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Primary Ciliary Dyskinesia

[*Immotile Cilia Syndrome*]

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Summary

Disease characteristics. Primary ciliary dyskinesia (PCD) is associated with: abnormal ciliary structure and function that result in retention of mucus and bacteria in the respiratory tract, leading to chronic oto-sino-pulmonary disease; situs abnormalities; and abnormal sperm motility. More than 75% of full-term neonates with PCD have 'neonatal respiratory distress' requiring supplemental oxygen for days to weeks. Chronic airway infection, apparent in early childhood, results in bronchiectasis that is almost uniformly present in adulthood. Nasal congestion and sinus infections, apparent in early childhood, persist through adulthood. Chronic/recurrent ear infection, apparent in most young children, can be associated with transient or later irreversible hearing loss. Situs inversus totalis (mirror-image reversal of all visceral organs with no apparent physiologic consequences) is present in 50% of individuals with PCD; heterotaxy (discordance of right and left patterns of ordinarily asymmetrical structures that can be associated with significant malformations) is present in about 6%. About 50% of males with PCD are infertile.

Diagnosis/testing. The diagnosis of PCD requires the presence of the characteristic clinical phenotype and either specific ciliary ultrastructural defects identified by transmission electron microscopy in biopsy samples of the respiratory epithelium or evidence of abnormal ciliary function. The two genes known to be associated with PCD are *DNAI1* (accounting for ~10% of PCD) and *DNAH5* (accounting for ~28% of PCD). Molecular genetic testing of select exons is available on a clinical basis. Mutations in other genes at other loci are thought to be causative as well, but have not yet been identified.

Management. *Treatment of manifestations:* aggressive measures to enhance clearance of mucus (chest percussion and postural drainage, oscillatory vest, breathing maneuvers to facilitate clearance of distal airways) and prompt antibiotic therapy for bacterial infections of the airways (bronchitis, sinusitis, and otitis media); consideration of lobectomy for localized bronchiectasis; lung transplantation for end-stage lung disease; sinus surgery for extensive sinus infections; consideration of PE tube placement for chronic otitis media; speech therapy

and hearing aids as needed. Surgical intervention as needed for congenital heart disease; ICSI (intracytoplasmic sperm injection) or artificial insemination by donor sperm (AIDS) for male infertility. *Prevention of secondary complications:* prevention of respiratory infections through routine immunizations. *Surveillance:* follow-up by a pulmonologist to assess pulmonary disease extent/progression; for those with chronic otitis media, routine hearing evaluation until the teenage years. *Agents/Circumstances to avoid:* cough suppressants; exposure to respiratory pathogens, tobacco smoke, and other air pollutants and respiratoty irritants.

Genetic counseling. PCD is inherited in an autosomal recessive manner. The parents of an affected individual are obligate heterozygotes and therefore carry one mutant allele. Heterozygotes (carriers) are asymptomatic. At conception, each sib of an affected individual has 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. Prenatal testing is available for families in which the disease causing mutations have been identified.

Diagnosis

Clinical Diagnosis

The diagnosis of primary ciliary dyskinesia (PCD) requires the presence of the following:

Characteristic clinical phenotype including but not limited to some of the following:

- **Chronic sinopulmonary disease**
  - Chronic cough and sputum production
  - Chronic wheeze and air trapping
  - Obstructive lung disease on lung function tests
  - Persistent colonization with pathogens commonly found in individuals with PCD
  - Chest radiograph with chronic abnormalities
  - Sinus radiograph with chronic abnormalities
  - Chronic otitis media
  - Neonatal respiratory distress
  - Chronic nasal congestion dating from the newborn period)
- **Situs inversus totalis** (mirror-image reversal of all visceral organs with no apparent physiologic consequences) or **heterotaxy** (discordance of right and left patterns of ordinarily asymmetrical structures, often categorized clinically as asplenia [predominant bilateral right-sidedness (right isomerism) or polysplenia [predominant bilateral leftsidedness (left isomerism)] [Zhu et al 2006].
- **Digital clubbing**

Specific ciliary ultrastructural defects identified by transmission electron microscopy. This "gold standard" diagnostic test for primary ciliary dyskinesia 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].

The most prevalent of the defined ultrastructural defects in primary ciliary dyskinesia are (Figure 1):

- Shortening and/or absence of dynein arms (inner, outer, or both) (~90%);
- Absence or disruption of the central apparatus (central microtubule pair and/or radial spokes) (~10%).

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. (2) Classic Kartagener syndrome with situs inversus, chronic sinusitis, and bronchiectasis in which no apparent ultrastructural defects are observed has been reported. (See Testing for other studies that may provide supportive evidence for PCD.)

Testing

Other studies have been used to provide supportive evidence for PCD, particularly in individuals with normal ciliary ultrastructure. These PCD variants may be missed if the diagnostic testing is restricted to ciliary ultrastructural analysis.

Other tests under evaluation as screening or 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].
- **Measurement of nasal nitric oxide production.** 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. Although measurement of nasal NO has promise as a screening test for PCD, better definition of normative NO values, particularly in young children, and definition of range of NO values in appropriate disease controls are needed.
- **Mucociliary clearance analysis of radiolabeled particles.** Mucociliary clearance has been measured by assessing clearance of radiolabelled particles from the nasal passages or from the lower airways [Coren et al 2002, De Boeck et al 2005]. For these studies, an aerosol containing radiolabeled particles is inhaled and then a gamma camera is used to track deposition and clearance of these insoluble particles.
- **Immunofluorescent staining of ciliary biopsy.** Immunofluorescent assays using *DNAH5* antibodies [Fliegauf et al 2005] hold promise for identifying outer dynein arm defects. The distribution of antibody staining along the ciliary axoneme differs between normal cilia and cilia from individuals with *DNAH5* mutations and outer dynein arm defects. Such testing is available on a research basis only.

Semen analysis. Sperm count is typically normal, but sperm are immotile or motility is severely limited [Afzelius 2004]. In some reports, up to 50% of males with PCD are fertile [Munro et al 1994].

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Genes. Two genes are known to be associated with primary ciliary dyskinesia (PCD):

- ***DNAI1*,** accounting for approximately 10% of PCD [Pennarun et al 1999, Guichard et al 2001, Zariwala et al 2001, Zariwala et al 2006]
- ***DNAH5*,** accounting for approximately 28% of PCD [Olbrich et al 2002, Hornef et al 2006]

Other loci. More than 60% of individuals with well-characterized PCD do not have an identifiable mutation in either of the two known genes.

Mutations in *DNAH11*, which encodes the protein ciliary dynein heavy chain 11, are a possible cause of PCD. One person with paternal uniparental isodisomy of chromosome 7, PCD and situs inversus (Kartagener syndrome), and cystic fibrosis was homozygous for the mutation (R2852X) in *DNAH11* and the mutation (F508del) in *CFTR* [Bartoloni et al 2002]. Because it is very difficult to distinguish between respiratory symptoms caused by cystic fibrosis and those caused by PCD, the authors concluded that mutations in *DNAH11* may cause one form of PCD or one form of situs inversus. Ultrastructural analysis of respiratory cilia from this individual shows normal dynein arms. Of six additional families with PCD who were tested, none had mutations in *DNAH11*. Recently, a family of German origin with PCD and the ciliary normal dynein arms was ascertained. Five affected individuals have situs solitus and one affected individual has situs inversus totalis. All six individuals harbored compound heterozygous mutations in *DNAH11* (Y4128X and A4518_A4523delinsQ). These data suggest the role of *DNAH11* in the causation of PCD [Schwabe et al 2008].

Evidence is also emerging that mutations in genes encoding dynein light chains, spoke head, and other axonemal components may be causative.

Other loci (15q24-q25, 15q13.1-q15.1, 16p12.1-p12.2, and 19q13.42-q13.43) have been implicated in PCD, but thus far no disease-causing genes have been identified (reviewed in Chodhari et al 2004).

Clinical testing

- **Targeted mutation analysis.** Testing involves a panel of previously reported mutations in *DNAI1* and *DNAH5* (Table 1).
- **Sequence analysis of select exons.** The common mutations associated with PCD reside in selected exons of *DNAI1* and *DNAH5* (Table 1). Sequencing of the selected exons shown in Table 1 is estimated to detect at least one mutation in 24% of individuals with PCD.

Research testing

- **Sequence analysis.** Full sequencing of *DNAI1* (20 exons) and *DNAH5* (80 exons), carried out on a research basis, is estimated to detect mutations in approximately 30%-38% of individuals who meet one of the following criteria [Pennarun et al 1999, Guichard et al 2001, Zariwala et al 2001, Zariwala et al 2006]:
  - One *DNAI1* or *DNAH5* mutation detected by targeted mutation analysis

    or
  - Outer dynein arm defects demonstrated by ultrastructural analysis

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Primary Ciliary Dyskinesia

Test Method	Mutations Detected	Mutation Detection Frequency by Gene and Test Method		Test Availability	
		Two Mutations	One Mutation		
Targeted mutation analysis	*DNAI1* and *DNAH5* panel of previously reported mutations [1]	38%		Clinical Testing	
Sequence analysis of select exons [2]	*DNAI1* sequence variants [3] *DNAH5* sequence variants [4]	13%	10%		
Full gene sequencing	*DNAI1* and *DNAH5*	30%	8%	Research only	

1. Panel of mutations may vary among laboratories.
2. The panel of exons for sequencing and the detection rates may vary among laboratories.
3. Exons 1, 13, 16, 17
4. Exons 34, 50, 63, 76, 77

Testing Strategy

To establish the diagnosis in a proband

- Clinical evaluation
- Ciliary ultrastructural analysis
- Ciliary beat frequency and pattern if available
- Nasal nitric oxide measurement if available
- For adult males with unexplained infertility, semen analysis

Carrier testing for at-risk relatives requires prior identification of the disease-causing mutations in the family.

Note: Carriers are heterozygotes for an autosomal recessive disorder and are not at risk of developing the disorder.

Prenatal diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutations in the family.

Genetically Related (Allelic) Disorders

To date, mutations in *DNAI1* and *DNAH5* are not known to be associated with phenotypes other than primary ciliary dyskinesia.

Clinical Description

Natural History

Primary ciliary dyskinesia (PCD) is associated with (1) abnormal ciliary structure and function that result in retention of mucus and bacteria in the respiratory tract and lead to chronic oto-sino-pulmonary disease and (2) abnormal flagellar structure that results in abnormal sperm motility.

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; however, few are diagnosed at this age [Coren et al 2002, Noone et al 2004].

Chronic airway infection is apparent in early childhood. Most children have chronic year-round cough, and chronic sinusitis and nasal congestion (frequently with mucostasis and prominent nasal drainage) beginning in the first months of life and often from birth. Sputum cultures typically yield oropharyngeal flora, *Hemophilus influenzae*, *Streptococcus pneumoniae*, and *Staphylococcus aureus* beginning in early childhood, after which *Pseudomonas aeruginosa* (first smooth and then mucoid) becomes more prevalent. Although rare in childhood, infection with non-tuberculous mycobacteria occurs in more than 10% of adults [Noone et al 2004].

Chronic airway infection results in bronchiectasis that may be apparent in some young children and is almost uniformly present in adulthood.

A subset of adults with chronic airway infection have calcium deposition in the lung and expectorate small calcium stones (lithoptysis) [Kennedy et al 2006].

Some develop end-stage lung disease in mid-adulthood and several have undergone lung transplantation.

While the onset of airway disease in PCD occurs early in childhood, the progression of lung disease can be slowed with appropriate therapy.

Nasal congestion and sinus infections. Nasal congestion and sinus infections become apparent in early childhood and persist through adulthood [Noone et al 2004, Leigh 2006].

Chronic/recurrent ear infection. Chronic/recurrent ear infection is apparent in most young children with PCD, but 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 [Hadfield et al 1997, Majithia et al 2005].

Infertility. Males with PCD may be infertile secondary to impaired sperm motility because the flagella of the sperm and cilia often (but not always) have the same ultrastructural and functional defects.

Some women with PCD have normal fertility, but others have impaired fertility and an 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 nearly 50% of individuals with PCD.
- **Heterotaxy** (also called "situs ambiguous") is present in at least 6% of individuals with PCD [Kennedy et al 2006]. Heterotaxy, discordance of right and left patterns of ordinarily asymmetrical structures, is distinct from situs inversus and is often categorized clinically as asplenia [predominant bilateral right-sidedness (right isomerism)] or polysplenia [predominant bilateral left-sidedness (left isomerism)].

  In those with heterotaxy, congenital cardiovascular malformations are common, 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 (IVC) and bilateral superior vena cavae (SVC) [Zhu et al 2006].

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 and the liver may be midline or may be reversed in its left and right lobes.

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 in some individuals with PCD and may reflect dysfunctional ependymal cilia [Kosaki et al 2003, Wessels et al 2003].

Genotype-Phenotype Correlations

Mutations in *DNAI1* and *DNAH5* associated with primary ciliary dyskinesia result exclusively in defects of the outer dynein arms of cilia [Pennarun et al 1999, Guichard et al 2001, Zariwala et al 2001, Zariwala et al 2006].

Genotype-phenotype correlation for the majority of mutations is not available.

One report correlated genotype and phenotype in individuals with *DNAH5* mutations [Kispert et al 2003]. A mutation causing premature translation termination resulted in complete absence of outer dynein arms whereas a splice site mutation resulted in shortened outer dynein arms.

Nomenclature

Terms used in the past to describe the condition currently known as primary ciliary dyskinesia (PCD) include dyskinetic cilia syndrome and acilia syndrome.

PCD associated with situs inversus totalis is known as Kartagener syndrome.

Prevalence

The incidence of PCD, estimated to be about 1:16,000 individuals in Norway and Japan, was extrapolated from radiographic surveys associating dextrocardia with clinical evidence of bronchiectasis [Torgersen 1950, Katsuhara et al 1972]. Based on these figures, the total number of individuals with PCD in the United States is estimated to be about 12,000 to 17,000.

The incidence may be higher in population isolates with a high rate of consanguinity.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Chronic sinopulmonary disease and bronchiectasis. Appropriate studies to exclude the following disorders should be performed during the evaluation for primary ciliary dyskinesia (PCD):

- Cystic fibrosis
- Immunodeficiency, such as immunoglobulin G (IgG) subclass deficiency
- Allergies

- Gastroesophageal reflux disease (GERD)
- Young syndrome: male infertility (obstruction of the epididymis by inspissated secretions) with chronic sinopulmonary infection [Handelsman et al 1984]
- Wegener's granulomatosis (upper- and lower-airway disease)

Situs abnormalities. Failure to establish normal left-right (L-R) asymmetry can result in a wide spectrum of congenital disorders including situs inversus totalis and heterotaxy syndrome (polysplenia and asplenia) that may be coincidentally associated with heart defects. More than 80 genes, including *DNAH5* and *DNAI1*, are required for the development of visceral asymmetry. Approximately 25% of individuals with situs inversus totalis have PCD [Zhu et al 2006]. Prevalence of PCD within the heterotaxy subclass is unknown but at least 6% of individuals with PCD have heterotaxy [Kennedy et al 2006].

Other. PCD is usually inherited in an autosomal recessive manner, but in rare instances other modes of inheritance have been reported. Narayan et al (1994) described a mother and her five sons from three different fathers (who were not related to the mother), all of whom had PCD; one affected child also had dextrocardia. This finding suggests either X-linked or autosomal dominant mode of inheritance.

Occasionally, mutations in *RPGR* (involved in X-linked retinitis pigmentosa) have been identified in males with retinitis pigmentosa cosegregating with PCD [Moore et al 2006 and references within].

A mutation in *OFD1* (involved in oral-facial-digital syndrome type 1) was found in a family in which X-linked mental retardation cosegregated with PCD [Budny et al 2006].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease 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)

Chronic/recurrent ear infections. Formal hearing evaluation (See Deafness and Hereditary Hearing Loss Overview for types of hearing evaluations available at different ages.)

Treatment of Manifestations

At present, there are no specific therapies to correct ciliary dysfunction. The therapies described in this section are empiric and aimed at treating consequences of dysfunctional cilia and sperm flagella. There is little evidence to support 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 such as vigorous exercise that promote deep breathing and cough.

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 multi-resistant organisms.)

For individuals with localized bronchiectasis, lobectomy has been performed in an attempt to decrease infection of the remaining lung; however, because this approach 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 patients 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 had offensive otorrhea following PE 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 IVF (in vitro fertilization) [Cayan et al 2001, Westlander et al 2003, Peeraer et al 2004].

Other options are artificial insemination by donor sperm (AIDS).

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

Measures to prevent respiratory illnesses include immunizations (annual influenza and pneumococcal vaccines and routine childhood immunization), as well as good hand hygiene and limitation of exposure to individuals with acute infections.

Surveillance

At follow-up visits with a pulmonologist, respiratory cultures, chest imaging studies, and spirometry are used to assess the extent and progression of the pulmonary disease.

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.

Testing of Relatives at Risk

Relatives with symptoms or findings suggestive of PCD such as neonatal respiratory distress despite term gestation, chronic oto-sino-pulmonary disease, bronchiectasis, situs inversus totalis, other situs abnormalities, and male infertility should undergo diagnostic evaluation for PCD.

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

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Because PCD is rare, multi-center trials will be necessary to include adequate numbers of individuals for clinical trials. Efforts to create a network of centers interested in PCD that could participate in multi-center trials are underway.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Primary ciliary dyskinesia (PCD) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has 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.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with PCD are obligate heterozygotes (carriers) for a disease-causing mutation.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier Detection

Carrier testing for at-risk family members is available on a clinical basis once the mutations have been identified in the family.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk and clarification of carrier status 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 or at risk.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for families in which biallelic disease-causing mutations have been identified is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Requests for prenatal testing for conditions such as PCD that do not affect intellect and have some treatment available are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Primary Ciliary Dyskinesia

Gene Symbol	Chromosomal Locus	Protein Name
DNAH5	5p15-p14	Ciliary dynein heavy chain 5
DNAI1	9p21-p13	Dynein intermediate chain 1, axonemal

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Primary Ciliary Dyskinesia

242650	PRIMARY CILIARY DYSKINESIA; PCD
244400	KARTAGENER SYNDROME
603335	DYNEIN, AXONEMAL, HEAVY CHAIN 5; DNAH5
604366	DYNEIN, AXONEMAL, INTERMEDIATE CHAIN 1; DNAI1

Table C. Genomic Databases for Primary Ciliary Dyskinesia

Gene Symbol	Entrez Gene	HGMD
DNAH5	1767 (MIM No. 603335)	DNAH5
DNAI1	27019 (MIM No. 604366)	DNAI1

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

Cilia, organelles present on almost every cell, emanate from one of the basal bodies, a modified centriole. Different categories of cilia include: motile cilia, non-motile primary cilia, and motile primary cilia (e.g., nodal cilia). The axoneme is a complex, highly conserved structure. Motile cilia are made up of approximately 250 proteins, each cilium has a '9+2' arrangement with nine peripheral microtubule doublets surrounding the central microtubule pair (Figure 1). The outer and inner dynein arms are present on the peripheral microtubules and are visible on transmission electron microscopic images of the ciliary cross sections. The outer and inner arm dyneins form a bridge between the doublet microtubules in the axoneme, and are the force-generating proteins responsible for ciliary beating [Afzelius et al 2001,El Zein et al 2003,Afzelius 2004,Zariwala et al 2007]. The outer dynein arm comprises several heavy,

intermediate, and light chains [Satir 1999]. The inner dynein arm is highly complex and varies along the entire length of the axoneme [Perrone et al 2000,DiBella & King 2001].

Defects in cilia have been associated with several human disorders including primary ciliary dyskinesia (PCD)/Kartagener syndrome, Bardet-Biedl syndrome (basal body of the cilia), autosomal dominant polycystic kidney disease, autosomal recessive polycystic kidney disease (defective renal monocilia), nephronophthisis (Senior-Loken syndrome), retinitis pigmentosa (photoreceptor connecting cilia), hydrocephalus, and Alstrom syndrome [Afzelius 2004, Badano et al 2006, Zariwala et al 2007]. Most of these disorders are genetically heterogeneous, with many genes remaining to be identified [Badano et al 2006].

PCD is characterized by abnormalities in the structure and function of cilia of the respiratory tract and flagella of sperm. Absent (or shortened) dynein arms occur in approximately 90% of individuals who have defined ultrastructural defects; about 10% have defective central complex or radial spoke or nexin links [Chilvers et al 2003, Noone et al 2004, Carlen & Stenram 2005]. Some individuals with PCD have no apparent ultrastructural abnormalities. Thus far, mutations causing autosomal recessive PCD have been clearly linked to two genes, *DNAI1* and *DNAH5*. Both genes encode the outer dynein arm proteins. The presence of situs inversus totalis in 50% of individuals with PCD provides evidence of the role for cilia in directing left-right asymmetry in the embryo.

The axonemal structure of a unicellular alga, *Chlamydomonas reinhardtii*, is similar to the structure of human cilia. Several motility-defective mutant strains of *Chlamydomonas* are known; their human counterparts could be candidates for PCD.

Homozygous deletion of *Mdnah5* in mouse resulted in the PCD phenotype including situs abnormalities, recurrent respiratory symptoms, ciliary immotility, hydrocephalus, and outer dynein arm defects by ultrastructural analysis [Ibanez-Tallon et al 2002].

Additionally, homozygous deletion of the motor domain of mouse *lrd* gene (ortholog of *DNAH11*) caused only situs inversus without the respiratory phenotype and normal ultrastructure of respiratory cilia [Supp et al 1999].

DNAI1

Normal allelic variants: The human *DNAI1* gene contains 20 exons and encodes a 699-amino acid protein.

Pathologic allelic variants: About 18 different mutations have been identified in *DNAI1*. Certain mutations appeared in two or more unrelated families including IVS1+2_3insT in intron 1 and the mutation cluster in exons 13, 16, and 17. The IVS1+2_3insT mutation accounts for about 55% of mutant alleles. Microsatellite marker analysis from the close proximity of *DNAI1* revealed IVS1+2_3insT to be a founder mutation [Zariwala et al 2006]. About 29% of mutations are present in exons 13, 16, and 17, the conserved WD repeat region of the gene.

Fifteen percent of mutations identified to date are missense and the remaining are nonsense and splice site mutations, insertions, and deletions [Zariwala et al 2006].

Normal gene product: Dynein axonemal intermediate chain 1 belongs to the large family of motor proteins [Pennarun et al 1999]. It contains five conserved WD repeat regions (containing tryptophane-aspartate) at the carboxy-terminal portion of the gene.

Abnormal gene product: The mutations in *DNAI1* gene lead to the defective (absent, or only shortened) outer dynein arms, as seen by ciliary ultrastructural analysis.

- The common mutation IVS1+2_3insT abrogates the splice donor site in cDNA, leading to the addition of intron 1 sequences, predicted to lead to premature translation termination [Pennarun et al 1999].
- Splice site mutation 1490G>A (R468_K523del) at the beginning of exon 16 is found to cause the in-frame deletion of exons 15 and 16, comprising 56 amino acids.
- The mutation IVS19+1G>A led to the in-frame deletion of exon 19 in cDNA [Zariwala et al 2006].

DNAH5

Normal allelic variants: The human *DNAH5* gene contains 79 exons with an alternative first exon.

Pathologic allelic variants: *DNAH5* mutations have been found in 28% of individuals with PCD [Olbrich et al 2002, Hornef et al 2006]. A total of 42 mutant alleles are known. Approximately 47% of the mutant alleles cluster in five exons (34, 50, 63, 76, 77). One mutation (10815delT) in exon 63 occurred in seven unrelated families. Deduced haplotype using a large number of intragenic single nucleotide polymorphisms indicated that 10815delT is a founder mutation. Fifteen percent of mutations were missense and the remaining were nonsense and splice site mutations, insertions, and deletions [Hornef et al 2006].

Normal gene product: *DNAH5* encodes ciliary dynein heavy chain 5, a 4624-amino acid protein. The N-terminal domain forms the stem domain of outer dynein arm complex and is involved in interaction with other heavy, intermediate and light chains. The C-terminal region that makes globular head contains six conserved 6 p-loop domains and conserved mictotubule binding site (MTB). The first p-loop domain is known to bind and hydrolyze the ATP [Olbrich et al 2002].

Abnormal gene product: In one individual, the splice mutation R577T led to the out-of-frame deletion of exon 13 predicted to cause premature translation termination signals [Hornef et al 2006]. Mutations in *DNAH5* lead to the defective outer dynein arms seen by ciliary ultrastructural analysis. Additionally, alteration in the distribution of the DNAH5 protein was observed by immunofluorescent analysis in individuals with mutations in *DNAH5*.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Kartagener's Syndrome and Primary Ciliary Dyskinesia Foundation
Email: nc-fuerleru@netcologne.de
www.kartagener-syndrome.org

PCD (Primary Ciliary Dyskinesia) Foundation
29252 N. 22nd. Lane
Phoenix AZ 85085
Phone: 623-215-2032; 612-396-1179
Fax: 623-215-6670
Email: info@pcdfoundation.org
www.pcdfoundation.org

Primary Ciliary Dyskinesia Family Support Group
67 Evendons Lane
Wokingham
Berks RG41 4AD
United Kingdom
Phone: 0118 9770258
www.pcdsupport.org.uk

American Lung Association
61 Broadway 6th Floor
New York NY 10006
Phone: 800-LUNGUSA (800-586-4871)
Primary Ciliary Dyskinesia

Genetic Diseases Of Mucocilliary Clearance Consortium Registry
7019 Thurston Bowles Bldg CB#7248
Chapel Hill NC 27599
Fax: 919-966-7524
Email: godwine@med.unc.edu
Genetic Diseases Of Mucocilliary Clearance Consortium Registry

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Suggested Readings

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Chapter Notes

Author Notes

Web site: www.med.unc.edu/dept_path.htm

Web site: www.med.unc.edu/cystfib/PCD.htm

Web site: www.med.unc.edu/dept_pediatrics.htm

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Revision History

- 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 to live Web site
- 19 July 2006 (mbz) Original submission

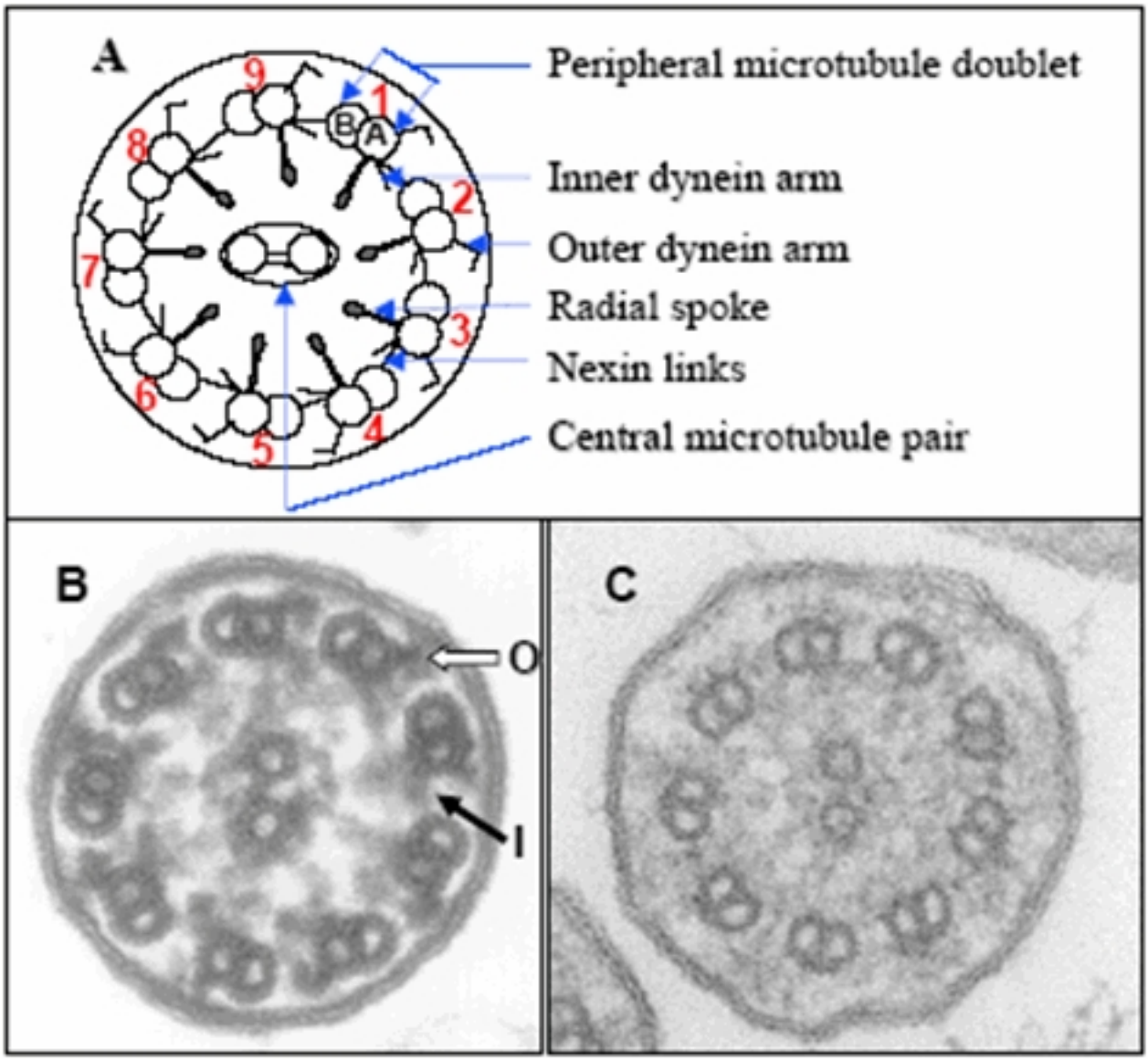

Figure 1. Cross section of the cilia

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

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.

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