

# Primary ciliary dyskinesia: mechanisms and management

Nadirah Damseh<sup>1</sup>

Nada Quercia<sup>1,2</sup>

Nisreen Rumman<sup>3</sup>

Sharon D Dell<sup>4</sup>

Raymond H Kim<sup>5</sup>

<sup>1</sup>Division of Clinical and Metabolic Genetics, <sup>2</sup>Department of Molecular Genetics, University of Toronto, Toronto, ON, Canada; <sup>3</sup>Pediatric Department, Makassed Hospital, Jerusalem, Palestine; <sup>4</sup>Division of Respiratory Medicine, Department of Pediatrics, Child Health Evaluative Sciences, Hospital for Sick Children, <sup>5</sup>Fred A Litwin Family Centre in Genetic Medicine, University Health Network and Mount Sinai Hospital, Department of Medicine, University of Toronto, Toronto, ON, Canada

**Abstract:** Primary ciliary dyskinesia is a genetically heterogeneous disorder of motile cilia that is predominantly inherited in an autosomal-recessive fashion. It is associated with abnormal ciliary structure and/or function leading to chronic upper and lower respiratory tract infections, male infertility, and situs inversus. The estimated prevalence of primary ciliary dyskinesia is approximately one in 10,000–40,000 live births. Diagnosis depends on clinical presentation, nasal nitric oxide, high-speed video-microscopy analysis, transmission electron microscopy, genetic testing, and immunofluorescence. Here, we review its clinical features, diagnostic methods, molecular basis, and available therapies.

**Keywords:** genetic testing, Kartagener's syndrome, primary ciliary dyskinesia

## Introduction

Primary ciliary dyskinesia (PCD) is a predominantly autosomal-recessive inherited disorder of mucociliary clearance secondary to ciliary dysfunction. The ciliary defect can be structural and/or functional, resulting in incompetent mucociliary clearance and mucus retention. It was first described clinically by Siewert in 1904 as a triad of chronic sinusitis, bronchiectasis, and dextrocardia.<sup>1</sup> PCD is associated with chronic upper and lower respiratory tract infections (otosinopulmonary disease), male infertility, and situs inversus. Respiratory distress in neonates, chronic suppurative lung disease, chronic serous otitis media, and chronic rhinosinusitis are the common respiratory presentations of PCD.<sup>2</sup> Situs inversus is present in half of PCD cases. Some patients also have other organ laterality defects and heterotaxis (laterality defects combined with heart lesions).<sup>3</sup> The estimated incidence of PCD is approximately one in 10,000–40,000 live births.<sup>4</sup> In a European survey, the prevalence in European countries ranged from 1.3 to 111 diagnosed cases per million children aged 5–14 years. The median age at diagnosis was 5.3 years and 3.5 years in children with situs inversus.<sup>4</sup> Additional surveys of patients with situs inversus and bronchiectasis in Norway and Japan estimated the incidence of PCD to be one per 10,000–20,000 births.<sup>5,6</sup> PCD is more common in certain ethnic groups with high rates of consanguinity, such as the Volendam population in the Netherlands, the British Asian population, and the Amish and Mennonite communities in the US.<sup>7–10</sup>

A diagnosis of PCD is confirmed by either biallelic mutations in a known PCD gene or a classic PCD ultrastructural ciliary defect observed by transmission electron microscopy (TEM).<sup>11,12</sup> However, in up to 30% of suspected PCD cases, genetic testing and TEM can be nondiagnostic. Therefore, many ancillary tests may help to clarify

Correspondence: Raymond H Kim  
Fred A Litwin Family Centre in Genetic Medicine, University Health Network, Mount Sinai Hospital, Department of Medicine, University of Toronto, Joseph and Wolf Lebovic Building, 60 Murray Street, Toronto, ON M5T 3L9, Canada  
Tel +1 416 586 4800 ext 4220  
Fax +1 416 619 5523  
Email raymond.kim@utoronto.ca

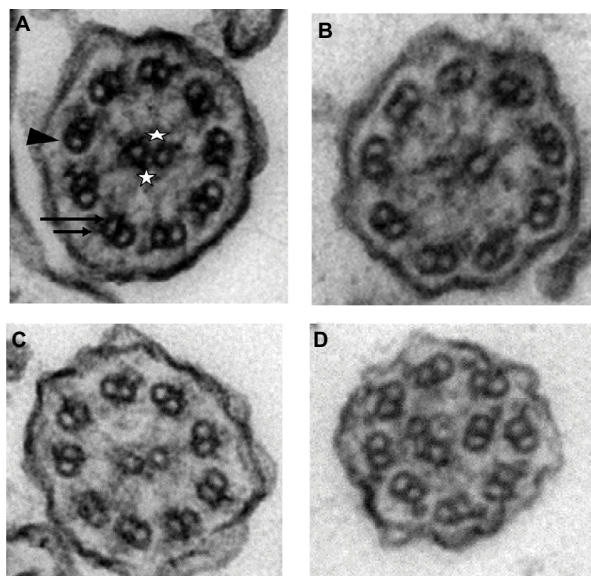
the diagnosis, including nasal nitric oxide (nNO), high-speed videomicroscopy analysis (HSVA), and immunofluorescence (IF). Despite the presence of these advanced technologies, diagnosing PCD can be very challenging and is best done at an expert center.<sup>13</sup> PCD may mimic other conditions that cause secondary ciliary dysfunction, like respiratory infections or airborne pollutant exposure (including cigarette smoke), and this may contribute to underdiagnosed or late-diagnosed cases in practice.<sup>14</sup> To date, there are 39 genes known to be associated with PCD. Two-thirds of PCD cases can be confirmed by identifying biallelic mutations in one of the PCD-causing genes.<sup>15</sup> The most common PCD-causing mutations are in *DNAH5* and *DNAH11*, which encode outer dynein arm (ODA) proteins.<sup>16</sup>

## Cilia structure

Respiratory epithelial cells have approximately 200 cilia per cell that beat in a synchronized manner to clear respiratory secretions. Cilia consist of a ring of microtubule scaffolding called the axoneme, which is covered by the cell membrane and anchored to the cell by a basal body. Motile cilia found on the surface of the respiratory tract have nine peripheral microtubule pairs that surround a central microtubule pair; this gives rise to the “9+2” arrangement of microtubules seen on cross-sections of an axoneme under electron microscopy. Each microtubule pair consists of one microtubule A and one microtubule B. ODAs and inner DAs (IDAs) are present along the peripheral microtubules and contain ATPase, which allows the peripheral microtubular pairs to slide relatively to one another (Figure 1). There are three linkage systems to hold the axoneme together: the inner sheath to support the central microtubules, nexin proteins that join adjacent outer microtubules, and radial spokes that connect the central microtubules to the peripheral microtubule A.<sup>17</sup>

Mucociliary clearance is an essential host-defense mechanism for the entire respiratory system. It has two main compartments: mucus production by mucus-producing goblet cells, which traps inhaled pollutants and infectious debris, and effective ciliary movement of ciliated cells, which clears the mucus outside the airways. Compromised mucociliary clearance predisposes to chronic respiratory diseases. In PCD, abnormal ciliary ultrastructure and orientation result in ciliary dysfunction.<sup>18</sup>

Another type of motile cilia, called nodal cilia, have a “9+0” microtubule arrangement and are present in embryonic nodal plate cells. These cilia lack the central microtubule pair, leading to rotatory motion of the motile nodal cilia, which produces a leftward flow of fluid across the surface



**Figure 1** (A) Normal ciliary ultrastructures, as seen on transmission electron microscopy. This shows the motile cilia characterized by a typical “9+2” arrangement with nine outer-microtubule doublets (arrowhead) and a central pair of microtubules (asterisk). The outer dynein arms (ODAs) and inner dynein arms (IDAs) (arrows) are present along the peripheral microtubules. (B) Absent ODAs. (C) Absent ODAs and IDAs. (D) Microtubular disorganization with IDAs.

**Note:** Courtesy of Patricia Goggin and Regan Doherty from the Southampton PCD Centre, University Hospital NHS Trust, Southampton.

of the embryonic node. This nodal flow establishes left–right body orientation, and if interrupted it may create laterality defects such as situs inversus totalis, situs ambiguus, and heterotaxis syndromes.<sup>19</sup> In PCD, organ orientation is a random event caused by dysfunctional nodal cilia responsible for laterality early in embryonic development, as evidenced by monozygotic female twins with PCD in which one twin has situs solitus and the other situs inversus totalis.<sup>20</sup> More than 250 proteins are involved in axonemal structure and function, which means that mutations in genes encoding for any of these proteins may result in PCD.<sup>15</sup>

## Clinical presentation

The clinical presentation of PCD is aspecific and overlaps with other common chronic respiratory diseases. However, there are some phenotypic clues that may lead physicians to early diagnosis of PCD and eventually early management and better prognosis.

Most PCD patients (73%–91%) present in the neonatal period with neonatal respiratory distress, which is commonly attributed to congenital pneumonia and transient respiratory distress (transient tachypnea of the newborn).<sup>21,22</sup> Chronic nasal congestion is another aspecific presentation that is considered one of the hallmark features of PCD, especially if present at birth.<sup>2</sup>

In a case–control study of PCD patients with a history of neonatal respiratory distress, PCD cases required more and longer oxygen therapy, had later onset of neonatal respiratory distress (at 12 hours of age compared to 1 hour in control cases), and had higher frequency of lobar collapse (78%) and situs inversus (48%). The authors recommended a pediatric pulmonologist referral for a PCD assessment in patients with a combination of any two of lobar collapse on chest radiography, situs inversus, and oxygen therapy for >2 days (87% sensitivity and 96% specificity for PCD).<sup>22</sup>

In early childhood, chronic upper and lower respiratory tract infections are the common presentation. In a cohort study of 118 PCD patients younger than 19 years from North America, clinical features included neonatal respiratory distress (82%), chronic daily wet cough (99%), chronic nasal congestion (97%), and chronic or recurrent otitis media (92%).<sup>2</sup> Another American cohort study of 78 PCD patients from different age-groups showed high prevalence of chronic rhinosinusitis (100%), recurrent otitis media (95%), neonatal respiratory symptoms (73%), and situs inversus (55%).<sup>21</sup>

Adulthood PCD manifestations are similar to those in childhood. However, recurrent otitis media become less frequent at school age. Most men with PCD have infertility secondary to sperm immotility as a result of defective sperm-flagella movement.<sup>23,24</sup> However, men with PCD due

to mutations in the *CCDC114* gene have preserved fertility, partly due to lower *CCDC114*-transcript expression in testes compared to the respiratory system.<sup>10</sup> Female fertility appears somewhat reduced, on account of egg transport relying at least partially on endometrial cilia.<sup>25</sup>

A large systemic review and meta-analysis was performed to quantify the variability in prevalence and severity of PCD clinical manifestations. A total of 52 studies were included, describing 1,970 patients of different age-groups. Except for the prevalence of congenital heart disease among PCD patients, the authors found considerable phenotypic heterogeneity in PCD manifestations between study cohorts.<sup>26</sup> This illustrates the need for larger, concerted, prospective studies to identify the spectrum of PCD manifestations.

The European Respiratory Society guidelines for the diagnosis of PCD recommend an evaluation for PCD if several of the following clinical features exist: persistent wet cough, situs anomalies, congenital cardiac defects, persistent rhinitis, chronic middle-ear disease with or without hearing loss, history in term infants of neonatal upper and lower respiratory symptoms, or neonatal intensive care admittance.<sup>11</sup> A recent consensus recommendation from the Genetic Disorders of Mucociliary Clearance Consortium in North America proposed PCD diagnostic criteria based on age (Table 1).<sup>12</sup>

**Table 1** Recommended PCD diagnostic criteria by age

| <b>Newborns (0–1 month of age)</b>  |
|---|
| Situs inversus totalis and unexplained neonatal respiratory distress at term birth plus at least one of the following: <ul style="list-style-type: none"> <li>• diagnostic ciliary ultrastructure on electron micrography</li> <li>• biallelic mutations in one PCD-associated gene</li> <li>• persistent and diagnostic ciliary waveform abnormalities on high-speed videomicroscopy, on multiple occasions</li> </ul>   |
| <b>Children (1 month to 5 years)</b>  |
| Two or more major PCD clinical criteria (see below) plus at least one of the following (nasal nitric oxide not included in this age-group, since it is not yet sufficiently tested): <ul style="list-style-type: none"> <li>• diagnostic ciliary ultrastructure on electron micrography</li> <li>• biallelic mutations in one PCD-associated gene</li> <li>• persistent and diagnostic ciliary waveform abnormalities on high-speed videomicroscopy, on multiple occasions</li> </ul>                                   |
| <b>Children 5–18 years of age and adults</b>  |
| Two or more major PCD clinical criteria (see below) plus at least one of the following: <ul style="list-style-type: none"> <li>• nasal nitric oxide during plateau &lt;77 nL/min on two occasions, &gt;2 months apart, with cystic fibrosis excluded</li> <li>• diagnostic ciliary ultrastructure on electron micrography</li> <li>• biallelic mutations in one PCD-associated gene</li> <li>• persistent and diagnostic ciliary waveform abnormalities on high-speed videomicroscopy, on multiple occasions</li> </ul> |
| <b>Major clinical criteria for PCD diagnosis*</b>   |
| 1. Unexplained neonatal respiratory distress (at term birth) with lobar collapse and/or need for respiratory support with CPAP and/or oxygen for >24 hours.   |
| 2. Any organ-laterality defect: situs inversus totalis, situs ambiguous, or heterotaxis.  |
| 3. Daily, year-round wet cough starting in first year of life or bronchiectasis on chest CT.  |
| 4. Daily, year-round nasal congestion starting in first year of life or pansinusitis on sinus CT.   |

**Notes:** \*Other diagnostic possibilities should have been considered, such as cystic fibrosis and immunodeficiencies, and diagnostic tests performed to rule out those disorders, as clinically indicated. Reproduced from Shapiro AJ, Zariwala MA, Ferkol T, et al. Diagnosis monitoring and treatment of primary ciliary dyskinesia: PCD Foundation consensus recommendations based on state of the art review. *Pediatr Pulmonol.* 2016;51:115–132.<sup>12</sup>

**Abbreviations:** PCD, primary ciliary dyskinesia; CPAP, continuous positive airway pressure; CT, computed tomography.

## Diagnostic testing

The clinical and genetic heterogeneity of PCD contribute to the challenges of diagnosis. The diagnosis of PCD is still difficult, despite the availability of sophisticated diagnostic tests. Currently, diagnosis incorporates multiple complex and expensive technologies, including nNO, HSVA, TEM, genetic testing, and IF of ciliary proteins. The diagnosis of PCD can be confirmed by genetic testing (biallelic mutations in known PCD genes) and/or finding a classic ultrastructural defect on TEM. However, if these diagnostic tests are not accessible or results are inconclusive, other investigations, such as nNO and HSVA, can play an essential role in making the diagnosis of PCD more likely, aiding in the management of putative PCD patients.

nNO is low in patients with PCD (10%–15% of normal values). There is no clear explanation for this, but some authors have suggested that impaired NO synthase 2 function may have a significant contribution.<sup>27</sup> The nNO test is a reliable PCD-screening test performed by measuring NO during a velum-closure maneuver, with good sensitivity and specificity in cooperative children (>5 years old) and adults. nNO can also be measured during tidal breathing in less cooperative children (<5 years old), but with lower sensitivity.<sup>28</sup> Sporadic cases of PCD have been reported, with normal nNO suggesting it is not 100% sensitive for PCD.<sup>27</sup> Cystic fibrosis (CF) and pulmonary hypertension are other conditions known to have low nNO levels, suggesting that nNO is not 100% specific for PCD.<sup>29</sup> A prospective North American study defined a disease-specific nNO-cutoff value of 77 nL/min, with sensitivity of 98% and specificity of 99.9%.<sup>30</sup>

HSVA is a subjective and qualitative analysis of ciliary beat pattern and frequency of ciliated epithelium-biopsy samples (eg, nasal or bronchoscopic brush). PCD and non-PCD patients show a degree of functional ciliary abnormalities in HSVA without culture. However, after air-liquid interface culture, normal ciliary beat pattern was seen in all non-PCD patients and was uniformly abnormal in PCD patients.<sup>31</sup> The test has excellent sensitivity (93%) and specificity (93%), and many European centers consider it a first-line test in the diagnostic algorithm of PCD.<sup>32</sup> However, HSVA requires great expertise to differentiate between primary and secondary abnormalities. In addition, some PCD mutations have been reported with subtle beating abnormalities, eg, *GAS8* mutations with radial spoke defects.<sup>33</sup> This raises the concern that despite high sensitivity and specificity, HSVA cannot be used as a stand-alone test.<sup>32</sup>

TEM was once considered the “gold standard” for the diagnosis of PCD. This has changed, since a substantial number of PCD cases are caused by mutations that are not

associated with ultrastructural defects, eg, *DNAH11* and nexin-link defects (*CCDC65*, *CCDC164*), and thus would not be identified by TEM.<sup>34,35</sup> While the detection rate of TEM is 83%, TEM has been estimated to miss the diagnosis of PCD in 26% of cases. Therefore, normal TEM does not rule out PCD. The prevalence of ultrastructural defects detected by TEM is 28% for ODA defect, 26% for both ODA and IDA defects, and 10% for microtubular defects.<sup>36</sup>

Genetic studies can provide a definitive diagnosis of PCD if biallelic mutations are identified in an autosomal-recessive PCD-causing gene or a hemizygous mutation is identified in an X-linked gene. However, genetic testing does not substitute other PCD functional studies, because in up to 35% of PCD cases, the genes are not yet known. So far, 39 PCD-causing genes have been identified. It is postulated that any of the >200 genes involved in ciliogenesis could contribute to PCD. Until now, only 65% of PCD patients have had a genetically confirmed diagnosis.<sup>37</sup>

IF is a form of indirect imaging that labels ciliary proteins using IF-linked antibodies and fluorescent or confocal microscopy. It helps in understanding the effect of genetic mutations on ciliary proteins. Using different fluorescence tags may provide further information regarding protein localization. IF is able to detect all ultrastructural abnormalities identifiable by TEM, in addition to abnormalities of nexin-link components.<sup>38</sup> Some authors support including IF in the routine diagnostic approach, especially if TEM equipment or expertise is not available.<sup>39</sup>

The European Respiratory Society proposed a PCD-diagnosis algorithm of three steps: 1) nNO and HSVA, 2) TEM, and 3) targeted genetic testing based on the presence or absence of TEM defects, and repeat HSVA  $\pm$  cell culture.<sup>11</sup> Abnormalities seen on HSVA can be secondary to damage during sampling and local infection or inflammation; therefore, a repeat sample after treating the patient might be needed. Reanalysis of cilia following culture and redifferentiation of epithelial cells at an air-liquid interface helps to eliminate these secondary abnormalities, hence aiding in the diagnosis.<sup>31</sup> With the decreasing costs of genetic sequencing and advances in massively parallel sequencing, genetic testing could emerge as a diagnostic alternative in centers that lack many of the other diagnostic investigations.<sup>40</sup>

## Genetics

### PCD genes and inheritance

PCD is primarily inherited in an autosomal-recessive fashion, and to date 39 PCD-associated genes have been identified. Around 65% of PCD patients have been identified to have biallelic mutations in one of these genes, and the majority

of PCD mutations have loss-of-function variants, including nonsense, frameshift, and splice-site mutations.<sup>15</sup> Recently, a study has demonstrated X-linked inheritance associated with point mutations and large deletions in *PIH1D3*, a cytoplasmic protein involved in dynein assembly.<sup>41</sup>

*DNAI1* was the first gene identified to be associated with PCD in 1999 through orthologue studies. *Chlamydomonas reinhardtii* is a single-cell alga with two flagella containing an axonemal structure similar to that of human respiratory cilia and sperm tails. Mutant *C. reinhardtii* carrying a defect in *IC78*, a gene that encodes the intermediate chain of dynein, has been found to have axonemal ultrastructural defects (absence of ODAs), similar to some patients with PCD. The human orthologue *DNAI1* was subsequently confirmed to be associated with PCD through a candidate-gene approach.<sup>42</sup> In addition to *DNAI1*, the most common identified causative genes of PCD include *DNAH5*, *DNAH11*, *CCDC39*, *CCDC40*, *DNAAF1*, *LRR6*, and *DNAI2* (Table 2).<sup>15, 43–45</sup> Other PCD genes include *ZMYND10*, *TTC25*, *SPAG1*, *RSPH9*, *RSPH4A*, *RSPH3*, *RSPH1*, *TXNDC3* (*NME8*), *HYDIN*, *HEATR2*, *GAS8*, *DYX1C1*, *CCDC164* (*DRC1*), *DNALI1*, *DNAJB13*, *DNAAF2* (*KTU*), *DNAAF3* (*C19orf51*), *CCNO*, *CCDC65* (*DRC2*), *CCDC151*, *CCDC114*, *CCDC103*, *C21orf59*, *ARMC4*, *STK36*, *DNAH6*, *DNAH8*, *MCIDAS*, *RPGR*, and *OFD1*.<sup>46–50</sup>

Ciliary ultrastructural defects are identified in the majority of PCD patients (70%). These include ultrastructural defects of ODA defects, IDA defects, central microtubular pair abnormalities and radial spoke defects. However, some PCD patients have normal ciliary ultrastructure, mainly those with *DNAH11*, *HYDIN*, *CCDC164*, and *CCDC65* mutations.<sup>34,44,53,55,56</sup>

## Genotype–phenotype correlation

Though limited, some genotype–phenotype correlations have been identified. For example, a previous study found

mutations in *RPGR* in patients with a complex X-linked phenotype of PCD and retinitis pigmentosa.<sup>57</sup> Another study reported a large family with X-linked recessive mental retardation syndrome. They presented with macrocephaly and ciliary dysfunction as a result of a frameshift mutation in the *OFD1* gene.<sup>58</sup>

*CCDC39* and *CCDC40* mutations are characterized by IDA defects and microtubular disorganization. Mutations in either gene lead to an indistinguishable clinical phenotype and ciliary defects. They are associated with earlier presentation, worse lung function, structural changes, and poorer nutritional status.<sup>2</sup> Mutations in *RSPH1* are associated with a milder disease phenotype, higher levels of nNO, and better lung function.<sup>59</sup> Mutations in *CCNO* lead to paucity or complete absence of motile cilia. Affected patients have early-onset and progressive PCD symptoms; situs inversus has not been observed, and few have infertility.<sup>60</sup> *CCDC114* mutations have no significant effect on fertility, and this has been attributed mainly to low transcript expression of *CCDC114* in testes compared to respiratory ciliated cells.<sup>10</sup>

Nodal cilia determine left–right asymmetry. They contain a 9+0 axonemal composition, and lack the components of central apparatus and radial spokes. Therefore, patients with mutations in genes that encode the central complex and radial spokes (eg, *RSPH1*, *RSPH3*, *RSPH4A*, *RSPH9*, and *HYDIN*) do not have situs abnormalities, as they still have the normal rotatory function, which is important for normal left–right asymmetry.<sup>55,61</sup>

## Genetic testing

PCD is a genetically heterogeneous disease. Traditionally, genes were sequentially analyzed using Sanger sequencing based on ciliary ultrastructure and the most prevalent PCD genes. The advent of next-generation sequencing and decreasing costs have led to the development of a number

**Table 2** Common genes associated with autosomal recessive PCD

| Gene name                     | Percentage of all PCD | Ciliary ultrastructural defect              | Percentage based on ultrastructural defect                      | References |
|-------------------------------|-----------------------|---|---|------------|
| <i>DNAH5</i>                  | 15%–21%               | ODA defect                                  | 27%–38% of PCD with ODA defects                                 | 15,51,52   |
| <i>DNAH11</i>                 | 6%–9%                 | Normal ultrastructure                       | 48% of PCD with normal ultrastructure                           | 15,51–53   |
| <i>CCDC39</i>                 | 2%–10%                | IDA defect and microtubular disorganization | 36%–65% of PCD with IDA defect and microtubular disorganization | 15,52      |
| <i>DNAI1</i>                  | 2%–10%                | ODA defect                                  | 4%–13% of PCD with ODA defects                                  | 15,16,52   |
| <i>CCDC40</i>                 | 2%–8%                 | IDA defect and microtubular disorganization | 24%–54% of PCD with IDA defect and microtubular disorganization | 15,52,54   |
| <i>DNAAF1</i> ( <i>LRR6</i> ) | 4%–5%                 | ODA and IDA defects                         | 17% of PCD with both ODA and IDA defects                        | 15,52      |
| <i>LRR6</i>                   | 3%                    | ODA and IDA defects                         | 11% of PCD with both ODA and IDA defects                        | 15         |
| <i>DNAI2</i>                  | 2%                    | ODA defect                                  | 4% of PCD with ODA defects                                      | 15,52      |

**Note:** Other PCD genes include *ZMYND10*, *TTC25*, *SPAG1*, *RSPH9*, *RSPH4A*, *RSPH3*, *RSPH1*, *PIH1D3*, *TXNDC3* (*NME8*), *HYDIN*, *HEATR2*, *GAS8*, *DYX1C1*, *CCDC164* (*DRC1*), *DNALI1*, *DNAJB13*, *DNAAF2* (*KTU*), *DNAAF3* (*C19orf51*), *CCNO*, *CCDC65* (*DRC2*), *CCDC151*, *CCDC114*, *CCDC103*, *C21orf59*, *ARMC4*, *STK36*, *DNAH6*, *DNAH8*, *MCIDAS*, *RPGR*, and *OFD1*, in addition to two linkage regions: *CILD4* and *CILD8*.

**Abbreviations:** PCD, primary ciliary dyskinesia; ODA, outer dynein arm; IDA, inner DA.

of gene panels based on massively parallel sequencing. However, the pace of PCD-gene discovery is quickly outdating currently available gene panels, suggesting alternative molecular genetic approaches may be needed.<sup>44</sup> It is likely that many more PCD-causing genes will be discovered, given the hundreds of genes that encode proteins for cilia structure and function.

The use of whole-exome sequencing (WES) and whole-genome sequencing (WGS) plays a significant role in novel-gene discovery in genetically heterogeneous diseases, such as PCD.<sup>62</sup> WES and WGS provide the advantage of analyzing all potential causative genes, including recently discovered genes that might not be included on PCD-gene panels.<sup>63</sup> As such, it has been suggested that WES could be more cost- and time-effective as a first-line molecular diagnostic test for PCD than clinical gene panels.<sup>13,64</sup> One limitation of WES is copy-number variant analysis, which can be a significant proportion of PCD mutations.<sup>62</sup> This may be overcome with more refined copy-number variant algorithms or with WGS.<sup>63</sup> WGS specifically analyzes noncoding regions that might be responsible for decreased expression of PCD genes, and could be used in conjunction with ciliary IF to correlated novel noncoding variants.

## Management

Proposed therapies for PCD lack randomized controlled trials, and as such are not evidence-based but mainly extrapolated from the field of CF. The aim of PCD treatment is to maintain or recover lung function by early detection and aggressive management of complications. The main objectives are the clearance of mucus, prevention of respiratory infections, and vigorous treatment of bacterial infections.

Measures used to enhance mucus clearance include positive pressure expiratory devices, intrathoracic oscillatory devices, high-frequency chest compression using vest therapy, manual chest physiotherapy, postural drainage, autogenic drainage, active cycle breathing, and exercise.<sup>65</sup> One study in children reported that physical exercise before physiotherapy is a more potent stimulus for bronchodilation than inhaled  $\beta_2$ -agonists.<sup>66</sup> Exercise may promote deep breathing and cough, which helps in mucus clearance. There is very limited evidence for using inhaled medications in PCD. A recent randomized clinical trial showed little evidence of quality-of-life improvement with the use of inhaled hypertonic saline in PCD patients.<sup>67</sup>

Prophylactic courses of antibiotics are used in some centers, but this is not routinely recommended. To address this, a multicenter European clinical trial is under way to assess the

efficacy and safety of azithromycin as maintenance therapy for 6 months in PCD patients. Azithromycin is known to have antibacterial, anti-inflammatory, and anti-quorum-sensing properties and is commonly used in chronic respiratory diseases, such as CF.<sup>68</sup>

The cornerstone of PCD management is the prompt treatment of respiratory tract infections. Management should be guided by microbiological studies using sputum culture, cough-swab culture, and sometimes bronchoalveolar lavage.<sup>38</sup> Commonly isolated pathogens from sputum culture in PCD patients are *Haemophilus influenzae* (most common, 65%), *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, and mucoid *P. aeruginosa*.<sup>68</sup>

Bronchiectasis is a prominent feature in PCD, and surgical resection with lobectomy or segmentectomy in patients with bronchiectasis is thought to decrease the risk of infection progressing into healthier lung tissue. However, there is controversy in the literature regarding the benefit of lung resection in PCD patients. PCD patients with severe localized bronchiectasis have been offered lobectomy where failed medical management has caused significant morbidity. In one cohort, 85% (eleven of 13) of lobectomized PCD patients reported subjective symptomatic improvement.<sup>69</sup> However, lobectomized PCD patients had the same prevalence of respiratory symptoms as the unlobectomized patients. Another cohort study showed that lobectomized patients had significantly worse forced expiratory volume in one second and forced vital capacity compared to unlobectomized patients. The authors considered lobectomy a poor prognostic factor for PCD in adults.<sup>69,70</sup>

A recent in vitro study demonstrated the efficacy of premature termination codon (PTC) read-through stimulation in PCD-causing mutations with aminoglycosides. PTC read-through has been shown to restore functional protein expression and reduce symptoms in several genetic disorders caused by loss-of-function mutations. In this study, three types of aminoglycosides were used to examine its effect on five PCD genes with PTC: *DNAH5*, *DNAH11*, *CCDC40*, *RSPH4A*, and *SPAG1*. The efficacy of each aminoglycoside in stimulating PTC read-through and protein production depended on the particular PTC, as well as on drug type and concentration. Among the examined PTCs, suppression was most efficient for the stop codon UGA. This precision medicine for PCD does show promise, but further studies are required to validate its efficacy, as it was a preclinical cell-line study.<sup>71</sup>

Lung transplantation has been described in a few case reports, and indicated increased 1-year mortality. More recently, an American study using a national registry

demonstrated that the survival outcome of a large group of patients with PCD and Kartagener's syndrome was similar to that of the general population with lung transplantation for common indications like COPD and CF.<sup>72</sup>

## Conclusion

PCD is a genetically heterogeneous recessive condition with defective ciliary motility. It is characterized by otosinopulmonary disease, male infertility, and situs inversus. A diagnosis of PCD depends on clinical presentation, nNO, HSVA, TEM, and genetic testing. The rapid development in PCD genetics is promising. In the near future, genetic testing could become the main diagnostic method, with minimal use of other expensive and effort-demanding diagnostic modalities. Due to its rarity and lack of clinical trials, the management of PCD remains challenging and mainly supportive. Understanding the biology of PCD with respect to ciliary function may allow for more targeted therapeutic agents in future.

## Disclosure

The authors report no conflicts of interest in this work.

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