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Ciliopathies: The Trafficking Connection

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Abstract

The primary cilium (PC) is a very dynamic hair-like membrane structure that assembles/disassembles in a cell-cycle dependent manner and is present in almost every cell type. Despite being continuous with the plasma membrane, a diffusion barrier located at the ciliary base confers the PC properties of a separate organelle with very specific characteristics and membrane composition. Therefore, vesicle trafficking is the major process by which components are acquired for cilium formation and maintenance. In fact, a system of specific sorting signals controls the right of cargo admission into the cilia.

Disruption to the ciliary structure or its function leads to multi-organ diseases known as ciliopathies. These illnesses arise from a spectrum of mutations in any of the more than 50 loci linked to these conditions. Therefore, it is not surprising that symptom variability (specific manifestations and severity) among and within ciliopathies seems to be an emerging characteristic. Nevertheless, one can speculate that mutations occurring in genes whose products contribute to the overall vesicle trafficking to the PC (*i.e.*, affecting cilia assembly) will lead to more severe symptoms, while those involved in the transport of specific cargoes will result in milder phenotypes. In this review, we summarize the trafficking mechanisms to the cilia and also provide a description of the trafficking defects observed in some ciliopathies which can be correlated to the severity of the pathology.

Keywords

Ciliopathies; vesicle trafficking; primary cilia; endocytic pathway; secretory pathway

Introduction

Non-motile cilia were first observed by Zimmerman (1) more than a century ago, and named ‘Primary cilium’ (PC) by Sergei Sorokin in 1968 (2). Initially, this plasma membrane-derived structure was thought to represent a vestigial swimming apparatus, and interest in it eventually faded away. Indeed, it was not until about a decade ago that the PC resurfaced as its presence was observed in virtually every cell type and its relevance for intracellular signaling and developmental diseases became clear (3).

The PC hosts a series of signaling pathways of critical importance for normal vertebrate development (Hedgehog (4), Wnt signaling pathways (5)), growth and differentiation (TGF-

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β (6), PDGF signaling (7)), sensory perception (Rhodopsin (8) and odorant receptors localization in the cilia (9)), hormonal regulation (Mchr1 and 5-HTr_6 (10), Sstr3 (11)) and mechanical transduction (Polycystin-1 and Polycystin-2 (12)). These crucial sensory functions of the PC rely on its high concentration of membrane receptors that interpret a plethora of chemical, mechanical and other extracellular cues. In consequence, deficiencies in the assembly or function of this specialized area of the plasma membrane have severe consequences on the development and overall physiology of the affected organism (13). Therefore, abnormal cilia have been linked to a heterogeneous group of diseases, attributed to single gene mutations in more than 50 loci, known as ciliopathies (14). These illnesses can be lethal and are characterized by overlapping phenotypes that may include retinal degeneration, kidney dysfunction, infertility, cognitive impairment, polydactyly, situs inversus, obesity, diabetes and other manifestations. In fact, it is in great part due to its medical relevance that in recent times we have witnessed an immense surge of research aimed to better understand the mechanisms of assembly, maintenance and function of the PC.

Assembly and Architecture of the PC

The PC is a sensory, cell surface-structure with a microtubule-based core (a non-motile 9+0 axoneme) originating from a basal body derived from the mother centriole, and ensheathed by the so-called ciliary membrane (Fig. 1A). For comprehensive descriptions of the PC organization, the reader is referred to excellent reviews available in the literature (3, 15, 16). Ciliogenesis in most cells is initiated by anchoring the basal body to the plasma membrane directly by the distal appendage protein C2cd3 that in turn leads other components namely Sclt1, Ccdc41, Cep89, Fbf1, and Cep164 to mark the position for assembly of the PC (17–19). Vesicles dock to the basal body and supply material for growth of the cilia. An alternative ciliary pathway begins in the cytosol, where vesicles dock onto the mother centriole, elongate the nascent cilium in the cytosol which is later inserted in the plasma membrane. In this case, the cilium remains partially buried under the plasma membrane, enclosed in a curved invagination of the plasma membrane called the ciliary pocket that continues with the ciliary membrane (20). Cilia elongation is mediated by a specialized bi-directional intraflagellar transport system (IFT) (see below under ‘Trafficking within the PC’).

Although the ciliary membrane presents continuity with the plasmalemma (Fig. 1A), the two have a very different composition when compared to each other (21, 22). The establishment of the primary cilia boundary is made possible by the presence of a barrier at the ciliary base whose components include the transition fibres (TFs), ciliary necklace and the ciliary pocket (Fig. 1A,B) that highly restricts protein diffusion to and from the ciliary membrane and the intraciliary space. Therefore, this barrier gives the cilia characteristics of a compartmentalized organelle and since there is no protein synthesis within the PC, it requires specialized trafficking machinery for the delivery and retrieval of components. Indeed, vesicle trafficking is essential for ciliogenesis (23).

This review will discuss the basics of ciliary transport to the base of the cilia, across the barrier and within the cilia. It will primarily highlight the role of genes affected in ciliopathies and involved in trafficking to and from the PC.

Vesicle trafficking in PC assembly, maintenance and function

Traffic Control: The Barrier

The most proximal line of defense against indiscriminate diffusion into the ciliary compartment is the periciliary membrane where distal appendages arising from the basal body, converted into the TFs, are attached. Transmission electron microscopy (TEM) has revealed a pin-wheel like structure for the TFs with inter-fiber space between the transition fibers too small for vesicles to pass through (24)(Fig. 1B). Instead, vesicles dock and fuse with the ciliary pocket (if present) and the periciliary membrane (20). The higher occurrence of endocytic events at the ciliary pocket sets it apart from the continuing plasma membrane (6) (Fig. 1A). Examination of the periciliary membrane by Laurdan Microscopy exhibited higher condensation of the membrane when compared to the ciliary membrane and the ciliary tip (22).

TEM also revealed, distal to the TFs, the presence of particles known as the ‘ciliary necklace’ circumferentially decorating the ciliary membrane (25). These membrane decorations were connected to the axoneme by champagne glass-shaped structures called “Y-links” (Fig. 1B). Many TZ (Transition Zone) proteins have been identified, namely the Nephronophthisis-Meckel Syndrome-Joubert Syndrome (NPHP-MKS-JBTS) complex and nucleoporins (26–31), and they have been proposed to be held in place by a septin barrier present between the periciliary and the ciliary compartments (30). In addition, isolation of the basal bodies from *Tetrahymena pyriformis* helped to identify a so-called ‘terminal plate’ which could serve as a ciliary partitioning system (32). Cryo-EM revealed that this ciliary pore complex has an outer ring, speculated to be the septin ring, with nine inner rings which are similar in size to the nuclear pore (32)(Fig. 1B). Indeed, similarities between the nuclear pore complex and the ciliary base have been proposed; however, whether nucleoporins form a pore complex at the ciliary base is still under debate (21, 31).

Membrane proteins—The septin ring was shown to prevent the lateral diffusion of membrane proteins to and from the PC, emerging as a major player in maintaining the ciliary membrane composition (33). The TZ seems to function as a ‘smart gate’ that validates the entry of cargo pre-loaded at the TFs on ‘IFT trains’ headed for the ciliary tip (34). Evidence points towards the existence of putative TZ resident proteins acting as ‘validating officers’ for each cargo to allow access to the ciliary membrane. Zhao et al (35) showed that the depletion of the components of the TZ zone B9d2 or Nephrocystin-5 (NPHP-5) affected the transport of the protein Opsin, but not Peripherin. Another example is the dramatic effect of depletion of the TZ proteins Tctn1, 2 and Cc2d2a on Smoothened (Smo), Polycystin-2 and Arl13 ciliary localization, but without consequences on Sstr3 trafficking to the cilia (27). In addition, depletion of more than one of its components led to ultrastructural defects in the TZ in *Caenorhabditis elegans* (29, 36).

Soluble proteins—The TZ also functions as a molecular sieve to restrict soluble proteins from moving across the barrier (Fig. 1A); although reports on the size-exclusion range vary, perhaps reflecting a cell-specific property (21, 31, 37). An extreme case of ciliary specialization is the photoreceptor, where the outer segment corresponds to the PC and is connected to the inner segment by a region analogous to the TZ. Nafaji et al (38) showed that the ability of soluble proteins to translocate into the photoreceptor cilia depended on their intrinsic size. However, the investigators proposed that the traffic of these proteins to the PC was controlled by steric hindrance exerted by layers of flattened membranous stacks present in the outer segment rather than by a diffusive barrier at the ciliary base (38).

Trafficking to the base of the PC

As mentioned above, vesicle trafficking is the major pathway by which cells deliver materials to the base of the cilia. Therefore, vesicle trafficking is required for the assembly, maintenance and functionality of the PC. This section summarizes different ciliary targeting mechanisms of ciliary lipids and proteins (Fig. 2).

Sorting of PC cargo at the Golgi apparatus—Among the earliest evidence that Golgi-derived vesicles carry structural components of the cilia was the demonstration that the Golgi-disrupting drug Brefeldin A was capable of impairing ciliogenesis (39, 40). Since the lipid composition of the ciliary compartment is distinct from the plasma membrane, ciliary specific lipids are believed to be pre-sorted at the TGN and packaged into vesicles for delivery to the site of cilia assembly (41). PC-destined proteins containing ciliary targeting signals (CTS) get incorporated into these vesicles. Further, a growing body of evidence suggests that proper localization to the PC requires the interplay between several CTS (see Table I) present in the protein cargo, and that different CTS can be recognized by different elements of the sorting machinery at different stations enroute to the PC.

Membrane proteins—The photoreceptor-enriched protein Rhodopsin has been a popular cargo to study trafficking to the PC (42–44), and a spatiotemporal model for the sorting of this protein has been proposed (45). Mazelova et al (42) identified a ternary complex composed of Arf4, ASAP1 and Rab11- FIP3 which functions at the TGN for the packaging of Rhodopsin into vesicles targeted to the cilia. Specifically, while a VXPX motif in Rhodopsin is recognized by the small GTPase Arf4, a FR signal is responsible for engaging the ARFGAP ASAP1. Disruption of either CTS prevented Rhodopsin localization to the PC (46). The BAR domain of ASAP1 is believed to confer the complex with the ability to deform membranes contributing to vesicle budding (47). FIP3, probably the last member of the complex to be recruited, stimulates the Arf4GAP activity of ASAP1 supporting the complex release from the TGN (48)(Fig. 2,I).

Although Polycystin-2 also contains a VXPX CTS (49), the membrane carriers containing this cargo pinch off from the cis-Golgi to reach the cilia without traversing the TGN (50). Interestingly, it has been demonstrated that full length Polycystin-2 and constitutively active Smo are routed towards the cilia at the cis-Golgi, whereas truncated Polycystin-2 and WT Smo found in the bulk of the plasma membrane are sorted at the trans-Golgi (50).

The tetrameric clathrin-associated adaptor complex AP1, clathrin and the Rab GTPase Rab8 contribute to the sorting of cargo to the PC at the exit of the TGN (9) (Fig. 2,I). Single AP1, clathrin or Rab8 mutants led to similar defects of ODR-10 trafficking, ciliary length and shape defects in *C.elegans* (9). However, AP1 and Rab8 seem to function at distinct steps during sorting because no co-localization was observed between them. Cargo seemed to move quickly through the AP1 compartment, but resided longer in the Rab8 compartment (9).

Rab8 was also found to interact with the inositol polyphosphate 5-phosphatase Ocrl1 (51). Ocrl1 is a protein capable of binding to several Rabs along the endocytic and secretory routes (51–53) and is required for membrane trafficking in both pathways (54). The loss of Ocrl1 was recently linked to deficient cilia assembly (43, 55). Coon et al (43) showed that Ocrl1 participates in the delivery of cargo to the PC *via* two routes: directly from the TGN involving Rab8 and an indirect route by internalizing cargo from plasma membrane and redirecting it from the endosomal compartment to the PC (Fig. 2,I and II). This latter mechanism involved Rab5 and the endosomal proteins IPIP27A/Ses. Some evidence suggested that both pathways coalesce at the base of the PC (43).

Additional evidence further supports the existence of an indirect, endocytosis- and recycling-dependent protein trafficking route to the PC (Fig. 2,II). For example knock-down of the tyrosine phosphatase PTPN2 in ht-RPE cells resulted in an accumulation of the typical PC-enriched protein Smo-EGFP in early endosomes (23). In addition, mice expressing a dominant negative version of the endocytic recycling protein Arl13b, displayed evidence of defective regulation of Smo in the PC and abnormal Sonic hedgehog (Shh) signaling (56, 57). Further, Arl13b was also shown to play a role in the ciliary targeting of the lipid phophatase Inpp5E (58). Similar to Arl13b's function at the ciliary base, another GTPase, Arl3, co-ordinates with its GAP RP2 the traffic of proteins to the ciliary base (59–62).

Soluble Proteins—Soluble cytoplasmic proteins reach the ciliary base by diffusion; however, evidence suggest that the dynein-mediated, microtubule (MT)-dependent transport is a parallel, faster route than diffusion, to reach the centrioles (63) (Fig. 2,III). Specifically, several centriolar components namely pericentrin, γ-tubulin, ninein, centrin and PCM-1 are localized by dynein-dynactin mediated and microtubule (MT) dependent transport (63, 64). These components were mislocalized following MT depolymerizing or by disrupting dynein (63, 64).

BBS4 interaction with PCM-1 and the p150 glued subunit of dynactin suggests that BBS4 is an adaptor linking cargo to the dynein-dynactin motor for MT mediated transport (65). Another adaptor protein that plays a role in maintenance of the centriolar structure and function is Hook2 which also exists in a complex with PCM-1 (66, 67). The proposed idea is that PCM-1 shuttles between the cytosol and the centriole delivering cargo to the ciliary base, whose dispersion away from the centriole is regulated by Cep290 (68)(Fig. 2,III).

As a whole, these results emphasize the existence of multiple mechanisms and routes participating in the sorting of proteins to the PC.

Vesicle docking and fusion at the base of the PC—Since vesicles are prevented from entering the cilia by the barrier located at the base of the PC, carriers must dock and fuse at the ciliary base.

Rab8 is one of the major players in ciliogenesis and the only Rab that localizes to the PC. Indeed, this Rab GTPase is required for the docking and fusion of vesicles at the base of the PC (69) and for maintaining ciliary membrane identity (70). Multiple proteins such as RPGR (71), Cep290 (72), Ahi1 (73) and PCM1 (68) and the Rab11-Rabin8 complex contribute to Rab8 recruitment to the base of cilia.

Also of outstanding importance for cilia assembly is Rab11, which is involved in the recruitment of the Rab8 activator Rabin8 on pericentrosomal vesicles, activity that requires the ASAP1 scaffolding function (46, 74, 75). The activation of Rab8 and localization to the PC by the Rab11-Rabin8 complex is coupled to ciliary growth. Once the required cilia length is achieved, Rabin8 is removed from the centrosomes which also stops the trafficking of Rab8 into the cilium (75).

The TRAPPII (transport protein particle II) complex co-localizes with Rabin8-Rab8 in vesicles and in the centriole (75). However, it seems to facilitate the tethering of the ciliary vesicles to the centriole rather than to the periciliary membrane (75). In addition, it was recently shown that distal appendage components can act as an anchor for ciliary vesicles (18, 19, 76, 77) and interact with the vesicle trafficking machinery.

The role for the exocyst in vesicle fusion at the periciliary membrane is supported by several observations. Members of the exocyst complex (Sec6 and Sec8) have been found at the base of the cilia (78, 79). Overexpression of the exocyst component Sec10 led to the formation of longer PC in MDCK cells likely due to the excess delivery of ciliary components (80). The observation that the Sec15 subunit of the exocyst interacts with Rab11 and Rabin8 (81), suggested that the exocyst is linked to the Rab11-binding ternary complex (Arf4-ASAP1-FIP3) and facilitates membrane fusion (45). In fact, Rab8 regulation was coupled to the exocyst-mediated ‘kiss and run’ discharge of the contractile vacuole in *Dictyostelium discoideum* (82), supporting their role in vesicle tethering and fusion. Exocyst components also were found in a complex with IFT components and cargo (Polycystin-2); and knock-down of Sec10 resulted in a mislocalization of the cargo suggesting that the exocyst directs the IFT particle and its associated cargo to the cilia (83).

Trafficking in and out of the PC

Membrane proteins—The octameric complex referred to as the BBSome, constitutes the first canonical coat complex known to be involved in specialized protein trafficking into the cilium (84, 85). Although the BBSome may also play a role in trafficking to the ciliary base (86, 87), it localizes to the plasma membrane via Arl6 (BBS3) and mediates cargo translocation through the ciliary barrier (85, 88)(Fig. 3A). Specifically, the BBSome interacts with the C-terminus of ciliary cargoes such as Smo and Sstr3 (85, 89) and somehow drags them across the barrier (90). The BBSome complex binds Rabin8 at the ciliary base and it has been suggested that this interaction is the key for BBSome ciliary entry along with its cargo (84). Regulators of BBSome ciliary trafficking have also been

reported, namely LZTFL1 and AZI1 which sequester the BBSome in the cytoplasm and the centriolar satellites respectively (91, 92).

There is also evidence that the BBSome is involved in the exit of proteins from the cilia. Loss of BBS proteins resulted in the accumulation of Smo and its negative regulator Patched (Ptch) in the cilia, leading to disruption of the essential development Shh signaling pathway (89, 91). These results suggested that BBS components are required for the regulated segregation of Smo from Ptch in the cilia, perhaps by facilitating the exit of the latter. Other studies indicated that the BBSome is required for the exit of Dopamine GPCRs from the primary cilia which could account for enhanced anxiety seen in BBS children (93, 94). It has also been suggested that the BBSome proteins controls cilia exit and entry by co-ordinating the IFT machinery (see below under 'Trafficking within the cilium'). In order to achieve the right ciliary volume, BBS and Rab8 deliver material to the ciliary compartment while the endocytic players help to remove material from the periciliary compartment (95).

Soluble proteins—Nucleoporins also have been found to localize at the base of the cilia (31) and the identification of a ciliary pore complex (32) emphasizes the similarities between the nuclear and ciliary transport mechanisms. The nuclear pore is a highly selective port of entry to the nucleus which only allows proteins with nuclear localization signals recognized by importins (soluble carriers), to be transported into the nucleus following a GTP-bound Ran gradient (96). Similar mechanisms have been proposed for the ciliary transport of soluble protein KIF17 and membrane proteins Crumbs and RP2 (97–99)(Fig. 3). Presence of a nuclear localization signal in these cargoes has been confirmed (see Table I). However, how these proteins are selectively localized in the cilia and not the nucleus is yet to be established. Other studies have showed that soluble proteins move into the cilia depending on their size (21, 37) by diffusion across a molecular sieve at the ciliary base. Therefore, it is possible that larger molecules require active transport to move across the cilia.

Trafficking within the PC

Once inside the cilia, movement is made possible by the IFT complexes A and B, responsible for retrograde and anterograde transport, respectively (12, 34, 100–103) (Fig. 3). Both complexes have been found to be in association as a single string of particles which are known as 'IFT trains', allowing constant bi-directional movement or helping each other to successfully complete a cycle of transport to and fro in the cilia (104). The IFT trains move in the space between the axoneme and the membrane and associate with both, as seen in the electron-tomographs of *Chlamydomonas reinhardtii* flagella (105). The IFT particles are carried in the anterograde direction by kinesin-2 motors and in the retrograde direction by cytoplasmic dynein-2 motors (105–107)(Fig. 3).

In *C.reinhardtii* and *C.elegans*, cargo gets loaded on IFT particles at the ciliary base (34) and again at the ciliary tip (108). A recent study in *C.reinhardtii* showed that cargo loading at the ciliary base is regulated by the size of the growing cilia (109). Up to date, no direct IFT-cargo interaction has been reported (110), however cargo has been observed hopping on and off the 'IFT trains' (111). Interestingly, Mukhopadhyay et al (112, 113) showed

evidence supporting the presence of an adaptor protein (Tulp-3) linking cargo and the IFT particle.

Investigations in *C.elegans* also suggested a role of the BBS proteins as co-ordinators of IFT particles and motors for efficient anterograde transport (114, 115)(Fig. 3). Specifically, *C.elegans* mutants of BBS7/8 displayed varying velocities of anterograde transport due to lack of co-ordination between the motors (114, 115). Similar roles have also been described for the ARL proteins Arl-3 and Arl-13 (116). How and whether these 2 families co-ordinate along the same pathway has not been determined. Further, loss of BBS proteins in *C.elegans* and *C.reinhardtii* led to the accumulation of IFT B particles and signaling molecules at the cilia tip (108, 117). Turnaround of IFT complexes and cargo loading at the ciliary tip occurred in a DYF-2 and BBS-1 dependent manner (108). This abnormality was also apparent in mouse models of BBS (BBS 1/2/4/6 null mice) showing bulged ciliary tip which points towards problems in the retrograde IFT transport (94, 118, 119).

Ciliopathies

Ciliopathies are a broad and heterogeneous group of diseases due to compromised cilium function or structure. Given that almost every cell type in our body assembles a PC at a certain moment, it is not surprising that most ciliopathies are multi-organ disorders.

Ciliopathies arise from different mutations in more than 50 genes, and mutations in some genes can lead to more than one ciliopathy with pleiotropic phenotypes that can vary from mild to severe. While Tables II–V summarizes the characteristics of different ciliopathies and their link to vesicle trafficking, the following section discusses the steps of ciliary trafficking specifically affected in each ciliopathy and assesses its correlation with the phenotypes/symptoms observed.

Renal ciliopathies

Among the ciliopathies, Polycystic kidney disease (PKD) and Nephronophthisis (NPHP) majorly involve renal malfunction.

PKD is caused by mutations in the renal-cilia specific signaling receptors Polycystin-1, Polycystin-2 or Fibrocystin (120). Abnormal function or PC targeting of these protein cargoes leads to mechanosensation defects which in turn conduces to cyst formation or tubulopathy (121).

NPHP is the leading cause of end stage renal disorder, the last stage of chronic kidney disease, a condition requiring immediate dialysis or kidney transplant. The products of the genes affected in NPHP are called nephrocystins, and are localized at the ciliary base. In addition to renal ciliopathies, some of these genes are also involved in multi-organ diseases (see below). NPHPs form distinct complexes with each other namely NPHP1-4-8, NPHP5-6, NPHP 2-3-9-16 found in the TZ (122). Although their specific functions are not known it is apparent that genes that cause the renal form of NPHP do not affect ciliogenesis (Table II). Some of the members of this protein family seem to play a role in signal transduction (123–125), for example Glis-2 is a negative regulator of the Wnt β-catenin

pathway by functioning as its negative regulator (126). In fact, suppression of the canonical Wnt signaling is required for normal renal development and maintenance (125, 127) which when disrupted in PKD and NPHP leads to cystogenesis or fibrosis.

Multi-organ ciliopathies

Senior-Løken Syndrome (SLSN)—Affected NPHP genes are also often found associated with retinal abnormalities, in which case the corresponding pathology is known as SLSN. NPHP-5 is the classical SLSN causal gene as 100% of the cases are associated with retinal-renal pathology. The link between nephrocystin genes and retinal degeneration is possibly due to the interaction of nephrocystins with RPGR which is required for the maintenance of the photoreceptor by trafficking of Opsins to the outer segment (128–131). RPGR acts as a GEF for Rab8 and is also required for Rab8 localization (71). The adaptor protein RPGRIP1L seems to mediate the interaction between the RPGR and different NPHP complexes namely NPHP1-2-5 and NPHP 4-6-8 (71, 132). A role of the nephrocystins in sorting and trafficking of Opsins by correct loading of IFT particles on trains has also been described (133).

Oculo-Cerebro-Renal syndrome of Lowe (OCRL) or Lowe Syndrome (LS)—LS is characterized by cataracts, mental retardation and renal abnormalities such as LMW proteinuria. This disease is caused by mutations in the *OCRL1* gene (see ‘Trafficking to the base of the PC’). However, *OCRL1* mutations can also lead to a renal tubulopathy called Dent disease. It has been proposed that these different pathologies might be due to mutations resulting in different truncated forms of the protein (134).

It has been shown that LS patient and Ocrl1 knock-down cells show abnormal cilia (43, 55, 135) with reduced Rhodopsin trafficking to the PC (43). A zebrafish model of LS showed symptoms typical of ciliary dysfunction with curved bodies, underdeveloped eyes, pronephro cilia abnormalities and neurological lesions (43, 55, 136). Importantly, Ocrl1 interacts with several Rabs (underscoring its role in vesicle trafficking); and with highest affinity for Rab8, highlighting its role in ciliary function (53). In fact, simultaneous overexpression of Ocrl1 and Rab8 led to abnormal traffic to the cilia and to the formation of bulged PC likely due to cargo accumulation (43). In addition, Ocrl1 lack of function leads to RhoGTPase activation abnormalities which could be a cause or consequence of ciliary dysfunction (137, 138). Although the specific mechanism is still unknown, these abnormalities led to defects in cell spreading, cell migration, and fluid phase uptake (139) which in turn may be responsible for some of the developmental defects observed in LS patients.

Bardet-Biedl Syndrome (BBS)—BBS is characterized by obesity, rod-cone dystrophy, renal abnormalities, polydactyly, male hypogonadism and learning disabilities; animal models of BBS faithfully reproduced these phenotypes (See Table III). Most of the BBS causative genes are part of the BBSome or are required for regulation, assembly or functioning of the BBSome. As discussed previously, the BBSome plays a role in trafficking of cargoes across the cilia (See Section on ‘Trafficking In and Out of the Cilia’). However, it does not seem to be playing a critical role in cilia assembly (87, 89, 117, 140)(Table III).

This is probably the reason why BBS is not characterized by severe phenotypes such as perinatal lethality. Indeed, BBS results in male infertility due to defective spermatogenesis caused by motile ciliary defect, not PC defect (140, 141).

Abnormal delivery of ciliary components for proper ciliary functioning can also lead to ciliary dysfunction, as it is apparent in the case of retinal degeneration due to mistrafficking of Rhodopsin. BBS proteins are required for maintenance of the photoreceptor by functioning at the connecting cilium; therefore, mutations in BBS components results in a degeneration of the photoreceptor. BBS proteins are also required for trafficking of neuronal cilia cargoes namely Sstr3, Mchr1 and D1 (87, 93, 94)(Table III). Defective Leptin receptor signaling and mistrafficking of the NeuropeptideY in the absence of the BBSome has been linked to obesity in these patients (86, 142)(Table III).

Lack of BBS protein functions led to structural ciliary defects with bulged ciliary tips due to accumulation of cargo along with IFT components (94, 118, 119). This is probably due to the role played by BBS in IFT co-ordination and turn-around in the cilia (108, 114, 115). Overall, these findings are suggestive of BBSome functioning in the delivery of cargo to the cilia in a cell-specific manner resulting in a degenerative disease.

Joubert Syndrome (JBTS)—JBTS is a multi-organ disorder with a characteristic hindbrain malformation (‘Molar tooth Sign’), along with ataxia and cognitive dysfunction. It is also frequently accompanied by renal and/or retinal symptoms. The animal models of JBTS display symptoms characteristic of ciliopathies: photoreceptor degeneration, brain malformations, laterality defects and cystic kidneys (133, 143–150)(Table IV).

Genes affected in JBTS are required for ciliogenesis (Table IV). Absence of PC or decreased PC length is observed upon mutations in *CSPP1, CEP41, TMEM237, TCTN1, KIF7, OFD1* and *AHI1*. Ciliary motility was also affected in animal models of JBTS: Nphp1 (151) and Cep41 (149). Ciliary defects were observed in several organs such as nodal cilia, connecting cilium of photoreceptors, neural tube cilia, limb bud mesenchyme and renal cilia (27, 143, 145–147) which accounts for the multi-organ disruptions associated with JBTS.

In addition, JBTS involves mutations in genes whose products are required in key vesicle trafficking processes during cilia assembly (Table IV). For example, the JBTS protein Cep164 is essential for ciliogenesis by docking the mother centriole to the apical membrane (148, 152) and vesicles to this structure (76). Ahi1 is required for vesicle delivery and fusion to the PC via its interaction with Rab8 (73). Arl13b is involved in trafficking material to the cilia (see ‘Trafficking to the base of the PC’) and its knockdown also resulted in a defective axoneme structure (56). Further, Arl13b, Cep164 and Pde6d form a complex that co-ordinates the localization of ciliary cargo (58), such as the lipid phosphatase Inpp5E. In turn, mutations in Inpp5E also lead to JBTS. Recently, the role of Inpp5E in ciliary development was demonstrated in morphant zebrafish (153). Although the exact mechanism of action is unknown; given its similarities to Ocrl1 in terms of substrate specificity (154, 155), Inpp5E may be also involved in vesicle transport to the PC. It is possible that this complex serves to transport more components to the cilia for its proper functioning (156). JBTS components

also play a role in the regulation of ciliary signaling pathways, such as the essential Shh pathway (56, 157).

JBTS proteins are also required for proper functional co-ordination of IFTs, as is apparent from the disruption of IFT-A and B subcomplexes in *ARL13b* mutant *C.elegans* (116). Lack of function of other JBTS proteins have also been linked to IFT transport, namely Ofd1 defective cells were affected for Ift-88 ciliary base localization (4) and Nphp1 mutant photoreceptors showed defective trafficking of Ift-88 and Wdr-19 (133). It can be speculated that each JBTS protein might be functioning with certain IFT particles and co-ordinating the movement of the IFT particle associated cargo into the PC; further, IFT particles might carry different cargoes depending on the cell type leading to a complex, multi-organ disease. Collectively, the evidence indicates that JBTS is caused by disrupted ciliogenesis or by trafficking of components essential for defining and maintaining the ciliary compartment characteristics thus leading to more severe phenotypes than BBS.

Meckel-Gruber Syndrome (*MKS*)—This is the most severe of the multi-organ ciliopathies, characterized by occipital encephalocele, perinatal lethality, renal cysts and hepatic ductal malformations. Animal models of MKS faithfully reproduce these defects (30, 123, 124, 158, 159)(Table V). Similar to JBTS, MKS mutants display overall ciliary disruption in multiple tissues namely, the nodal cilia, neural cilia, limb-bud cilia and retinal degeneration (27, 30, 124, 129, 158, 160) (Table V).

MKS proteins are involved in early ciliogenic events which involves establishment of the barrier at the base which controls protein trafficking to and from the PC. Most of these proteins are localized in the TZ and co-operate to form an intact TZ (29, 30)(Table V). Mutations in the corresponding TZ genes resulted in stunted cilia with abnormal membrane composition, due to loss of the ability to maintain the membrane diffusional barrier between the plasma and the ciliary membrane (29, 30). Other functions described for these MKS proteins involve basal body docking by Mks1 and Mks3 (161). Cep290 and Cc2d2a are required for Rab8 localization, which is the ciliary compartment identifier (68, 162). Taken together, mutations in these genes disrupt global ciliogenesis leading to severe phenotypes.

Overlap among ciliopathies—Lack of or abnormal function of certain genes can lead to the onset of several ciliopathies (See Fig. 4). For example, mutations in some MKS-causing genes (*CEP290*) also can lead to milder phenotypes resulting in NPHP, BBS or JBTS (See Table V). This spectrum in phenotype has been attributed to specific mutations and mutational load. Hypomorphic mutations in *MKS1* and *CC2D2A* have shown to cause milder diseases categorized as BBS and JBTS respectively (163, 164). In the case of *TMEM67*, the position and nature of the mutation determines the severity of the disease (165). Interestingly, Cep290 is a protein that when mutated can manifest a varied spectrum of disorders (130), possibly due to the number and type of interactors that it has, namely, BBS proteins, Cc2d2a, Nphp5 and Rab8 (68, 166–168).

In addition, there are also reports that even the same mutation may lead to scenarios of different severity. For example, Ocrl1 mutations can cause LS, but also Dent's disease (lacking mental retardation and ocular abnormalities) (169). The mechanisms responsible for

this variability are not fully established yet, but the existence of critical genetic modifiers and the differential impact of specific mutations have been suggested.

Conclusions

Broadly, ciliopathies can be divided in isolated (PKD, NPHP) versus multi-organ disorders (SLSN, BBS, JBTS, LS and MKS). Whereas specific ciliary signaling pathways are disrupted in NPHP and PKD, multi-organ ciliopathies display a more global effect on PC function. Importantly, the severity of the disease seems to depend on whether ciliogenesis is affected or not (Fig. 5). In the case of the milder BBS, while the cilia are intact, specific functions are disrupted due to mistrafficking of ciliary receptors (Fig. 5B). On the more severe end of the disease spectrum are LS, JBTS and MKS in which ciliogenesis is disrupted or affected (Fig. 5C and D).

In summary, this review emphasized the importance of vesicle trafficking and protein sorting for the assembly and function of the primary cilia. As a whole, the evidence discussed also highlights the correlation between the impact of the mutation (depending on factors such as gene redundancy and the presence of genetic modifiers) on the PC (e.g., altering traffic of specific cargo vs. PC assembly deficiencies) and the severity of the corresponding ciliopathy. We speculate that in the near future, these emerging trends will contribute to our ability to make predictions in terms of gene product function or ciliopathy mechanism.

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Synopsis

The receptor-rich, signaling organelle known as Primary cilium (PC) has been implicated in a multitude of diseases collectively denominated as ciliopathies. The presence of a defined barrier at its base makes the PC an isolated compartment that needs vesicle trafficking for maintenance and function. This review discusses the major players involved in trafficking to the PC and highlights evidence correlating the severity of the ciliopathy to the trafficking defect involved. Specifically, mild and severe symptoms arise from specific ciliary receptor mislocalization and generalized ciliogenesis defect, respectively.

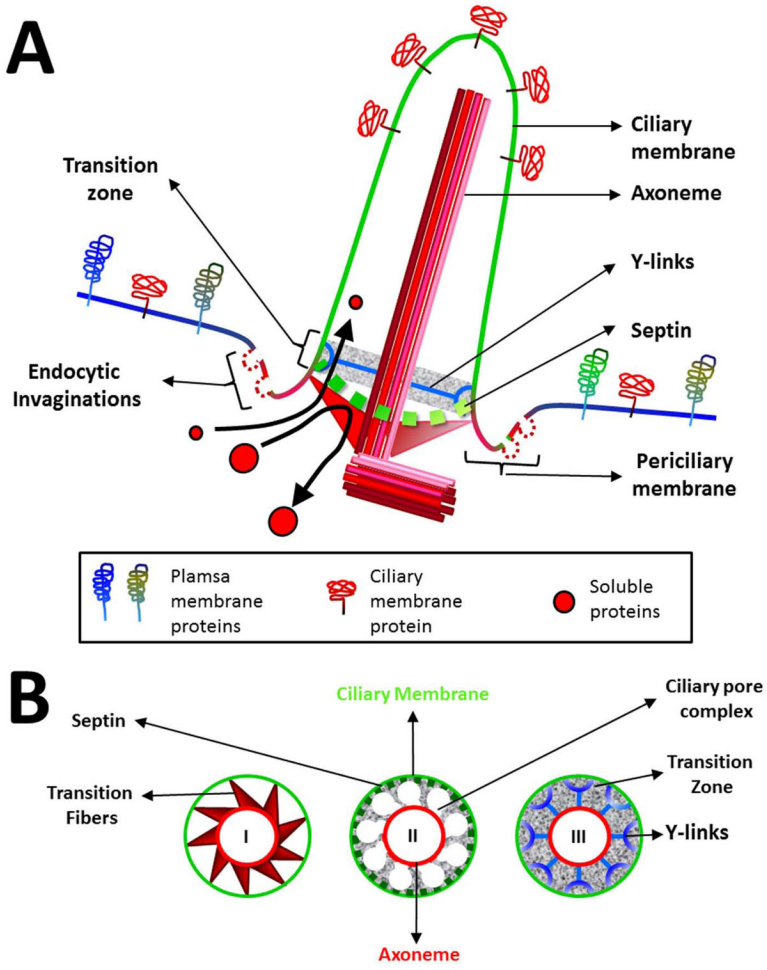

Figure 1. The PC is an isolated domain

(A) The barrier at the ciliary base gives the ciliary membrane its unique identity in terms of lipid and protein composition (see text for details). **(B)** Cross-sections bottom up of the ciliary base depicting the proximal transition fibres (I), Septin ring and the ciliary pore complex (II) and the distal Y-links (III) (See text for details).

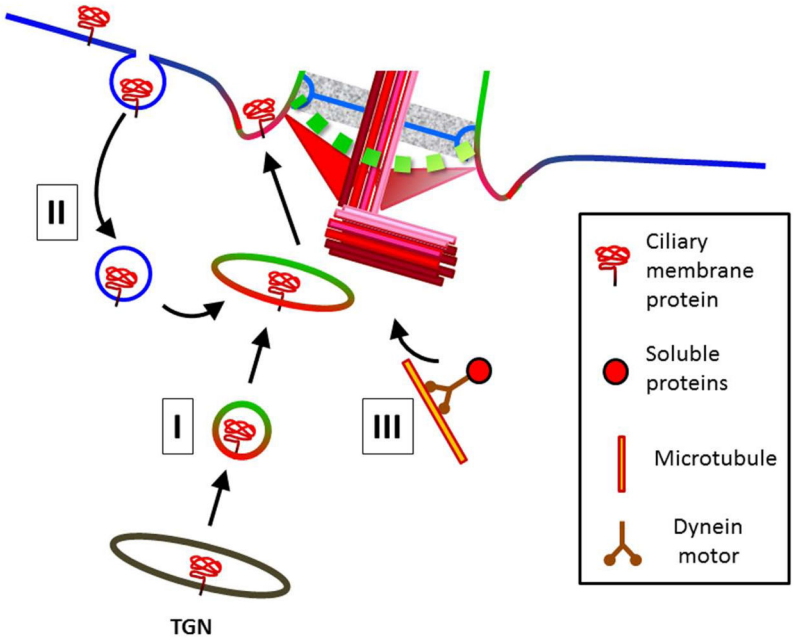

Figure 2. Pathways for transport of material to the base of the cilia

Secretory pathway **(I)** Endocytic-recycling pathway **(II)** Dynein-Dynactin complexes **(III)**. (See text for details)

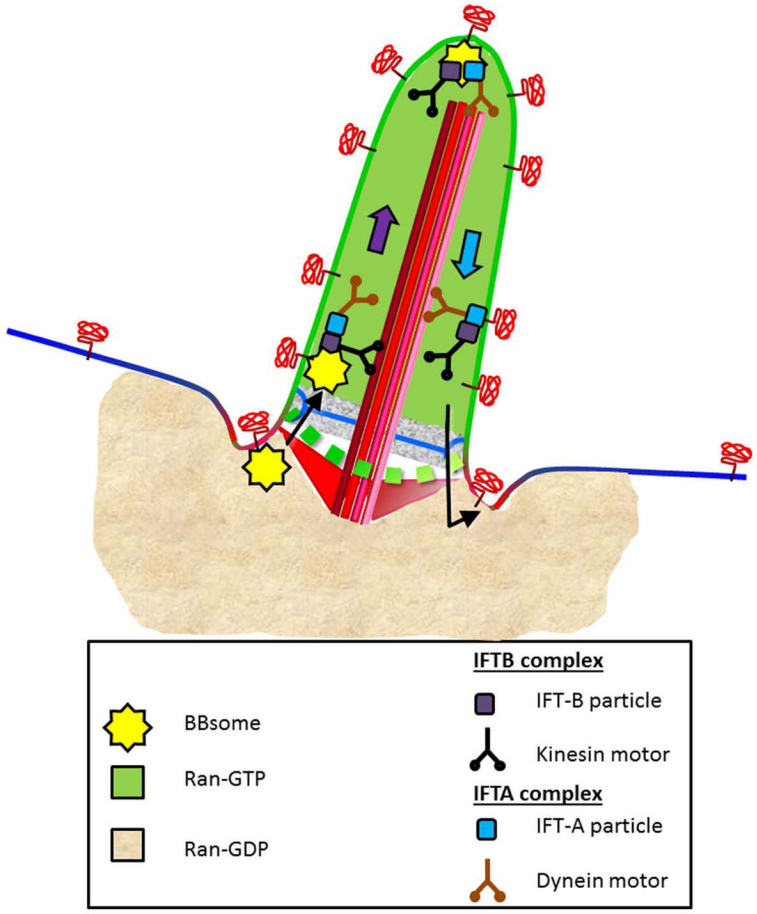

Figure 3. Transport of Material across and within the cilia

Movement across the cilia mediated by the BBSome and activated Ran gradient system. Co-ordination of IFT inside the cilia by the BBSome for anterograde and retrograde trafficking (See text for details).

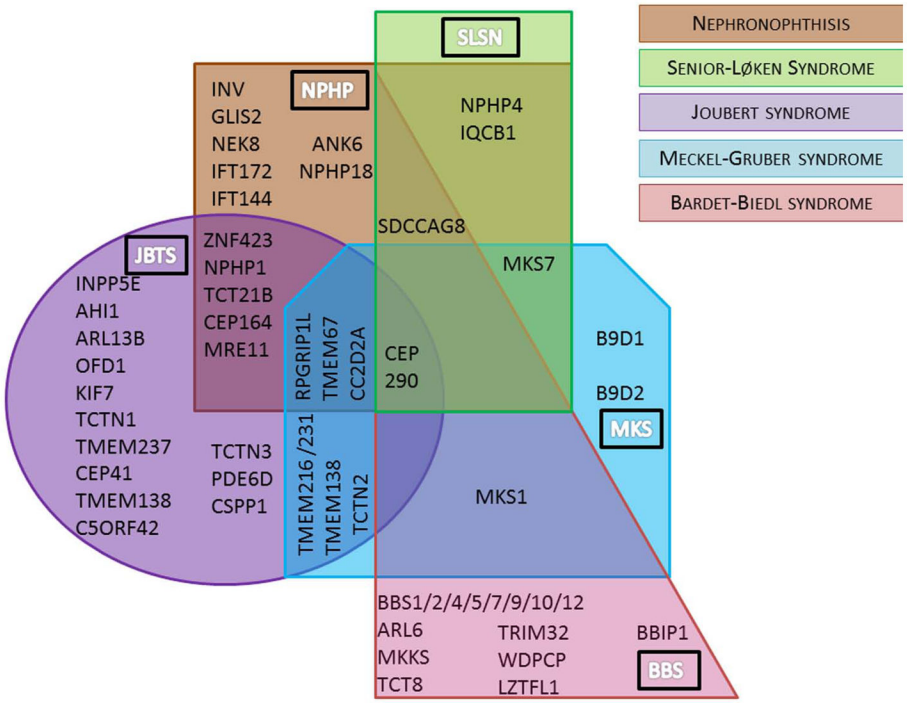

Figure 4.

A Graphical Representation of the overlap of genes involved in ciliopathies.

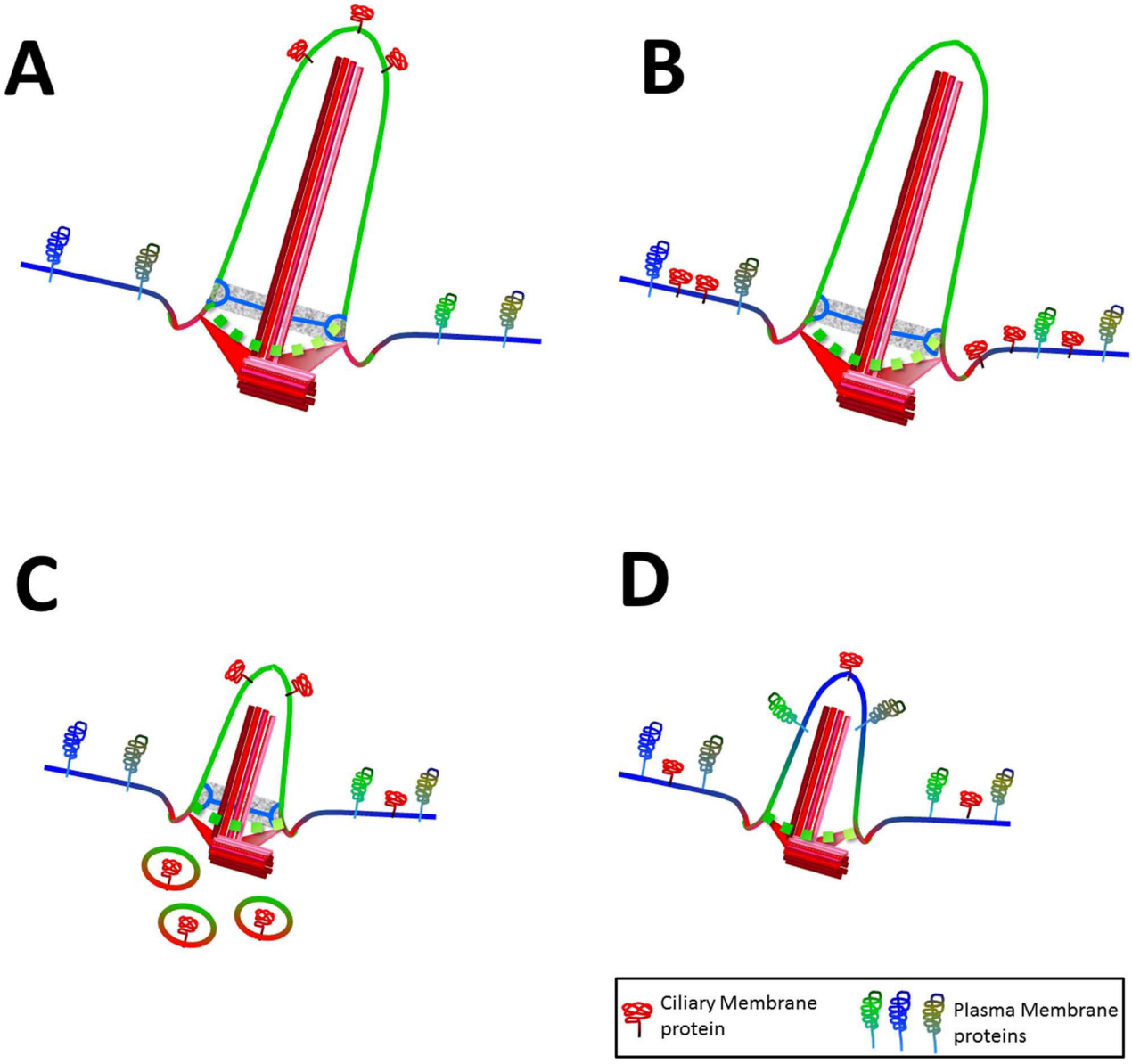

Figure 5. Ciliary trafficking defects in ciliopathies

(A) Normal Cilia. **(B)** NPHP and BBS: no ciliogenesis defect, specific ciliary cargo trafficking defect. **(C)** LS and JBTS: ciliogenesis affected due to defective material delivery for ciliary construction. **(D)** MKS: TZ components missing resulting in the loss of ciliary boundary

Table I

Ciliary targeting consensus sequences present in cargos

Cargo	Protein type	Organism	Signal1 (Consensus)[a]/binding partner	Signal2 (Consensus)[a]/binding partner
ODR-10	GPCR	*C.elegans*	FR (ØB)/ND[b](170)	
STR-1	GPCR	*C.elegans*	YR (ØB)/ND (170)	
SSTR3	GPCR	Mammalian	FK (ØB)/BBSome (4)	APSCQ (AX[S,A]XQ)/ND (171)
HTR6	GPCR	Mammalian	FK (ØB)/ND (4)	ATAGQ (AX[S,A]XQ)/ND (171)
Rhodopsin	GPCR	Mammalian	FR (ØB)/ASAP1 (4, 46, 170)	QVSPA ([K,R,Q]VXPX)/Arf4 (42, 44)
Smoothened	GPCR	Mammalian	WR (ØB)/ND (4)	
MCHR1	GPCR	Mammalian	APASQ (AX[S,A]XQ)/ND (171, 172)	
GPR161	GPCR	Mammalian	[I,V]KARK/ND (113)	
Polycystin-1	GPCR	Mammalian	KVHPSST ([K,R,Q]VXPX)/ND (173)	
PGR15L	GPCR	Mammalian	[R,K][I,L]W/ND (142)	
GPR83	GPCR	Mammalian	[R,K][I,L]W/ND (142)	
NPY2R	GPCR	Mammalian	[R,K][I,L]W/ND (142)	
Polycystin-2	6 TM domains	Mammalian	RVQPQ ([K,R,Q]VXPX)/ND (49)	
Fibrocystin	Single-pass TM	Mammalian	CLVCCWFKKSKTRKIKP/Rab8 (174)	
RP2	Membrane-associated protein	Mammalian	Consensus M9 sequence/Importin β2 (99)	
CNGB1b	Ion channel	Mammalian	RVSPG ([K,R,Q]VXPX)/ND (175)	
KIF17	Soluble	Mammalian	KRKK (Similar to NLS)/Importinβ2 (98)	

[a] Amino acids are indicated using the 1-letter code (e.g., Y=Tyrosine; N=Asparagine). “X” represents a position occupied by any amino acid. Ø= amino acid with a bulky-hydrophobic side chain (L, I, M, V, F). Amino acids within brackets indicate that one or the other can be found in that position within the consensus.

[b] Not determined

Table II

Ciliary defects and phenotypes characteristic of Renal/Retinal-renal ciliopathies

Genes	Other names	Ciliopathy	Cilia presence	Ciliary signaling functions	Other functions/defects	Animal model phenotypes
INV	NPHP2	NPHP	Inv/inv mutant mice: Renal cilia not affected (176), structure of the nodal cilia not affected (177).	Negative regulator of Wnt/β-catenin pathway (178), required for cilia disassembly (179).	inv/inv mutant mice: Sustained cell proliferation in the kidney(180).	KO[a] mice: Situs inversus (181), renal fibrosis (182).
NPHP7	GLIS2	NPHP	KD[b] in zebrafish: Required for ciliary motilify (183)	Negative regulator of Wnt/β-catenin pathway (126)	Required for kidney architecture (127, 184)	KO mice: Tubular atrophy and fibrosis leading to kidney failure (127, 184)
NPHP9	NEK8	NPHP	KO mice: Not required for ciliogenesis (185).	Suggestive of Polycystin-2 dependent signaling from the cilia (185, 186).	Required for the kidney tubule maintenance (187), regulator of Hippo signaling (188).	KO mice: Die at birth due to situs inversus, cardiac anomalies, glomerular cysts (185). KD in zebrafish: pronephric cysts (189).
NPHP4	Nephroretinin	NPHP, SLSN	Nphp4 mutant mice: No overall ciliogenesis defect, photoreceptor degeneration reported (190)	Negatively regulate Wnt/β-catenin pathway (191)	Negative regulator of Hippo pathways (188)	
NPHP5	IQCB1	NPHP, SLSN	Nphp5 KD: Decreased number of renal cilia (192)	Rhodopsin trafficking (192)		KO mice: Apoptosis, fibrosis and cysts (192)

[a] Knockout;

[b] Knockdown

Table III

Ciliary defects and phenotypes characteristic of Bardet-Biedl Syndrome (BBS)

Genes	Other names	Ciliopathy	Cilia presence	Ciliary signaling and trafficking functions	Phenotypes in animal models
BBS1		BBS	KO[a] mice: Defective olfactory epithelium (193). Bbs1 M390R knockin mice: abnormally swollen distal end in their ependymal cilia, airway epithelial cilia, photoreceptor degeneration (118, 119)	Component of BBSome (85), leptin signaling (86), Hh signaling (89), required for turnaround of IFT particles (108).	Bbs1 M390R knock-in mice: ventriculomegaly, obesity,retinopathy, higher heart rate (118). KO mice: Embryonic lethal, anosmia (193).
BBS2		BBS	KO mice: Global cilia assembly not affected, photoreceptor degeneration, defective sperm flagella (140), bulged ciliary tips in airway epithelia (119), not required for ciliogenesis in the brain(87). MO[b] injected zebrafish: progressively defective KV[c] cilia (194).	Component of BBSome (85), Leptin signaling (86), Sstr3 and Mchr1 neuronal cilia localization (87), Dopamine receptor ciliary exit (93), Rhodopsin photoreceptor localization (140)	KO mice: obesity (86, 140), ventriculomegaly (118), retinopathy, male infertility, neurosensory phenotypes (140).
BBS3	ARL6	BBS	MO injected zebrafish: Defective KV (195, 196). Mutant Arl6 overexpression in hTERT-RPE cells: increased ciliary length (88)	Required for BBSome targeting to the cilia (85), Hh signaling (91), Wnt/β-catenin signaling (88).	KO mice: Retinopathy (196).
BBS4		BBS	KO mice: Global cilia assembly not affected, defective olfactory epithelium, photoreceptor degeneration, defective sperm development (141, 193, 197), not required for ciliogenesis in the brain (87), bulged ciliary tips in airway epithelia(119), longer renal cilia (198). MO injected zebrafish: Progressive defective KV cilia (194). Full length flagella assembled in the absence of BBSome components (117).	Component of BBSome (85), Leptin signaling (86), Rhodopsin, Arrestin and Transducin photoreceptor localization (197). Sstr3 and Mchr1 neuronal cilia localization (87). Dopamine receptor ciliary exit (93). Required for transport of PCM1 and its associated cargo to the ciliary base (65). Aberrant Rho A signaling (199).	KO mice: Neurosensory phentoypes (140), anosmia (193), male infertility (141).
BBS5		BBS	MO injected zebrafish: Progressive defective KV cilia (194, 200).	Component of BBSome (85), Hh signaling (91), interacts with the Dopamine receptor (93).	MO injected zebrafish: Altered heart looping, defective melanosome transport (200).
BBS6	MKKS	BBS	KO mice: retinal degeneration (201, 202), Olfactory epithilium cilia affected, bulged ciliary tips in airway epithelia (119). MO injected zebrafish: Progressive defective KV cilia (194).	Required for BBSome assembly (203), Leptin signaling (86).	KO mice: obesity (86), ventriculomegaly (118), retinal degeneration (201, 202).
BBS7		BBS	KO mice: ependymal cilia abnormally bulged at the tips, photoreceptor degeneration (94). MO injected zebrafish: Progressive defective KV cilia (194). BBS7 null mice MEFs[d]: Cilia not affected (89)	Component of BBSome (85), Dopamine receptor ciliary exit (93). Co-ordination of IFT (114, 115).	KO mice: retinal degeneration, obesity, ventriculomegaly and male infertility (94).
BBS8	TCT8	BBS	KO mice: Olfactory cilia affected (204). MO injected zebrafish: Progressive defective KV cilia (194).	Component of BBSome (85). Required for OSM-9 localization in *C.elegans* (205), ACIII and SLP3 localization in olfactory sensory neuronal cilia (204). Co-ordination of IFT (114, 115).	KO mice: Olfactory cilia affected (204)

Genes	Other names	Ciliopathy	Cilia presence	Ciliary signaling and trafficking functions	Phenotypes in animal models
BBS9	PTHB1	BBS	MO injected zebrafish: defective KV. KD[e] in IMCD3 cells: absence of cilia (206).	Component of BBSome (85)	
BBS10		BBS		Required for BBSome assembly (203)	
BBS11	TRIM32	BBS	MO injected zebrafish: progressive defective KV cilia (207)		KO mice: Myopathy and neurodegeneration (208)
BBS12		BBS		Required for BBSome assembly (203)	
BBS17	LZTFL1	BBS		Negative regulator of BBSome, Hh signaling (91)	
BB1P10	BBS18	BBS		NPY2R ciliary localization (142)	KO mice: Obesity, hyperphagia, retinal degeneration, male sterility (142).
BBS15	WDPCP, Fritz	BBS	Mutant mice: Kidney collecting duct, neuroepithelium and MEFs have defective ciliogenesis (209). KD in Xenopus: fewer and shorter cilia (210).		Mutant mice: anophthalmia, central polydactyly, kidney cysts, complex congenital heart defects, cloacal septal defects (209).
SDCCAG8	BBS16, NPHP10	BBS, NPHP, SLSN	KO mice: No global ciliogenesis defect, photoreceptor degeneration (211).	Rhodopsin trafficking, DNA Damage signaling response (211).	MO injected zebrafish: body axis curvature, kidney cysts, hydrocephalus (212).

[a]Knockout;

[b]Morpholino;

[c]Kupffer's vesicle;

[d]Mouse Embryonic Fibroblasts;

[e]Knockdown

Table IV

Ciliary defects and phenotypes characteristic of Joubert Syndrome (JBTS)

Genes	Other names	Ciliopathy	Cilia presence	Ciliary signaling and trafficking functions	Phenotypes in animal models
Inpp5E	JBTS1	JBTS	Mutant mice MEFs[a]: Prematurely destabilized cilia in response to growth factor stimulation (155). MO injected zebrafish: decreased cilia in KV[c] and pronephric ducts (153)		*INPP5E* mutant mice: Embryonic lethal, skeletal abnormalities, kidney cysts, cerebral defects, hexadactyly (155). MO[b] injected zebrafish: microphthalmia, pronephros cysts, pericardial effusion, and left-right body axis asymmetry (153).
AHI1	JBTS3	JBTS	Mutant mice: Photoreceptor degeneration (145, 146), normal cilia in kidneys and MEFs (213, 214). Ahi 1 KD[d] in IMCD3 cells and mutant mice MEF: affected for ciliogenesis (73, 147). Ahi1 morphant zebrafish: Defective ciliation in KV and in the pronephros cilia (147).	Wnt signaling (214), Shh signaling (56), Rab8 localization, vesicle docking and fusion (73), Opsin (145), Transducin and Rom1 trafficking (146).	KO mice: fibrosis, cystic kidney, midline fusion defect (213, 214), photoreceptor degeneration (145, 146). MO injected zebrafish: ear, hindbrain and eye abnormalities, cardiac-looping, cloacal dilation (147).
ARL13B	JBTS8	JBTS	Mutant mice: Ciliary axoneme structure affected (56)	Hh signaling (56), Inpp5E, Polycystin-2 and ODR-10 ciliary localization (58, 116). Co-ordination of IFT (215).	KO mice: Embryonic lethal, open neural tube, randomized heart looping, polydactyly, abnormal eyes (56). Mutant zebrafish: curved bodies, pronephric cysts (144).
OFD1	JBTS10	JBTS	Mutant mice: nodal cilia and kidney cilia affected (143). Ofd1 mutant ES[e] cell lines: affected for ciliogenesis (216).	Required for the recruitment of Ift88 to the centrosome (216).	KO mice: embryonic lethal, left-right axis asymmetry, cystic kidneys (143).
KIF7	JBTS12, COS2	JBTS	KD in hTERT-RPE cells: reduced number of cilia (217).	Hh signaling (157, 218)	KO mice: skeletal abnormalities, Preaxial polydactyl (218), expanded motor neuron domain, embryonic lethal (157).
TCTN1	JBTS13	JBTS	KO mice: nodal and neural tube cilia affected (27).	Hh signaling, Ciliary localization of AC3, Polycystin-2 and Arl13b (27, 219)	KO mice: Embryonic lethal, defective limb bud patterning, neural tube patterning defects, cerebral abnormalities, holoprosencephaly (219)
TMEM237	JBTS14	JBTS	Patient fibroblasts failed to produce cilium (36).	Wnt signaling disrupted (36).	
CEP41	JBTS15	JBTS	Mutant zebrafish: kindey cilia motility was affected. Patient fibroblasts had a fewer percentage of cilia (149).		Mutant mice: embryonic lethal, brain malformation, laterality defects; MO injected zebrafish: laterality defects (149).
PDE6D		JBTS		Inpp5E ciliary localization (58).	
CSPP1		JBTS	Patient fibroblasts affected for ciliogenesis (150).	Ciliary localization of ACIII and Arl13b (150)	MO injected zebrafish: curved bodies, pronephric cysts, cerebellar abnormalities (150).
Cep164	NPHP15	NPHP, JBTS	KD in hTERT-RPE blocked docking of mother centrioles, docking of vesicle to the mother centriole and ciliogenesis (76, 148, 152)	Interacts with Rab8 (76), Inpp5E ciliary localization (58). Defective DNA damage response (148).	
NPHP1	JBTS4	NPHP, JBTS	Mutant mice: sperm development affected (220), photoreceptor degeneration (133), respiratory cilium motility defects (151).	Trafficking of Ift88, Rhodopsin and Transducin ciliary localization (133).	Nphp1 mutant mice: male sterility, retinal degeneration (133, 220).

[a] Mutant Embryonic Fibroblats,

[b] Morpholino,

[c] Kupffer's vesicle,

[d] Knockdown,

[e] Embryonic stemcells

Table V

Ciliary defects and phenotypes characteristic of Meckel-Gruber Syndrome (MKS)

Genes	Other names	Ciliopathy	Cilia presence	Ciliary signaling and trafficking functions	Phenotypes in animal models
B9D1	MKS9, MKSR-1	MKS	KO[a] mice: reduced cilia in kidney tubules (221), ciliogenesis affected in rapidly dividing tissues (30). KD[b] in IMCD3 cells: disrupted ciliogenesis (222).	Hh signaling, Ciliary localization of Arl13b, ACIII (221). MKS-1/MKSR-1/MKSR-2/ MKS-3/MKS-6 along with NPHP1 and 4 are required for the formation of an intact barrier in *C.elegans* cilia (29).	KO mice: Embryonic lethal, polydactyly, kidney cysts, ductal plate malformation, abnormal neural tube patterning (221), microphthalmia, polydactyly, severe vascular defects (30).
B9D2	MKS10, MKSR-2,Stumpy	MKS	KO mice: Ependymal cilia affected (159). KD in IMCD3 cells: disrupted ciliogenesis (222)	MKS-1/MKSR-1/MKSR-2/MKS-3/MKS-6 along with NPHP1 and 4 are required for the formation of an intact barrier in C.elegans cilia (29).	KO mice: hydrocephalus, cystic kidneys (159).
MKS1	BBS13	BBS, MKS	Mutant mice: Cilia numbers were affected in most epithelial and mesenchymal tissues (160), MEFs[c] and kidney (223). KD in IMCD3: ciliogenesis disrupted, by blocking centriole migration to the apical membrane (28, 161).	Hh signaling (28, 160). MKS-1/MKSR-1/ MKSR-2/MKS-3/MKS-6 along with NPHP1 and 4 are required for the formation of an intact barrier in *C.elegans* cilia (29).	Mks1 mutant mice: embryonic lethal, biliary duct malformation, kidney cysts, polydactyly, occipital encephalocoele, hydrocephaly, skeletal defects (160); craniofacial defects, polydactyly, congenital heart defects, polycystic kidneys and randomized left-right patterning (223).
CEP290	BBS14, MKS4, JBTS5, NPHP6	BBS, MKS, JBTS, NPHP, SLSN	Mutant mice: Retinal degeneration (129). KD in IMCD3 and hTERT-RPE cells: Critical for ciliogenesis (28, 68)	Component of Y-links (26). Required for Rab8 localization (68), Rhodopsin and Arrestin ciliary localization (129).	Cep 290 null mice: Midline fusion defect (214). Cep290 mutant mice: retinal degeneration (129).
TMEM216	JBTS2, MKS2	JBTS, MKS	KD in IMCD3: ciliogenesis defects, centrosomal docking was prevented (224)	MKS-1/MKSR-1/MKSR-2/MKS-3/MKS-6 along with NPHP1 and 4 are required for the formation of an intact barrier in *C.elegans* cilia (29).	
TMEM67	JBTS6, MKS3, NPHP11, Meckelin	JBTS, MKS, NPHP	Mutant mice: kidney tubule cilia affected (27), photoreceptor degeneration (225). KD in IMCD3 cells: ciliogenesis affected by blocking centriole migration to the apical membrane (161).	Ciliary localization of ACIII, Arl13b, Rhodopsin, Rom1, Transducin and Arrestin (27, 225). MKS-1/MKSR-1/MKSR-2/ MKS-3/MKS-6 along with NPHP1 and 4 are required for the formation of an intact barrier in *C.elegans* cilia (29).	KO mice: kidney ciliary defects, kidney cysts (27), photoreceptor degeneration (225).
RPGRIP1l	JBTS7, MKS5, NPHP8, FTM	NPHP, JBTS, MKS,	Mutant mice: Fewer cilia in the neural tube and limb buds (158). Mutant C.elegans: ciliogenesis affected (29).	Hh signaling (158).	KO mice: death, craniofacial dysmorphology, microphthalmis, polydactyly, heterotaxia (158)
CC2D2A	JBTS9, MKS6	NPHP, JBTS, MKS,	KO mice: nodal and neural tube cilia formation affected (27).	Required for ciliary localization of ACIII, Polycystin-2, Arl13b (27), opsin (162). MKS-1/MKSR-1/MKSR-2/MKS-3/MKS-6 along with NPHP1 and 4 are required for the formation of an intact barrier in *C.elegans* cilia (29).	KO mice: embryonic lethal, neural tube ciliary defects, laterality defects, holoprosencephaly, microphthalmia (27). Mutant zebrafish: photoreceptor degeneration (162).

Genes	Other names	Ciliopathy	Cilia presence	Ciliary signaling and trafficking functions	Phenotypes in animal models
TMEM138	JBTS16	JBTS, MKS		Marks vesicles which are ciliary bound (226).	
TMEM231	JBTS20	JBTS, MKS	KO mice ciliogenesis defects in rapidly dividing tissues (30).	Hh signaling, required for diffusion barrier integrity (30).	KO mice: Microphthalmia, polydactyly, lethal due to severe vascular defects (30).
TCTN2	MKS8	JBTS, MKS	KO mice: nodal and neural tube cilia formation affected (27).	Hh signaling, required for ciliary localization of ACIII, Polycystin-2, Arl13b (27).	KO mice: Embryonic lethal, affected nodal cilia, neuronal cilia and limb bud mesenchyme cilia (27).
NPHP3	MKS7	NPHP, MKS, SLSN	MO[d] injected zebrafish: KV[e] cilia affected (124).	Wnt signaling (123, 124)	KO mice: Embryonic lethal, Situs inversus, renal-hepatic, pancreatic dysplasia, heart defects, tapetoretinal degeneration (123). MO in zebrafish: hydrocephalus, situs inversus (124).

[a]Knockout,

[b]Knockdown,

[c]Mouse embryonic fibroblasts,

[d]Morpholino,

[e]Kupffer's vesicle