

Ciliopathies and the Kidney: A Review

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Primary cilia are specialized sensory organelles that protrude from the apical surface of most cell types. During the past 2 decades, they have been found to play important roles in tissue development and signal transduction, with mutations in ciliary-associated proteins resulting in a group of diseases collectively known as ciliopathies. Many of these mutations manifest as renal ciliopathies, characterized by kidney dysfunction resulting from aberrant cilia or ciliary functions. This group of overlapping and genetically heterogeneous diseases includes polycystic kidney disease, nephronophthisis, and Bardet-Biedl syndrome as the main focus of this review. Renal ciliopathies are characterized by the presence of kidney cysts that develop due to uncontrolled epithelial cell proliferation, growth, and polarity, downstream of dysregulated ciliary-dependent signaling. Due to cystic-associated kidney injury and systemic inflammation, cases result in kidney failure requiring dialysis and transplantation. Of the handful of pharmacologic treatments available, none are curative. It is important to determine the molecular mechanisms that underlie the involvement of the primary cilium in cyst initiation, expansion, and progression for the development of novel and efficacious treatments. This review updates research progress in defining key genes and molecules central to ciliogenesis and renal ciliopathies.

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Introduction

Cilia are evolutionarily conserved organelles that protrude apically from the surface of nearly all quiescent mammalian cell types.¹ Synonymous with flagella, these hair-like structures have diverse physiologic and context-dependent roles, from determination of left-right asymmetry, cell proliferation, and differentiation, to tissue morphogenesis and signal transduction.²

Presently, more than 950 cilia-related genes and their respective ciliary proteins have been discovered, mutations in which can be associated with human disease.³ Dysfunctional cilia typically result in pleiotropic clinical manifestations that are reflected by widespread distribution and varied functionality. A broad spectrum of more than 35 human genetic diseases, known as “ciliopathies,” have been linked to more than 180 established ciliopathy-associated proteins.^{1,4,5} The number of mutated genes shown to be involved in various ciliopathies continues to increase along with progressive developments in sequencing technology. This may eventually warrant a shift toward functional categorization of ciliopathies as a continuum of disorders rather than as distinct syndromes to provide better definitions and more suitable diagnoses for patients and clinicians.^{6,7}

Importantly, the growing number of proteins recognized as being cilia associated demands further studies to understand their precise roles in ciliogenesis and in the specialized cell and physiologic functions supported by these enigmatic organelles. Ciliopathies are often characterized by and commonly affect the renal organ system, which is the focus of this review.^{5,8} Renal ciliopathies are frequently observed as a consequence of mutations in 1 or more ciliary-associated proteins.

This review outlines the basic biology of cilia, the range of ciliary genes in which mutations can be associated with renal ciliopathies, and new advances in knowledge that

increasingly instruct the march toward personalized therapies for patients with genetic kidney disease.

Primary Cilia and Ciliogenesis

Cilia are specialized microtubule-based projections that are classified by their axonemal architecture as motile (9+2) or nonmotile (9+0; Fig 1).⁹ Although 75% of structural components are shared, only the latter, distinguished by a lack of a central microtubule (MT) doublet, are ubiquitously present throughout the human body.¹⁰ These nonmotile or “primary cilia” are principally sensing and signal transduction organelles, often referred to as cellular antennae.¹¹ Receptors and signaling molecules are concentrated within primary cilia and sequestered from the rest of the plasma membrane. Nachury¹² notes that primary cilia have a surface area 500 times less than the whole plasma membrane of a cell and a volume 5,000 times smaller than the cytoplasm. This distinctive characteristic is conducive to their role as a communication hub, allowing the cilia to transduce extracellular information into downstream intracellular signaling pathways to trigger appropriate physiologic responses.¹²

The formation of cilia, or ciliogenesis, occurs in quiescent cells and is suppressed in proliferating cells.¹³ Notably, primary cilia are erected at the onset of the G1 phase and then completely disassembled again before cell division.¹⁴ Following cell division, a pair of mother and daughter MT-based centrioles are released from their position within the mitotic spindle and migrate to a sub-plasma membrane site, where they mature to form the basal body.¹⁰ Also referred to as the MT organizing center, the basal body, specifically the mother centriole, acts as an anchor and docking site at the base of the cilia, supporting nucleation of the axoneme outward from the apical surface of the cell.^{13,15,16} Ciliogenesis is then sustained through

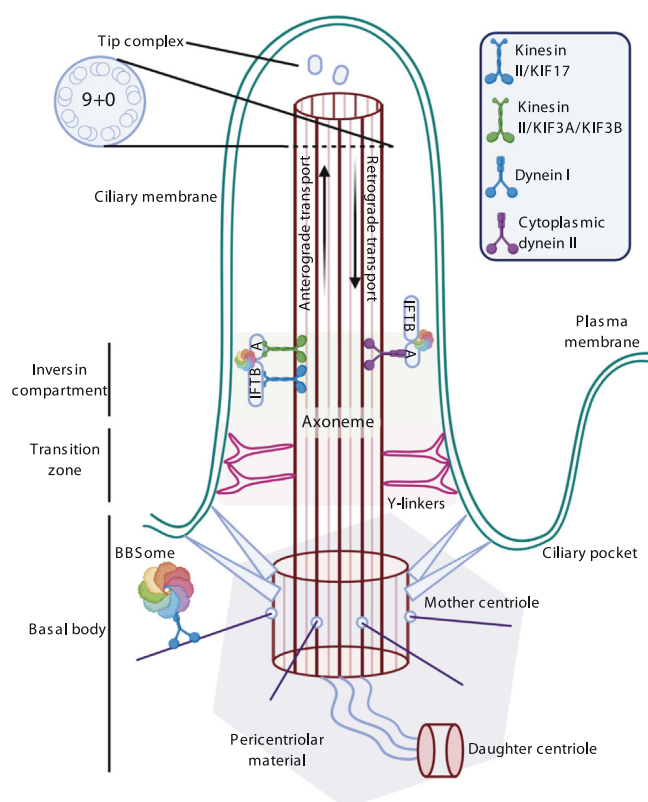


Figure 1. The key structural components of the primary cilium based around the central axoneme. This nonmotile cilium has 9 outer microtubule doublets but no central doublet. Ciliary components, receptors, and signaling proteins are trafficked in anterograde and retrograde directions on the axoneme by intraflagellar transport (IFT) complexes, IFTA and IFTB, which engage dynein II and kinesins (blue box), respectively. The BBSome complex assists traffic at the base of the cilium and then cooperates with IFTs. The cilium grows out of the mother centriole within the basal body and the base of the cilium is segregated from the cytoplasm by the transition zone, defined by the presence of Y-linkers. The primary cilium is erected in quiescent cells and disassembled before cell division. Abbreviation: KIF, Kinesin family members. Created with BioRender.com.

vesicular transport of membrane and membrane proteins from the Golgi complex to the base of the cilium.

Due to the inability of cilia to synthesize their own proteins, the ciliary-specific intraflagellar transport system (IFT) uses IFT transporters or “trains” for vesicular trafficking of these proteins throughout the cilia. These motor-based trains, IFT-A and -B, move along the MT axoneme to perform anterograde and retrograde transport of ciliary proteins, respectively.¹⁵ The IFT system regulates protein entry and exit, which is required for ciliary maintenance and growth and to continuously populate the organelle with functional receptors and other sensory and mechanosensory proteins.¹⁷ Mutations that affect IFT function result in ciliary defects and have been implicated in a range of ciliopathies.¹⁷

A transition zone (TZ) separates the cilia from the rest of the plasma membrane, requiring vesicle transport for movement into and out of this zone.¹⁸ Located toward the distal end of the basal body and defined by the presence of Y-linkers and transition fibers, the TZ is a diffusion barrier that controls the entry and exit of more than 700 ciliary proteins into the cilium, including axonemal precursors, associated signaling molecules, and other diverse cargoes.^{19,20} The inversin compartment, distal to the TZ, is a distinct molecular subsection of the primary cilia characterized by the localization of the inversin protein (INV), which is encoded by NPHP2, a prominent gene associated with nephronophthisis (NPHP).^{21,22} Therefore, somewhat unsurprisingly, this proximal region of the cilium has been implicated as an important controller of ciliogenesis and ciliary protein composition.²² Within the TZ, a variety of large supramolecular protein complexes mediate cilia formation, function, and trafficking. These complexes are named after diseases or ciliopathies associated with their specific gene mutations and they include the Bardet-Biedl syndrome (BBS), Meckel syndrome (MKS), and NPHP complexes.^{18,23} The functions of these complexes are only broadly understood and are summarized below.

Through a cadre of specifically localized cilia-associated receptors including Wnt, Hedgehog, transforming growth factor β (TGF β), and platelet-derived growth factor receptors (PDGFRs), cilia sense extracellular signals such as growth factors, hormones, and other stimuli and convert them into signaling cascades to trigger locally enriched effectors that bring about downstream effects to control tissue differentiation and homeostasis, cell proliferation and growth, and organ development and function.^{11,24} Disruptions in these signaling pathways are associated with ciliopathies.²⁴

Cilia have also been implicated in the regulation of planar cell polarity. The major signaling pathway controls oriented cell division that is crucial for establishing renal tubule development, perturbations of which are often observed in cystic kidney diseases.^{25–27} However, the explicit pathophysiologic changes that occur as a result of dysregulated cilia-associated planar cell polarity and give rise to cystogenesis remain poorly correlated.^{25,27}

Although the exact mechanisms that underlie the organization of signaling cascades from the primary cilia are still unknown, it is clear that the structure of the cilia, from the physical compartmentalization and protein localization to its intricate IFT machinery, is fundamental for its function as a sensory organelle.⁸ When defective, this results in the broad and overlapping morphologic features observed within the associated diseases or ciliopathies (Fig 2). However, ciliopathies are characterized by the involvement of a core set of tissues: retinal, cerebral, and renal, of which the latter are the main focus of this review.⁵

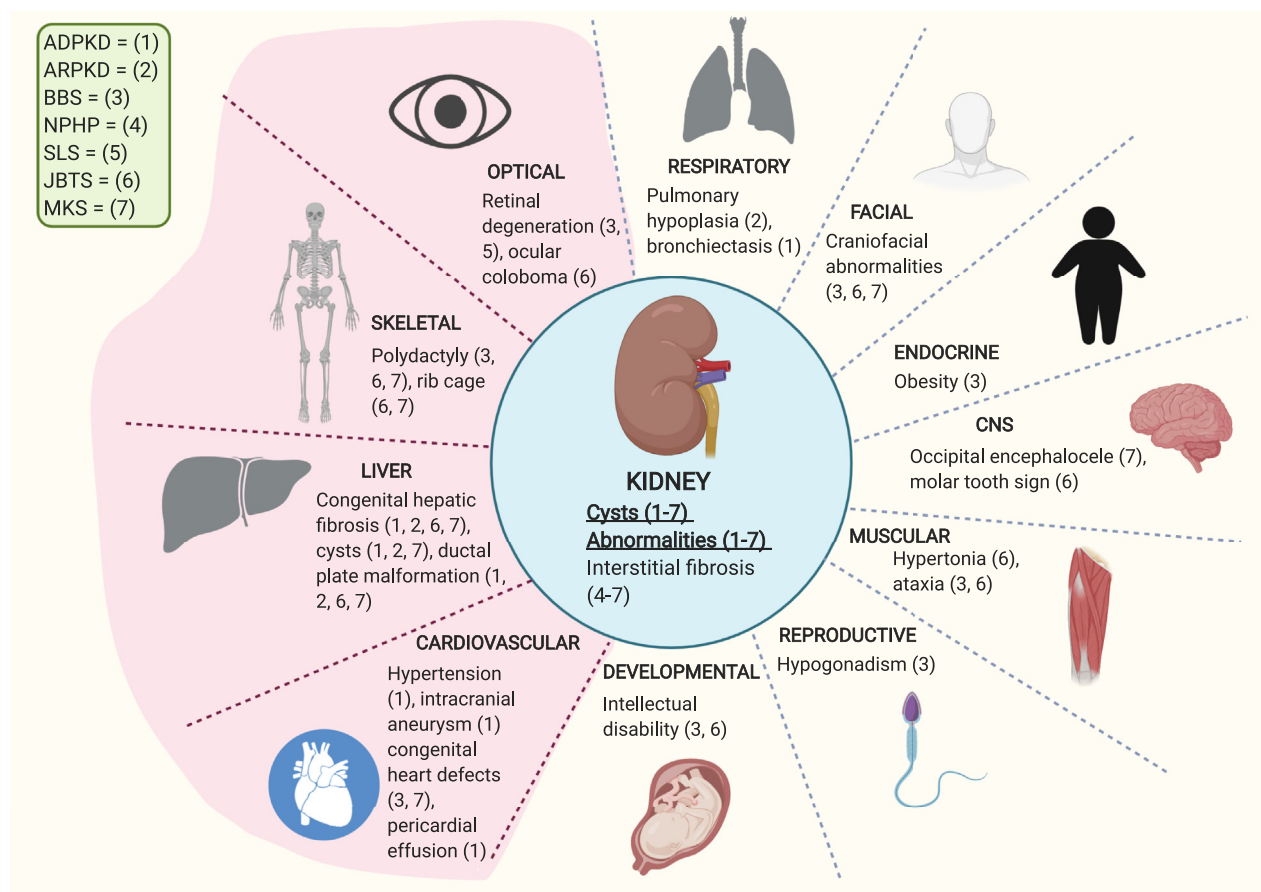


Figure 2. Renal ciliopathies and clinical phenotypes. Ciliopathies arising from gene mutations in ciliary proteins often affect the kidney and multiple other systems. Primary (highlighted in pink) and secondary clinical phenotypes are depicted here for common renal ciliopathies. Phenotypic overlap within the clinical presentations of these renal ciliopathies is discussed throughout this review. Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; BBS, Bardet-Biedl syndrome; CNS, central nervous system; JBTS, Joubert syndrome; MKS, Meckel-Gruber syndrome; NPHP, nephro-nophthisis; SLS, Senior-Loken syndrome. Created with BioRender.com based on information in²⁸⁻³².

Renal Ciliopathies

Primary cilia are present on polarized epithelial cells that line the renal tubules, where they project into the tubule lumen to execute their sensory roles.³³ The link between primary cilia and cystic kidney diseases first became evident on studies in the roundworm *Caenorhabditis elegans* that showed localization of polycystic kidney disease (PKD)-associated protein homologues to the organelle.³⁴ Focused research has since identified additional ciliary genes and proteins associated with cystic pathologic states in the kidney (Fig 3^{28,35-40}). Consequently, cilia have since been implicated in the core features that characterize renal ciliopathies, including cyst initiation, development, and the progression to kidney failure.^{8,33} We briefly describe the renal ciliopathies that present as a result of dysregulated cilia-dependent processes following mutations in other ciliary-associated proteins.

Polycystic Kidney Disease

PKD is characterized by the bilateral presence of numerous fluid-filled cysts in the renal parenchyma that continue to enlarge and develop throughout a patient's lifetime.⁴¹ Cysts form from the tubular epithelial cells as a result of abnormally high rates of misoriented cellular proliferation, the expression of a secretory phenotype, decreased apoptosis, fluid accumulation, and altered protein sorting.^{33,42} The cysts progressively displace renal parenchyma, compressing the microvasculature and resulting in PKD-associated kidney injury stimulating systemic inflammatory changes.^{43,44} This creates a positive feedback loop that destroys renal homeostasis, causing kidney failure that necessitates kidney transplantation, preferably preemptively.⁴⁵ Inheritance in both a dominant (autosomal dominant PKD [ADPKD]) and recessive (autosomal recessive PKD [ARPKD]) manner is possible, with

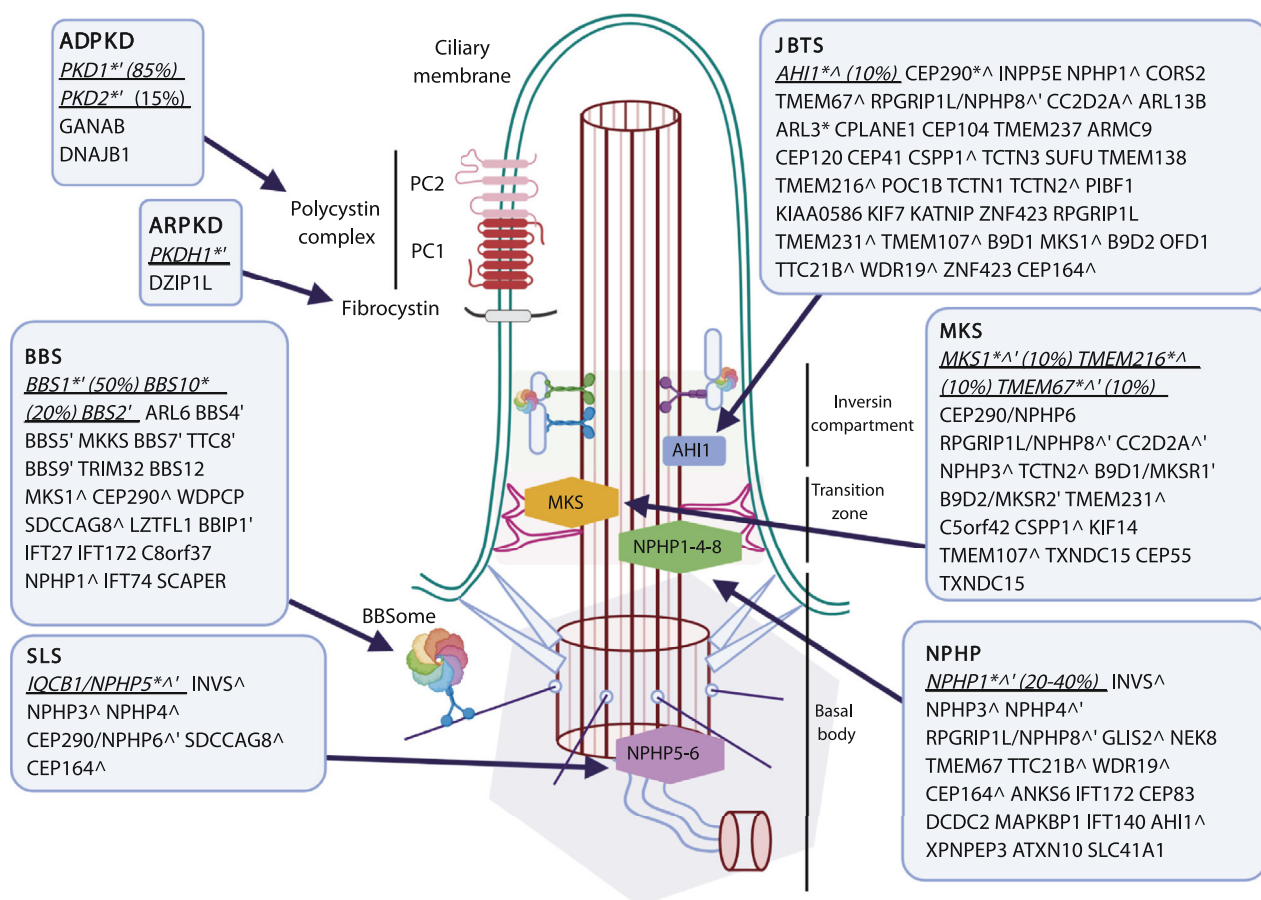


Figure 3. Renal ciliopathies and associated genotypes. The known reported genes mutated in the renal ciliopathies outlined in this review overlaid on a primary cilium schematic (see Fig 1). *Main associated genes. ^Mutated in another renal ciliopathy. 'Part of displayed protein/protein complex. Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; BBS, Bardet-Biedl syndrome; JBTs, Joubert syndrome; MKS, Meckel-Gruber syndrome; NPHP, nephronophthisis; PC1(2), polycystin 1(2); SLS, Senior-Loken syndrome. Created with BioRender.com based on information in^{28,35–40}.

considerations for additional genetic and environmental influences.^{4,6}

Autosomal Dominant PKD

The most common inherited cause of kidney failure, ADPKD is a systemic ciliopathy that presents with progressive renal cyst expansion and extrarenal manifestations following loss-of-function mutations in the genes *PKD1* and *PKD2* (Fig 3).^{4,7} The cognate renal ciliary proteins, polycystin 1 (PC1) and polycystin 2 (PC2), form heterodimeric receptor-ion channel complexes that localize to the primary cilia, prompting intensive study into their role as an underlying cause of common renal ciliopathies.^{4,8,49} PC1 is a large G-protein coupled receptor (GPCR), of which the ligand(s) and activating stimuli are still unknown.⁵⁰ It has a particularly large amino-terminal extracellular domain (3,704 amino acids) containing a GPCR proteolytic site (GPS domain), 11 transmembrane domains, and a short carboxy-terminal coiled-coil domain

(197 amino acids).⁵¹ PC2 is a member of the transient receptor potential (TRP) superfamily of ion channels, commonly referred to as TRPP2, and serves as a receptor-coupled nonselective calcium-permeable channel.⁵² Resolved in 2017, the cryogenic electron microscopy structure revealed that the 968-amino acid PC2 consists of 6 transmembrane segments and a cytoplasmic carboxy terminal tail containing a variety of domains involved in calcium (Ca^{2+}) binding, protein-protein interactions, and modulation of the Ca^{2+} -dependent channel activity.⁵³ Therefore, somewhat unsurprisingly, PC2 is regulated by a range of stimuli including pH, phosphorylation, membrane stretch, voltage, lipids, and internal and external Ca^{2+} concentration.⁵³ Together, PC1 and PC2 colocalize to the ciliary membrane to form the polycystin complex.⁵¹

Determination of the high-resolution polycystin complex structure by cryogenic electron microscopy in 2018 provided details as to the assembly of the heterooligomeric complex, confirming that incorrect folding and/or trafficking of the receptor to the membrane of the

primary cilium could be pathogenic.⁵⁴ Based on studies in several experimental settings, it was initially proposed that in PKD, the polycystin complex would act as a mechanoresponsive sensor for calcium signaling, reflecting a role for PC2 in sensing nodal flow for left-right determination in embryonic development and fluid-shear stress.⁵⁵⁻⁵⁷ This was the prime example widely cited to portray the proposed mechanosensory function of cilia. However, a more recent study by Delling et al⁵⁸ found a lack of mechanically induced cilia-specific Ca^{2+} influx. Although primary cilia are one of the possible mechanosensors in renal tubules, their role and that of the polycystin complex in flow-induced calcium signaling is yet to be fully understood under normal physiologic conditions and in the context of disease.^{59,60}

Germline mutations in the polycystin complex result in the onset of ADPKD, with some evidence to suggest that additional “somatic second hit” mutations may play a role in the high levels of inter- and intrafamilial variability observed.⁶¹ This is supported by the focal and monoclonal nature of the renal cysts that are thought to occur following reduction in levels of PC1 and PC2 below a critical threshold, though this is somewhat debated.^{62,63} A myriad of effector pathways lie downstream of the polycystin complex, including canonical Wnt/ β -catenin and noncanonical β -catenin-independent Wnt, cyclic adenosine monophosphate, intracellular Ca^{2+} , GPCR, cystic fibrosis transmembrane conductance regulator (CFTR), epidermal growth factor receptor (EGFR), mitogen-activated protein kinase (MAPK), Janus kinase/signal transducers and activators of transcription (JAK-STAT pathway), mammalian target of rapamycin (mTOR), and cell cycle signaling.⁶⁴⁻⁶⁶ These reflect the cystic phenotype associated with ADPKD, following mutations within PKD1 and/or PKD2, due to the dysregulation of transepithelial fluid secretion and tubular cell proliferation and disruption of cellular polarity and differentiation.^{26,64,67}

Although fully penetrant, there is considerable phenotypic variability associated with ADPKD influenced by both unalterable maleficent factors (sex and type of mutation) and acquired conditions such as additional kidney injury and hypertension.⁶⁸ As discussed, mutations in PKD1 and PKD2 result in the onset of PKD. However, both loci present with high levels of allelic heterogeneity.⁶⁹ Furthermore, mutations in additional cystic genes and cystic kidney disease modifier genes have been identified within ADPKD populations.⁷⁰ Together, these observations may provide an explanation for the extreme variation in both presentation and disease outcome that have come to characterize ADPKD.⁶⁹

Autosomal Recessive PKD

ARPKD is a rare inherited hepatorenal cystic disease, with 50% of patients developing kidney failure and requiring kidney replacement therapy by the age of 10 years.⁷¹ Subcellularly, fibrocystin is located at apical structures

of kidney epithelial structures, colocalizing with the ADPKD protein, PC2, at the plasma membrane and apical primary cilium.^{72,73} First identified in 1994, mutations in the polycystic kidney and hepatic disease 1 (PKHD1) gene have since been attributed to the majority of ARPKD cases (Fig 3).⁷⁴

The exceptionally large PKHD1 gene extends over 470 kilobases to produce a 4,074-amino acid protein.⁷⁵ PKHD1 is highly expressed in renal tissue and at lower levels in the liver, where it encodes the protein product fibrocystin.^{72,75} Fibrocystin (or polyductin) is a type 1 transmembrane protein that localizes to the primary cilium, in keeping with other ciliary proteins linked to cystic kidney disease or “cystoproteins.”⁷³ During embryogenesis, fibrocystin is expressed and is required for normal branching morphogenesis of the ureteric bud for embryonic kidney development and is also present in adult and fetal kidney, liver, and pancreatic tissue.⁷⁶ Fibrocystin functions as a key regulator of cell proliferation, apoptosis, and polarization.⁷¹ Consequently, when mutated, fibrocystin can no longer serve these roles, resulting in the onset of cystic kidney disease and a range of extrarenal manifestations together constituting ARPKD (Fig 2).⁶⁴

Both ADPKD and ARPKD are characterized by the presence and development of kidney cysts, following mutations in their respective ciliary localized cystoproteins. Interestingly, this distinct phenotypic abnormality of cystic kidney epithelia is shared within a group of diseases that are collectively referred to as renal ciliopathies. In the next 2 sections of this review, we outline other members of this disease grouping, namely BBS and NPHP.

Bardet-Biedl Syndrome

BBS is an inherited autosomal recessive disorder that results in a plethora of developmental and multiorgan defects. A considerable proportion of patients with BBS present with cystic kidney disease that commonly results in kidney failure.³⁵ Presently, biallelic mutations in 22 pathogenic genes have been identified to cause BBS (Fig 3), with individuals presenting with archetypal features of the disease. We provide a brief overview of the main proteins involved and their association with primary cilia, with more extensive reviews available.^{8,35}

The evolutionarily conserved BBS proteins, BBS1, BBS2, BBS4, BBS5, BBS7, BBS8, BBS9, and BBS18, form the stable 438-kDa BBSome complex that links the cause of BBS to the primary cilium.^{77,78} The BBSome functions as a cargo adaptor to maintain, stabilize, and assemble IFT particles, supporting protein import and export from the primary cilium.⁷⁸ Subcellular localization studies have shown the position of BBS proteins to be at the basal body and/or within the cilia itself (Fig 1), supporting a role for the proteins in the trafficking of ciliary signaling proteins and related functions; mutations in these proteins result in mislocalization of key molecules and disruption of critical downstream cellular signaling pathways.^{48,78}

Consequently, this can alter ciliary-dependent signaling to affect cell-cycle regulation, developmental patterning, planar cell polarity, and cell proliferation, reflecting the primary pathogenic symptoms of BBS outlined in Fig 2.¹

Mutations within the major BBS-associated genes, BBS1 through BBS18, have been identified in 70% to 80% of the total number of reported BBS cases, with BBS1 boasting the highest mutational load; along with BBS2, BBS4, and BBS7, it has been shown to interact with renal tissue-specific proteins.^{79,80} Interestingly, interactions of the BBSome with other major ciliary cystoproteins are wide ranging. The complex has been shown to mediate ciliary targeting of both PC1 and PC2, and NPHP-associated proteins have been linked to the regulation of BBSome integrity and trafficking.⁸¹ This apparent interactome of ciliary proteins, when coupled to additional complex genetic interactions, provides a possible explanation for why ciliopathies such as BBS commonly display extreme phenotypic variation downstream of single locus mutations.⁸ This is often reflected by the clinical heterogeneity observed in BBS, specifically related to the specificity and severity of the presenting clinical manifestations (Fig 2).^{8,82}

Nephronophthisis

NPHP is an autosomal recessive tubulointerstitial disease that results in kidney failure by the third decade of life and accounts for ~5% of children with kidney failure.⁸³ Traditional classifications of NPHP are based on the age when kidney replacement therapy is required—infantile, juvenile, and adolescent/adult—with juvenile being the most common and referred to as the classic form.⁸⁴ Juvenile NPHP is typified by the presence of cystic kidneys coupled with renal fibrosis and interstitial inflammation that significantly contribute to the development of the disease (Fig 2).^{85,86}

Currently, mutations to the 25 known NPHP-related pathogenic genes account for only a third of diagnosed NPHP families (Fig 3); most of these gene products colocalize to the primary cilia, basal bodies, or centrosomes in kidney epithelial cells.⁸⁷ Proteomic studies have shown that these genes and their protein products are linked within an interaction network into macromolecular complexes, also known as nephrocystin modules: NPHP1-4-8 (the NPHP complex), NPHP5-6, NPHP2-3-9-ANKS6, NPHP5-6, and MKS.^{36,87-90} These complexes have been shown to work in parallel with one another to support ciliogenesis and ciliary function, contributing toward the wide phenotypic spectrum observed within NPHP.^{90,91} Additionally, digenic and triallelic inheritance have been shown to occur in NPHP, affecting the ciliopathy protein complexes and their resultant biochemical and genetic interactions that further modify observed NPHP phenotypes.^{84,91} Exploratory studies have been used to determine additional pathogenic mechanisms underlying NPHP; specific metabolic networks and DNA damage repair pathways have since been implicated.^{36,92,93}

Mutations in NPHP1 are the most common cause of juvenile NPHP and represent 20% to 25% of cases.⁹⁴ Nephrocystin 1 (also known as nephrocystin and NPHP1), encoded for by NPHP1, is an adaptor protein that localizes both to the primary cilia and the apical surface of kidney epithelial cells, where it associates with molecules involved in cell adhesion, signaling, and maintenance and with other cystoproteins, polycystin being the most pertinent.⁸⁶ Interactions occur with other nephrocystins, namely nephrocystin 4 (NPHP4) and nephrocystin 8 (NPHP8/RPGRIP1L), to form the nephrocystin complex.⁸⁹ These 3 nephrocystin proteins are found to localize to the TZ, governed by NPHP8, and have been determined to regulate ciliary protein composition and ciliogenesis.²² This apparent interaction network of ciliopathy-associated proteins is required to establish basal-body and TZ membrane associations and restrict the accumulation of nonciliary components within the cilium, disruptions to which can modulate downstream signaling to cause renal cystogenesis.³⁶

Renal Ciliopathies With Extrarenal Manifestations

Although renal ciliopathies are typically classified according to characteristic kidney pathologic states, they often exhibit extrarenal manifestations as a result of the ubiquitous and multiorgan presence of primary cilia throughout the body.

Extrarenal manifestations are commonly present alongside the renal ciliopathies outlined in this review, thought to be a direct result of the superfluity and widespread distribution of primary cilia throughout the body. ADPKD often presents with additional cystic involvement of multiple organs, including the liver, seminal vesicles, and pancreas, coupled with connective tissue abnormalities and intracranial aneurysms.⁹⁵ These manifestations also occur in 10% to 20% of NPHP cases, referred to as NPHP-related ciliopathies, and cause dysplasia or degeneration to a broad set of organs including but not limited to the eye, nervous system, and liver.⁸⁶ Mutations in NPHP proteins have been associated with retinitis pigmentosa (Senior-Loken syndrome [SLS]), central nervous system malformations (Joubert syndrome and related disorders [JSRD]), and more severe NPHP-renal pathologies that often result in perinatal lethality (MKS) due to extreme multiorgan involvement (Fig 2).^{85,90} Because this summary is focused on renal manifestations of ciliopathies, more extensive information can be found in a review from Hildebrandt and Zhou.⁹⁶

SLS is an oculoretinal condition that is observed in ~10% of NPHP cases, characterized by tapetoretinal degeneration with severe visual loss. The most commonly associated mutations in SLS are found within the IQ-domain protein (also known as NPHP5 and encoded by IQCB1), a protein that has been found to play a role in cilia functioning as part of a multimeric protein complex with retinitis pigmentosa guanosine triphosphatase regulator

and calmodulin, and within an additional complex alongside CEP290 (NPHP5-6).^{37,87}

Joubert syndrome is characterized by a marked neurodevelopmental phenotype, hypotonia, and most critically, the presence of the molar tooth sign.⁹⁷ This key neuro-radiologic hallmark, when observed alongside the manifestation of any additional non-neurologic feature, is referred to as JSRD. Although JSRD displays extreme genetic heterogeneity, all associated genes and their pathogenic variants encode proteins that localize to the primary cilium and/or basal body, hence JSRD is considered to be an archetypal ciliopathy.^{97,98}

MKS is a rare severe ciliopathy characterized by a severe multiorgan phenotype that often results in embryonic or postnatal mortality.^{28,99} To date, causative genes corresponding to 60% of MKS cases have been identified, with the remaining molecular causes yet to be determined, hypothesized to exist either as uncommon or private mutations within single families.²⁸ MKS displays allelism with a variety of ciliopathic syndromes and presents with considerable genetic heterogeneity, multiple widespread organ involvement, and phenotypic overlap, reflective of the ubiquitous presence of cilia within the body. However, because this summary is focused on the renal manifestations of ciliopathies, more information on the extrarenal manifestations of MKS can be found in the review from Hildebrandt and Zhou.⁹⁶

Current and Potential Therapies

Recent advances in genomic sequencing technology are transforming the field of clinical diagnostics, something exemplified within the area of kidney disease. Next-generation sequencing and genomic approaches are now both more accessible and affordable, supporting their successful transition and implementation from the research laboratory into the clinic.⁷ The field of kidney genomics has progressed from gene identification to disease modeling, genetic screening, and patient diagnosis.⁷ However, even with advances in sequencing technology and clinical diagnostics, few curative, disease-modifying, or prophylactic treatments have been determined for the range of cystic kidney diseases outlined in this review. The sole targeted, yet non-cilia-directed, therapy to date is the US Food and Drug Administration–approved tolvaptan for ADPKD, a vasopressin V₂ receptor inhibitor that has been shown to delay decline in estimated glomerular filtration rate.¹⁰⁰ Hence, it is important to further elucidate the molecular pathways that underpin this highly heterogeneous and overlapping group of pathologic disorders for the development of effective treatments.

To do this, technological advances in structural, genomic, stem cell, and cell biology are increasingly being used to develop personalized therapeutic approaches. For instance, since their development in 2015, kidney organoids, derived from human and now specifically patient-derived induced pluripotent stem cells, have been used

to model kidney development, injury, and personalized therapeutic approaches and have contributed to our understanding of PKD by highlighting the importance of modifying and environmental factors in disease progression.¹⁰¹⁻¹⁰³

Additionally, a range of molecular genetic studies have added to our understanding of these diseases through the identification of novel ciliary-associated genes and proteins, as highlighted throughout this review. This knowledge could and should now be used toward the development of specific cilia-associated therapies. By targeting this cellular antenna, the creation of novel pharmacologic agents to modulate cilia-associated proteins and signaling pathways in a symptomatic or even curative manner may be possible.

Conclusions

Research is steadily filling in the gaps of our understanding by revealing how gene mutations translate to aberrant proteins and defects in ciliary structure and function with consequential effects on kidney epithelial tissue formation and structure. As our knowledge of the molecular and functional aspects of primary cilia increases, so does our comprehension of the ciliary landscape and with it the understanding that mutations in ciliary genes cause widespread dysfunction in the kidneys and beyond. These discoveries and further exploration of this sensory organelle can hopefully be translated and used for the development of novel and effective treatments for renal ciliopathies.

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