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Understanding primary ciliary dyskinesia and other ciliopathies

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Abstract

Ciliopathies are a collection of disorders related to cilia dysfunction. Cilia are specialized organelles that project from the surface of most cells. Motile and primary (sensory) cilia are essential structures and have wide ranging functions. Our understanding of the genetics, pathophysiology, and clinical manifestations of motile ciliopathies, including primary ciliary dyskinesia (PCD), has rapidly advanced since the disease was linked to ciliary ultrastructural defects nearly five decades ago. We will provide an overview of different types of cilia, their role in child health and disease, focusing on motile ciliopathies, and describe recent advances that have led to improved diagnostics and may yield therapeutic targets to restore ciliary structure and function.

Keywords

primary ciliary dyskinesia; bronchiectasis; cilia; basal body; dynein

CILIA STRUCTURE AND FUNCTION

Cilia and flagella are evolutionarily conserved structures from simple unicellular algae to humans. *Chlamydomonas reinhardtii,* a biflagellated single cell organism, has been a powerful model to study motile cilia. The similarities between algal flagella and eukaryotic motile cilia have yielded new insights into the genetics and biological functions of proteins in human cilia. Many genes linked to primary ciliary dyskinesia and other ciliopathies have *Chlamydomonas* orthologues.

There are two general classes of cilia: motile cilia and immotile cilia. All eukaryotic cilia extend from basal bodies, docked at the surface of the cell (Figure 1). They share similar structures, including the axoneme, a cytoskeletal scaffold that forms their central core[1]. The axoneme is composed of nine microtubule doublets that extend the length of the cilium, maintaining structural integrity and direct components into and from cilia, using a process

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known as intra-flagellar transport (IFT). The axoneme is anchored to the cell by a basal body, a protein structure derived from the centriole. Although different types of cilia share a basic structural blueprint (Figure 2), they differ in their function and distribution.

Motile cilia are organelles that are found on the apical epithelial surface of upper and lower respiratory tracts. Motile cilia are anatomically and functionally oriented organelles that rhythmically beat, moving fluid, mucus, and trapped bacteria along the epithelial surface. Approximately 200 motile cilia cluster on the surface of airway epithelial cells, and they must undergo a complex process of centrosomal amplification to produce hundreds of basal bodies. Mucociliary clearance is a critical defense of the respiratory tract and is dependent on a highly coordinated ciliary function. Defects in clearance lead to chronic infection and inflammation in the upper and lower respiratory tracts. Normal beat frequency in the airway typically ranges between 8 to 14 Hertz. However, beat frequency can be modulated in response to external stimuli such as changes in redox conditions, infection, or exposure to pollutants, including cigarette smoke[2–5]. In addition to the respiratory tract, motile cilia are present elsewhere. The brain ependyma and fallopian tubes are lined by motile ciliated cells, and the spermatozoan flagellum have the same core structure and fundamentally similar motility characteristics as cilia.

Motile cilia have multimeric dynein arms that extend from the A microtubule of the outer doublets and attach to the adjacent B microtubule (Figure 2). These elements are critical for motion through adenosine triphosphatase activity. The outer dynein arm generates the force that translates into a sliding motion of two neighboring tubules, whereas the inner dynein arms control ciliary motion through the nexin-dynein regulatory complex, which coordinates activity of various dynein proteins[6]. Motile cilia also have a central microtubular pair, creating the “9+2” configuration seen on transmission electron micrographs. The central apparatus maintains structural integrity, transfers force during cilia beating, and aligns adjacent cilia, ensuring ciliary motility is maintained in the same direction along the airway. Radial spokes connect the central apparatus and inner dynein arms, sending signals to the dynein regulatory complex to regulate dynein activity [7].

Another motile cilium is only expressed during fetal development. Nodal cilia (Figure 3) are transiently localized to the ventral node of the gastrula, and unlike multi-ciliated cilia on airway epithelial cells, they exist as monocilium and do not have a central pair, creating a “9+0” microtubular arrangement. Because they lack a central pair, their motion is rotatory, thus producing leftward flow of extra-cellular fluid across the surface of the embryonic node, which in turn activates a signaling cascade that establishes left-right sidedness and body laterality[8–10]. When motile cilia are defective and flow is absent, body laterality occurs at random, and can lead to *situs inversus totalis* and heterotaxy.

In contrast, primary cilia are usually *immotile monocilia*, present on the surface of many non-dividing differentiated cells. Unlike motile cilia, most primary cilia have a “9+0” microtubule configuration, lacking the central apparatus and dynein arms. There are few exceptions, such as the kinocilium in the cochlea and olfactory cilia (Figure 3). Primary cilia are sensory organelles that sense the extracellular environment and can act as surface mechano- or chemo-receptors. Other primary cilia detect changes in

osmolality, light, temperature, and gravity. Furthermore, they have critical roles in normal development and tissue differentiation, and express many essential receptors on their surface, including sonic hedgehog, epidermal growth factor receptor, and platelet derived growth factor receptor[11–13]. As a result of their ubiquitous distribution, primary ciliary defects are associated with wide-ranging syndromes and diseases that involve multiple systems, referred to as primary ciliopathies (Table). For instance, Bardet-Biedl syndrome (BBS) is a rare, autosomal recessive disorder, caused by defective BBS proteins that localize to the basal body of primary cilia.[14, 15] It can present with intellectual disabilities, obesity, retinal degeneration, polycystic kidneys, polydactyly, diabetes mellitus, and cardiovascular anomalies. Other primary ciliopathies include cranioectodermal dysplasia, Sensenbrenner syndrome, short-rib polydactyly, and Jeune syndrome, conditions that have overlapping clinical features, including skeletal dysplasia that result in chest deformities, pulmonary restriction, and respiratory compromise[16].

Most primary ciliopathies do not affect the function of motile cilia, though there have been rare reports of syndromes that have features of both primary and motile cilia dysfunction[17–19]. In some families, *RPGR* mutations, which cause retinitis pigmentosa due to primary cilia dysfunction, can also lead to PCD-like symptoms due motile cilia dysfunction in the airway [18]. Both motile and immotile cilia share many proteins and structures, and there are several lines of evidence indicating that the motile cilia have sensory and signaling functions [20].

CLINICAL FEATURES OF PRIMARY CILIARY DYSKINESIA (PCD)

PCD is a rare inherited disease in which genetic mutations impair motile cilia function[21]. It is widely found across ethnic groups, without racial or gender predilection. The reported frequency of PCD in the general population varies between 1 in 10,000–20,000 live-born children, but some have reported its prevalence as high as 5% in children with repeated respiratory infections[22].

Primary ciliary dyskinesia typically presents early in life. Roughly 80% of full-term infants with PCD present with respiratory distress within 24 hours of birth, requiring supplemental oxygen or mechanical ventilator support for days or even weeks. Chest imaging often reveals atelectasis, mainly involving the morphological right middle lobe or lingua. Children with PCD also develop daily, year-round “wet” or productive cough that usually begins under 6-months of age, and is related to impaired mucociliary clearance, which leads to chronic airway infection, inflammation, progressive airway obstruction, and bronchiectasis, even early in life[23]. Patients with PCD have frequent upper airway involvement, manifested as persistent rhinosinusitis with watery nasal discharge that begins in early infancy [24]. Nasal polyposis is relatively uncommon, reported in less than 15% of children[25]. Middle ear involvement is nearly universal in PCD, with recurrent acute and chronic otitis media. Conductive hearing loss is common, and 75% of children with PCD have some degree of hearing loss. Interestingly, some children have sensorineural or mixed hearing loss[26]. These chronic respiratory symptoms negatively affect the lives of people with PCD, and delayed diagnosis has been associated with poorer quality of life [27].

Roughly half of all patients with PCD have left-right laterality abnormalities, including *situs inversus totalis* and heterotaxy syndromes, which can be associated with congenital heart disease, asplenia, or polysplenia[28]. Male and female infertility or subfertility are other non-respiratory complications, related to sperm dysmotility and ciliary dysfunction in the fallopian tubes, respectively. Rarer manifestations of PCD include prenatal hydrocephalus[29] and blindness due to *RPGR* gene mutations[18, 30].

GENETICS OF PRIMARY CILIARY DYSKINESIA

Because of the large number of proteins involved in cilia function and assembly, PCD is genetically heterogeneous, primarily an autosomal-recessive disease, but autosomal-dominant and X-linked inheritance patterns are known. Most of the genes associated with PCD encode proteins that are involved in axonemal motors, structure and regulation, or ciliary assembly and preassembly. The rate of discovery of new genes has accelerated during the past decade, and nearly 50 genes have been linked to disease (Figure 4, available online). Over 70% of all patients tested have biallelic mutations within one of these genes. Through the efforts of international, collaborative consortia, that number will surely rise.

Genetic studies have yielded unexpected insights into the disease. Approximately 30% of people with PCD and ciliary dysmotility have normal ciliary ultrastructure. For example, airway cilia from people who have mutations in *DNAH11*, which encodes an outer dynein arm protein, appear structurally normal, but have a rapid beat frequency with abnormal waveform[31, 32]. Individuals who have mutations in genes encoding for dynein regulatory complex proteins may have only subtle ciliary changes which can be missed on transmission electron microscopy[33, 34]. Recently, a mutation in an inner dynein arm protein was associated with PCD[35], with a normal ultrastructure and subtle changes in cilia beat.

Mutations in several genes that encode cytoplasmic proteins have been associated with PCD. Often, these mutations result in both outer and inner dynein arm defects and cilia immotility[36–40]. Pathogenic mutations in *NEK10*, a gene that encodes a ciliated cell-specific kinase, results in pathologically shortened motile cilia and impaired mucociliary clearance[41]. Other mutations can affect cilia orientation, such as mutations in *GAS2L2* that cause ciliary disorientation and asynchronous beating[42]. More commonly, though, ciliary disorientation follows viral infections and airway injury, causing an acquired ciliopathy that impairs mucociliary clearance.

Motile ciliopathies distinct from classical PCD have been described. For instance, people with biallelic mutations in *CCNO* and *MCIDAS*, two proteins required for centriole production, have clinical features similar to PCD but are characterized by oligocilia with normal ultrastructure on airway epithelial cell surface. People harboring mutations in these genes are reported to have greater lung disease compared with those who have dynein arm proteins defects [43, 44]. Moreover, individuals with *MCIDAS* mutations have higher incidence of hydrocephalus [43, 45]. *De novo*, single mutations in *FOXJ1*, a vital transcription factor that regulates cilia gene expression, cause reduced number of motile cilia and are associated with hydrocephalus, recurrent respiratory infections, and laterality defects[46].

Finally, PCD exists as a clinical spectrum, and genotype-phenotype associations have emerged. Studies have shown that children who have biallelic mutations in *CCDC39* or *CCDC40*, two genes involved in assembly of the ciliary scaffold and spacing of radial spokes, have greater lung disease and more rapid pulmonary function decline when compared with individuals with dynein arm protein defects[47, 48]. Conversely, people with *RSPH1* defects tend to have milder lung disease, situs solitus, and less middle ear involvement [49].

DIAGNOSING PRIMARY CILIARY DYSKINESIA

Historically, the diagnosis of PCD has been challenging, but newer tools have improved accuracy. Testing should be performed only in patients who have a clinical phenotype consistent with the disease. There are four clinical features that discriminate PCD from other more common respiratory diseases of childhood, which include neonatal respiratory distress in full-term infants, laterality defects, daily non-seasonal nasal congestion, and daily, year-round wet cough that begins before 6 months of age. If two of these findings are present, the sensitivity and specificity for PCD are 80% and 72%, respectively[50]. Although persistent middle ear effusions and chronic otitis media are common in PCD, the high prevalence of recurrent otitis media in the general pediatric population makes this feature less reliable. The combination of respiratory distress with situs abnormalities recognized in a term infant without congenital heart disease would be consistent with PCD and should prompt the clinician to pursue further evaluation. These clinical features are the basis of published diagnostic algorithms[51, 52]. Other clinical diagnostic tools have been created and validated to estimate the probability of a positive diagnosis based on clinical features[53].

It is important to remember that no single test will diagnose every patient with PCD. Since axonemal ultrastructural defects were first recognized over 40 years ago, transmission electron microscopy to assess axonemal ultrastructure has been the “gold” diagnostic standard. Four ultrastructural defects have been described in primary ciliary dyskinesia: outer dynein arm defects; inner and outer dynein arm defects; microtubular disorganization with inner dynein arm defects; and radial spokes and central apparatus defects. Inner dynein arm defects alone are rarely associated with disease, and to date, only one gene encoding an inner dynein arm protein has been associated with disease[35]. With advances in genetic tools, the limitations of electron microscopy have become obvious. About 30% of patients with genetically confirmed PCD have normal or near-normal ultrastructure, related to mutations in genes that encode structural proteins that do not affect the integrity of the dynein arms. Moreover, nonspecific changes in ciliary ultrastructure may be observed after airway infections and environmental pollutant exposures, resulting in an erroneous diagnosis of PCD. Recently, British investigators have found that immunofluorescent staining of specific markers can accurately identify abnormal axonemal ultrastructure and may overcome some limitations of electron microscopy[54]. This approach is frequently used by many PCD centers in Europe, but has not been widely adopted in the United States. With further standardization and optimization of antibody panels, this approach may become a first-line diagnostic test.

Another screening tool arose from the reproducible observation that most people with PCD have reduced nasal nitric oxide levels. Low levels of nasal nitric oxide measurements are sensitive and specific for the diagnosis of PCD in children five years and older, when combined with supportive clinical features[55, 56], with sensitivity and specify of 98% and 99%, respectively[55]. The mechanism by which nitric oxide production is reduced is not entirely understood. Many of the nitric oxide synthase and regulatory enzymes localize to the proximal ciliary axoneme and basal bodies, and their function may be affected when cilia are dysmotile[57–59]. Despite its usefulness, it is important to note that reduced nasal nitric oxide measurements alone are never sufficient to make the diagnosis[52]. Indeed, low nasal nitric oxide levels can be found in individuals with cystic fibrosis and primary immunodeficiencies, two conditions that share clinical features with PCD, and must be excluded.

High-speed video microscopy that assess cilia beat frequency and patterns is an alternative diagnostic tool used in Europe[60, 61]. Although this approach has value, it also has limitations. The technique requires substantial experience and should be performed at specialized center [62]. Some centers perform non-standardized ciliary beat analyses using standard brightfield microscopy to determine whether further testing is warranted. This approach can be misleading, however, and should *never* be used as a screen or diagnostic tool for PCD.

During the last decade, large-scale parallel sequencing of regions of interests and whole exome sequencing have been used to successfully identify candidate genes associated with PCD. These advances have also transformed diagnostic testing for PCD, and there are currently several commercially available gene panels that provide coverage of most known genes associated with PCD[36, 63, 64]. genetic testing, which has become a first-line diagnostic, is one of many available diagnostic tools, and its use should be limited to patients that fulfill clinical diagnostic criteria for PCD. In some cases, mutations are identified that have no clear effect on the function of the protein, termed variants of unknown significance (VUS). Interpretation of these variants requires experience and often confirmatory functional testing to determine their contribution to disease. Furthermore, it has become evident that different mutations in the same gene may lead to different clinical presentations[65]. Some children should be referred to specialized PCD centers to confirm or establish the diagnosis.

MANAGEMENT OF PRIMARY CILIARY DYSKINESIA

Despite recent advances, this knowledge has not been translated into disease-specific therapies. Currently, there are no treatments that have been shown to correct or restore cilia function in people with PCD.

Management strategies of children with PCD have been extrapolated largely from other forms of bronchiectasis such as cystic fibrosis. Airway clearance techniques and systemic antibiotics, guided by routine surveillance sputum cultures, are cornerstones of therapy, used to clear purulent secretions, mobilize secretions and control bacterial burden of the lower respiratory tract, particularly during acute exacerbations. Patients with PCD have varying levels of bronchiectasis associated with chronic bacterial overgrowth. Bacterial organisms

that are frequently detected include *Haemophilus influenzae, Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa.*[66, 67]. Though data is lacking, there is some evidence that chronic colonization with mucoid *P. aeruginosa* may be associated with greater lung function decline. [67, 68]

A multicenter, European clinical trial examined the efficacy of routine thrice weekly azithromycin as an anti-inflammatory agent in a selected PCD subpopulation[69]. Macrolide therapy resulted in modest reduction in frequency of respiratory exacerbations, but quality-of-life and pulmonary function measures did not improve. The benefits of other therapies, such as alternate-month inhaled antimicrobials, nebulized hypertonic saline, or mucolytics have not been established.

Management of the sinonasal and middle ear disease is largely derived from other conditions, because large clinical trials are lacking. Myringotomy tubes are frequently placed in infants and young children with PCD, often before the underlying diagnosis is made. Although several studies have reported that myringotomy tube placement improves hearing thresholds, others did not find any improvement. Additionally, prolonged otorrhea and persistent tympanic membrane perforation are relatively common complications[70] that have led to recommendations against the routine use of myringotomy tubes in children with PCD. Treatment of sinonasal disease in PCD is largely based on management of chronic rhinosinusitis, consisting of various medical and surgical therapies. Antibiotics are also used to treat upper respiratory tract infections, especially during exacerbations, and in some instances, long-term suppressive antibiotic therapy is used. Occasionally, surgical interventions are required, including adenoidectomy, polypectomy, and functional endoscopic sinus surgery, but usually reserved for cases of failed medical therapy.

SUMMARY

Primary ciliary dyskinesia is a rare inherited disease of the motile cilia, one of a growing collection of genetic disorders known as ciliopathies. Children with PCD have diverse clinical manifestations, and usually present early in life with neonatal respiratory distress, persistent sinonasal and middle ear disease, hearing loss, chronic daily cough, bronchiectasis, and left-right laterality defects. Our understanding of the genetics of PCD has advanced, and nearly 50 different disease-associated genes have been identified, encoding axonemal, cytoplasmic, and regulatory proteins that are involved in the assembly, structure, and function of motile cilia. This knowledge has translated into new insights into the clinical heterogeneity of motile ciliopathies and revolutionized our approach toward diagnostic testing for PCD. This progress has not translated into therapeutics, but undoubtedly new disease targets will be identified and treatments will follow.

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Abbreviations:

PCD	primary ciliary dyskinesia
VUS	variant of unknown significance

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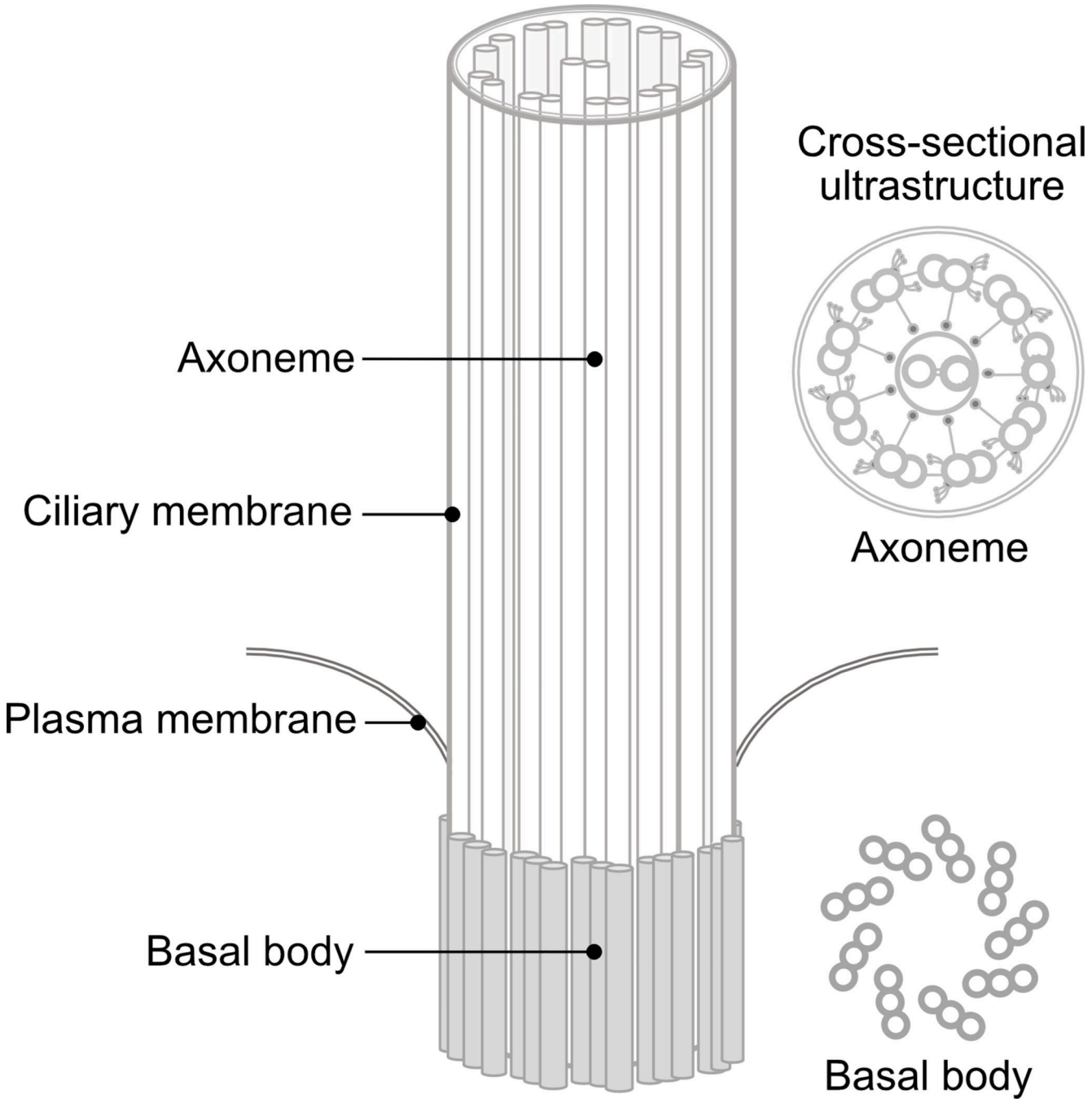

Figure 1.
Schematic diagram of a ciliary axoneme and basal body.

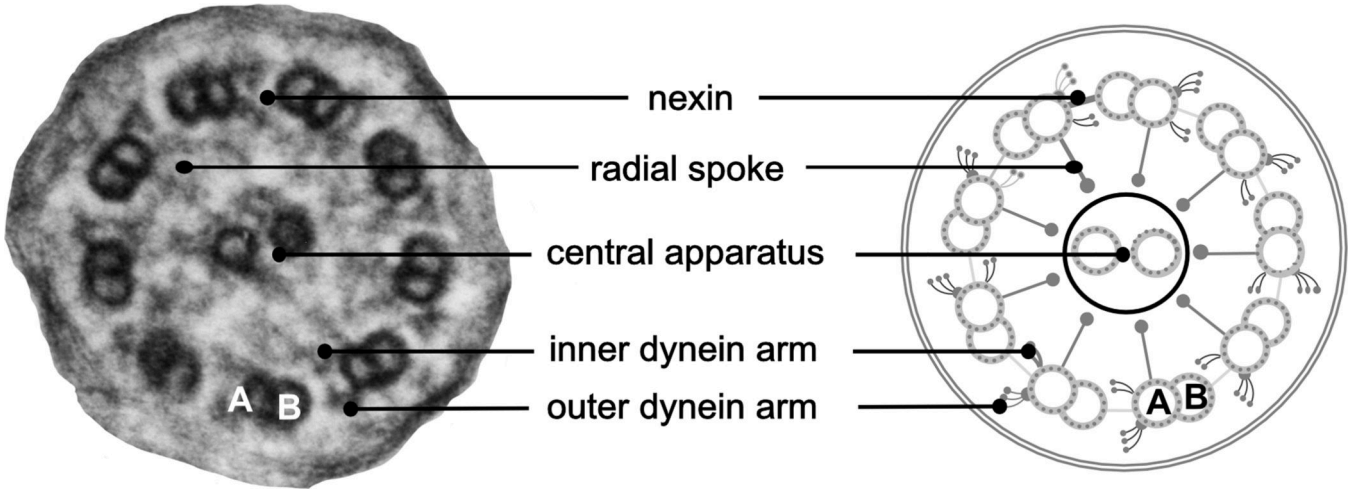

Figure 2.
Electron photomicrograph and diagram showing ultrastructural features of the motile cilium.

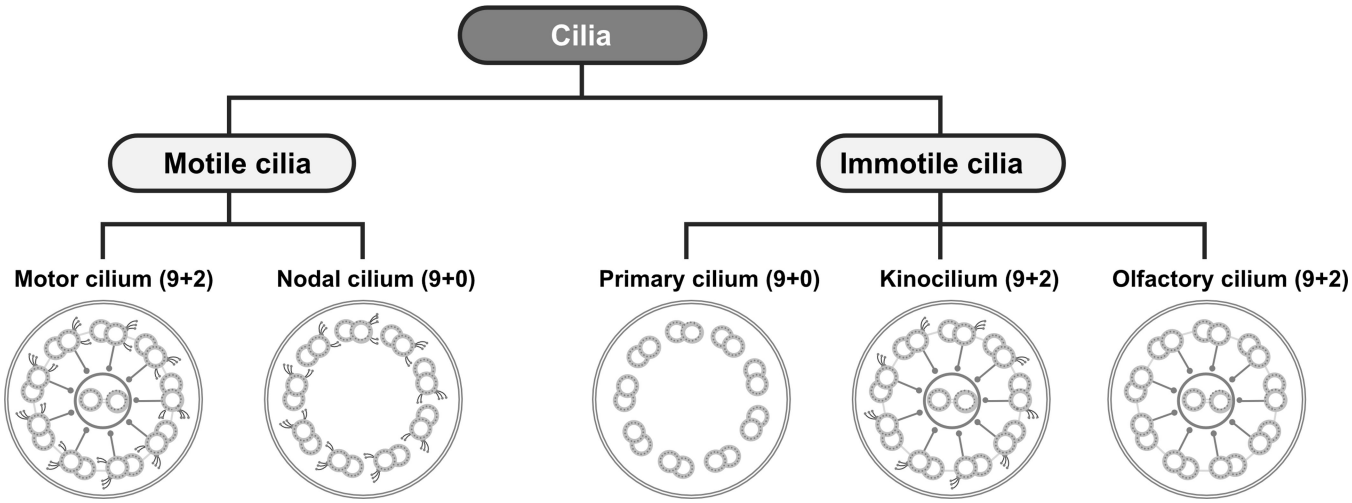

Figure 3.

Schematic diagrams depicting the general classification of motile and immotile cilia based on ultrastructural configuration and function.

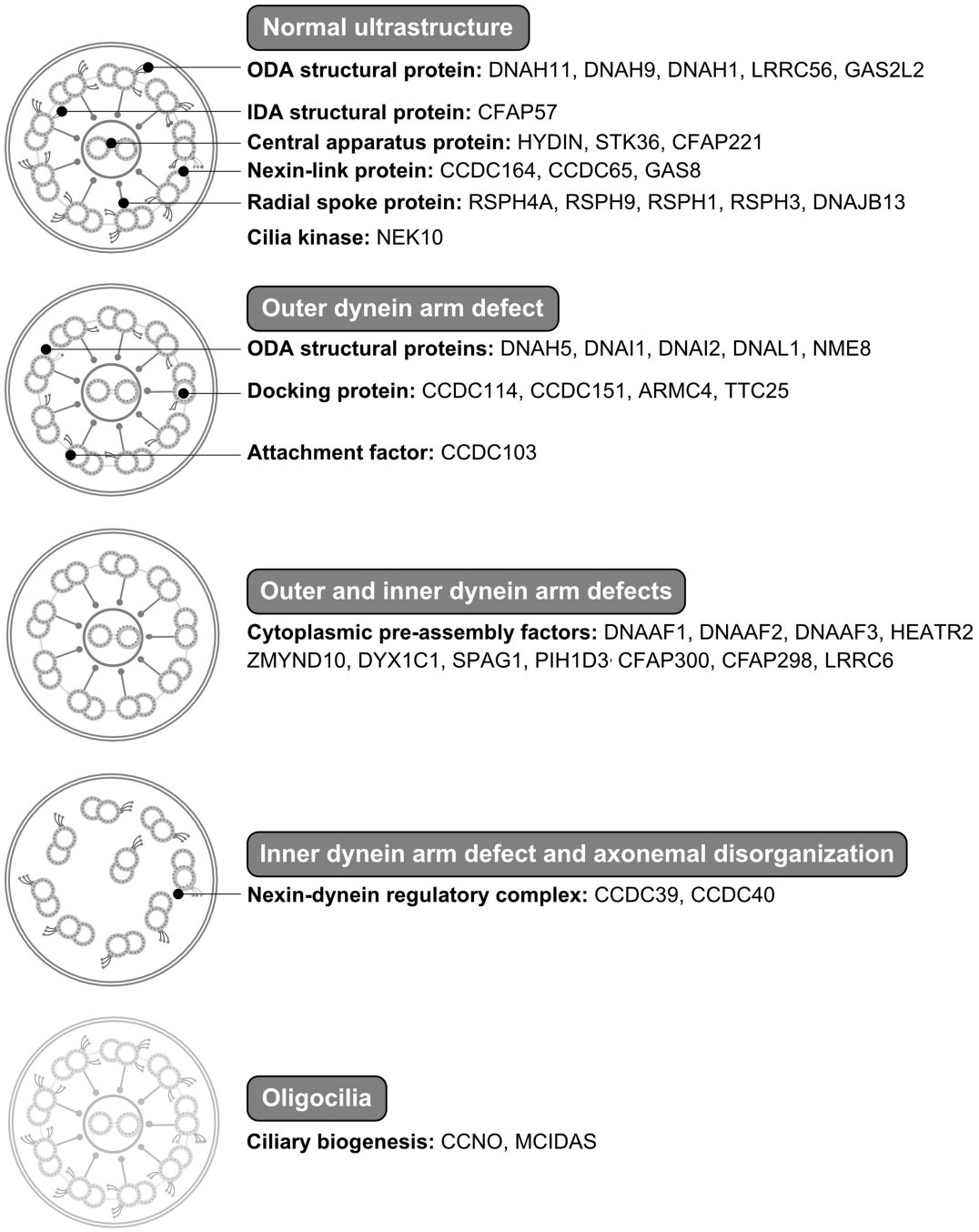

Figure 4.

Classification of ultrastructural defects of the motile ciliary axoneme and genes associated with primary ciliary dyskinesia. IDA: inner dynein arm; ODA: outer dynein arm.

TABLE.

Genes and clinical symptoms associated with selected primary ciliopathies

Disease or syndrome	Clinical features	Associated genes
Alstrom syndrome	Obesity, retinitis pigmentosa, diabetes mellitus, hypothyroidism, hypogonadism, skeletal dysplasia, cardiomyopathy, pulmonary fibrosis	*ALMS11*
Bardet-Biedl syndrome	Obesity, polydactyly, developmental delay, retinitis pigmentosa, renal anomalies, anosmia, hypogonadism, congenital heart disease	*ARL6, BBS1–12, CEP290, MKKS, MKS1, MKS3, SDCCAG8, TRIM32, WDPCP*
Ellis van Creveld syndrome	Chondrodystrophy, polydactyly, ectodermal dysplasia, congenital heart disease	*EVC, EVC2*
Jeune syndrome	Thoracic cage deformities, renal cysts, retinitis pigmentosa, skeletal dysplasia, polydactyly	*DYNC2H1, IFT80, IFT139, IFT140, IFT144, WDR35*
Joubert syndrome	CNS anomalies, developmental delay, ataxia, retinitis pigmentosa, polydactyly, cleft lip, cleft palate	*ATXN10, AHI1, ARL13B, C5ORF42, CC2D2A, CEP41, CEP290, CORS2, INPP5E, JBTS1, JBTS3, JBTS4, KIF7, NPHP1, NPHP3, RPGRIP1L, TCTN1, TCTN2, TMEM67, TMEM138, TMEM216, TMEM237*
Meckel-Gruber syndrome	Renal cysts, polydactyly, developmental delay, CNS anomalies, congenital heart disease, cleft lip, cleft palate	*B9D1, B9D2, CC2D2A, CEP290, MKS1–6, MKKS, NPHP3, RPGRIP1L, TCTN2, TMEM67, TMEM216*
Nephronophthisis	Renal cysts, interstitial nephritis, hepatic fibrosis, retinitis pigmentosa	*ALMS1, ATXN10, CEP290, GLIS2, IFT139, INVS, NEK8, NPHP1–11, TCTN2, TTC21B, TTC8, WDR19, XPNPEP3*
Orofaciodigital syndrome type 1	Polydactyly, syndactyly, cleft lip, cleft palate, brain anomalies, developmental delay, renal cysts	*OFD1*
Polycystic kidney disease	Early onset renal cysts, hepatic fibrosis	*PKHD1*