et al 2005].

### Infertility

Virtually all males with PCD are infertile as a result of abnormal sperm motility.

Some women with PCD have normal fertility; others have impaired fertility and are at increased risk for ectopic pregnancy because of impaired ciliary function in the oviduct [Afzelius 2004].

### Situs Abnormalities

**Situs inversus totalis** (mirror-image reversal of all visceral organs with no apparent physiologic consequences) is observed in 40%-50% of individuals with PCD.

**Heterotaxy** (also called "situs ambiguous") is present in approximately 12% of individuals with PCD [Kennedy et al 2006, Shapiro et al 2014]. Heterotaxy (discordance of right and left patterns of ordinarily asymmetric

structures) is distinct from situs inversus and is often categorized clinically as asplenia (predominant bilateral right-sidedness, or right isomerism) or polysplenia (predominant bilateral left-sidedness, or left isomerism).

In those with heterotaxy, congenital cardiovascular malformations are common and complex, and often the cause of death. Specific cardiovascular defects associated with heterotaxy include atrial isomerism, transposition of the great vessels, double outlet right ventricle, anomalous venous return, interrupted inferior vena cava, and bilateral superior vena cava [Shapiro et al 2014].

Pulmonary isomerism, usually asymptomatic, can be right isomerism (a trilobed pulmonary anatomy bilaterally with bilateral eparterial bronchi) or left isomerism (both lungs have the lobar and hilar anatomy characteristic of a normal left lung).

The stomach may be displaced to the right; the liver may be midline, or the left and right lobes may be reversed.

Abnormal rotation of the intestinal loop can result in obstruction or volvulus (vascular obstruction).

CNS, skeletal, and genitourinary malformations may also be seen.

## Other

Hydrocephalus may occur on rare occasion in individuals with PCD and may reflect dysfunctional ependymal cilia [Wessels et al 2003, Kosaki et al 2004].

## Establishing the Clinical Diagnosis of Primary Ciliary Dyskinesia

Recently published consensus recommendations [Shapiro et al 2018] have defined a panel of tests for the diagnosis of PCD including key clinical features, nasal nitric oxide measurement, and transmission electron microscopy. The four key clinical features for detection in childhood include the following [Leigh et al 2016]:

- Unexplained neonatal respiratory distress
- Laterality defect
- Early-onset, year-round wet cough
- Early-onset, year-round, nasal congestion

The diagnosis of PCD is highly likely if two or more of these key clinical features are present. Identification of a specific mendelian form by molecular genetic testing (see Table 1) may confirm the diagnosis; however, 20%-30% of individuals with well-characterized PCD do not have identifiable pathogenic variants in any of associated genes. Transmission electron microscopic analysis of ciliary biopsy can also be performed; however, it should be noted that an estimated 30% of individuals with PCD do not have ultrastructural abnormalities of the cilia. Nasal nitric oxide measurement can be performed as an adjunctive test in children older than age five years to provide additional support for the diagnosis of PCD.

## Differential Diagnosis of Primary Ciliary Dyskinesia

### Chronic Sinopulmonary Disease and Bronchiectasis

Like PCD, the following disorders are associated with chronic sinopulmonary disease and bronchiectasis. Unlike PCD, these disorders are not associated with situs abnormalities:

- Cystic fibrosis
- Immunodeficiency, such as immunoglobulin G (IgG) subclass deficiency [Zysman-Colman et al 2019]
- Allergic rhinitis
- Gastroesophageal reflux disease
- Wegener's granulomatosis (upper- and lower-airway disease)

## Sinopulmonary disease

- X-linked retinitis pigmentosa and sinorespiratory infections, with or without deafness (OMIM 300455) can be considered in the differential diagnosis of PCD; however, PCD is not likely if the affected individual has isolated retinitis pigmentosa and no respiratory manifestations.
- Cri-du-chat syndrome (OMIM 123450) is caused by a segmental chromosome 5p deletion that usually includes *DNAH5* (a gene known to be associated with PCD). PCD co-occurs in cri-du-chat syndrome when a PCD-causing pathogenic variant is detected in the remaining allele of *DNAH5*. Cri-du-chat syndrome is associated with chronic sinopulmonary disease but not situs abnormalities.

**Situs abnormalities.** Multiple genes are associated with visceral heterotaxy (see [Phenotypic Series: Visceral heterotaxy](#) for genes associated with this phenotype in OMIM). PCD is not likely if the affected individual has visceral heterotaxy but no associated respiratory manifestations.

## 2. Causes of Primary Ciliary Dyskinesia

To date, pathogenic variants in 45 genes are known to cause primary ciliary dyskinesia (PCD). PCD is inherited in an autosomal recessive manner with the exception of *FOXJ1*-PCD (which is autosomal dominant) and *PIH1D3*-PCD and *OFD1*-PCD (which are X-linked). However, 20%-30% of individuals with well-characterized PCD do not have identifiable pathogenic variants in any of the associated genes (Table 1).

**Table 1.** Molecular Genetics of Primary Ciliary Dyskinesia

Gene <sup>1</sup>	% of PCD Caused by Pathogenic Variants in Gene <sup>2, 3</sup>	Distinguishing Clinical Features	Findings on Ciliary Ultrastructure Analysis	OMIM Phenotype / References
<i>ODAD2</i> ( <i>ARMCA</i> )	<3% <sup>4</sup>	Situs abnormalities	ODA defects	615451
<i>CCDC39</i>	4%-9%	Situs abnormalities; worse lung function; ↑ bronchiectasis; poor weight gain	IDA defects+MTD	613807
<i>CCDC40</i>	3%-4%	Situs abnormalities; worse lung function; ↑ bronchiectasis; poor weight gain	IDA defects+MTD	613808
<i>CCDC65</i> <sup>5</sup>	Rare	Situs abnormalities not reported	Normal ciliary ultrastructure	615504
<i>CCDC103</i>	<4% <sup>4</sup>	Situs abnormalities	ODA defects	614679
<i>ODAD1</i>	Rare	Situs abnormalities	ODA defects	615067
<i>ODAD3</i> ( <i>CCDC151</i> )	<3% <sup>4</sup>	Situs abnormalities	ODA defects	616037
<i>CCNO</i>	Rare	Situs abnormalities not reported	Oligocilia <sup>6</sup>	615872
<i>CFAP221</i>	Rare	Situs abnormalities not reported	Normal ciliary ultrastructure	Bustamante-Marín et al [2020]
<i>CFAP298</i>	Rare	Situs abnormalities	ODA+IDA defects	615500

Table 1. continued from previous page.

Gene <sup>1</sup>	% of PCD Caused by Pathogenic Variants in Gene <sup>2, 3</sup>	Distinguishing Clinical Features	Findings on Ciliary Ultrastructure Analysis	OMIM Phenotype / References
<i>CFAP300</i> ( <i>C11orf70</i> )	Rare	Situs abnormalities	ODA+IDA defects	618063 / Fassad et al [2018a], Höben et al [2018]
<i>DNAAF1</i>	Rare	Situs abnormalities	ODA+IDA defects	613193
<i>DNAAF2</i>	Rare	Situs abnormalities	ODA+IDA defects	612518
<i>DNAAF3</i>	Rare	Situs abnormalities	ODA+IDA defects	606763
<i>DNAAF4</i>	Rare	Situs abnormalities	ODA+IDA defects	615482
<i>DNAAF5</i>	Rare	Situs abnormalities	ODA+IDA defects	614874
<i>DNAAF11</i> ( <i>LRRC6</i> )	Rare	Situs abnormalities	ODA+IDA defects	614935
<i>DNAH1</i>	Rare	Situs abnormalities	Ciliary ultrastructure not defined	617577
<i>DNAH5</i>	15%-29%	Situs abnormalities	ODA defects	608644
<i>DNAH8</i>	Rare	Situs status unknown	Ciliary ultrastructure not defined	Watson et al [2014]
<i>DNAH9</i> <sup>7</sup>	Rare	Situs abnormalities	Subtle ODA defects	618300 / Fassad et al [2018b], Loges et al [2018]
<i>DNAH11</i> <sup>8</sup>	6%-9%	Situs abnormalities	Normal ciliary ultrastructure	611884
<i>DNAI1</i>	2%-10%	Situs abnormalities	ODA defects	244400
<i>DNAI2</i>	Rare	Situs abnormalities	ODA defects	612444
<i>DNAJB13</i>	Rare	Situs abnormalities not reported	CP defects	617091 / El Khouri et al [2016]
<i>DNAL1</i>	Rare	Situs abnormalities	ODA defects	614017
<i>DRC1</i> <sup>5</sup>	Rare	Situs abnormalities not reported	Normal ciliary ultrastructure	615294
<i>FOXJ1</i>	Rare	Situs abnormalities; AD MOI	Normal ciliary ultrastructure	602291 / Wallmeier et al [2019]
<i>GAS2L2</i>	Rare	Situs abnormalities not reported	Normal ciliary ultrastructure	618449
<i>GAS8</i>	Rare	Situs abnormalities not reported	Normal ciliary ultrastructure.	616726 / Olbrich et al [2015]
<i>HYDIN</i> <sup>9</sup>	Rare	Situs abnormalities not reported	Normal ciliary ultrastructure.	608647
<i>LRRC56</i> <sup>10</sup>	Rare	Situs abnormalities	Normal ciliary ultrastructure	618254
<i>MCIDAS</i>	Rare	Situs abnormalities not reported	Oligocilia <sup>6</sup>	Boon et al [2014]

Table 1. continued from previous page.

Gene <sup>1</sup>	% of PCD Caused by Pathogenic Variants in Gene <sup>2, 3</sup>	Distinguishing Clinical Features	Findings on Ciliary Ultrastructure Analysis	OMIM Phenotype / References
<i>NME8</i>	Rare	Situs abnormalities	ODA defects (~66% of cross sections)	<a href="#">610852</a>
<i>OFD1</i> <sup>11</sup>	Rare	Situs abnormalities; dysmorphic features; hypotonia; worse lung function; ↑ bronchiectasis; poor weight gain; XL MOI	Normal ciliary ultrastructure	Hannah et al [2019]
<i>PIH1D3</i>	Rare	Situs abnormalities; XL MOI	ODA+IDA defects	<a href="#">300991</a> / Olcese et al [2017], Paff et al [2017]
<i>RSPH1</i>	Rare	Milder lung disease; situs abnormalities not reported	CP defects	<a href="#">615481</a>
<i>RSPH3</i>	Rare	Situs abnormalities not reported	CP defects	<a href="#">616481</a>
<i>RSPH4A</i>	Rare	Situs abnormalities not reported	CP defects	<a href="#">612649</a>
<i>RSPH9</i>	Rare	Situs abnormalities not reported	CP defects	<a href="#">612650</a>
<i>SPAG1</i>	<4% <sup>4</sup>	Situs abnormalities	ODA+IDA defects	<a href="#">615505</a>
<i>SPEF2</i> <sup>9</sup>	Rare	Situs abnormalities not reported; can present w/ isolated male infertility	Normal ciliary ultrastructure	<a href="#">610172</a> / Cindrić et al [2020], Liu et al [2020], Liu et al [2019], Sha et al [2019]
<i>STK36</i>	Rare	Situs abnormalities not reported	CP defects	<a href="#">607652</a> / Edelbusch et al [2017]
<i>TTC25</i>	Rare	Situs abnormalities	ODA defects	<a href="#">617092</a> / Wallmeier et al [2016]
<i>ZMYND10</i>	<2%-4% <sup>4</sup>	Situs abnormalities	ODA+IDA defects	<a href="#">615444</a>

AD = autosomal dominant; CP defects = central pair defects (note that most cilia may appear normal); IDA defects+MTD = inner dynein arm defects+microtubular disorganization; MOI = mode of inheritance; ODA defects = outer dynein arm defects; ODA+IDA defects = outer+inner dynein arms defects; XL = X-linked

1. Genes are listed in alphabetical order.

2. Rare = pathogenic variants in this gene reported in  $\leq 2\%$  of individuals with PCD

3. Some estimates are extrapolations based on defects in ciliary structure (see Ciliary Ultrastructural Analysis).

4. Gene was screened in a large cohort in a single study. Percentage may be an overestimate if the study cohort was selected on the basis of prior molecular genetic testing results (i.e., individuals with biallelic pathogenic variants in previously known genes were excluded).

5. Encodes component of Nexin-Dynein regulatory complex

6. Cilia biogenesis defect

7. Encodes protein localized to the distal end of cilia

8. Encodes outer dynein arm protein

9. Encodes component of central pairs

10. Encodes component of intraflagellar transport machinery

11. *OFD1* is implicated in classic [oral-facial-digital syndrome type I](#), an X-linked disorder typically associated with male lethality, as well as additional phenotypes including Simpson-Golabi-Behmel syndrome type 2 (OMIM [300209](#)). Hannah et al [2019] describe findings consistent with both PCD and Simpson-Golabi-Behmel syndrome in hemizygous males.



### 3. Evaluation Strategy to Identify the Genetic Cause of Primary Ciliary Dyskinesia

The diagnosis of a specific mendelian form of primary ciliary dyskinesia (PCD) **is established** in a proband with the above Clinical Characteristics and biallelic pathogenic or likely pathogenic variants (or a heterozygous pathogenic variant in *FOXJ1*, or a hemizygous pathogenic variant in *PIH1D3* or *OFD1* in a male) identified in one of the genes listed in Table 1.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis.

Molecular testing approaches can include a combination of **gene-targeted testing** (multigene panel, targeted analysis for pathogenic variants, serial single-gene testing) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype:

- **A multigene panel** that includes *DNAH5*, *DNAH11*, *CCDC39*, *DNAI1*, *CCDC40*, *CCDC103*, *SPAG1*, *ZMYND10*, *ODAD2 (ARMC4)*, *ODAD3 (CCDC151)*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

- **Targeted analysis** for pathogenic variants in a particular gene can be performed first in individuals of a specific ethnicity/ancestry if appropriate. See [Table 2](#) (pdf).
- **Comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) may be considered. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

### Other Testing

#### Ciliary Ultrastructural Analysis

Transmission electron microscopy to identify ciliary ultrastructural defects requires a biopsy of the respiratory epithelium, typically obtained by brushing or scraping the inferior surface of the nasal turbinate or brushing the bronchial surface via bronchoscopy [MacCormick et al 2002, Chilvers et al 2003]. Approximately 30% of individuals with a clinical phenotype strongly suggestive of PCD and low levels of nasal nitric oxide have normal ciliary ultrastructure (in many of whom the diagnosis has been confirmed by identification of biallelic pathogenic variants in one of the genes listed in Table 1) [Knowles et al 2013].

The dynein arm defects are often specific for the mutated gene (see Table 1). The most prevalent of the defined ultrastructural defects in primary ciliary dyskinesia are the following (Figure 1) [Knowles et al 2013, Davis et al 2015]:

- Shortening and/or absence of outer dynein arms alone (~55% with defined ultrastructural defects, or 38.5% of all PCD)
- Shortening or absence of both outer and inner dynein arms (~15% with defined ultrastructural defects, or 10.5% of all PCD)
- Microtubular (axonemal) disorganization associated with absence of the inner dynein arm and central apparatus defect (5%-20% of defined ultrastructural defects, or ~14% of all PCD)
- Absence or disruption of the central apparatus (central microtubule pair and/or radial spokes) (~10% of defined ultrastructural defects, or 7% of all PCD)
- Shortening and/or absence of inner dynein arms alone (rare)
- Oligocilia (presence of only few cilia) with or without normal ultrastructure (rare).

Note: (1) Expertise in evaluation of ciliary ultrastructure is needed to distinguish primary (genetic) defects from acquired defects that result from exposure to different environmental and infectious agents.

## Nasal Nitric Oxide Measurement

Nitric oxide (NO), produced by the respiratory cells, is present in much higher concentrations in the upper airway than in the lower airway. For unknown reasons, individuals with PCD have very low nasal NO production that is approximately one tenth of control values. In individuals older than age five years who can cooperate with palate closure maneuvers and with a cut-off value of 77 nL/min, this test is 98% sensitive and 99% specific for identifying individuals with PCD [Leigh et al 2013, Shapiro et al 2017]. Rare individuals with PCD and approximately 50% of those with biallelic pathogenic variants in *RSPH1* have values above the cut-off (77 nL/min) [Leigh et al 2013, Knowles et al 2014]. Nasal NO values may be falsely low if there is any bleeding in the nasosinal cavity and may be low in other disorders including acute viral infections and cystic fibrosis. Therefore, nasal NO testing should be performed (1) after [cystic fibrosis](#) has been ruled out by appropriate testing (sweat test or *CFTR* genetic testing) and (2) when the individual is at baseline health status. Testing should be repeated if there is concern about recent or current viral infection [Leigh et al 2013].

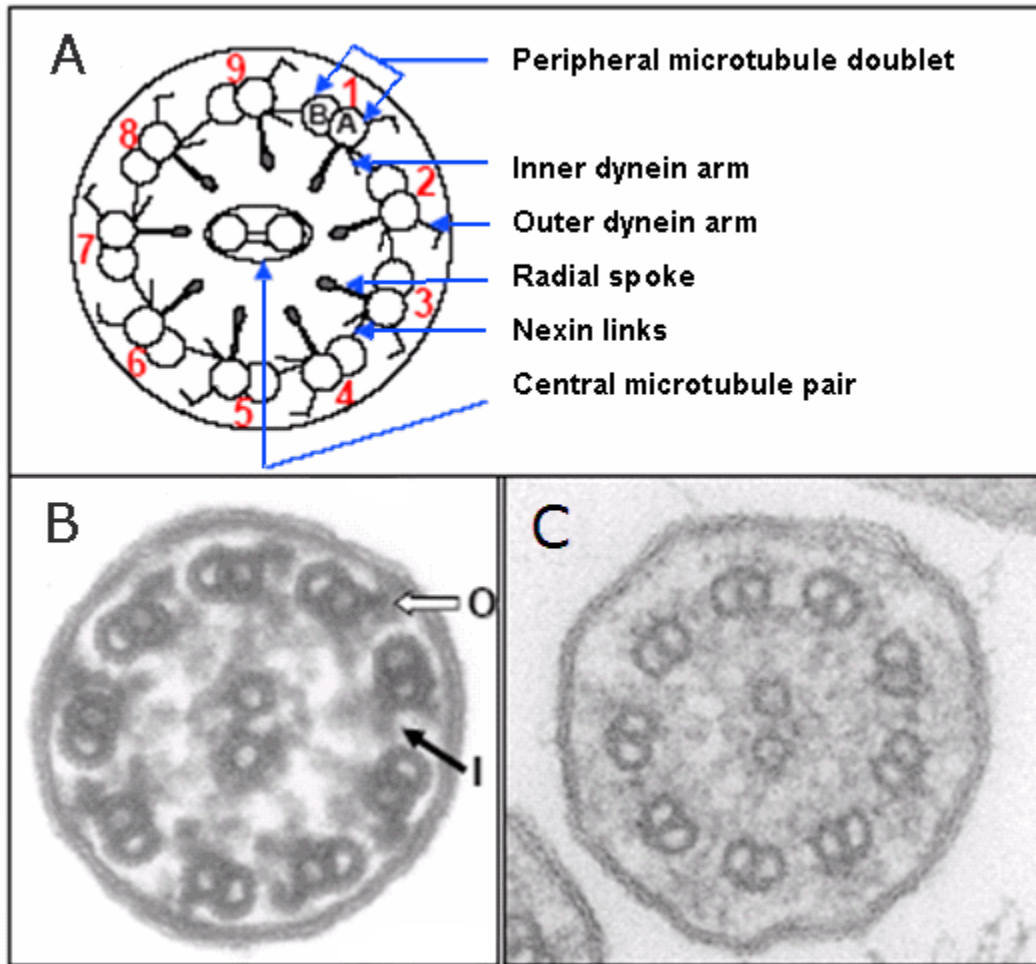
## Other Tests Under Evaluation as Supportive Tests for PCD

**High-speed videomicroscopy of ciliary motility.** Evaluation of ciliary beat frequency and ciliary beat pattern requires high-speed videomicroscopy of freshly obtained ciliary biopsies that are maintained in culture media under controlled conditions. Specific immotility/dysmotility patterns associated with PCD can be identified [Chilvers et al 2003, Toskala et al 2005, Raidt et al 2014]. Note: It is now recognized that ciliary videos must be repeated multiple times (including studies on cultured ciliary cells) in order to establish the diagnosis of PCD using ciliary waveform analyses.

**Mucociliary clearance analysis of radiolabeled particles.** Mucociliary clearance has been measured by assessing clearance of radiolabeled particles from the nasal passages or from the lower airways [De Boeck et al 2005, Marthin et al 2007]. For these studies, an aerosol containing radiolabeled particles is inhaled and a gamma camera is used to track deposition and clearance of these insoluble particles.

**Immunofluorescent staining of ciliary biopsy.** Immunofluorescent assays using antibodies specific to the ciliary components can be used to identify the specific ciliary ultrastructural defect. For example, individuals with outer dynein arm (ODA) defects on electron microscopic analysis and/or biallelic pathogenic variants in ODA-related genes such as *DNAH5* or *DNAI2* show absence of ciliary staining using anti-DNAH5 or anti-DNAI2 antibodies [Fliegauf et al 2005, Loges et al 2008]. Inner dynein arm (IDA) defects, nexin-dynein regulatory complex defects, and radial spokes/central pair defects can be ascertained using IDA-specific anti-





**Figure 1.** Cross section of the cilia

A. Schematic diagram of a cilium revealing "9+2" arrangement of nine peripheral microtubule doublets surrounding a central microtubule pair

B. Representative electron microscopic image of a normal cilium from the nasal epithelium of a control. "O" represents the outer dynein arm (open arrow) and "I" represents the inner dynein arm (solid arrow). The central pair and radial spokes are also visible.

C. Representative electron microscopic image of a cilium from the nasal epithelium of an individual with PCD demonstrating absence of dynein arms

DNALI1, nexin-related anti-GAS8/GAS11 antibodies, and radial spokes-related anti-RSPH1, anti-RSPH4A, and anti-RSPH9, respectively [Becker-Heck et al 2011, Merveille et al 2011, Frommer et al 2015]. Limited information is available about utility of immunofluorescent staining as a diagnostic test [Shoemark et al 2017].

**Semen analysis.** Sperm count is typically normal, but sperm are immotile or motility is severely limited [Afzelius 2004].

## 4. Genetic Counseling of Family Members of an Individual with Primary Ciliary Dyskinesia

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic*

*status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.*

## Mode of Inheritance

Primary ciliary dyskinesia (PCD) is usually inherited in an autosomal recessive manner. *PIH1D3*-PCD and *OFD1*-PCD are inherited in an X-linked manner. *FOXJ1*-PCD is inherited in an autosomal dominant manner.

## Autosomal Recessive Inheritance – Risk to Family Members

### Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one PCD-causing pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a PCD-causing pathogenic variant and to allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

### Sibs of a proband

- If both parents are known to be heterozygous for a PCD-causing pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

**Offspring of a proband.** The offspring of an individual with autosomal recessive PCD are obligate heterozygotes (carriers of a PCD-related pathogenic variant).

**Other family members.** Each sib of the proband's parents is at a 50% risk of being a carrier of a PCD-related pathogenic variant.

**Carrier detection.** Carrier testing for at-risk relatives requires prior identification of the PCD-related pathogenic variants in the family.

## X-Linked Inheritance – Risk to Family Members

### Parents of a male proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the *PIH1D3* or *OFD1* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote (carrier). Note: If a woman has more than one affected child and no other affected relatives and if the pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote (carrier) or the affected male may have a *de novo* *PIH1D3* or *OFD1* pathogenic variant, in which case the mother is not a carrier.

**Sibs of a male proband.** The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has a either *PIH1D3* or *OFD1* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes (carriers) and will usually not be affected.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *PIH1D3* or *OFD1* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is greater than that of the general population because of the possibility of maternal germline mosaicism.

**Offspring of a male proband.** Affected males transmit the *PIH1D3* or *OFD1* pathogenic variant to:

- All of their daughters who will be (heterozygotes) carriers and will usually not be affected;
- None of their sons.

**Other family members.** A male proband's maternal aunts may be at risk of being carriers for the pathogenic variant and the aunts' offspring, depending on their sex, may be at risk of being carriers for the pathogenic variant or of being affected.

**Heterozygote detection.** Molecular genetic testing of at-risk female relatives to determine their genetic status requires prior identification of the *PIH1D3* or *OFD1* pathogenic variant in the family.

## Autosomal Dominant Inheritance – Risk to Family Members

### Parents of a proband

- To date, all individuals with *FOXJ1*-PCD whose parents have undergone molecular genetic testing have had the disorder as the result of a *de novo* *FOXJ1* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the pathogenic variant most likely occurred *de novo* in the proband; another possible explanation is germline mosaicism in a parent.
- The family history of some individuals diagnosed with *FOXJ1*-PCD may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has been performed on the parents of the proband.

**Sibs of a proband.** The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the pathogenic variant but are clinically unaffected, sibs are still presumed to be at increased risk for PCD because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

**Offspring of a proband.** Each child of an individual with *FOXJ1*-PCD has a 50% chance of inheriting the pathogenic variant.

**Other family members.** The risk to other family members depends on the status of the proband's parents: if a parent has the *FOXJ1* pathogenic variant, the parent's family members may be at risk.

## Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

### Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being affected or carriers.

## Prenatal Testing and Preimplantation Genetic Testing

Once the PCD-related pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

## Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).*

- **Genetic Disorders of Mucociliary Clearance Consortium**  
[www1.rarediseasesnetwork.org/cms/gdmcc](http://www1.rarediseasesnetwork.org/cms/gdmcc)
- **Kartagener's Syndrome and Primary Ciliary Dyskinesia Foundation**  
Lärchenweg 14  
Ettlingen 76275  
Germany  
**Phone:** 07243 39338  
**Email:** [info@kartagener-syndrome.de](mailto:info@kartagener-syndrome.de); [erafra@web.de](mailto:erafra@web.de)  
[www.kartagener-syndrome.org](http://www.kartagener-syndrome.org)
- **PCD (Primary Ciliary Dyskinesia) Foundation**  
10137 Portland Avenue South  
Minneapolis MN 55420  
**Phone:** 952-303-3155; 612-386-1261  
**Fax:** 952-303-3178  
**Email:** [info@pcdfoundation.org](mailto:info@pcdfoundation.org)  
[www.pcdfoundation.org](http://www.pcdfoundation.org)
- **Primary Ciliary Dyskinesia Family Support Group**  
15 Shuttleworth Grove  
Wavendon Gate Milton Keynes MK7 7RX  
United Kingdom  
**Phone:** 01908 281635

**Email:** [chair@pcdsupport.org.uk](mailto:chair@pcdsupport.org.uk)  
[www.pcdsupport.org.uk](http://www.pcdsupport.org.uk)

- **American Lung Association**  
**Phone:** 800-586-4872 (Toll-free HelpLine)  
**Fax:** 202-452-1805  
**Email:** [info@lung.org](mailto:info@lung.org)  
[www.lung.org](http://www.lung.org)
- **Ciliopathy Alliance**  
 United Kingdom  
[ciliopathyalliance.org](http://ciliopathyalliance.org)

## 5. Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with primary ciliary dyskinesia (PCD), the following evaluations are recommended:

- **Pulmonary disease**
  - Respiratory cultures (typically sputum cultures) to define infecting organisms and to direct antimicrobial therapy. Specific cultures for non-tuberculous mycobacteria should be included for older children and adults.
  - Chest radiographs and/or chest CT to define distribution and severity of airway disease and bronchiectasis
  - Pulmonary function tests (spirometry) to define severity of obstructive impairment
  - Pulse oximetry, with overnight saturation studies if borderline
- **Nasal congestion and/or sinus symptoms.** Sinus imaging (sinus x-rays or preferably sinus CT examination)
- **Chronic/recurrent ear infections.** Formal hearing evaluation (See [Deafness and Hereditary Hearing Loss Overview](#) for hearing evaluations available at different ages.)
- **Other.** Clinical genetics consultation

### Treatment of Manifestations

To date, no specific therapies can correct ciliary dysfunction. The therapies described in this section are empiric and aimed at treating consequences of dysfunctional cilia and sperm flagella. Little evidence supports use of specific therapeutic modalities in PCD.

**Pulmonary disease.** Management of individuals with PCD should include aggressive measures to enhance clearance of mucus, prevent respiratory infections, and treat bacterial infections.

Approaches to enhance mucus clearance are similar to those used in the management of [cystic fibrosis](#), including chest percussion and postural drainage, oscillatory vest, and breathing maneuvers to facilitate clearance of distal airways. Because cough is an effective clearance mechanism, patients should be encouraged to cough and engage in activities that promote deep breathing and cough (e.g., vigorous exercise).

Routine immunizations to protect against respiratory pathogens:

- Pertussis
- Haemophilus influenzae type b
- Pneumococcal vaccine

- Annual influenza virus vaccine

Prompt institution of antibiotic therapy for bacterial infections of the airways (bronchitis, sinusitis, and otitis media) is essential for preventing irreversible damage. Sputum culture results may be used to direct appropriate choice of antimicrobial therapy. In those individuals in whom symptoms recur within days to weeks after completing a course of antibiotics, extended use of a broad-spectrum antibiotic or even prophylactic antibiotic coverage may be considered. (Consideration of chronic antibiotic therapy must include assessing the risk of selecting for multiresistant organisms.)

For individuals with localized bronchiectasis, lobectomy has been performed in an attempt to decrease infection of the remaining lung. This approach, however, is controversial; consultants with expertise in PCD should be involved in the decision-making process.

Lung transplantation has been performed in persons with end-stage lung disease.

**Nasal congestion and sinus infections.** In some persons with extensive sinus disease, sinus surgery can facilitate drainage and relieve symptoms.

**Chronic/recurrent ear infection.** For chronic otitis media unresponsive to antibiotic therapy, PE tube placement may be helpful; however, some individuals with PCD have persistent mucoid discharge following PE tube placement [Hadfield et al 1997].

Speech therapy and hearing aids may be necessary for children with hearing loss and delayed speech.

**Male infertility.** A couple in which the male has PCD-related infertility has the option of in vitro fertilization using ICSI (intracytoplasmic sperm injection). In this procedure, spermatozoa retrieved from ejaculate (in males with oligozoospermia) or extracted from testicular biopsies (in males with obstructive azoospermia) are injected into a harvested egg by in vitro fertilization [Sha et al 2014].

Another option is artificial insemination by donor sperm.

**Situs abnormalities.** Typically, situs abnormalities do not require intervention unless physiologic dysfunction (e.g., congenital heart disease) requiring surgical intervention is present.

## Prevention of Secondary Complications

Appropriate preventive measures:

- Routine immunizations (including influenza vaccine and pneumococcal vaccine) to prevent respiratory infections
- Education about infection control including attention to hand washing, avoidance of sick contacts, proper cleaning/disinfecting of respiratory devices, and early use of antibiotics for respiratory illnesses (directed by prior respiratory cultures)

## Surveillance

Follow up by a pulmonologist to monitor lung function and pathogens in sputum cultures as well as to assess pulmonary disease extent/progression is indicated.

For young children with chronic otitis media, routine hearing evaluation is essential, and should be continued until the teenage years, by which time hearing is usually normal [Majithia et al 2005]. Typically, the ear disease improves in later childhood and hearing screening is not necessary.



## Agents/Circumstances to Avoid

Cough suppressants should not be used because cough is critical for clearing secretions.

Exposure to respiratory pathogens, tobacco smoke, and other pollutants and irritants that may damage airway mucosa and stimulate mucus secretion should be avoided.

## Evaluation of Relatives at Risk

It is appropriate to evaluate the older and younger sibs of a proband in order to identify as early as possible those who would benefit from initiation of treatment and preventive measures.

- If the pathogenic variants in the family are known, molecular genetic testing can be used to clarify the genetic status of at-risk sibs.
- If the pathogenic variants in the family are not known, a rigorous clinical history and physical examination accompanied by chest imaging and nasal nitric oxide measurements can be used to clarify the disease status of at-risk sibs.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Pregnancy Management

For a female with PCD, any pulmonary infections and pulmonary functional status should be rigorously evaluated by an expert in PCD (or cystic fibrosis) to define the risk associated with child bearing.

## Chapter Notes

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- 28 February 2013 (cd) Revision: *DNAAF3*, *CCDC103*, and *LRRC6* mutation testing clinically available; mutations in *HYDIN* and *HEATR2* associated with PCD

- 7 June 2012 (cd) Revision: nomenclature change: *TXNDC3* → *NME8*; clarifications to Molecular Genetics
- 8 March 2012 (cd) Revision: deletion of part or all of *DNAAF1* and an exon deletion in *DNAH5* reported
- 12 January 2012 (cd) Revision: multi-gene panels for primary ciliary dyskinesia now listed in the GeneTests™ Laboratory Directory
- 10 November 2011 (cd) Revision: sequence analysis and prenatal testing available clinically for *DNAL1*
- 15 September 2011 (me) Comprehensive update posted live
- 6 October 2009 (me) Comprehensive update posted live
- 1 February 2008 (cd) Revision: targeted mutation analysis (mutation panel includes 61 mutations in *DNAH5* and *DNAI1*) and prenatal diagnosis available clinically
- 13 June 2007 (cd) Revision: sequence analysis of select exons of *DNAI1* and *DNAH5* available clinically
- 24 January 2007 (me) Review posted live
- 19 July 2006 (mbz) Original submission

## References

### Literature Cited

- Afzelius BA. Cilia-related diseases. *J Pathol.* 2004;204:470–7. PubMed PMID: 15495266.
- Becker-Heck A, Zohn IE, Okabe N, Pollock A, Lenhart KB, Sullivan-Brown J, McSheene J, Loges NT, Olbrich H, Haeffner K, Fliegauf M, Horvath J, Reinhardt R, Nielsen KG, Marthin JK, Baktai G, Anderson KV, Geisler R, Niswander L, Omran H, Burdine RD. The coiled-coil domain containing protein CCDC40 is essential for motile cilia function and left-right axis formation. *Nat Genet.* 2011;43:79–84. PubMed PMID: 21131974.
- Boon M, Wallmeier J, Ma L, Loges NT, Jaspers M, Olbrich H, Dougherty GW, Raidt J, Werner C, Amirav I, Hevroni A, Abitbul R, Avital A, Soferman R, Wessels M, O’Callaghan C, Chung EM, Rutman A, Hirst RA, Moya E, Mitchison HM, Van Daele S, De Boeck K, Jorissen M, Kintner C, Cuppens H, Omran H. MCIDAS mutations result in a mucociliary clearance disorder with reduced generation of multiple motile cilia. *Nat Commun.* 2014;5:4418. PubMed PMID: 25048963.
- Bustamante-Marin XM, Shapiro A, Sears PR, Charng WL, Conrad DL, Leigh MW, Knowles MR, Ostrowski LE, Zariwala MA. Identification of genetic variants in CFAP221 as a cause of primary ciliary dyskinesia. *J Hum Genet.* 2020;65:175–80. PubMed PMID: 31636325.
- Chilvers MA, Rutman A, O’Callaghan C. Ciliary beat pattern is associated with specific ultrastructural defects in primary ciliary dyskinesia. *J Allergy Clin Immunol.* 2003;112:518–24. PubMed PMID: 13679810.
- Cindrić S, Dougherty GW, Olbrich H, Hjejij R, Loges NT, Amirav I, Philipsen MC, Marthin JK, Nielsen KG, Sutharsan S, Raidt J, Werner C, Pennekamp P, Dworniczak B, Omran H. *SPEF2*- and *HYDIN*-mutant cilia lack the central pair-associated protein *SPEF2*, aiding primary ciliary dyskinesia diagnostics. *Am J Respir Cell Mol Biol.* 2020;62:382–96. PubMed PMID: 31545650.
- Davis SD, Ferkol TW, Rosenfeld M, Lee H-S, Dell SD, Sagel SD, Milla C, Zariwala MA, Pittman JE, Shapiro AJ, Carson JL, Krischer J, Hazucha MJ, Cooper ML, Knowles MR, Leigh MW. Clinical features of childhood primary ciliary dyskinesia by genotype and ultrastructural phenotype. *Am J Respir Crit Care Med.* 2015;191:316–24. PubMed PMID: 25493340.
- De Boeck K, Proesmans M, Mortelmans L, Van Billoen B, Willems T, Jorissen M. Mucociliary transport using 99mTc-albumin colloid: a reliable screening test for primary ciliary dyskinesia. *Thorax.* 2005;60:414–417. PubMed PMID: 15860718.
- Edelbusch C, Cindrić S, Dougherty GW, Loges NT, Olbrich H, Rivlin J, Wallmeier J, Pennekamp P, Amirav I, Omran H. Mutation of serine/threonine protein kinase 36 (*STK36*) causes primary ciliary dyskinesia with a central pair defect. *Hum Mutat.* 2017;38:964–969. PubMed PMID: 28543983.

- El Khouri E, Thomas L, Jeanson L, Bequignon E, Vallette B, Duquesnoy P, Montantin G, Copin B, Dastot-Le Moal F, Blanchon S, Papon JF, Lorès P, Yuan L, Collot N, Tissier S, Faucon C, Gacon G, Patrat C, Wolf JP, Dulioust E, Crestani B, Escudier E, Coste A, Legendre M, Touré A, Amselem S. Mutations in DNAJB13, encoding an HSP40 family member, cause primary ciliary dyskinesia and male infertility. *Am J Hum Genet.* 2016;99:489–500. PubMed PMID: 27486783.
- Fassad MR, Shoemark A, le Borgne P, Koll F, Patel M, Dixon M, Hayward J, Richardson C, Frost E, Jenkins L, Cullup T, Chung EMK, Lemullois M, Aubusson-Fleury A, Hogg C, Mitchell DR, Tassin AM, Mitchison HM. C11orf70 mutations disrupting the intraflagellar transport-dependent assembly of multiple axonemal dyneins cause primary ciliary dyskinesia. *Am J Hum Genet.* 2018a;102:956–72. PubMed PMID: 29727692.
- Fassad MR, Shoemark A, Legendre M, Hirst RA, Koll F, le Borgne P, Louis B, Daudvohra F, Patel MP, Thomas L, Dixon M, Burgoyne T, Hayes J, Nicholson AG, Cullup T, Jenkins L, Carr SB, Aurora P, Lemullois M, Aubusson-Fleury A, Papon JF, O'Callaghan C, Amselem S, Hogg C, Escudier E, Tassin AM, Mitchison HM. Mutations in outer dynein arm heavy chain DNAH9 cause motile cilia defects and situs inversus. *Am J Hum Genet.* 2018b;103:984–94. PubMed PMID: 30471717.
- Fliegau M, Olbrich H, Horvath J, Wildhaber JH, Zariwala MA, Kennedy M, Knowles MR, Omran H. Mislocalization of DNAH5 and DNAH9 in respiratory cells from patients with primary ciliary dyskinesia. *Am J Respir Crit Care Med.* 2005;171:1343–9. PubMed PMID: 15750039.
- Hadfield PJ, Rowe-Jones JM, Bush A, Mackay IS. Treatment of otitis media with effusion in children with primary ciliary dyskinesia. *Clin Otolaryngol Allied Sci.* 1997;22:302–6. PubMed PMID: 9298603.
- Frommer A, Hjej R, Loges NT, Edelbusch C, Jahnke C, Raidt J, Werner C, Wallmeier J, Große-Onnebrink J, Olbrich H, Cindrić S, Jaspers M, Boon M, Memari Y, Durbin R, Kolb-Kokocinski A, Sauer S, Marthin JK, Nielsen KG, Amirav I, Elias N, Eitan K, Shoseyov D, Haeffner K, Omran H. Immunofluorescence analysis and diagnosis of primary ciliary dyskinesia with radial spoke defects. *Am J Respir Cell Mol Biol.* 2015;53:563–573. PubMed PMID: 25789548.
- Hannah WB, DeBrosse S, Kinghorn B, Strausbaugh S, Aitken ML, Rosenfeld M, Wolf WE, Knowles MR, Zariwala MA. The expanding phenotype of OFD1-related disorders: Hemizygous loss-of-function variants in three patients with primary ciliary dyskinesia. *Mol Genet Genomic Med.* 2019;7:e911. PubMed PMID: 31373179.
- Höben IM, Hjej R, Olbrich H, Dougherty GW, Nöthe-Menchen T, Aprea I, Frank D, Pennekamp P, Dworniczak B, Wallmeier J, Raidt J, Nielsen KG, Philipsen MC, Santamaria F, Venditto L, Amirav I, Mussaffi H, Prenzel F, Wu K, Bakey Z, Schmidts M, Loges NT, Omran H. Mutations in C11orf70 cause primary ciliary dyskinesia with randomization of left/right body asymmetry due to defects of outer and inner dynein arms. *Am J Hum Genet.* 2018;102:973–84. PubMed PMID: 29727693.
- Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. *Nature.* 2017;549:519–22. PubMed PMID: 28959963.
- Kennedy MP, Leigh MW, Dell S, Morgan L, Molina PL, Zariwala M, Minnix S, Noone PG, Knowles MR. Primary ciliary dyskinesia and situs ambiguus/heterotaxy: Organ laterality defects other than situs inversus totalis. *Proc Am Thorac Soc.* 2006;3:A399.
- Knowles MR, Daniels LA, Davis SD, Zariwala MA, Leigh MW. Primary ciliary dyskinesia: recent advances in diagnostics, genetics, and characterization of clinical disease. *Am J Respir Crit Care Med.* 2013;188:913–22. PubMed PMID: 23796196.

- Knowles MR, Ostrowski LE, Leigh MW, Sears PR, Davis SD, Wolf WE, Hazucha MJ, Carson JL, Olivier KN, Sagel SD, Rosenfeld M, Ferkol TW, Dell SD, Milla CE, Randell SH, Yin W, Sannuti A, Metjian HM, Noone PG, Noone PJ, Olson CA, Patrone MV, Dang H, Lee HS, Hurd TW, Gee HY, Otto EA, Halbritter J, Kohl S, Kircher M, Krischer J, Bamshad MJ, Nickerson DA, Hildebrandt F, Shendure J, Zariwala MA. Mutations in RSPH1 cause primary ciliary dyskinesia with a unique clinical and ciliary phenotype. *Am J Respir Crit Care Med*. 2014;189:707–17. PubMed PMID: 24568568.
- Kosaki K, Ikeda K, Miyakoshi K, Ueno M, Kosaki R, Takahashi D, Tanaka M, Torikata C, Yoshimura Y, Takahashi T. Absent inner dynein arms in a fetus with familial hydrocephalus-situs abnormality. *Am J Med Genet A*. 2004;129A:308–11. PubMed PMID: 15326634.
- Leigh MW, Ferkol TW, Davis SD, Lee HS, Rosenfeld M, Dell SD, Sagel SD, Milla C, Olivier KN, Sullivan KM, Zariwala MA, Pittman JE, Shapiro AJ, Carson JL, Krischer J, Hazucha MJ, Knowles MR. Clinical features and associated likelihood of primary ciliary dyskinesia in children and adolescents. *Ann Am Thorac Soc*. 2016;13:1305–13. PubMed PMID: 27070726.
- Leigh MW, Hazucha MJ, Chawla KK, Baker BR, Shapiro AJ, Brown DE, Lavange LM, Horton BJ, Qaqish B, Carson JL, Davis SD, Dell SD, Ferkol TW, Atkinson JJ, Olivier KN, Sagel SD, Rosenfeld M, Milla C, Lee HS, Krischer J, Zariwala MA, Knowles MR. Standardizing nasal nitric oxide measurement as a test for primary ciliary dyskinesia. *Ann Am Thorac Soc*. 2013;10:574–81. PubMed PMID: 24024753.
- Leigh MW, Pittman JE, Carson JL, Ferkol TW, Dell SD, Davis SD, Knowles MR, Zariwala MA. Clinical and genetic aspects of primary ciliary dyskinesia/Kartagener syndrome. *Genet Med*. 2009;11:473–87. PubMed PMID: 19606528.
- Liu C, Lv M, He X, Zhu Y, Amiri-Yekta A, Li W, Wu H, Kherraf ZE, Liu W, Zhang J, Tan Q, Tang S, Zhu YJ, Zhong Y, Li C, Tian S, Zhang Z, Jin L, Ray P, Zhang F, Cao Y. Homozygous mutations in SPEF2 induce multiple morphological abnormalities of the sperm flagella and male infertility. *J Med Genet*. 2020;57:31–7. PubMed PMID: 31048344.
- Liu W, Sha Y, Li Y, Mei L, Lin S, Huang X, Lu J, Ding L, Kong S, Lu Z. Loss-of-function mutations in SPEF2 cause multiple morphological abnormalities of the sperm flagella (MMAF). *J Med Genet*. 2019;56:678–84. PubMed PMID: 31151990.
- Loges NT, Antony D, Maver A, Dearnorff MA, Güleç EY, Gezdirici A, Nöthe-Menzen T, Höben IM, Jelten L, Frank D, Werner C, Tebbe J, Wu K, Goldmuntz E, Čuturilo G, Krock B, Ritter A, Hjeij R, Bakey Z, Pennekamp P, Dworniczak B, Brunner H, Peterlin B, Tanidir C, Olbrich H, Omran H, Schmidts M. Recessive DNAH9 loss-of-function mutations cause laterality defects and subtle respiratory ciliary-beating defects. *Am J Hum Genet*. 2018;103:995–1008. PubMed PMID: 30471718.
- Loges NT, Olbrich H, Fenske L, Mussaffi H, Horvath J, Fliegauf M, Kuhl H, Baktai G, Peterffy E, Chodhari R, Chung EM, Rutman A, O'Callaghan C, Blau H, Tiszlavicz L, Voelkel K, Witt M, Zietkiewicz E, Neesen J, Reinhardt R, Mitchison HM, Omran H. DNAI2 mutations cause primary ciliary dyskinesia with defects in the outer dynein arm. *Am J Hum Genet*. 2008;83:547–58. PubMed PMID: 18950741.
- MacCormick J, Robb I, Kovesi T, Carpenter B. Optimal biopsy techniques in the diagnosis of primary ciliary dyskinesia. *J Otolaryngol*. 2002;31:13–7. PubMed PMID: 11881766.
- Majithia A, Fong J, Hariri M, Harcourt J. Hearing outcomes in children with primary ciliary dyskinesia--a longitudinal study. *Int J Pediatr Otorhinolaryngol*. 2005;69:1061–4. PubMed PMID: 16005347.
- Marthin JK, Mortensen J, Pressler T, Nielsen KG. Pulmonary radioaerosol mucociliary clearance in diagnosis of primary ciliary dyskinesia. *Chest*. 2007;132:966–76. PubMed PMID: 17646235.
- Merveille AC, Davis EE, Becker-Heck A, Legendre M, Amirav I, Bataille G, Belmont J, Beydon N, Billen F, Clément A, Clercx C, Coste A, Crosbie R, de Blic J, Deleuze S, Duquesnoy P, Escalier D, Escudier E, Fliegauf M, Horvath J, Hill K, Jorissen M, Just J, Kispert A, Lathrop M, Loges NT, Marthin JK, Momozawa Y, Montantin G, Nielsen KG, Olbrich H, Papon JF, Rayet I, Roger G, Schmidts M, Tenreiro H, Towbin JA,

- Zelenika D, Zentgraf H, Georges M, Lequarré AS, Katsanis N, Omran H, Amselem S. CCDC39 is required for assembly of inner dynein arms and the dynein regulatory complex and for normal ciliary motility in humans and dogs. *Nat Genet.* 2011;43:72–8. PubMed PMID: 21131972.
- Mullowney T, Manson D, Kim R, Stephens D, Shah V, Dell S. Primary ciliary dyskinesia and neonatal respiratory distress. *Pediatrics.* 2014;134:1160–6. PubMed PMID: 25422025.
- Noone PG, Leigh MW, Sannuti A, Minnix SL, Carson JL, Hazucha M, Zariwala MA, Knowles MR. Primary ciliary dyskinesia: diagnostic and phenotypic features. *Am J Respir Crit Care Med.* 2004;169:459–67. PubMed PMID: 14656747.
- Olbrich H, Cremers C, Loges NT, Werner C, Nielsen KG, Marthin JK, Philipsen M, Wallmeier J, Pennekamp P, Menchen T, Edelbusch C, Dougherty GW, Schwartz O, Thiele H, Altmüller J, Rommelmann F, Omran H. Loss-of-function GAS8 mutations cause primary ciliary dyskinesia and disrupt the nexin-dynein regulatory complex. *Am J Hum Genet.* 2015;97:546–54. PubMed PMID: 26387594.
- Olcese C, Patel MP, Shoemark A, Kiviluoto S, Legendre M, Williams HJ, Vaughan CK, Hayward J, Goldenberg A, Emes RD, Munye MM, Dyer L, Cahill T, Bevillard J, Gehrig C, Guipponi M, Chantot S, Duquesnoy P, Thomas L, Jeanson L, Copin B, Tamalet A, Thauvin-Robinet C, Papon JF, Garin A, Pin I, Vera G, Aurora P, Fassad MR, Jenkins L, Boustred C, Cullup T, Dixon M, Onoufriadis A, Bush A, Chung EM, Antonarakis SE, Loebinger MR, Wilson R, Armengot M, Escudier E, Hogg C, Amselem S, Sun Z, Bartoloni L, Blouin JL, Mitchison HM, et al. X-linked primary ciliary dyskinesia due to mutations in the cytoplasmic axonemal dynein assembly factor PIH1D3. *Nat Commun.* 2017;8:14279. PubMed PMID: 28176794.
- Paff T, Loges NT, Aprea I, Wu K, Bakey Z, Haarman EG, Daniels JMA, Siermans EA, Bogunovic N, Dougherty GW, Höben IM, Große-Onnebrink J, Matter A, Olbrich H, Werner C, Pals G, Schmidts M, Omran H, Micha D. Mutations in PIH1D3 cause X-linked primary ciliary dyskinesia with outer and inner dynein arm defects. *Am J Hum Genet.* 2017;100:160–8. PubMed PMID: 28041644.
- Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. *Nat Genet.* 2016;48:126–33. PubMed PMID: 26656846.
- Raidt J, Wallmeier J, Hjeij R, Onnebrink JG, Pennekamp P, Loges NT, Olbrich H, Häffner K, Dougherty GW, Omran H, Werner C. Ciliary beat pattern and frequency in genetic variants of primary ciliary dyskinesia. *Eur Respir J.* 2014;44:1579–88. PubMed PMID: 25186273.
- Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 2015;17:405–24. PubMed PMID: 25741868.
- Sha Y, Liu W, Wei X, Zhu X, Luo X, Liang L, Guo T. Biallelic mutations in Sperm flagellum 2 cause human multiple morphological abnormalities of the sperm flagella (MMAF) phenotype. *Clin Genet.* 2019;96:385–93. PubMed PMID: 31278745.
- Sha YW, Ding L, Li P. Management of primary ciliary dyskinesia/Kartagener's syndrome in infertile male patients and current progress in defining the underlying genetic mechanism. *Asian J Androl.* 2014;16:101–6. PubMed PMID: 24369140.
- Shapiro AJ, Davis SD, Ferkol TF, Dell SD, Rosenfeld M, Olivier KN, Sagel SD, Milla C, Zariwala MA, Wolf W, Carson JL, Hazucha MJ, Burns K, Robinson B, Knowles MR, Leigh MW. Laterality defects other than situs inversus totalis in primary ciliary dyskinesia: Insights into situs ambiguus and heterotaxy. *Chest.* 2014;146:1176–86. PubMed PMID: 24577564.
- Shapiro AJ, Davis SD, Polineni D, Manion M, Rosenfeld M, Dell SD, Chilvers MA, Ferkol TW, Zariwala MA, Sagel SD, Josephson M, Morgan L, Yilmaz O, Olivier KN, Milla C, Pittman JE, Daniels ML, Jones MH, Janahi IA, Ware SM, Daniel SJ, Cooper ML, Noguee LM, Anton B, Eastvold T, Ehrne L, Guadagno E, Knowles

- MR, Leigh MW, Lavergne V, et al. Diagnosis of primary ciliary dyskinesia. An official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2018;197:e24–e39. PubMed PMID: 29905515.
- Shapiro AJ, Josephson M, Rosenfeld M, Yilmaz O, Davis SD, Polineni D, Guadagno E, Leigh MW, Lavergne V. Accuracy of nasal nitric oxide measurement as a diagnostic test for primary ciliary dyskinesia. A systematic review and meta-analysis. *Ann Am Thorac Soc*. 2017;14:1184–96. PubMed PMID: 28481653.
- Shoemark A, Frost E, Dixon M, Ollosson S, Kilpin K, Patel M, Scully J, Rogers AV, Mitchison HM, Bush A, Hogg C. Accuracy of Immunofluorescence in the Diagnosis of Primary Ciliary Dyskinesia. *Am J Respir Crit Care Med*. 2017;196:94–101. PubMed PMID: 28199173.
- Toskala E, Haataja J, Shiraski H, Rautiainen M. Culture of cells harvested with nasal brushing: a method for evaluating ciliary function. *Rhinology*. 2005;43:121–124. PubMed PMID: 16008067.
- Wallmeier J, Frank D, Shoemark A, Nöthe-Menchen T, Cindric S, Olbrich H, Loges NT, Aprea I, Dougherty GW, Pennekamp P, Kaiser T, Mitchison HM, Hogg C, Carr SB, Zariwala MA, Ferkol T, Leigh MW, Davis SD, Atkinson J, Dutcher SK, Knowles MR, Thiele H, Altmüller J, Krenz H, Woste M, Brentrup A, Ahrens F, Vogelber C, Morris-Rosendahl DJ, Omran H. De novo mutations in FOXJ1 result in a motile ciliopathy with hydrocephalus and randomization of left/right body asymmetry. *Am J Hum Genet*. 2019;105:1030–9. PubMed PMID: 31630787.
- Wallmeier J, Shiratori H, Dougherty GW, Edelbusch C, Hjej R, Loges NT, Menchen T, Olbrich H, Pennekamp P, Raidt J, Werner C, Minegishi K, Shinohara K, Asai Y, Takaoka K, Lee C, Griese M, Memari Y, Durbin R, Kolb-Kokocinski A, Sauer S, Wallingford JB, Hamada H, Omran H. TTC25 deficiency results in defects of the outer dynein arm docking machinery and primary ciliary dyskinesia with left-right body asymmetry randomization. *Am J Hum Genet*. 2016;99:460–9. PubMed PMID: 27486780.
- Watson CM, Crinnion LA, Morgan JE, Harrison SM, Diggie CP, Adlard J, Lindsay HA, Camm N, Charlton R, Sheridan E, Bonthron DT, Taylor GR, Carr IM. Robust diagnostic genetic testing using solution capture enrichment and a novel variant-filtering interface. *Hum Mutat*. 2014;35:434–41. PubMed PMID: 24307375.
- Wessels MW, den Hollander NS, Willems PJ. Mild fetal cerebral ventriculomegaly as a prenatal sonographic marker for Kartagener syndrome. *Prenat Diagn*. 2003;23:239–42. PubMed PMID: 12627427.
- Zysman-Colman ZN, Kaspery KR, Alizadehfar R, Mykamp KR, Zariwala MA, Knowles MR, Vinh DC, Shapiro AJ. Nasal nitric oxide in primary immunodeficiency and primary ciliary dyskinesia: Helping to distinguish between clinically similar diseases. *J Clin Immunol*. 2019;39:216–224. PubMed PMID: 30911954.

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