Primary Ciliary Dyskinesia: An Update on New Diagnostic Modalities and Review of the Literature

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Primary ciliary dyskinesia (PCD) is a genetic condition affecting approximately 1 in 15,000–20,000 individuals, and the majority of cases exhibit an autosomal recessive inheritance pattern. However, genetic heterogeneity is seen in PCD and reflects the complexity of ciliary structure and biogenesis. There have been many recent advances in the diagnosis and management of PCD in the last few years, including advanced genetic sequencing, nasal nitric oxide assay, and ciliary motility tests. This article focuses on the ultrastructure and pathophysiology of ciliary dyskinesias, along with a review of clinical features, screening, and diagnostic tests. It also reflects upon the diagnostic challenge caused by the diverse clinical presentation, which will be of great value to pediatricians for considering PCD in their differential list, henceforth leading to early recognition and management, along with awareness of the recent advances in the field of genetics and other techniques for diagnosis of this condition.

Introduction

PRIMARY CILIARY DYSKINESIA (PCD) is a heterogeneous genetic disorder characterized by abnormal ciliary ultrastructure or function leading to impaired mucociliary clearance and recurrent respiratory infections, which may result in decline in lung function over time.¹ Inheritance usually follows autosomal recessive pattern, though X-linked inheritance² has been reported. The estimated prevalence of PCD is 1 in 15,000–20,000 individuals, though experts believe this is an underestimate. PCD is often under diagnosed or misdiagnosed because symptoms may overlap with other more common respiratory conditions, leading to an underestimation of the actual prevalence rate, especially in children. There is some evidence from observational data that early diagnosis and management of patients with PCD in a specialized PCD clinic may improve long-term lung function outcomes.¹ In order to avoid delays in diagnosis and potentially to improve outcomes, it is imperative to consider referral to a disease-specific treatment center.

Historical Perspective

Siewart first described an association of sinusitis, bronchiectasis, and situs inversus in 1904.³ This triad of symptoms was again described in 1933⁴ by Kartagener and became known as Kartagener's triad. In the mid-1970s, Afzelius^{5,6} recognized altered ciliary ultrastructure, specifically noting a deficiency of dynein arms, decreased muco-

ciliary clearance, and a lack of ciliary motion in patients with immotile sperm and recurrent sinopulmonary infections. His team ultimately coined the term “immotile cilia syndrome” and noted that situs inversus occurred in half of the patients.⁷ Simultaneously and subsequently, many different ultrastructural changes in cilia were described to cause the syndrome.^{8–11} Afzelius et al. noted functional ciliary impairment without ultrastructural deformity,¹² as well as motile cilia with grossly abnormal movement pattern, in patients with immotile cilia syndrome.^{13–15} These observations led to a renaming of the disorder to “primary ciliary dyskinesia.”¹⁶

Structure and Function of Cilia

Cilia are membrane-bound structures that project from the cell surface and are found on almost all cell types in humans. In the respiratory tract, the density of cilia decreases from upper to lower airways, with virtually no cilia in alveoli and air sacs.¹⁷ Mammalian cilium consists of a basal body, which attaches the cilium to the cell, a trunk, and the apex or crown. The trunk consists of a microtubule cytoskeleton—the axoneme that is surrounded by a specialized ciliary membrane. The axoneme consists of a circular arrangement of nine microtubule doublets surrounding a central pair of microtubule singlet (9+2), or with an arrangement where the central pair is absent (9+0).¹⁸ The ciliary axonemes can be broadly classified in these categories: 9+2 motile cilia with dynein arms (in respiratory

epithelium), 9+0 nonmotile cilia lacking dynein arms (in kidney tubules), and 9+0 motile cilia with dynein arms (in the embryonic node, which are thought to be necessary for left-right positioning of organs^{18–21}; Fig. 1). However, there are exceptions to these rules. Both motile 9+0 cilia¹⁸ and immotile 9+2 cilia²⁰ have been described.

The peripheral microtubules are linked each other by nexin links and to the central tubules via radial spokes. Attached to the nine outer doublets are two distinct dynein arms: an inner dynein arm (IDA) and an outer dynein arm (ODA). A major component of these dynein arms are adenosine triphosphatases (ATPases) that act as the molecular motors of cilia and cleave adenosine triphosphate (ATP) to promote the sliding of microtubules.

Apart from the lower respiratory epithelium, 9+2 motile cilia are found along the upper respiratory epithelium (such as paranasal sinuses and eustachian tubes), sperm tail,¹⁸ female reproductive tract, and on ependymal cells lining the brain ventricles. Cilia with the 9+0 arrangement, also referred to as “primary cilia,” are also found on kidney epithelial cells in the kidney, bile duct, endocrine pancreas, and thyroid, as well as nonepithelial cells, such as chondrocytes, fibroblasts, smooth muscle cells, and neurons. Based on their widespread distribution, abnormal cilia have been implicated in various diseases such as PCD, infertility, hydrocephalus,²² situs inversus, polycystic kidney disease, retinal degeneration, skeletal defects, and several other conditions. Many of these conditions have overlapping phenotypic features because they are genetically heterogeneous, and the manifestations likely depend on the specific defect, the pattern of expression of the altered gene, and the functional dependency of the tissue. Collectively, these disorders are referred to as ciliopathies.^{20,23}

Motile cilia in the airway are surrounded by thin, watery periciliary fluid. Overlying the periciliary layer is a more viscous layer of mucus. Particles become trapped in the mucous layer and are propelled toward the oropharynx by the coordinated (metachronal) movement of cilia.²⁴ The efficacy of this function depends on the viscosity and composition of periciliary fluid and overlying mucus, the integrity of airway epithelium, and the synchrony and beat frequency of the cilia.

Cilia beat and move by a three-dimensional, synchronous sliding action of the microtubules. Ciliary beat frequency

ranges from 8 to 20 Hz under normal conditions. The frequency of ciliary beating is variable and correlates with the mucus thickness in the different parts of the tracheobronchial tree. These movements occur by hydrolysis of ATP generated by IDAs and ODAs, which are connected to ATPases. Thus, dynein arms are responsible for ciliary motion, whereas radial spokes determine the direction of ciliary beating by restricting the degree of sliding. The sliding of the microtubules is synchronous and controlled, initially involving the dynein arms on only one side of cilia, allowing the cilia to bend. There is an effective stroke and a recovery stroke leading to ciliary beat. In the airway, the effective stroke is vertical. This causes movement of the cilia in the overlying mucus layer propelling mucus toward the oropharynx. The recovery stroke is horizontal. This allows cilia to stand upright again in the periciliary fluid layer underneath the mucus.^{18–20,25}

In contrast to the waveform sliding motion of 9+2 cilia, motile nodal 9+0 cilia beat with a vertical motion generating leftward nodal flow. It is postulated that this motion of nodal cilia in the extra-embryonic fluid determines the normal left-right axis of symmetry of the viscera. The absence or dysfunction of ciliary motility causes randomization of rotation and may result in situs inversus. Mutations affecting the left-right dynein (*Lrd*) gene have been shown to cause left-right asymmetry in the inversus viscerum (*iv/iv*) mouse model.²⁶

Apart from the primary defect in ciliary structure and/or function, many extrinsic factors such as tobacco smoke²⁷ and certain microbes^{28,29} have been implicated in alteration of ciliary function either directly or via release of inflammatory mediators leading to clinical consequences of mucociliary dysfunction.³⁰ These disorders are collectively referred to as acquired or secondary ciliary dyskinesia (SCD).

Clinical Features

The clinical phenotype in PCD is extensive and overlaps with more common disorders based on the organ system involvement.^{31–33} Patients with classic PCD typically present with chronic respiratory symptoms.³⁴ Age at presentation ranges from birth to adulthood. In the most extensive recent North American review of a case series of 78 patients diagnosed with PCD, all patients reported chronic cough with upper airway symptoms and rhinitis. Nearly two-thirds of the pediatric patients had situs inversus totalis compared to approximately half of the adult patients. Almost all patients (95%) had a history of recurrent otitis media. Neonatal respiratory symptoms were a common presentation, with 74% of patients reporting this. The majority of patients had evidence of bronchiectasis based on clinical and radiographic criteria.^{35,36} The clinical symptoms reported in this case series were similar to symptoms reported in an earlier case series review including fewer patients.^{36–38}

In the neonatal period, patients with PCD may present with tachypnea, respiratory distress, hypoxia, or neonatal pneumonia without any obvious predisposing factors.³¹ Many patients present with continuous rhinorrhea, with parents describing that it started on the first day of life.³⁹ Other associated features include disorders of laterality,^{36,38} complex congenital heart disease,³⁸ heterotaxy,⁴⁰ dextrocardia,³⁸ hydrocephalus,^{22,37,41} biliary atresia,⁴² and esophageal abnormalities.³⁸ Of note, PCD should be

FIG. 1. Cilia and flagella structure reproduced with the courtesy of Molecular Expressions, National High Magnetic Field Laboratory, The Florida State University. Color images available online at www.liebertpub.com/ped

considered prenatally in patients with any of the above associated defects noted on antenatal ultrasound.³⁹ Though situs inversus totalis has been described in almost 50% of the patients with PCD,⁷ heterotaxy (situs ambiguous) has been described in approximately 6% of patients in one study.⁴⁰ This study also reported that the prevalence of congenital heart disease with heterotaxy is 200 times higher in PCD patients compared to the general population.⁴⁰

In infants and older children, PCD manifests as a chronic productive or wet-sounding cough, recurrent upper and lower respiratory tract infections, shortness of breath, chronic chest congestion, chronic rhinosinusitis (rarely, nasal polyps), non-cystic fibrosis (non-CF) bronchiectasis, severe gastroesophageal reflux, and recurrent otitis media with effusion, often requiring multiple interventions.^{31,43} Many are misdiagnosed as having asthma, recurrent pneumonia, or bronchitis.

Adolescents or adults with PCD present similarly to younger children, but bronchiectasis is more evident and clubbing may be present. The presence of abnormal cilia in the fallopian tubes of adolescent or adult females with PCD can lead to subfertility and increased risk of ectopic pregnancy.⁴⁴ Males frequently present with infertility due to abnormal sperm motility or ciliary dyskinesia of the vas deferens, but a significant percentage of males are fertile.⁴⁵

Radiological Findings

The most common findings noted on chest x-rays of patients with PCD are hyperinflation and variable degree of bronchial wall thickening. Less frequent findings include atelectasis and/or consolidation.⁴⁶ Dextrocardia is identified in approximately half of the patients with PCD.

High-resolution computed tomography (HRCT) of the chest is considered the gold-standard imaging technique for evaluation of early airway changes and parenchymal abnormalities in chronic lung conditions such as PCD.⁴⁷ The most common HRCT findings in patients with PCD include peribronchial thickening, mucus plugging, and bronchiectasis, but consolidation, ground-glass opacities, focal air trapping, and mosaic attenuation are also observed^{48,49} (see Fig. 2). The radiographic abnormalities in various studies

FIG. 2. Noncontrast computed tomography (CT) scan of the thorax in a patient with primary ciliary dyskinesia (PCD) showing dextrocardia with left lingular bronchiectasis and mild bronchial wall thickening throughout both lungs.

have shown basal predilection, with severity scores highest in the middle and the lingular lobes.⁴⁹ HRCT has thus remained the diagnostic modality of choice for localization and assessment of severity of the disease. However, the accumulation of radiation doses in relation to frequent follow-up in such patients, and the fact that children are more sensitive to radiation compared to adults,⁵⁰ limits the utility.

It has been recently shown in a small study that chest high-field 3.0-T magnetic resonance imaging (MRI) is equally effective as HRCT in evaluating the magnitude and severity of pulmonary abnormalities in children with non-CF chronic lung disease, including PCD, without exposure to radiation.⁵¹ However, limited spatial resolution, lengthy study duration, high cost, and lack of randomized clinical trials preclude its use. Studies have shown persistent abnormal ventilation-perfusion scans in more than two-thirds of patients with PCD, but this imaging modality is not routinely used to monitor disease progression.⁵²

Lung Function in PCD

The lung function abnormalities in PCD are thought to result from recurrent airway infections resulting in scarring with airway remodeling. The most frequently observed abnormality is an obstructive ventilatory defect with air trapping. However, a mixed pattern has been described. The obstructive defect can progress to end-stage lung disease in some patients. A recent study showed an average decline in forced expiratory lung volume in 1 second (FEV1) of 0.8% per year in patients with PCD.³⁵

A longitudinal study in 1997 showed that lung function was significantly lower in PCD patients entering a standardized treatment cohort in adulthood as compared to those entering during childhood. This study also showed that lung function remained stable in most patients after diagnosis, suggesting that regular follow-up and treatment could alter progression.¹ The largest longitudinal study to date examining lung function over time in patients with PCD followed at a tertiary care center has cast doubts on these earlier conclusions. This study demonstrated abnormal lung function in a third of patients diagnosed at preschool age. It also showed no correlation between age at diagnosis, lung function at the time of diagnosis, and pattern of lung function over time.⁵³ In a recent case series, three children diagnosed before 3 years of age demonstrated abnormal infant pulmonary function test (PFT) measurements, raising concern that irreversible lung damage can be present at a very early age.⁵⁴

Controversy exists in determining the best way to monitor lung function changes over time. Studies have shown significant correlation between pulmonary function tests (forced vital capacity [FVC] and FEV1) and CT scan findings in patients with PCD.⁴⁸ However, a recent retrospective study evaluated HRCT and spirometry at baseline (stable lung disease) and during respiratory exacerbation (unstable lung disease), and no relationship was found between HRCT and spirometry results. The structural lung disease, as evidenced by CT, worsened in patients with PCD, though spirometry results were stable, suggesting that spirometry was less accurate than CT scan in assessing the progression of lung disease in PCD.⁵⁵

Results from the ongoing multicenter, prospective studies of the lung function and disease progression, coordinated

from the University of North Carolina (ClinicalTrials.gov Identifier: NCT00450918 and NCT00722878) have not yet been posted.

Diagnosis

PCD presents a diagnostic challenge due to range of phenotypic presentations and specialized expertise required to conduct and interpret available diagnostic testing. The American Thoracic Society sponsored a workshop in 2005 to review the diagnosis and management of PCD, and it is expected that a consensus statement will be published. The European Respiratory Society published an excellent consensus statement on the diagnosis and management of patients with PCD in 2009.³⁹

The following section will review the various tests that can be used to support the diagnosis of PCD. Screening tests include saccharin testing, radioaerosol testing, and nasal nitric oxide (NO) testing. Children with clinical findings of PCD, radiographic findings (bronchiectasis, bronchial wall thickening), or heterotaxy should be screened, and diseases with similar features excluded (e.g., CF, immunodeficiency, chronic aspiration). Diagnostic testing includes electron microscopy analysis of ciliary structure, ciliary beat pattern and frequency analysis, and genetic testing. Any positive screening testing warrants confirmatory diagnostic testing.

Saccharin test

In this screening test, a 1–2 mm tablet of saccharin is placed on the inferior turbinate, and the time taken to taste the saccharin is recorded, which gives a rough estimation of nasal mucociliary clearance. It requires a great deal of cooperation from the subject. Hence, it is challenging to perform in children, and there are no acceptable reference values available in children. This test is inexpensive, but can be unreliable and miss cases of dyskinetic cilia.⁵⁶

Radioaerosol tests

Reduced pulmonary mucociliary function estimated by airway clearance of radioactive tracer labeled aerosols has been used for screening of PCD. The sensitivity of this test is high, but specificity is low, and therefore a negative test can be valuable to rule out PCD in suspected cases.^{53,57} It has been used in children over the age of 5 years, although no reference values are available for children. The test is time intensive, involves exposure to radiation, and can result in inconclusive results in the presence of a cough.⁵³

Nasal NO assay

Nasal NO testing has proved to be a useful noninvasive screening test for PCD. NO is produced from the amino acid L-arginine by the enzyme NO synthase (NOS). The upper respiratory tract contributes the majority of exhaled NO in healthy individuals, whereas a small portion originates from the lower respiratory tract.⁵⁸ NO has been shown to increase ciliary beat frequency⁵⁹ and also contributes to host defense. NOS is induced in the setting of inflammation or infection, and elevated levels of exhaled NO are found in conditions such as asthma,⁶⁰ bronchiectasis,⁶¹ and upper airway infections.⁶² Glucocorticoids inhibit NOS.⁶³ For reasons that are poorly understood, reduced levels of exhaled NO are

observed in PCD,^{64–66} CF,^{65,67} nasal polyposis, chronic sinusitis,^{68,69} and systemic sclerosis with pulmonary hypertension.⁷⁰

Multiple studies have shown that nasal NO is significantly lower in adult patients with PCD compared to healthy controls and disease controls (CF, idiopathic bronchiectasis, sinusitis, and Young's syndrome), making it a useful screening tool for PCD.⁷¹

There have been very limited data in the literature regarding the use of nasal NO in the pediatric population with PCD. Recently, a large prospective trial evaluated nasal NO levels by three different sampling methods; breath holding (BH-nNO), oral exhalation against resistance (OE-R-nNO), and tidal breathing (TB-nNO) in 282 subjects, including those with PCD, healthy controls, and disease controls (CF), ranging from infancy to adulthood. All the methods reliably and significantly distinguished PCD subjects from non-PCD patients and healthy controls. The study also showed that in children younger than 6 years of age, nasal NO measurement via OE-R-nNO is more reliable.⁷²

In addition to the challenges in test administration and the cost associated with this test, there are no agreed screening cutoff values available, and currently there are no FDA-approved devices for nasal NO measurements available in United States.⁷³ However, one of the recent multicentric prospective trials conducted by investigators in the Genetic Disorders of Mucociliary Clearance Consortium (GDMCC) across seven geographical locations in North America used a standardized protocol for measuring nasal NO to establish cutoff values specific to PCD. Their results showed that a disease-specific nasal NO cutoff value of 77 nL/min had a sensitivity of 0.98 and a specificity of >0.999 in identifying patients with PCD.⁷⁴ Despite these limitations, nasal NO measurement is likely to emerge as a widely used screening tool for PCD in the future.

Ciliary function analysis

Ciliary beat pattern assessment and measurement of ciliary beat frequency (CBF) serves as an important diagnostic marker for PCD. Strips of epithelium containing cilia obtained by nasal brushing as well as biopsy are visualized under light microscope and ciliary beat frequency is calculated by counting the number of frames per second for completing a full beat cycle in slow-motion replay.³⁹

As patients can have normal beat frequency with ultrastructural defects and ineffective motility, measurement of beat frequency alone will result in a higher rate of false negative testing.⁷⁵ Recent data confirm that high-speed video imaging can be used successfully for analysis of both CBF^{76,77} and pattern analysis.⁷⁸ Digital high-speed imaging studies of ciliary beat do show correlation of abnormalities with specific ultrastructural defects.^{78,79}

Although analysis of ciliary beat is a useful diagnostic test, this test must be used along with structural and genetic analysis to confirm the diagnosis. Limited centers in the United States have the ability to perform this analysis.

Structural assessment of cilia

Electron microscopy (EM) to evaluate the ultrastructure of cilia is considered to be the gold standard for the diagnosis of PCD. Various ciliary ultrastructural defects have been described, including the absence of or alteration in

IDAs or ODAs (most common), absence of the central pair, or defect of radial spokes.^{8,80–82} EM diagnosis is complicated by the observation that ciliary ultrastructural changes can occur in the setting of inflammation in non-PCD patients. For the same reason, ciliary biopsy or brushing should be delayed until approximately 8 weeks after an acute inflammatory or infectious process. Secondary causes of ciliary dyskinesia can demonstrate similar structural changes, but lack of uniform effect on all cilia distinguishes it from PCD.⁸³ Studies have shown 3–10% prevalence of defective cilia in the airways of healthy individuals.^{75,84} Also, normal ultrastructure is observed in up to 15% of PCD cases.⁸⁵ Additionally, EM testing requires an adequate sample, technically difficult processing and fixation steps, a sophisticated electron microscope, and technical expertise.⁷⁵ In patients with phenotypic features of PCD and ultrastructural abnormalities on EM, a comprehensive evaluation is still recommended to avoid misdiagnosis.

Genetics in PCD and recent advances

The respiratory cilia are highly complex structures composed of approximately 250 protein complexes.⁸⁶ Because abnormalities in any of these proteins may result in PCD, it is a genetically heterogeneous disorder. Currently available genetic testing only identifies a subset of patients, and interpretation can be difficult because of the high number of genes involved and frequent identification of gene variants of unknown significance. The most common pattern of inheritance in PCD is autosomal recessive, which means that the sibling of an affected individual carries a 25% risk of inheriting the disease.⁸⁷ Out of those diagnosed, approximately 50% have situs inversus. Other organ system involvement, although rare, does occur. Also, it should be emphasized to parents while counseling that the affected child carries the risk of infertility in the future. Thus, molecular genetic testing of PCD mutations is important for improving diagnostic outcomes and to enable successful counseling.

Based on complexity of ciliary structure and numerous genes that can cause the disease,⁸⁸ PCD genetics have been studied by animal models with a presumption that the ciliary axonemal structure is largely unchanged in other species, referred to as evolutionary conservation. The human orthologs of the genes causing specific defects in various species forms are an interesting facet of PCD genetic research. *Chlamydomonas reinhardtii* (an unicellular eukaryotic protozoan) is widely studied due to its structural resemblance to mammalian cilia and similarity in mutant sequencing.⁸⁹

Mutations of any of the genes encoding the important components of ciliary ultrastructure (axoneme) can cause PCD. However, two-thirds of patients have mutations causing a defect in ODAs. The heterogeneity of the disease can be understood by the fact that mutations in different genes can result in a similar structural defect.

DNAI1 and DNAH5 mutations constitute the disease causing mutation in 25% of patients with PCD and 50% of patients with PCD and ODA defects. Table 1 describes the genes currently implicated in the pathogenesis of PCD.

Genetic sequencing

PCD next gen (next generation) sequencing is commercially available for clinical use.⁹⁰ It differs from DNA se-

quencing in that it not only identifies the precise order of nucleotides within a DNA molecule, but also evaluates thousands or millions of gene sequences simultaneously and in parallel. The commercially available test screens for 11 genes associated with PCD, which accounts for approximately 56% of patients with a clinical diagnosis of PCD as compared to 38% via traditional genetic testing. Currently clinical genetic testing identifies only a subset of patients, and interpretation can be difficult because of the high number of genes involved and frequent discovery of gene variants of unknown significance.

One recent study has shown encouraging potential of massively parallel sequencing of targeted genes in clinical settings for diagnosis of heterogeneous disorders such as PCD.^{91–93} Another study included gene mutation identification based on large deletions, along with identification of polymorphism by microsatellite markers, in patients with confirmed diagnosis of PCD.⁹⁴ An ongoing prospective cohort study conducted at the same institute aims to identify genes that are necessary for normal functioning of respiratory cilia and the pathogenesis of these genetic mutations affecting ciliary function in patients with a confirmed diagnosis as well as those with strong clinical suspicion of PCD. These studies will hopefully provide a better understanding of genetic variability and its impact on long-term disease progression.⁹⁵

In vitro cultures

In vitro culturing of respiratory epithelial cells can provide a reliable and significant platform for analyzing the inherited defects in structure and function of cilia in the absence of offending environmental factors, thereby distinguishing between PCD and SCD.^{96,97} It can help delineate the relationship between a particular genotype of PCD and its associated phenotype.

Immunofluorescent analysis

Analysis and localization of ciliary proteins such as DNAH5 by immunofluorescence microscopy (IFM) may aid as a diagnostic marker for PCD. In Germany, a blinded trial revealed absence of DNAH5 staining within the ciliary axoneme and intracellular accumulation of DNAH5 in the microtubular region from the nasal epithelia cells in PCD patients with ODA defects in contrast to control patients (which included healthy controls and disease controls), who had normal DNAH5 staining along the ciliary shaft.⁹⁸ It is not affected by secondary ciliary abnormalities. However, there are limited studies in the literature on IFA, and it requires ciliary protein-specific antibodies.

Standard of care

There is limited literature evaluating the management of PCD in the pediatric population. Treatment strategies for PCD are generally based on CF therapeutic protocols. Generally, therapy is directed to minimize symptoms, and to prevent or delay the progression of lung damage. There are no therapies that have been adequately studied to prove definitively their efficacy in the treatment of PCD.⁹⁹

Aggressive airway clearance with chest physiotherapy and mucolytics remains the cornerstone of therapy, supplemented by appropriate antibiotics to treat recurrent

TABLE 1. GENES IMPLICATED IN THE PATHOGENESIS OF PCD

<i>Gene</i>	<i>Basic defect</i>	<i>Estimated prevalence</i>	<i>Locus</i>	<i>Phenotype</i>	<i>Defective structure</i>
DNAI1 ⁸⁸⁻⁹⁰	20 exons mutation	9% of PCD	9p21-p23	PCD + SI	ODA
DNAH5 ⁹¹⁻⁹³	5 exons mutation	28% of PCD 50% with ODA defect	5p15	PCD + SI	ODA, dynein heavy chain
DNAI2 ^{94,95}	Splicing and stop mutations	2% of PCD 4% with ODA defect	17q25.1	PCD + SI	ODA
TXNDC3 ^{96,97}	TXNDC mutation	Not known	7p14.1	PCD + SI	ODA*
CCDC39 ⁹⁸	Biallelic/novel mutations	Not known	3q26.33	PCD	IDA, dynein regulatory defect
CCDC40		75% of IDAs	17q25.3		
RSPH4A ⁹⁹	Inframe deletion	Not known	6q22	PCD	Central pair absent
RSPH9	Inframe deletion		6p21	PCD	Central pair displaced
KTU/DNAAF2 ¹⁰⁰	3 exon mutation	Not known 12% with ODA + IDA defect	14q21.3	PCD + PCKD + Immotile sperm + SI	IDA + ODA defects
DNAH11 ^{73,101-103}	Loss of function mutation in 20%	ODA heavy chain + other defects	7p15.3-21	PCD	Normal ciliary ultrastructure**
DNAAF3 ¹⁰⁴	Missense mutation, nonsense mutation	IDA + ODA defect	19q13	PCD	IDA + ODA defects
DNAAF1/ODA7/LRRC50 ⁹⁵	Loss of function point mutation, genomic rearrangement	5% with dynein arm defects	16q23.3-q24.1	PCD + SI	IDA + ODA defects
LRRC6 ¹⁰⁵	Loss of function mutation	Dynein arm defects	8q24.22	PCD, male infertility	IDA + ODA defects
DNAL1 ¹⁰⁶	Homozygous point mutation	ODA defect	14q24.3	PCD	Absent or markedly shortened ODA
HYDIN ^{107,108}	Homozygous mutation in the HYDIN gene	Central pair defect	16q22	PCD, sperm immotility	Normal ciliary ultrastructure on EM, Central pair defects on high resolution EM
CCDC ^{103,109}	Homozygous mutation in CCDC103 gene	Dynein arm defects	17q21.3	PCD ± SI	Variable IDA + ODA defects, reduced beat amplitude, complete cilia paralysis
HEATR2 ^{110,111}	Homozygous mutation in HEATR2 gene	ODA defect	7p22.3	PCD, sperm immotility ± SI	IDA + ODA defects

*It is expressed in testicular cells and respiratory epithelium, and is a human ortholog of sea urchin gene coding a part of the sperm DNA.

**Though this gene was initially identified in a patient with cystic fibrosis (CF), situs inversus, and uniparental disomy of chromosome 7, recent literature describes other mutations in DNAH11 causing PCD. The patients with these mutations usually have normal ciliary ultrastructure. However, the ciliary beating pattern is hyperkinetic. It therefore poses a diagnostic dilemma, as electron microscopy shows normal dynein arms.

CCDC39, coiled-coil domain-containing protein 39; CCDC40, coiled-coil domain-containing protein 40; CCDC103, coiled-coil domain-containing protein 103; DNAAF1, dynein axonemal assembly factor 1; DNAAF2, dynein axonemal assembly factor 2; DNAAF3, dynein axonemal assembly factor 3; DNAH5, dynein axonemal heavy chain 5; DNAH11, dynein axonemal heavy chain 11; DNAI1, dynein axonemal intermediate chain 1; DNAI2, dynein axonemal intermediate chain 2; DNAL1, dynein axonemal light chain 1; HEATR2, heat repeat containing protein 2; HYDIN, hydrocephalus inducing; IDA, inner dynein arm; LRRC6, leucine-rich repeat-containing protein 6; LRRC50, leucine-rich repeat-containing protein 50; ODA, outer dynein arm; PCD, primary ciliary dyskinesia; RSPH4A, radial spoke head 4A; RSPH9, radial spoke head 9; SI, situs inversus; TXNDC3, thioredoxine nucleoside diphosphate kinase 3.

respiratory tract infections. Periodic clinical evaluations, imaging, sputum culture, and pulmonary function tests can guide the long-term management. A multidisciplinary approach involving coordination of care with pediatrician, pulmonologist, otolaryngologist, physiotherapist, nutritionist, and social worker should be systematized.

Summary

PCD is a heterogeneous disorder presenting with signs and symptoms that overlap with many common disorders or illnesses challenging us to recognize those patients requiring further evaluation. Making the diagnosis of PCD is difficult

and involves clinical expertise, sophisticated testing, and collaboration between multiple providers. No gold-standard test for screening exists, and the currently available genetic testing results can be difficult to interpret. Fortunately, considerable effort is being coordinated by the Primary Ciliary Dyskinesia Foundation to establish PCD centers nationally.

We think that the characterization and treatment of patients with PCD in a cohort fashion by multidisciplinary centers will likely lead to heightened awareness of PCD, better understanding of phenotypic subgroups, further elucidation of molecular pathology, enhanced diagnostic algorithms, development of therapeutic research trials, implementation of evidence-based treatment protocols, and ultimately improved patient outcomes/quality of life.

Author Disclosure Statement

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