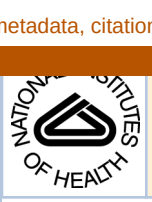

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Clinical and Genetic Aspects of Primary Ciliary Dyskinesia / Kartagener Syndrome

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Abstract

Primary ciliary dyskinesia (PCD) is a genetically heterogeneous disorder of motile cilia. Most of the disease-causing mutations identified to date involve the heavy (*DNAH5*) or intermediate (*DNAI1*) chain dynein genes in ciliary outer dynein arms, although a few mutations have been noted in other genes. Clinical molecular genetic testing for PCD is available for the most common mutations. The respiratory manifestations of PCD (chronic bronchitis leading to bronchiectasis, chronic rhino-sinusitis and chronic otitis media) reflect impaired mucociliary clearance owing to defective axonemal structure. Ciliary ultrastructural analysis in most patients (>80%) reveals defective dynein arms, although defects in other axonemal components have also been observed. Approximately 50% of PCD patients have laterality defects (including situs inversus totalis and, less commonly, heterotaxy and congenital heart disease), reflecting dysfunction of embryological nodal cilia. Male infertility is common and reflects defects in sperm tail axonemes. Most PCD patients have a history of neonatal respiratory distress, suggesting that motile cilia play a role in fluid clearance during the transition from a fetal to neonatal lung. Ciliopathies involving sensory cilia, including autosomal dominant or recessive polycystic kidney disease, Bardet-Biedl syndrome, and Alstrom syndrome, may have chronic respiratory symptoms and even bronchiectasis suggesting clinical overlap with PCD.

Keywords

Primary ciliary dyskinesia; PCD; Kartagener syndrome; situs inversus; dynein

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Conflicts of Interest:
None

OVERVIEW

Primary ciliary dyskinesia (PCD) (MIM#244400) is a genetically heterogeneous, typically autosomal recessive, disorder characterized by ciliary dysfunction and impaired mucociliary clearance, resulting in an array of clinical manifestations, including chronic bronchitis leading to bronchiectasis, chronic rhino-sinusitis, chronic otitis media, situs inversus (in approximately 50% of cases), and male infertility. The incidence of PCD is estimated at 1/16,000 births, based on prevalence of situs inversus and bronchiectasis.[1,2] However, few PCD patients carry a well-established diagnosis, which reflects, the limited ability to diagnose this disorder.

The first cases, reported in the early 1900's, and characterized by a triad of symptoms that included chronic sinusitis, bronchiectasis and situs inversus,[3] became known as Kartagener syndrome. Subsequently, patients with Kartagener syndrome, as well as other patients with chronic sinusitis and bronchiectasis, were noted to have “immotile” cilia and defects in the ultrastructural organization of cilia.[4-6] Initially, the term “immotile cilia syndrome” was used to describe this disorder; however, later studies showed that most cilia were motile, but exhibited a stiff, uncoordinated and/or ineffective beat. The name was changed to “primary ciliary dyskinesia” to more appropriately describe its heterogeneous genetic base and the ciliary dysfunction, as well as to distinguish it from the secondary ciliary defects acquired following multiple causes of epithelial injury.

The “gold-standard” diagnostic test for PCD has been electron microscopic ultrastructural analysis of respiratory cilia obtained by nasal scrape or bronchial brush biopsy. Recent studies have identified mutations in several genes encoding structural and/or functional proteins in cilia. Limited clinical genetic testing is currently available, but a multi-center, international collaboration is focused on defining additional PCD-specific gene mutations in order to expand PCD genetic testing. Recently, nasal nitric oxide (NO) measurement has been used as a screening test for PCD, because nasal NO is extremely low (10-20% of normal) in PCD patients.[7-10] As an adjunct test, nasal NO measurement can identify individuals with probable PCD (even if ciliary ultrastructure appears normal) to target for genetic testing. We anticipate that genetic testing for PCD will soon become the “gold standard” diagnostic test in a growing number of cases.

In summary, we are in the midst of a revolution for the diagnosis, and understanding of genotype/phenotype correlations in PCD. This effort has greatly benefited from an NIH-sponsored Rare Disease Network (url: http://rarediseasesnetwork.epi.usf.edu/), and a consortium focused on studying genetic disorders of mucociliary clearance, including PCD (url: http://rarediseasesnetwork.epi.usf.edu/gdmcc/index.htm).

CILIARY STRUCTURE AND FUNCTION

Normal ultrastructure of motile cilia

Cilia and flagella are evolutionarily ancient organelles whose structure and function have been rigidly conserved across the phylogenetic spectrum. Historically recognized for their role in cell motility and transport of fluids over mucosal surfaces, cilia have recently been recognized to have a sensory function that modulates elements of development and cell function. Both motile and sensory cilia are composed of highly organized arrays of microtubules and attendant accessory elements and their classification is depicted in Fig. 1. Microtubules are formed from α- and β- monomers of tubulin configured into helical patterns of protofilaments. The peripheral microtubules in the canonical 9+2 microtubular pattern of motile cilia are studded with dynein arms that contain ATPases and act as molecular motors to effect the sliding of the peripheral microtubular pairs relative to one

another. The outer dynein arms (ODA) are positioned proximal to the ciliary membrane and the inner dynein arms (IDA) proximal to the central apparatus of the A microtubule. The dynein arms are large protein complexes each comprised of several heavy, light, and intermediate chains as shown in Fig. 2. In *Chlamydomonas*, and likely other eukaryotic cilia and flagella-bearing cells, the IDA and ODA are spaced in specific linear repeats of 96 nm and 24 nm, respectively[11,12] along the axis of each microtubular pair, where they undergo an attachment, retraction, and release cycle with the neighboring microtubular pair that imposes a sliding motility of the pairs relative to one another. The A microtubule in cross-section is comprised of thirteen protofilaments and shares three protofilaments with the B microtubule. Studies of isolated axonemes depleted of accessory structures have shown that in the presence of ATP the microtubular pairs slide upon one another to visible light extinction. It is thought that some of the accessory structures, including the nexin links, radial spokes, and ciliary membrane provide shear forces that transition the sliding event to the bending characteristic of ciliary waveform. In contrast to the 9+2 pattern of motile cilia with dynein motors, there are structural variants without dynein motors that have a 9+0 microtubular pattern,[13] which are called “primary” cilia. Unlike the numerous motile cilia present on airway epithelial cells, these primary cilia are borne as solitary appendages. Historically thought to be non-functional or vestigial, they have been rediscovered in recent years as structures central to organ positioning during embryologic development and to the detection of mechanical and chemical gradients. Thus, primary cilia are now recognized as structures modulating detection, orientation, and positioning. Virtually all cells are capable of producing a single primary cilium, which lacks dynein arms and is immotile. However, it has been suggested that populations of both non-motile primary cilia and specialized motile cilia are present in nodal cells, and that dyneins on the motile populations confer a whirling motility to the organelle that is distinct from the waveform motility typical of 9+2 motile cilia. Thus, there are three basic groups of cilia; motile 9+2 cilia with attendant dynein arm structures (e.g. respiratory epithelial cells), non-motile 9+0 primary cilia lacking dynein arms (e.g. kidney tubules), and motile 9+0 primary cilia possessing dynein arms (e.g. embryonic node). In addition to the highly specialized organization of the core of the cilium, the ciliary membrane exhibits a specialized structure, the ciliary necklace at the base of the axonemal shaft.[14] The ciliary necklace has been speculated to be a docking/assembly site for axonemal elements, since nascent organizing structures of these arrays have been reported on the luminal membranes of cells in early stages of ciliogenesis.[15]

Normal ciliary beat frequency

Two distinctive types of motility are representative of 9+2 and 9+0 motile cilia. Ciliated epithelial cells bear approximately 200 motile (9+2) cilia that move with both intracellular and intercellular synchrony. The pattern of beat in 9+2 motile cilia occurs in a waveform having a forward effective stroke followed by a return stroke. The direction of stroke is a function of the directional orientation of the central microtubules. In addition to moving in synchrony, individual cilia in normal cells are very plastic and move fluidly, sometimes deforming briefly upon encountering resistance and/or particles being transported over the mucosal surface. Cilia are embedded in a watery periciliary fluid of low viscosity, which facilitates the rapid beat cycle to move the more viscous overlying layer of mucus. Ciliary beat frequency ranges from approximately 8-20 Hz under normal conditions, but may be accelerated by exposure to irritants such as tobacco smoke.[16] The mechanism whereby beat frequency is accelerated has been suggested to be regulated through the activity of nitric oxide synthases localized in the apical cytoplasm. While baseline ciliary beat frequency is not thought to be under NO regulation, NO accelerates ciliary beat frequency in response to challenge through soluble adenylyl or guanylyl cyclase to form their respective cyclic nucleotides with activation of protein kinase G (PKG) and A (PKA) to accelerate beat

frequency.[17,18] Increases in intracellular calcium fluxes[19,20] may also play a role in accelerating ciliary beat frequency.

In contrast to the forward/return waveform of 9+2 cilia, motile nodal 9+0 cilia beat with a vertical motion. This type of motility is thought to direct nodal flow "leftward" across the node, which is necessary for establishment of proper left/right asymmetry.

Cilia composition and conservation across species

The ciliary genome is highly conserved across the phylogenetic spectrum from simple unicellular eukaryotes and lower animals to functionally complex mammalian cells and tissues. The genomes for many of organisms are already characterized and the simple organisms are easily grown in the substantive quantities and manipulated in the laboratory setting to facilitate structural, functional, and genetic studies. This provides opportunities to identify cilia-specific mutations that may represent candidate genes for human ciliopathies.[21] Indeed, mutations conferring outer dynein arm defects in primary ciliary dyskinesia have orthologs in *Chlamydomonas*.[22] Moreover, genes encoding polycystins and intraflagellar transport proteins in *Chlamydomonas* also have orthologs with relevance to polycystic kidney disease.[23,24] Hence studying orthologous genes across the various species is valuable in order to decipher the candidate genes for human ciliopathies.

GENETICS

Genetic heterogeneity; challenges and methods to identify disease-causing genes

Dysfunction of the axonemal structure has been linked to the emerging class of disorders collectively known as "ciliopathies" which includes PCD / Kartagener syndrome, Bardet-Biedl syndrome, hydrocephalus, polycystic kidney disease, polycystic liver disease, nephronophthisis, Meckel-Gruber syndrome, Joubert syndrome, Alstrom syndrome, Jeune syndrome, and laterality defects.[25-28] PCD was the first human disorder linked to the dysfunction of motile cilia and that will be discussed in detail in this chapter.

Axonemal structure, which is conserved through evolution, is complex and comprised of multiple proteins; hence, it is not surprising that PCD is a genetically heterogeneous disorder posing challenges for defining causative genes. Conventional family based genome wide linkage studies have failed to identify PCD causing genes,[29] because combining data from multiple families limits power when dealing with a genetically heterogeneous disorder, such as PCD. Multiple other methodologies alone, or in combination, have been successfully applied to elucidate the genetic basis of PCD, including functional candidate gene testing,[30-34] homozygosity mapping[35-37] followed by positional candidate gene analysis, and comparative computational analysis involving comparative genomics, transcriptomics and proteomics.[38-43] Thus far, mutations have been identified in eight genes (Table 1) in PCD (*DNAI1*, *DNAH5*, *DNAH11*, *DNAI2*, *KTU*, *RSPH9*, *RSPH4A* and *TXNDC3*) but no genotype/phenotype associations have been defined and these genes are discussed in detail below:

DNAI1—*DNAI1* (dynein axonemal intermediate chain 1) (MIM#604366), was the first PCD-causing gene to be identified based on the candidate gene approach. This approach takes advantage of the fact that the axoneme is highly conserved through evolution, and human orthologs of the genes known to cause specific ultrastructural and functional defect in other species are candidates for PCD. *Chlamydomonas* is a bi-flagellate, unicellular algae with well studied genetics and multiple motility mutants. One such mutant (*oda9*) had a mutation in the *IC78* (intermediate chain 78) gene, resulting in a flagellar ODA defect. The human ortholog of *IC78* (*DNAI1*) was cloned and tested in 6 unrelated PCD patients with

ODA defects and biallelic mutations were identified in one PCD patient.[33] Two studies reported biallelic mutations in three additional unrelated patients with PCD.[44,45] Subsequently, a large study comprising of 179 unrelated patients revealed 9% (14 with biallelic and 2 with only monoallelic mutations) of all PCD patients carry mutations in *DNAI1*.[46] Thus, taken together from all published literature, mutations in *DNAI1* were seen in approximately 10% (22 of 226) of all PCD patients and it increased to 14%, if only patients with ODA defects were considered.[33,44-46] Despite allelic heterogeneity, the IVS1+2_3insT founder mutation represented 55% of all the mutant alleles, as well as mutation clusters were seen in other exons (exons 13, 16, and 17), and these observations became the basis for the clinical molecular genetic test for PCD.[33,44-47] In addition, IVS1+2_3insT founder mutation appears to be more common in individuals of the Caucasian descent.[46] A recent study from Europe in 104 PCD patients (without phenotypic preselection) revealed biallelic mutations in *DNAI1* in only 2% of the patients.[48] Interestingly, these authors also observed 3 unrelated PCD patients harboring the IVS1+2_3insT founder mutation in *DNAI1*.

DNAH5—The *DNAH5* (dynein axonemal heavy chain 5) (MIM#603335) gene was identified as a causative gene for PCD using homozygosity mapping. This approach requires the analysis of a large affected inbred family and assumes that the recessive disorder is caused by a homozygous mutation that is inherited from the common ancestor. Using a large Arab inbred family with PCD, Omran and colleagues found the locus on chromosome 5, which included *DNAH5* within the shared interval.[49] *DNAH5* was a candidate gene for PCD because the mutation in its ortholog γ-HC (gamma-heavy chain) in *Chlamydomonas* caused flagellar immotility and ODA defects; and indeed, mutations were observed in 8 unrelated PCD families.[36] Subsequently, the same group carried out large scale studies using 134 unrelated PCD patients and found that ~28% of all PCD patients harbor mutations in *DNAH5*.[50,51] Despite allelic heterogeneity, mutation clusters were observed in five exons (exons 34, 50, 63, 76 and 77), which assisted in the development of the first clinical molecular genetic test for PCD.[47] Immunofluorescence studies on the respiratory epithelium and sperm flagella of patients known to harbor biallelic *DNAH5* mutations showed that the mutant protein is present in the microtubule organizing center (MTOC) of the respiratory epithelial cells, but failed to localize along the axonemal shaft.[28,52] Interestingly, sperm analysis from a male patient showed normal immunofluoresence staining pattern; thus, DNAH5 is not mislocalized in the sperm flagella.[52]

DNAI2—The *DNAI2* (dynein axonemal intermediate chain 2) (MIM#605483) is an intermediate chain dynein of the ODA that was cloned and characterized utilizing the candidate gene approach. Mutations in the *Chlamydomonas* ortholog (*IC69*) caused an immotile mutant strain (*oda6*) which had loss of ODA.[34] Initial studies showed no disease causing mutations in 16 PCD families, including 6 families with microsatellite marker alleles concordant for loci on chromosome 17q23-ter (locus for *DNAI2*).[34,53] Very recently, Loges et al[35] used homozygosity mapping and identified linkage to the *DNAI2* locus in a consanguineous Iranian Jewish family, and a homozygous splice mutation (IVS11+1G>C) in all the affected individuals. Subsequently, they sequenced an additional 105 unrelated patients (48 with ODA defects) and identified a homozygous splice mutation (IVS3-3T>G) in a Hungarian PCD family and a homozygous stop mutation (R263X) in a German patient. Thus, *DNAI2* mutations are found in ~ 2% of all PCD families and 4% of PCD families with documented ODA defects.[35]

DNAH11—Genetics of *DNAH11* (dynein axonemal heavy chain 11) (MIM#603339) are still emerging. A patient with uniparental isodisomy of chromosome 7 presented with cystic fibrosis due to the common homozygous mutation (deltaF508) in *CFTR* (MIM# 602421). In

addition, this patient had situs inversus, which is not part of the spectrum of cystic fibrosis.[30] Upon investigation of the region near *CFTR* on chromosome 7, *DNAH11* emerged as a candidate gene because mutations in the ortholog β-HC (beta-heavy chain) dynein and left right dynein (*lrd*) caused motility defects in *Chlamydomonas oda4* mutant strain (reviewed in reference[22]) and situs inversus in mice[54,55] respectively. Sequencing of *DNAH11* in this cystic fibrosis patient with situs inversus revealed a homozygous nonsense mutation (R2852X).[30] Because this patient had airways disease due to cystic fibrosis and no defined ciliary ultrastructural defect, it was not certain if the patient also had PCD, or only isolated situs inversus; hence, the status of *DNAH11* as a PCD causing gene remained undefined. Very recently, a large German family with 5 affected individuals (and Kartagener syndrome) was found to harbor biallelic compound heterozygous truncating mutations in *DNAH11*.[37] Although, the electron microscopic analysis and immunofluorescence localization in these patients showed normal dynein arms, they had abnormal ciliary beat patterns. Since PCD patients with normal dynein arms are difficult to diagnose, it will be important to carry out large scale genetic studies of *DNAH11* in PCD subjects to decipher if *DNAH11* plays an important role in PCD patients with normal DA.

TXNDC3—Thioredoxin-nucleoside diphosphate (*TXNDC3*) (MIM#607421) ortholog in *Chlamydomonas* (*LC3* (Light chain 3) and *LC5* (light chain 5)) and sea urchin ((*IC1* (intermediate chain 1)) is a component of sperm ODA. Due to the involvement of *TXNDC3* in the ODA, it was considered a candidate gene and tested in 41 unrelated PCD patients.[31] Only one patient harbored a nonsense mutation (L426X) on one allele inherited from the mother[31] and a common intronic variant (c.271-27C>T) on the trans allele. Although this variant is present in 1% of non-PCD control subjects, it occurs near the branch point in the intron that is involved in the splicing. *TXNDC3* encodes two transcripts, one full length isoform and a novel short isoform TXNDC3d7 (inframe deletion of exon 7) that is thought to bind microtubules. The authors concluded that the variant was pathogenic in the patient with a nonsense mutation on one allele and the variant on the other allele because the levels of the short isoform (TXNDC3d7) were reduced in this PCD patient thereby affecting the ratio of the two isoforms.[31]

KTU—A truncating homozygous mutation in *Ktu* (previously known as Kintoun or *knt*) (MIM#612517) in Medaka fish causes laterality defects, polycystic kidney disease and impaired sperm motility in male fish. Ultrastructural analysis of the cilia of Kupffer's vesicle (functionally equivalent to the mouse node) and flagella of sperm from the fish revealed ODA+IDA defects.[32] Similar ultrastructural defects were found in the paralyzed flagella mutant strain of *Chlamydomonas* (*pf13*) that harbored mutation in the *PF13* gene (ortholog of *KTU*), required for the ODA assembly.[32] *KTU* does not belong to the dynein family genes, but it is a cytoplasmic protein that is required for the assembly of the dynein complex and hence was considered a candidate gene for PCD.[32] A total of 112 unrelated PCD patients were tested for the mutations in *KTU* and two unrelated inbred families were found to harbor truncating mutations; the ciliary ultrastructural analysis revealed ODA+IDA defects. Of the 112 PCD families tested, only 17 had defined ODA+IDA defects; thus, mutations in *KTU* occur in 12% PCD patients with ODA+IDA defects.[32] Interestingly, *KTU* mutations caused PCD in humans, but polycystic kidney disease in fish, perhaps due to the difference in the origin of the kidneys that are mesonephric in fish and metanephric in mammals.

RSPH9—Very recently, Castleman et al[56] identified the mutations in *RSPH9* (radial spoke head protein 9). The authors carried out homozygosity mapping and identified the disease interval on chromosome 6 and subsequently discovered the inframe deletion (K268del) in *RSPH9* in two Arab Bedouin families. The ultrastructural analysis from the patients who

harbored mutations was the mixture of 9+2 or 9+0 microtubular configuration in one family and the normal dynein arms in the other family.[56] Interestingly, *Chlamydomonas* motility defective mutant; *pf17* that harbors mutation in the orthologous gene *RSP9*, shows the absence of entire radial spoke head and the central pair displacement.[57]

RSPH4A—Another PCD causing gene that has emerged very recently is *RSPH4A* (radial spoke head protein 4A).[56] This gene was identified by the virtue of homozygosity mapping in three inbred Pakistani families. Homozygous nonsense mutation (Q154X) was identified in all three inbred and one out-bred Pakistani families in RSPH4A. In addition, one family of a Caucasian descent was compound heterozygous for the mutations (Q109X + R490X) in this gene. Ultrastructural analysis in all of the five PCD families with the mutation showed transposition defects with the absence of central pair and 9+0 or 8+1 microtubule configurations.[56] *RSPH4A* is orthologous to the *Chlamydomonas RSP4* and *RSP6*. However, *Chlamydomonas* motility defective mutants *pf1* and *pf26* lacking *RSP4* or *RSP6* respectively, show absence of radial spoke head.[58]

Genes tested and found to be negative in PCD

A number of other PCD candidate genes have been tested and found to be negative in PCD patients. These genes include DNAH9 (dynein axonemal heavy chain 9), *DNAH17* (dynein axonemal heavy chain 17), *DNAL1* (dynein axonemal light chain 1), *DNAL4* (dynein axonemal light chain 4), *TCTE3* (T complex-associated testis-expressed 3), *DYNLL2* (dynein light chain 2), *DNALI1* (dynein axonemal light intermediate polypeptide 1 (*HP28*)), *DNAH3* (dynein axonemal heavy chain 3), *DNAH7* (dynein axonemal heavy chain 7), *SPAG6* (sperm-associated antigen 6), *SPAG16* (sperm-associated antigen 16), *DPCD* (deleted in PCD), and *FOXJ1* (forkhead box J1 (*HFH-4*)). The details about the number of patients tested for each of these genes is given in Table 2. Some of these genes may still be candidates for PCD as they were either tested in a small cohort of patients or the patients were not preselected based on ultrastructural findings to test for the appropriate axonemal component gene.

PCD co-segregating with other syndromes (*OFD1* and *RPGR*)

In a few instances, PCD cosegregates with other genetic conditions and the causative genes primarily do not affect ciliary motor function. A large inbred Polish kindred was identified with a novel X-linked mental retardation syndrome, together with the compatible clinical PCD phenotype and dyskinetic cilia. Linkage studies followed by comparative genomic analysis identified the locus on the X chromosome including *OFD1* (formerly known as *CXORF5*) (MIM# 311200). Mutation analysis confirmed the frameshift mutation in *OFD1* in all the affected individuals tested from the Polish family.[59] OFD1 is localized to the centrosomes and the basal body of the primary cilia and does not affect ciliary motor function.[60,61] The index patient with the *OFD1* mutation had disorganized ciliary beat suggesting the role of OFD1 in the respiratory epithelial ciliary function.[59]

A family consisting of two probands has been described by Moore et al.,[62] with the X-linked retinitis pigmentosa (xlRP) (MIM# 268000), oto-sino-pulmonary symptoms consistent with PCD, and multiple abnormalities of all the ciliary components by ultrastructural analysis. Upon sequencing, both patients harbored a 57 bp deletion that is predicted to cause a truncated protein in *RPGR* that resides on the X chromosome (MIM# 312610).[62] Furthermore, Zito et al.,[63] described a patient with PCD and mild hearing loss together with xlRP. They detected a frameshift mutation in *RPGR*. In addition, Iannaccone et al.[64] report a family with PCD and otitis media with bronchitis together with xlRP and the presence of a missense mutation in *RPGR*. RPGR protein is expressed in rods and cones and is essential for photoreceptor maintenance and viability.[65] RPGR is also expressed in cochlear,

bronchial and sinus epithelial lining cells,[64,66] indicating a possible functional role for the broad phenotype in patients with *RPGR* mutations.

Animal models for PCD

Animal models for PCD are available that are either naturally occurring or constructed via genetic manipulations. They include dogs,[67-71] cats,[72] pigs,[73] rats[74] and mice. Causative genes in the animal models other than the mouse models are not yet known. Several axonemal component gene knock-out mice have been created including *Mdnah5* (mouse dnah5),[75,76] *lrd*,[54,55,77-79] *Dpcd*/*poll* (deleted in PCD/polymerase lambda),[80] *Pcdp1* (PCD protein 1),[81] *hydin*,[82-85] *Tektin-t*,[86] *Mdhc7* (mouse dynein heavy chain 7, human ortholog (*DNAH1; dynein axonemal heavy chain 1*)),[87,88] *Foxj1/Hfh4*,[89] *Spag16*,[90-92] *Spag6*,[90,93] and *Spag16*/*Spag6* double knock-outs.[94] None of these mice models presented with the classic PCD phenotype, except for the *Mdnah5* and *Dpcd*/*poll*. None of these genes harbored mutations in the human orthologs (see Tables 1 and 2) in the PCD patients, except for the *Mdnah5* and *lrd* (discussed in detail, below).

Mdnah5 deficient mouse

Mdnah5 nullizygous mice were generated by transgenic insertional mutagenesis that led to a frameshift mutation. These mice presented with the classical features of PCD, including respiratory infections, situs abnormalities, immotility of the cilia and ultrastructural analysis revealing absent ODA.[75] Consistent with the autosomal recessive mode of inheritance, only homozygous mutant mice presented with the PCD phenotype. Almost all homozygous mutant mice developed hydrocephalus leading to perinatal lethality and indeed partial ODA defects were noted in the ependymal cells that are lining the brain ventricles and the aqueduct.[95] Recently, another group identified the homozygous mice with an inframe deletion of 593 amino acids (exons 7-17) during the ENU (ethylnitrosourea) mutagenesis screen.[76] These mice, (known as Dnahc5del593), presented with dyskinetic cilia and ODA defects in respiratory cilia. Mice presented with situs inversus totalis (35%) and heterotaxy (40%) with congenital heart defects leading to post-natal lethality. *DNAH5* is the only gene thus far known to cause PCD in humans and mice.[36,51]

Other interesting mouse models

Another mouse model with the classic PCD phenotype is *Dpcd*/*poll* knock out mice presenting with sinusitis, situs inversus, hydrocephalus, male infertility and ciliary IDA defect.[80] The initial study considered the mouse phenotype to be caused by the homozygous deletion of *poll*,[80] but later it was discovered that another gene known as *Dpcd* was also deleted in these mice.[96] In addition, mice generated with the catalytic domain of *poll* did not have a PCD phenotype.[97] Thus; taken together, it appears that *poll* is not a candidate for the PCD phenotype in these mice that may be due to the *Dpcd* deletion. The human ortholog (*DPCD*) was tested in 51 patients with PCD (15 with IDA defects) and no mutations were discovered.[96] A note-worthy model is for the *left-right-dynein* (*lrd*) deficient mice (*lrd* mice, *iv* mice and *lgl* mice) where classic PCD phenotype is not observed, but these mice present with the situs abnormalities and normal dynein arms by ultrastructural analysis.[54,55,77-79] Interestingly, mutations have been observed in the human ortholog of *lrd* (*DNAH11*) in PCD patients.[30,37]

CLINICAL FEATURES

Introduction

Ciliated cells line the airways of the nasopharynx, middle ear, paranasal sinuses, and lower respiratory tract from the trachea to the terminal airways.[98] Each ciliated cell has approximately 200 cilia projecting from its surface in the same orientation. Coordinated

movement of the cilia sweeps the periciliary fluid and overlying mucus, resulting in vectoral movement of mucus out of the lower respiratory tract. The mucociliary escalator is the primary defense mechanism of the airways,[99,100] and any functional disruption, primary or acquired, can lead to chronic sino-pulmonary symptoms.

Early clinical manifestations

The clinical features of PCD manifest early in life (Table 3). Most PCD patients (70-80%) present in the neonatal period with respiratory distress, which suggests that motile cilia are critical for effective clearance of fetal lung fluid.[9,101-103] Several case reports have emphasized unexplained atelectasis or pneumonia in term newborns, which can present with hypoxemia or even acute respiratory failure requiring mechanical ventilation. Despite this early clinical feature, the association of newborn respiratory distress with PCD has been under-recognized and diagnosis is often delayed. In a retrospective review, investigators have found the mean age of PCD diagnosis was more than 4 years of age despite these early pulmonary manifestations.[104] Persistent rhinitis and chronic cough are present since early infancy. Chronic cough is consistently reported in the majority of subjects (84-100%), and typically characterized as wet and productive.[9,105,106] The infant may also exhibit poor feeding and failure to thrive in the early years of life,[107] similar to cystic fibrosis, thus, making the diagnosis a challenge.

Laterality defects

A classic phenotypic feature of PCD that may be detected at birth are left-right laterality defects. The prevalence of situs inversus totalis tends to be over 60% in the pediatric population, as opposed to 50% in the adult population, suggesting that situs abnormalities may serve as a marker to aid in disease diagnosis.[9,105,106,108,109] Without functional nodal cilia in the embryonic period, thoracoabdominal orientation is random and not genetically pre-programmed.

Heterotaxy and congenital cardiovascular defects

Patients with Kartagener syndrome have a greater incidence of congenital cardiovascular defects, and recent studies have found that approximately 6% of PCD patients have heterotaxy (situs ambiguus or organ laterality defects other than situs inversus totalis),[110] which is associated with increased morbidity due to complex cardiovascular anomalies. Heterotaxia syndromes include abdominal situs inversus, polysplenia (left isomerism) and asplenia (right isomerism and Ivemark) syndromes.[111] It is therefore recommended that patients with anomalies consistent with situs ambiguuus or heterotaxy, including congenital heart disease, with neonatal respiratory distress or chronic respiratory tract infections be referred for PCD screening.

Upper respiratory tract

The upper respiratory tract is frequently involved in PCD. Rhinosinusitis (100%) and otitis media (95%) are cardinal features of the disease, are responsible for much of the morbidity associated with PCD in early childhood.[9,104] Nasal congestion and/or rhinorrhea are very common, and some patients have nasal polyposis. Middle ear disease is described in virtually all cases of PCD with varying degrees of chronic otitis media and persistent middle ear effusions, such that patients are often first referred to an otolaryngologist, who must have a high index of suspicion for the disease. The middle ear disease often leads to multiple sets of pressure-equalization (PE) tubes in early childhood,[9,105,112] which can be complicated by persistent, purulent otorrhea. Middle ear disease often leads to conductive hearing loss.

Lower respiratory tract

Most patients (and their family members) report a chronic, productive cough as a prominent symptom of PCD, since cough compensates for the lack of effective mucociliary clearance. Physiologic data have shown that “effective” coughs can produce effective lung clearance, almost equal to normal mucociliary clearance over short time periods, even in PCD subjects with severe ciliary defects.[113] Impaired mucociliary clearance of the lower respiratory tract leads to recurrent episodes of pneumonia or bronchitis. Bacterial cultures of lower respiratory secretions most commonly yield non-typeable *Haemophilus influenzae*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*. *Pseudomonas aeruginosa* infection, including mucoid strains, has also been reported, most often in older individuals.[9]

Bronchiectasis; severity of disease

Clinical and radiographic evidence of bronchiectasis develops as the disease progresses, often accompanied by digital clubbing. Review of high-resolution computerized tomography (CT) findings of the lungs showed that bronchiectasis primarily involves the middle and lower lobes (100% adults and 55% pediatric patients).[114,115] Bronchiectasis and obstructive impairment may be apparent in preschool children.[106,116] When compared to cystic fibrosis (CF), pulmonary involvement is generally milder in PCD when controlled for age and gender. Studies examining lung function decline suggest that forced expiratory volume in one second (FEV_1) in a cross-section of PCD patients decreases slower than that seen in CF.[9,117] PCD patients can develop chronic respiratory impairment (25% in one series) as defined by hypoxemia or an FEV_1 less than 40% predicted for age and some may eventually require lung transplantation.[9,118] Pulmonary involvement also adversely impacts quality of life as PCD patients mature, and is increasingly recognized as both medical and public understanding in ciliopathies increase.[119]

Infertility

Men with PCD are typically infertile as a result of impaired spermatozoa motility secondary to defective sperm flagella, although it is not a universal finding.[120,121] Males with PCD may occasionally have intact spermatozoa motility, suggesting sperm tails may retain some function or could have different genetic control than cilia.[120] Female fertility is more variable; with reduced fertility in some that report delay in conception following unprotected intercourse, presumably due to abnormal ciliary function in the Fallopian tube.[120,122]

Other clinical manifestations

Other clinical manifestations of PCD are rare and less well understood. Several reports have linked hydrocephalus with PCD, hypothetically due to impaired cerebrospinal fluid flow secondary to dysfunctional motile cilia that line the ventricular ependymal cells.[123,124] Hydrocephalus is frequently found in murine PCD models, but its incidence or clinical relevance in PCD patients is unclear. Retinitis pigmentosa has recently been linked to some forms of PCD,[62-64,125] and recently, bronchiectasis was reported in 37% of patients who have autosomal-dominant polycystic kidney disease.[126] Findings in these studies suggest phenotypic overlap between sensory and motile ciliopathies.

DIFFERENTIAL DIAGNOSIS

The diagnosis of primary ciliary dyskinesia is often delayed until late childhood or adulthood as a consequence of the heterogeneous nature of the disease, lack of physician knowledge of disease characteristics and the technical expertise required for an accurate diagnosis.[9,104] Several clinical presentations warrant consideration of PCD in the differential diagnosis, including infants with unexplained respiratory distress and/or

laterality defect, and infants and children who present with chronic cough, nasal drainage and sino-pulmonary disease.

(a) Neonatal respiratory distress

The differential diagnosis for neonatal respiratory distress in a term infant is extensive, and includes transient tachypnea of the newborn (TTNB), neonatal pneumonia and meconium aspiration,[127] as well as rarer causes such as surfactant protein deficiency[128] and interstitial lung disease. Infants with PCD are often misdiagnosed with TTNB or neonatal pneumonia in the newborn period. Surfactant protein deficiency, a rare form of interstitial lung disease (see below), presents in infancy with severe tachypnea and hypoxia, often requiring mechanical ventilation. These children typically have diffuse interstitial disease on chest CT and alveolar proteinosis on bronchoalveolar lavage, neither of which are seen in PCD.[129,130]

(b) Laterality defects

Situs inversus totalis occurs in approximately 50% of patients with PCD;[9,131] approximately 25% of subjects with situs inversus have PCD.[132] Other situs anomalies (heterotaxy), such as abdominal situs inversus, polysplenia, and right and left isomerism, may also be found in PCD;[110,133] and, in conjunction with neonatal respiratory distress, should prompt an evaluation for PCD. Congenital heart disease, especially involving defects of laterality, may also be present in subjects with PCD;[110,131,133] however, respiratory distress secondary to PCD may be difficult to distinguish from distress secondary to cardiac defects, thereby, delaying diagnosis.

(c) Chronic cough, nasal congestion and sino-pulmonary disease

The differential diagnosis includes CF, asthma, allergic rhinitis, gastroesophageal reflux disease (with or without aspiration), immunodeficiency, interstitial lung disease, and idiopathic bronchiectasis (see Table 4).[9,131,134]

Cystic Fibrosis

Both PCD and CF are characterized by chronic, productive cough, obstructive impairment on lung function testing,[116,135-137] and radiologic changes including hyperinflation, subsegmental atelectasis, and bronchiectasis.[9,134,135,138] Parents of PCD children often note that cough was present from birth, which may distinguish these patients from those with CF.[9,134] Digital clubbing, chronic sinusitis and nasal polyps can occur in both diseases.[9,131,134] The gastrointestinal and nutritional issues commonly seen in CF (e.g. failure to thrive, steatorrhea, and liver disease) are not typical of PCD.[134,138] In contrast, chronic otitis media is a hallmark of PCD, occurring in 90-100% of PCD patients, while the incidence of otitis media in CF is not increased compared to the general population.[9,131] CF can be ruled out by pilocarpine sweat electrolyte testing and/or by *CFTR* gene mutation analysis.[139]

Asthma and Allergic Rhinitis

PCD and asthma can both be characterized by chronic cough; however, this cough is usually dry and non-productive in asthma as opposed to the wet cough of PCD.[140-142] Atelectasis is a common finding in both PCD and asthma, often associated with hyperinflation.[143,144] Obstructive impairment on pulmonary function testing is seen in both PCD and asthma; however, bronchodilator responsiveness, a common feature in asthma, is not typical in children with PCD.[131,141]

Gastroesophageal reflux disease and aspiration

Gastroesphageal reflux disease (GERD) may present with a variety of pulmonary and upper respiratory tract symptoms, including cough, wheeze, rhinorrhea, sneezing, and recurrent pneumonia.[145,146] Aspiration pneumonia (chemical pneumonitis) can occur as a result of GERD typically involves upper lobes on chest radiograph,[147] while radiologic findings in PCD have a predilection for the right middle lobe and lingula.[134]

Immunodeficiency

Primary immunodeficiencies often present with chronic sino-pulmonary infections, resulting in a distinct overlap in symptoms with PCD.[148,149] The antibody deficiencies seen with humoral diseases result in increased susceptibility to encapsulated bacteria (*Staphylococcus aureus, Streptococcus pneumoniae,* and *Haemophilus influenzae*), and lead to recurrent pneumonia, sinus infection, and otitis media with symptoms which overlap with PCD.

Interstitial Lung Disease

Interstitial lung disease (ILD) is a descriptive term that encompasses a spectrum of over 100 lung diseases of both known and unknown etiology, all of which involve damage of the alveolar wall, accumulation of extracellular matrix within the pulmonary interstitium, and destruction of normal alveolar-capillary complexes, with progression towards pulmonary fibrosis.[130,150] Patients with ILD may present in infancy or childhood with pulmonary infiltrates, hypoxia, cough, tachypnea, and frequent infections.[129,130,150] Pulmonary function testing in ILD typically shows restrictive impairment[129] that is distinct from the obstructive impairment seen in PCD. Typical findings on high-resolution chest CT (HRCT) in ILD include ground-glass opacities, septal thickening, geographic hyperlucency, consolidation, and cysts or nodules,[129] all of which are distinct from the hyperinflation, atelectasis, infiltrates, bronchial thickening, and bronchiectasis seen in PCD.[9,105]

DIAGNOSTIC APPROACH

The diagnostic approach to PCD is evolving. Until recently, the only definitive diagnostic test had been electron microscopy to define ultrastructural defects in cilia supported by light microscopic analysis demonstrating obvious ciliary dysfunction (immotile or profoundly dyskinetic cilia). Emerging diagnostic tests include genetic testing, nasal nitric oxide measurement, immunofluorescent analysis, and high-speed videomicroscopy to define subtle ciliary dysmotility. At this point, these specialized diagnostic tests are not standardized or readily available; therefore, referral to research centers may be needed. A systematic research approach to diagnosing PCD has defined some individuals with normal ciliary ultrastructure, who have PCD based on identification of disease-causing mutations in a ciliary genes associated with subtle defects in ciliary motility (as described above). It is conceivable that ultrastructural defects may represent a small fraction of individuals with a genetic defect of cilia in PCD.

DIAGNOSTIC TESTS

Ultrastructural changes in PCD

Ultrastructural defects of cilia associated with mucociliary dysfunction was first described in 1975 by Afzelius et al.[4,151] These reports identified absent and dysmorphic dynein arms in spermatozoa and airway cilia of affected individuals and subsequent reports have supported these observations. Current ciliary ultrastructural diagnostic criteria include absence or structural modification of either inner or outer dynein arms individually, or of both dynein arms[152-155] (Fig. 3). Cilia with defective radial spokes and transposition of a peripheral pair of microtubules to occupy the central axis also have been associated with disease consistent

with PCD, although such cases appear to be rare.[156,157] Although a variety of other ciliary ultrastructural defects such as axonemal changes, are reported in respiratory disease, these changes are "secondary" and can be traced to infection, inflammation, or irritant exposure.[158,159] These abnormalities are distinguished from the index ultrastructural lesions of PCD by their lack of universality in all cilia of affected individuals. Indeed, studies of healthy airways have demonstrated a background of 3-5% defective cilia even in airways of healthy individuals.[160] Ultrastructural analysis is cumbersome requiring technical expertise, sophisticated electron optical imaging, and is only available at a limited number of centers.

While ultrastructural analysis has proved invaluable in the diagnosis of PCD and has been considered the "gold standard", new studies[37] are emerging to demonstrate that affected individuals can exhibit the clinical phenotype of PCD, and mutations in ciliary genes, but have normal ciliary ultrastructure. This observation points to the broadening definition of PCD which is being brought about by advances in molecular genetics. These molecular studies are important, as they support a growing awareness among researchers that PCD is an underreported syndrome perhaps, in part, because of the limitation of ciliary ultrastructural analysis.[161]

Ciliary motility abnormalities in PCD

The first reports by Afzelius et al.[4,151] indicated spermatozoa and airway cilia from the affected individuals were totally immotile, which led to the early descriptive name, "immotile cilia syndrome". Subsequent studies among other affected individuals reported motile, but dyskinetic, ciliary activity, which led to adoption of "primary ciliary dyskinesia (PCD)". PCD more correctly described the typical pattern of motility, and implied heterogeneous genetic basis of the syndrome. Motile, but dyskinetic, cilia usually beat out of synchrony relative to neighboring cilia. Typically, dyskinesia is accompanied by markedly attenuated ciliary beat frequency (<3 Hz at 22°C) although cases of vigorous motility have been documented. Ongoing research is studying relationships between ciliary kinetics and beat frequency, specific ultrastructural characteristics, and specific dynein mutations conferring PCD.

Nasal Nitric Oxide testing

Nasal nitric oxide (NO) measurements is emerging as a non-invasive screening test for PCD, based on multiple studies demonstrating that nasal NO production is markedly reduced (5-20% of normal) in patients with PCD.[7-10,162] The exact mechanism for reduced nasal NO in PCD has yet to be elucidated, and the biologic function of nasal NO has not been fully defined. Postulated functions include regulation of ciliary motility[163] and antimicrobial activity.[164] Nasal NO, produced predominantly in the paranasal sinuses, is much more abundant (10 – 50 fold greater) than in the lower airways.[10,162,165] Consequently, accurate measurement of nasal NO production requires specific techniques for palate closure, in order to ensure that there is no dilution of the nasal NO by air from the lower airways.[134,165] While nasal NO is extremely low in patients with PCD, it is also reduced (though not as low) in patients with cystic fibrosis.[134,165] Sinus disease (acute or chronic) may result in falsely diminished nasal NO levels in otherwise healthy subjects.[165] Because no FDA-approved devices for measurement of nasal NO are available, nasal NO measurement is used predominantly in research studies in the United States, but has become part of the diagnostic clinical testing at centers in Europe.[166] Normal values are published for children as young as six years of age.[167] Recent studies have focused on standardizing techniques for measuring nasal NO especially in children under 6 years of age who are unable to cooperate with maneuvers to close the soft palate.[168,169]

Immunofluorescent analysis

Immunofluorescent analysis for ciliary proteins holds diagnostic potential for PCD. Recent studies showed that PCD patients with ODA defects had absence of DNAH5 staining from the entire axoneme or from the distal portion and accumulation of DNAH5 at the microtubule-organizing center, in contrast to all control individuals, including disease controls (recurrent respiratory infections unrelated to PCD) who had normal DNAH5 staining along the ciliary axoneme.[52,170] This method is performed on nasal epithelial cells obtained via non-invasive trans-nasal brushing. The main advantage of this method is that it can detect the changes along the entire length of the ciliary axoneme. At present immunofluorescent staining is available at one research laboratory in Germany with limited supply of ciliary protein specific antibodies.

Genetic testing

The diagnosis of PCD is challenging due to the requirement of cumbersome ultrastructural or immunofluorescent analyses, and only a few laboratories can offer those tests. Defining biallelic mutations in trans (inheriting a mutation from each parent) in a PCD patient in the causative gene would confirm the diagnosis. But, genetic diagnosis for PCD is also challenging due to the genetic heterogeneity and the large size of PCD-causing genes. In addition, despite the identification of several of PCD causing genes, the number of PCD patients harboring mutations in some of these genes is small and thus, limits the development of a robust clinical genetic test. *DNAI1* and *DNAH5* appear to be major causative genes in almost 30-38% of all PCD families.[33,36,44-46,48,51] Since mutations in these genes have been exclusively identified in patients with ODA defects, the mutation detection rate is higher (~50-60%) in PCD patients with ODA defects. Despite allelic heterogeneity in *DNAI1* and *DNAH5*, mutation clusters were observed in 9 exons of *DNAI1* (exons 1, 13, 16, and 17) and *DNAH5* (exons 34, 50, 63, 76 and 77). Based on published reports, we estimate that analysis of the 9 exons would lead to the identification of at least one mutant allele in approximately 24% of all PCD patients. The DNA from these patients can then be sequenced to test for the second mutation. The first PCD clinical genetic assay was developed that required sequencing of only 9 exons (out of 100 exons),[28,47] and a commercial laboratory subsequently developed a genetic assay that tests for the known 60 mutant alleles of *DNAI1* and *DNAH5*. For the full listing of the laboratories offering PCD genetic tests please check (url: http://www.genetests.org/). Sequence based assays are expensive; hence, alternative approaches, are being considered such as melting curve analysis and microarray chips. The benefit of these alternative methods is the ease of addition of the new genetic mutations as they are discovered, which can assist in further increase in specificity of the genetic test.

MANAGEMENT

Medical management of lung disease

Currently, there are no therapies that have been adequately studied to definitively prove their efficacy in the treatment of PCD. Treatments that are used in clinical practice tend to be extrapolated from CF clinical trials. There is evidence, however, from the observational data of clinical case series, that early diagnosis and management of patients with PCD in a specialized PCD clinic may improve long term lung function outcomes.[171] The disease management approach reported by Ellerman and Bisgaard[171] followed an algorithm very similar to the CF disease management approach. A number of high quality randomized controlled trials of therapy have been published to help establish an evidence based approach to care of CF.[172] CF medical management practices which have some biological rationale for extrapolation to PCD, include daily airway clearance, judicious use of antibiotics, infection control and attention to nutritional status. Generally antibiotics are used

acutely with disease exacerbation and are prescribed according to bacteria grown in the last sputum culture. Chronic suppressive use of antibiotics would be considered, if a patient is repeatedly growing *Pseudomonas aeruginosa* in the sputum. There are no data to recommend for or against agents that improve mucociliary clearance or inflammation in PCD. Clinical utility of bronchodilators has not been demonstrated in PCD. Monitoring for progression of lung disease should be an important part of the regular clinic visit. At present, there are no clinical practice guidelines to direct frequency of clinic visits or additional testing. Based on the PCD management approach reported by Ellerman and Bisgaard [171] and clinical practices used for cystic fibrosis, tests to consider include lung function testing and respiratory cultures every 3-6 months and lung imaging on an annual or biannual basis. Consideration should be given for obtaining a chest CT, instead of a plain chest radiograph, at the time of diagnosis or at intervals during follow-up, since chest CT is the gold standard for diagnosing bronchiectasis.[173] The additional radiation of a chest CT must be weighed against the potential "benefit" of early recognition of bronchiectasis.

Surgical management of lung disease

Lobectomy is generally not recommended since PCD is a generalized airway disease. However, lobectomy has been shown to improve symptoms and to have low perioperative mortality in case series of selected patients with PCD[174] and idiopathic bronchiectasis.[175] Consideration for lobectomy should be limited to selected patients with severe localized bronchiectasis with frequent febrile episodes or, severe hemoptysis and failure of conservative medical management with antibiotics, airway clearance and embolotherapy.[174] Surgery should only be performed in centers with specialized expertise. Lung transplantation is an option once a patient has reached end-stage lung disease. There are at least 9 reported cases of successful lung transplantation in patients with PCD.[176] There are no longitudinal survival data published in order to develop criteria for referral for lung transplantation in PCD.

Management of chronic otitis media

The management of serous otitis and recurrent otitis media in PCD is controversial. While some otolaryngologists argue that myringotomy tubes can be harmful and should be avoided, others argue that myringotomy tubes allow hearing and speech to develop in the infant or toddler with hearing loss due to chronic serous otitis. The proponents against tubes suggest that they cause annoying chronic mucopurulent drainage of the middle ear, pose a risk of chronic middle ear perforation and that the natural history of hearing loss is that it normalizes by age 12 years, making these procedures unnecessary.[177] On the other hand, mucopurulent drainage responds to treatment with local antibiotics and there is no hard data to show that chronic middle ear perforation is a common complication. In addition, delayed speech development can have profound effects on language development and subsequent school performance. Hearing aids may be used instead of myringotomy tubes, however they are sometimes not well tolerated in the preschool age group.

Specialized PCD diagnostic and treatment centers

A multi-disciplinary "disease management" approach to chronic disease is now well recognized to be the most successful strategy for improving patient outcomes.[178] Key elements of advancing disease management include research, performance measurement and quality improvement.[179] When one considers that PCD is a chronic airways disease with many similarities to CF including a similar (albeit slower) progression of lung function deterioration and lower airways bacterial colonization with age,[9] the notion of a need for specialty "PCD Centers" seems obvious. Improvement in survival and quality of life over the last 30 years for patients with CF can be largely attributed to the better treatment developed at major CF centers.[180] In addition to improved clinical outcomes, disease-

specific centers are generally regarded favorably by patients and have numerous psychosocial benefits, including the opportunity to meet other families/patients with the same rare disease and share experiences.[181] Finally, major CF centers also provide a natural infrastructure for the conduct of clinical research to further improve outcomes.[139] Good medical management in a specialized PCD diagnostic and treatment center will probably provide the PCD patient with the best chance for preservation of lung function over time.

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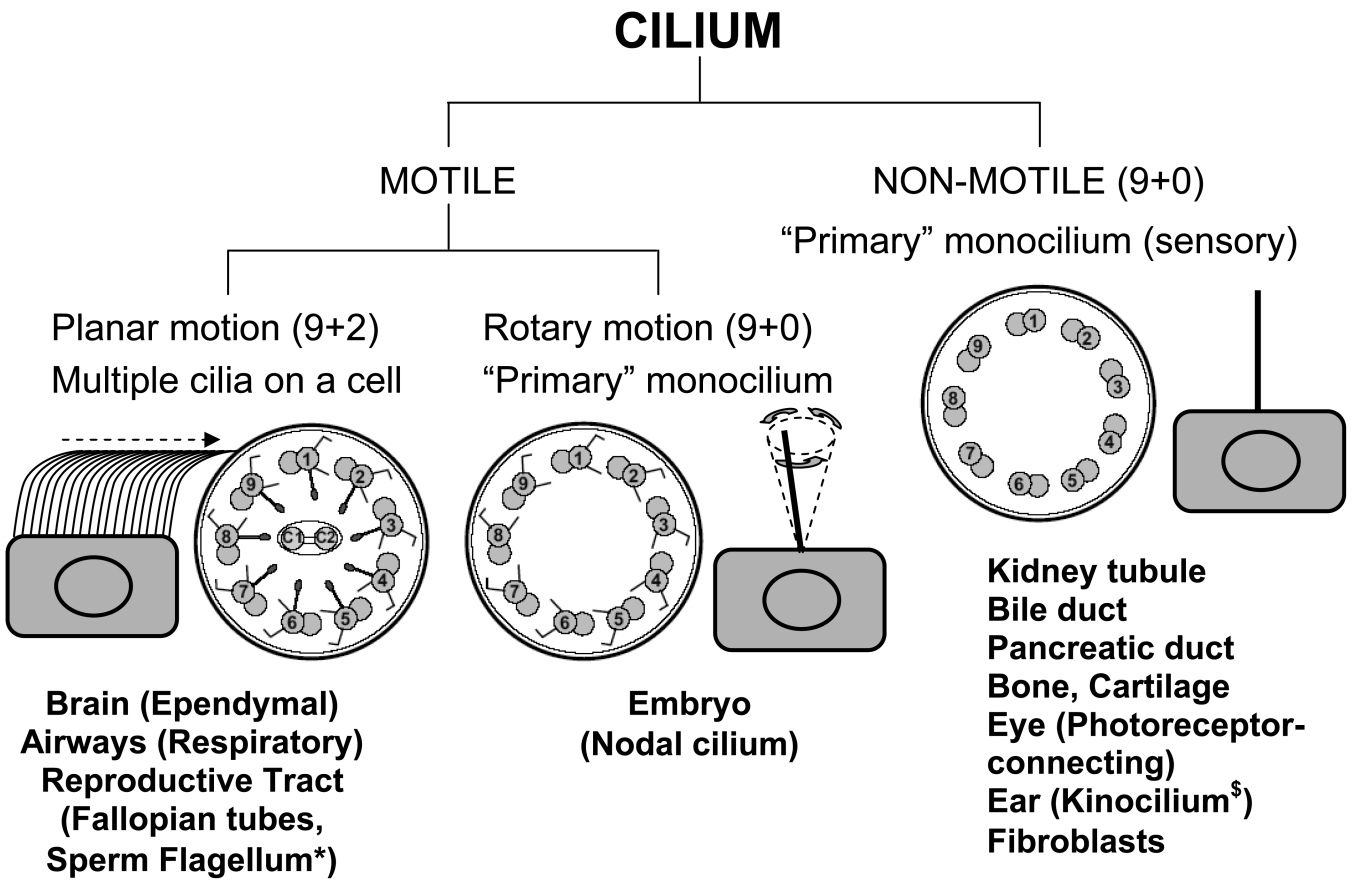

Figure 1.

Diversity of ciliary axoneme. Cross section of non motile (9+0 arrangement) and motile cilia (9+2 and 9+0 arrangement) are shown.[27,182] Studies to date have not determined whether the 9+0 monocilium has radial spokes. The model showing synchronous motion of motile (9+2), rotatory motion of motile monocilium (9+0) and immotile monocilium (9+0) is also shown.

* Solitary axoneme in the sperm mirrors the structure of the cilium

§ Subcellular structure of the kinocilium is debatable. Some reports indicate 9+0 while others indicate 9+2 configuration. The function of the kinocilium is also not clear as it disappears during the mammalian early postnatal period.[183]

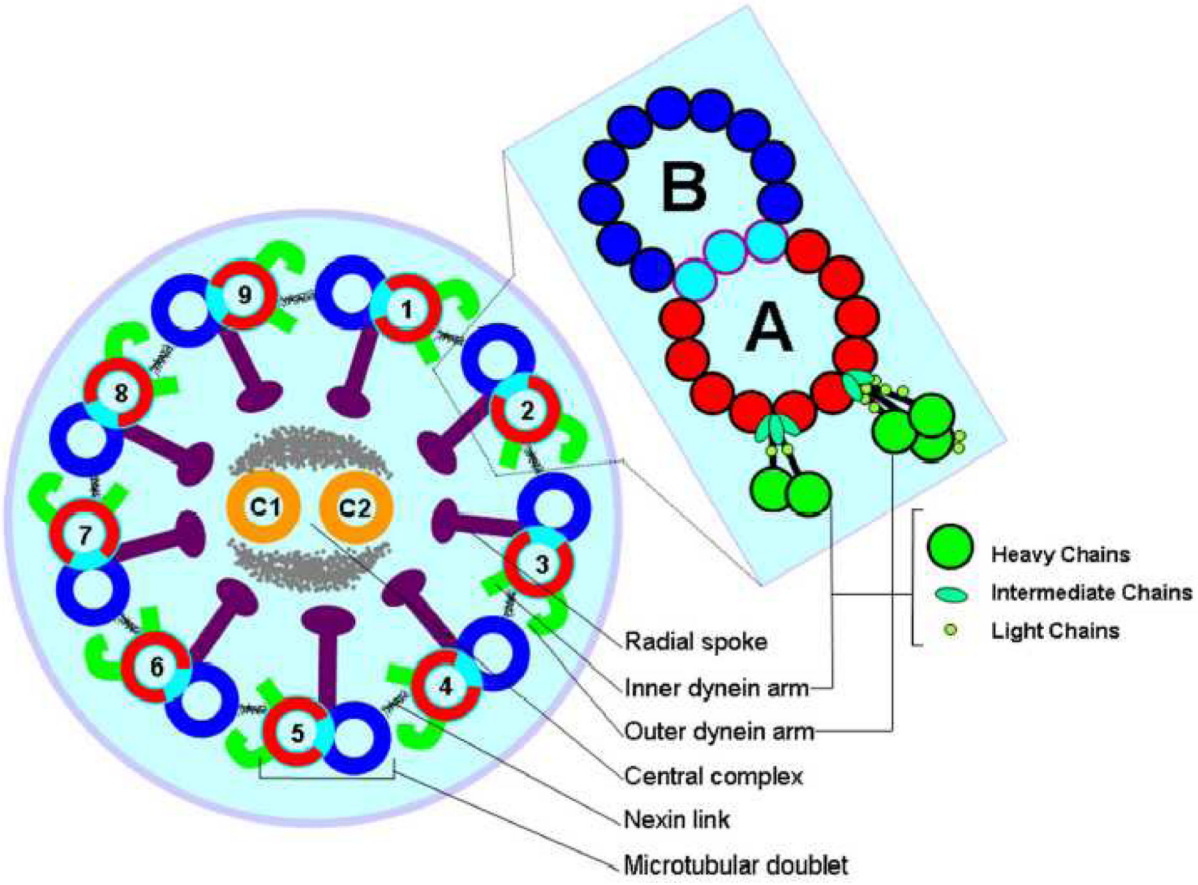

Figure 2.

Schematic diagram of the eukaryotic cilium. Cross-section illustrates the 9+2 configuration of nine peripheral microtubular doublets surrounding a central pair microtubule complex. The expanded view of a microtubular doublet schematically depicts cross-sections of the tubulin protofilaments including those shared by the A and B tubules. The dynein arms in the expanded view are rendered to schematically depict several light, intermediate, and heavy chains comprising each of these structures. While the outer arm exhibits a specific distribution of dyneins, being uniformly composed of three heavy, two intermediate and at least 8 light chains, the distribution of dyneins in the inner arm is thought to be more variable.

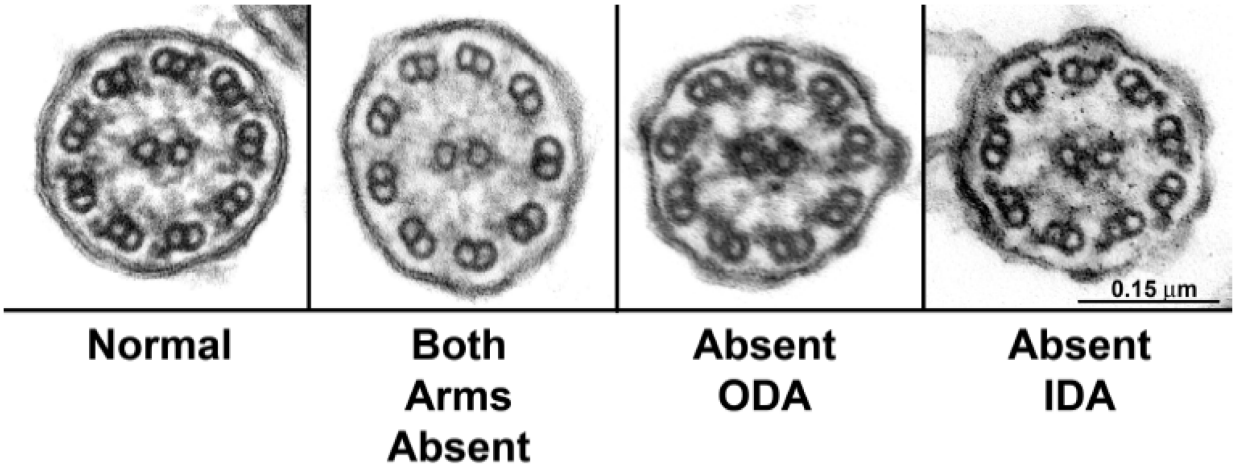

Figure 3.
Electron micrographs of nasal cilia from patients with primary ciliary dyskinesia (PCD) illustrating dynein defects. Far left panel illustrates ultrastructure of a normal cilium from nasal epithelium of a healthy, clinically unaffected subject. The adjacent panels from three different PCD patients illustrates defects in both dynein arms, isolated defects of outer dynein arms only, and isolated defects of inner dynein arms only.

Table 1

Candidate genes tested and found to be mutated in PCD patients

Human Gene	Axonemal component	# of PCD families tested	# of PCD families with biallelic mutations	# of PCD families with only monoallelic mutations	References
DNAH5	ODA-HC	134	28	10	36,50,51
DNAH11	ODA HC	2	2	0	30,37
DNAI1	ODA IC	226	20	2	33,44-46
		104	2	2	48
DNAI2	ODA IC	10	0	0	34
		6	0	0	53
		106	3	0	35
TXNDC3	ODA LC/IC	41	1	0	31
KTU	cytoplasmic *	112	2	0	32
RSPH9	RS	2	2	0	56
RSPH4A	RS	5	5	0	56

Abbreviations:

ODA: outer dynein arm, IDA: inner dynein arm, HC: heavy chain, IC: intermediate chain, LC: light chain, RS: radial spoke

* = cytoplasmic protein requires for the dynein arms assembly

Table 2

Candidate genes tested and found negative in PCD patients

Human Gene	Axonemal component	# of PCD families tested	# of PCD families with biallelic mutations	# of PCD families with only monoallelic mutations	References
DNAH9	ODA HC	2	0	0	184
DNAH17	ODA HC	4	0	0	185
DNAL1	ODA LC	86	0	0	186
DNAL4	ODA LC	54	0	0	187
TCTE3	ODA LC	36	0	0	188
DYNLL2	ODA LC	58	0	0	53
DNALI1 (HP28)	IDA LC	61	0	0	187,189
DNAH3	IDA HC	7	0	0	190
DNAH7	IDA HC	1	0	0	191
DPCD	IDA gene	51	0	0	96
SPAG6	CA	54	0	0	185
SPAG16	CA	5	0	0	192
FOXJ1/HFH-4	expressed*	8	0	0	89

Abbreviations:

ODA: outer dynein arm, IDA: inner dynein arm, HC: heavy chain, IC: intermediate chain, LC: light chain, CA: central apparatus

* = expressed in respiratory cilia

Table 3

Clinical Features of PCD

Middle ear
Chronic otitis media
Conductive hearing loss
Nose and Paranasal sinuses
Neonatal rhinitis
Chronic nasal congestion and mucopurlent rhinitis
Chronic pansinusitis
Nasal polyposis
Lung
Neonatal respiratory distress
Chronic cough
Recurrent pneumonia
Bronchiectasis
Genitourinary tract
Male (and possibly female infertility)
Laterality defects
Situs inversus totalis
Heterotaxy (± congenital cardiovascular abnormalities
Central nervous system
Hydrocephalus
Eye
Retinitis pigmentosa

Table 4

Differential Diagnoses, Presenting Symptoms, and Findings

SYMPTOMS	PCD	CF	Asthma	Allergic Rhinitis	GERD	ILD
Cough	+++	+++	++	++	++	++
frequency	chronic, daily	chronic	intermittent	intermittent	intermittent	intermittent
character	wet	wet	dry	dry or wet	dry or wet	dry or wet
time of year	year-round	year-round	often seasonal	often seasonal	year-round	year-round
Nasal congestion	+++	++	*w/ allergic*	++	−	−
frequency	chronic, daily	intermittent	*rhinitis*	intermittent		
time of year	year-round	year-round		often seasonal		
Otitis media	+++	−	−	−	+	++
Sinus disease	+++	+++	−	++	−	−
Neonatal respiratory distress	+++	−	−	−	−	+++
FINDINGS						
Chest imaging	hyperinflation, infiltrates, atelectasis, peribronchial thickening, bronchiectasis	hyperinflation, infiltrates, atelectasis, peribronchial thickening, bronchiectasis	hyperinflation, infiltrates, rare atelectasis,	normal	normal, or infiltrates with aspiration, rare bronchiectasis	ground-glass opacities, hyperlucency, consolidation, septal thickening, cysts, nodules
Pulmonary Function Testing	obstructive, later mixed	obstructive, later mixed	obstructive	normal	normal	restrictive

DEFINITIONS:

+++ Occurs in over 75% of patients with classic disease

++ Occurs in many patients with classic disease

+ Occurs in some patients with classic disease

− Occurs at same frequency as in general population

Abbreviations:

PCD: primary ciliary dyskinesia, CF: cystic fibrosis, GERD: gastroesophageal reflux disease, ILD: interstitial lung disease (examples of ILD presenting in neonatal period include surfactant protein C deficiency and neuroendocrine cell hyperplasia)