Cilia

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Photoreceptor sensory cilia and ciliopathies: focus on CEP290, RPGR and their interacting proteins

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Abstract

Ciliopathies encompass a broad array of clinical findings associated with genetic defects in biogenesis and/or function of the primary cilium, a ubiquitous organelle involved in the transduction of diverse biological signals. Degeneration or dysfunction of retinal photoreceptors is frequently observed in diverse ciliopathies. The sensory cilium in a photoreceptor elaborates into unique outer segment discs that provide extensive surface area for maximal photon capture and efficient visual transduction. The daily renewal of approximately 10% of outer segments requires a precise control of ciliary transport. Here, we review the ciliopathies with associated retinal degeneration, describe the distinctive structure of the photoreceptor cilium, and discuss mouse models that allow investigations into molecular mechanisms of cilia biogenesis and defects. We have specifically focused on two ciliary proteins – CEP290 and RPGR – that underlie photoreceptor degeneration and syndromic ciliopathies. Mouse models of CEP290 and RPGR disease, and of their multiple interacting partners, have helped unravel new functional insights into cell type-specific phenotypic defects in distinct ciliary proteins. Elucidation of multifaceted ciliary functions and associated protein complexes will require concerted efforts to assimilate diverse datasets from *in vivo* and *in vitro* studies. We therefore discuss a possible framework for investigating genetic networks associated with photoreceptor cilia biogenesis and pathology.

Keywords: Ciliopathy, Retinal degeneration, Primary cilium, Sensory cilia, CEP290, RPGR, Bardet–Biedl syndrome, Leber congenital amaurosis, Joubert syndrome, Nephronophthisis

Introduction

As the field of cilia biology has exploded over the past decade, our understanding has evolved from the initial realization of cilia as important cellular structures to the knowledge that defects in these organelles constitute a unifying framework in numerous syndromic diseases, collectively called ciliopathies. More recently, distinct sets of genes have been identified as causing overlapping symptom clusters, making it possible to link specific genetic mutations to clinical diagnosis. Amidst this rapid progress, confusion arose because disease conditions manifest as a continuum of disorders with varying severity and organ involvement rather than cleanly segregated entities. As a result, even identical gene mutations can give rise to distinct clinical manifestations, while a well-defined clinical syndrome can trace its etiologic origin to a multitude of gene defects. The goal of this review is to focus on the differences among ciliopathies based on molecular and genetic characteristics and on the realization that assigning a specific clinical diagnosis is only the starting point for identifying the culprit gene. In reaching a clear understanding of molecular mechanisms and future therapeutic strategies, correlating specific symptoms to genetic mutation(s) should provide valuable insights.

We have focused on ciliopathies that include retinal degeneration as part of the clinical spectrum in order to provide a comprehensive analysis of their mutations, phenotypes, subcellular localization of the gene products, and functional insights from respective mouse models. In addition to summarizing the current state of knowledge, we have attempted to define gaps in our understanding of cilia biology and suggested approaches for future investigations.

An overview of ciliogenesis and cilia function

Cilia can be categorized as primary, sensory or motile. Nearly all cells develop a primary cilium, which serves

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either as a precursor to a cluster of motile cilia (in cells such as ventricular ependyma and tracheal epithelium) [1,2] or remains as an environmental sensor. Given that most primary cilia are now known to enable cells to interact with and respond to their environment [3], the distinction between primary and sensory cilia has lost much of its meaning. These cilia are highly specialized organelles that have developed to mediate perception of light, sound, odorants, osmolarity, pressure, flow, circulating hormones, and position within the plane of a tissue (via gradients of morphogens); these perceptions are then transmitted into the cell via signaling pathways to mediate distinct responses. For example, photoreceptor outer segments are filled with stacks of membranous discs densely packed with rhodopsin, the receptor molecule that initiates a transduction cascade turning photons into electrical signals. In the cochlea, the kinocilium serves as a transient anchor point for positioning the stereocilia bundles. In olfactory epithelium, the multiple cilia in each cell converge odorant receptors in the membrane and orchestrate G-protein coupled receptor signaling in response to environmental stimuli. Many recent reviews have summarized ciliogenesis and signaling pathways in cilia [4-13], motile cilia [14], mechanosensory cilia mechanics [15], cilia as stress and flow sensors [16], and clinical manifestations and diagnosis of neuronal pathology [17,18].

Ciliopathies and associated pleiotropic phenotypes

Kartagener's syndrome was one of the earliest descriptions of a motile cilia disorder [19]. While Bardet–Biedl syndrome (BBS) was recognized as a distinct collection of phenotypes at least 60 years ago [20] and Joubert syndrome (JBTS) as early as 1968 [21], ciliopathies have become recognized to have sensory cilia as a unifying theme only during the last decade [22,23]. Clinical entities that affect motile cilia only, such as Kartagener's syndrome/primary ciliary dyskinesia, manifest *situs inversus*, bronchiectasis and sinus/respiratory complications, but lack other clinical features commonly seen in ciliopathies. The etiology of primary ciliary dyskinesia lies in genetic defects that inactivate selected molecular motors or structures within the cilia critical for motility, usually in dyneins or radial spoke components [24], thereby explaining more uniform and limited manifestations. Interestingly, defects in the sensory ciliopathies encompass a broader spectrum of gene functions including cilia biogenesis and structure, receptor trafficking and signaling, implying that sensory roles of cilia are more complex and critical to life.

Ciliopathies share an overlapping conglomeration of features, exhibiting retinal degeneration, cognitive impairments, cerebellar dysmorphogenesis, kidney cysts, hepatic fibrosis, polydactyly, situs inversus, obesity, skeletal/thoracic dysmorphology, genitourinary defects, cardiorespiratory abnormalities, neural tube patterning defects, and/or hydrocephalus (Figure 1) [25-27]. Although various syndromes may have unique symptom clusters, the distinction among clinical entities is often blurred. Clinical diagnosis alone thus provides little insight into disease etiology. Adding molecular diagnosis to classical clinical findings can be valuable in clarifying possible pathogenic mechanism(s). For example, the distinction between nephronophthisis (NPHP) and Senior–Løken syndrome (SLSN) depends on the presence of retinal findings in SLSN; however, individuals in NPHP pedigrees can also manifest ocular defects [28]. Similarly, the distinction between COACH syndrome (Joubert syndrome with congenital hepatic fibrosis) and JBTS is blurry. With a goal to establish a link between clinical features, syndromes, and genetic causes, we have summarized relevant details of many ciliopathies and their causative genes based on information from the Online Mendelian Inheritance in Man database in Figure 1.

In contrast to motile cilia, sensory cilia are uniquely modified to carry out a particular function in a specific organ. As each tissue is designed to mediate a different sensory function, the associated pathways are more complex and slow to unravel (see Table 1). To comprehend the significance of cilia involvement, it would be helpful to delineate the pathological process in each tissue; for example, kidneys may have either massive polycystic disease or glomerulonephritis, differing pathologies that probably represent distinct etiologies. Cellular pathology and dysfunction in sensory ciliopathies may result from absent, shortened or otherwise morphologically abnormal cilia; from normal cilia structure but no transport/function; or from different cell types/tissues affected in various conditions. In photoreceptors, for example, mutations in various ciliopathy genes result in a number of distinct phenotypes, ranging from complete failure of connecting cilium formation [29] and curtailed outer segment biogenesis [30], to abnormalities of disc assembly [31]. All of these defects should eventually be traceable to a stage in ciliogenesis, transport or maintenance. Photoreceptors thus offer a unique opportunity to evaluate the contribution of ciliary proteins.

Photoreceptor structure, modified cilium and transport

The dense stacks of rhodopsin-laden discs in photoreceptor outer segments represent a highly complex and unique example of sensory cilia specialization, enlarged to house the machinery of phototransduction. As the vast majority of photoreceptors in mouse and human retina are rods, our remarks are directed primarily towards rod photoreceptors. Four ciliary compartments can be defined in photoreceptors, based on expression and other studies (Figure 2 and legend); these include the distal cilium (operationally defined as the domain occupied by Rp1 and Mak), the proximal cilium or transition zone (known

GENES	BBS	MKS	JBTS	NPHP	SLSN	LCA/RP	COACH	MKKS	JATD	ALMS	PKD
BBS1	✓										
BBS2	✓										
BBS4	✓										
BBS5	✓										
BBS7	✓										
BBS9 /PTHB1	✓										
BBS10/C12ORF58/ FLJ23560	✓										
TRIM32 /BBS11	✓										
BBS12	✓										
MKKS/BBS6	✓							✓			
ARL6 /BBS3/RP55	✓					✓					
TTC8/ BBS8/RP51	✓					✓					
WDPCP/C2ORF86/ BBS15/FRITZ	✓	(✓)									
MKS1 /BBS13	✓	✓									
CEP290/NPHP6/ BBS14/JBTS5	✓	✓	✓	✓	✓	✓					
TMEM67/MKS3/ JBTS6/NPHP11	(✓)	✓	✓	✓			✓				
RPGRIP1L/JBTS7/ NPHP8/MKS5		✓	✓	✓		✓	✓				
CC2D2A /JBTS9/MKS6		✓	✓				✓				
TMEM216 /MKS2/JBTS2		✓	✓								
NPHP3 /MKS7		✓		✓							
TCTN2 /MKS8		✓									
B9D1 /MKS9		✓									
B9D2 /MKS10		✓									
NPHP1/JBTS4/ SLSN1			✓	✓	✓						
TTC21B/JBTS11/ NPHP12/ATD4			✓	✓					✓		
ARL13B /JBTS8 (ARL2L1)			✓								
INPP5E /JBTS1			✓								
AHI1 /Jouberin/JBTS3			✓								
KIF7 /JBTS12	(✓)		✓								
TCTN1 /JBTS13			✓								
OFD1/CXORF5 /JBTS10			✓								
SDCCAG8 /SLSN7/NPHP10				✓	✓						
NPHP4/SLSN4				✓	✓						
GLIS2/NPHP7				✓							
WDR19/ NPHP13/ATD5				✓					✓		
NEK8 /NPHP9				✓							
INVS/NPHP2				✓							
IQCB1/NPHP5/ SLSN5					✓	✓					
RPGR /RP3						✓					
LCA5/lebercilin						✓					
RP1						✓					
RP2						✓					
RPGRIP1						✓					
MAK						✓					
ATD1									✓		
IFT80/ATD2									✓		
DYNC2H1/ATD3									✓		
ALMS1										✓	
PC1 (PKD1)											✓
PC2 (PKD2)											✓

Figure 1 (See legend on next page.)

(See figure on previous page.)
Figure 1 Ciliopathy genes with syndromic manifestations. Information from Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim). ALMS, Alstrom syndrome; BBS, Bardet–Biedl syndrome; COACH, Joubert syndrome with congenital hepatic fibrosis; JATD, Jeune asphyxiating thoracic dystrophy; JBTS, Joubert syndrome; LCA/RP, Leber congenital amaurosis/retinitis pigmentosa; MKKS, McKusick-Kaufman syndrome; MKS, Meckel–Gruber syndrome; NPHP, nephronophthisis; PKD, polycystic kidney disease; SLSN, Senior–Lø1ken syndrome.

in photoreceptors as the connecting cilium), the basal body, and the periciliary ridge complex or periciliary membrane complex [75,76], which is analogous to what is referred to as the ciliary pocket in general cilia literature [77]. Expression of ciliopathy-associated proteins is generally restricted to one of these four domains (Figure 2). Thus, it is now possible to divide ciliopathy proteins by discrete anatomical localization and to contemplate understanding molecular mechanisms based on precise expression data from confocal images. These proteins are identified as being expressed in specific compartments. Axo: INV/NPHP2 [43], NPHP3 [43], NPHP9/NEK8 [43], RP1, SDCCAG8 [78], MAK [79]; TZ/CC: NPHP1 [43], NPHP4 [43], NPHP8/RPGRIP1L [43], NPHP5/IQCB1 [43], NPHP6/CEP290 [43], RPGR RPGRIP1 [80-82], AHI1 [83], RP2 [84], Lebercilin [85], IFT88 [85]; BB: BBS1, BBS2, BBS3, BBS4, BBS5, BBS7, BBS9, MKKS/BBS6 [31]; PC/PCC: USH2A/usherin [75], DFNB31/USH2D/whirlin, [75], VLGR1 [75]. Having immuno-electron micrograph images of protein expression in relationship to microtubule bundles, basal body, and transition zone will further advance our understanding of protein function.

Compartment 1, the distal cilium or axoneme, contains proteins that primarily modulate cilium length; these include MAK [79], RP1 [87], RP1L1 and IFT20 [88]. In photoreceptors, compartment 1 delineates the base of the outer segment (Figure 2B,E). Compartment 2 is referred to as the connecting cilium in photoreceptors and is equivalent to the transition zone of motile and primary cilia. Proteins in this zone include CEP290 [30,89-91], RPGR [30,92-99], RPGRIP1 [80], RPGRIP1L [100-105], IFT88 [106-108], KIF3A [109], KIF7 [110], and LCA5/Lebercilin [85]. Although intraflagellar transport proteins mediate ciliary transport along the length of the cilium, antibody localization via immunohistochemistry identifies them in specific compartments. We believe that the appearance of being concentrated in a particular subzone may reflect a bottleneck in transit. Compartment 3 comprises the basal bodies and the pericentriolar material. The proteins in this domain include BBS1 [111], BBS4 [111], BBS3 [112], MKKS [113], TTC8/BBS8 [114], and RAB8A [115]. In addition to these three core compartments, a peripheral component contributing to ciliopathies is the periciliary ridge (Compartment 4). The analogous structure in non-photoreceptor cells is the ciliary pocket [77]. The periciliary ridge was originally described in frog photoreceptors by scanning electron microscopy [76]. The same structure is not visible in mammalian photoreceptors; however, three USH2 proteins (usherin, whirlin and VLGR1) mark a functionally equivalent region, referred to as the periciliary membrane complex, to indicate a highly specialized membrane microdomain [75,116]. Distal to the basal body are structures called rootlets, which provide support for the basal bodies and cilia. A notable

Table 1 Molecular pathways associated with ciliary pathology in each affected tissue

Organ/tissue/cell type	Signaling/biogenesis pathway(s)Wnt, Shh, PDGF, PCP	Reviews and other references
Retina – photoreceptors	Ciliogenesis and transport	[32,33] [34]
Cognition – brain	GPCR trafficking to neuron cilia	[35,36] JBTS: [37] [38,39]
Cerebellum – granule cells?	IFT, Wnt, Shh	[40-42]
Kidney cysts	Wnt/PCP, Shh, mTOR, Ca^{2+}; mechanosensation, fluid pressure, proliferation	[43-50]
Hepatic fibrosis[a]	Ductal plate malformation – PCP?; receptors expressed on cilia; cysts – hyperproliferation	[51-57] [46]
Polydactyly	Shh	[58]
Situs inversus	Nodal, PCP	[59]
Obesity	Neuronal cilia receptors Shh	[60] [46]
Skeletal/thoracic	Mechanical sensation, Shh, IFT	[58,61-66]
Genitourinary	Ca^{2+}	[67]
Cardiorespiratory	Heart – Shh, cardiogenesis; lung – primary cilia precede motile cilia	[1,68] [69] [70] [71]
Neural tube defects/ hydrocephalus	Shh, PCP	[72] [73,74]

GPCR, G-protein coupled receptor; IFT, intraflagellar transport; JBTS, Joubert syndrome; PCP, planar cell polarity; PDGF, platelet-derived growth factor. [a]Note the importance of distinguishing primary (for example, PCP/ductal plate malformation) and secondary (for example, hepatic fibrosis and congestion) characteristics.

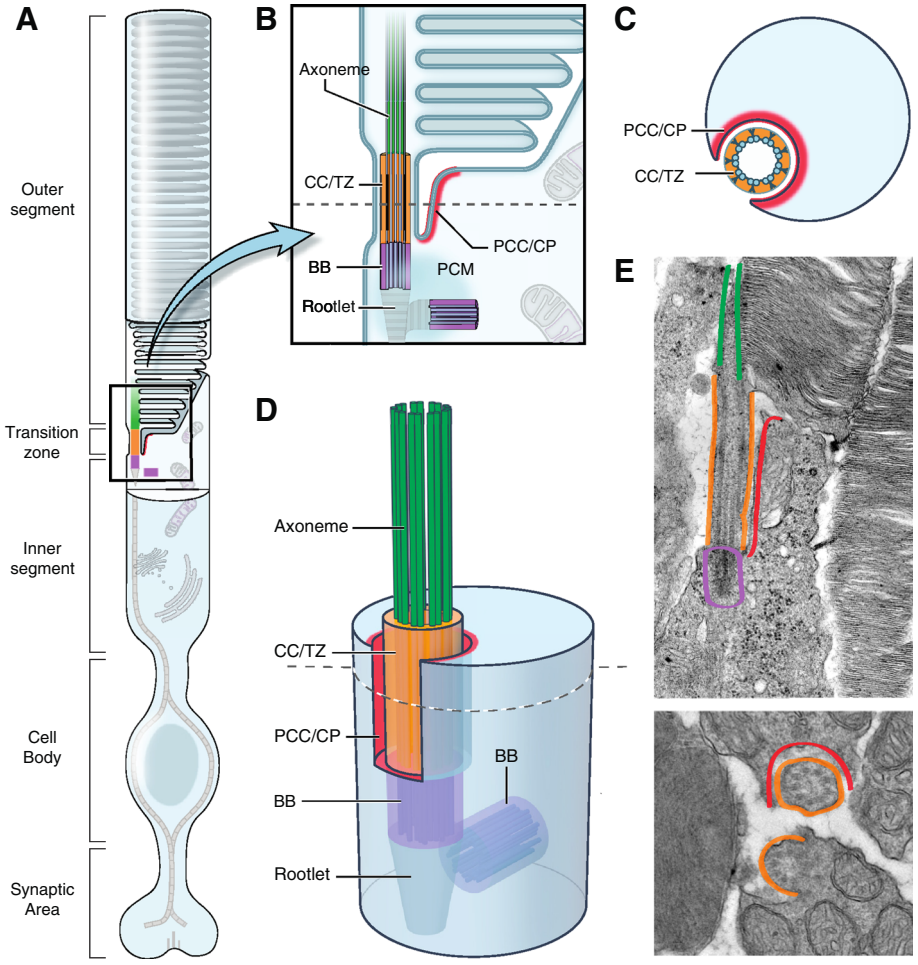

Figure 2 Four distinct compartments in photoreceptor primary cilia, indicating known proteins that define their respective extent. The four compartments are: (1) distal cilium or axoneme (Axo; green); (2) connecting cilium/transition zone (CC/TZ; orange); (3) basal body (BB; purple); and (4) periciliary complex or ciliary pocket (PCC/CP; red). These compartments serve discrete functions in the cilium. (**A**) Schematic of a photoreceptor, showing specialized domains of the cell. The primary cilium elaborates into stacks of outer segment disks packed with rhodopsin, which serves as the primary light sensors of the cell. (**B**) Enlargement of the photoreceptor transition zone in two dimensions showing the four structural and functional domains in which most ciliary proteins are expressed. These domains are identified by known protein markers, such as acetylated α-tubulin (Axo + CC/TZ) and γ-tubulin (BB). Note: illustration of outer segment is based on a traditional model of disc morphogenesis in which nascent discs are open to the extracellular milieu, but a newer model posits that new discs form within the enclosure of outer segment plasma membrane [86]. (**C**) Cross-section through the CC/TZ of the photoreceptor showing the relationship between the microtubules of the cilium and the inner segment, via the PCC/CP. (**D**) Three-dimensional representation of the transition zone and adjacent domains shown in (B). Note the manner in which the PCC surrounds the TZ. Note also that the TZ is the one compartment that contacts all other compartments. (**E**) Electron micrographs showing longitudinal (top) and cross-section (bottom) views of mouse photoreceptors. Functional domains are highlighted with the corresponding colors shown in the other panels.

protein in this compartment is CROCC (rootletin) [117]. While several not strictly ciliary proteins have been included in the list of ciliopathy proteins (Figure 1) as mutations in these cause cilia-related phenotypes, a number of cilia proteins are not included – for example, trafficked cargos that are integral for outer segment function or cytoskeletal proteins that are general features of all ciliated cells.

Knowing the compartmental localization of individual proteins within the cilium will lead to new insights into cilia biogenesis and function. For example, groups of cilia proteins expressed in the same compartment, such as CEP290 and RPGR, may function in related pathways (Figure 3). Other documented interactions between proteins expressed in adjacent compartments (CEP290 and MKKS [31]; NPHP1 and NPHP4 [43]; RPGR and USH2 [118]) might provide clues to how proteins in different compartments cooperate in mediating transport or signaling. Interesting and non-exclusive possibilities are: the expression patterns indicate pools of protein accumulation

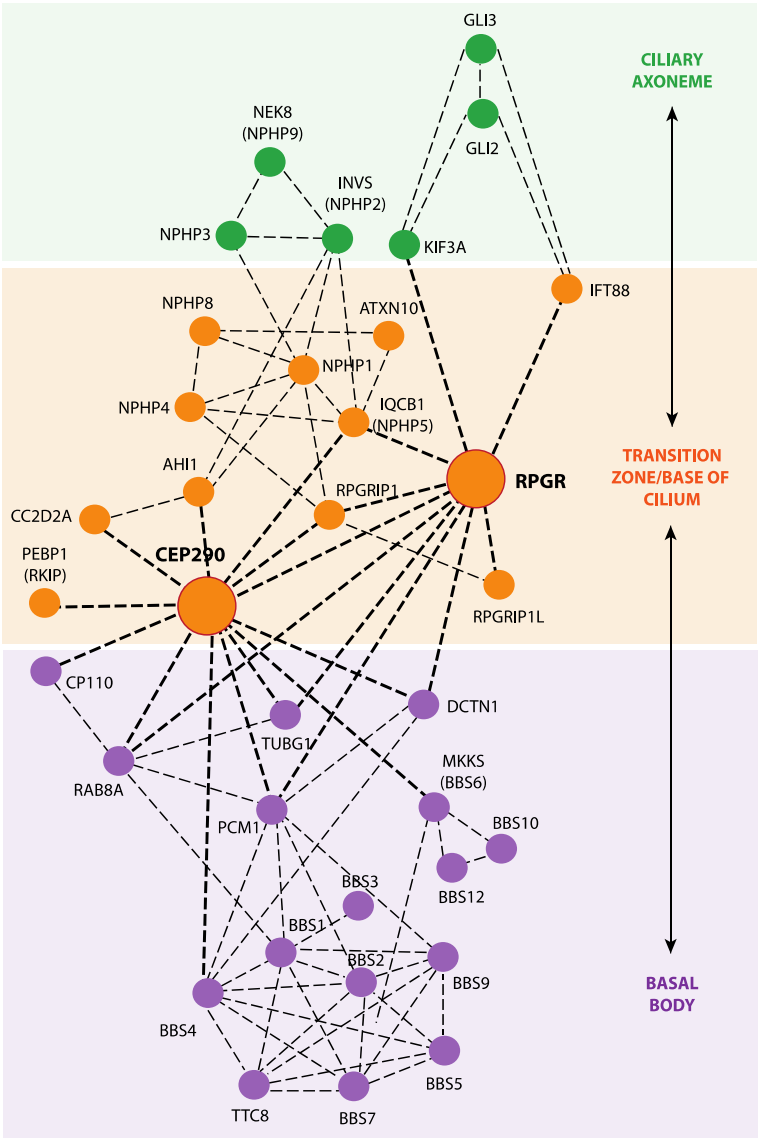

Figure 3 Interactome of ciliary proteins directly or indirectly connected to CEP290 and RPGR. Ciliary proteins directly (bold dotted lines) or indirectly (thin dotted lines) connected to CEP290 and RPGR. Ciliary expression domains are colored as in Figure 2. This network shows representative interactions.

rather than absolute boundaries; a system of protein relays transports cargo or signaling from the cell body to the cilia and back; interacting proteins are part of larger multi-protein complexes with overlapping boundaries; and/or discrete molecules of a given protein (for example, CEP290) form complexes within its primary compartment (transition zone), while other CEP290 domains interact with separate complexes in other compartments (for example, basal body). Given the predicted three-dimensional structure of CEP290 as a long, fibrillar coiled-coil protein, and the plethora of its interactors (Figure 3), a central role in transport and communication is suspected.

Retinal degeneration in clinical ciliopathies

Loss or dysfunction of photoreceptors is a moderately penetrant phenotype in ciliopathies. In the clinic, the retinal defect is called retinitis pigmentosa (RP), and in cases with an early childhood onset clinicians frequently give the diagnosis of Leber congenital amaurosis (LCA). Differences among ciliopathy phenotypes reflect both the causative gene and specific mutations within each gene. Retinal degeneration in BBS [25,119] tends to be slower compared with other ciliopathies. Patients with Meckel–Gruber syndrome have severe neural tube closure defects and early lethality; vision is thus not generally assessed in

these patients [120,121]. Many JBTS patients develop a degree of childhood vision impairment [101,110,120]. Alstrom syndrome patients develop vision loss in young adulthood [122]. Like JBTS cases, patients with SLSN tend to exhibit early vision loss [34,123-125]. Visual impairment in a child can be the presenting feature of Jeune syndrome (Jeune asphyxiating thoracic dystrophy) [126].

Mouse models of human ciliopathies with retinal degeneration

Integration of biochemical, cell biologic, protein interactions and human genetic/clinical datasets with genetic mutations in mice provides deeper insight into each gene function as it relates to cilia and pathogenic processes. Animal studies can also explain the pleiotropic nature of ciliopathies and apparent variability in clinical and disease manifestations; these may include spatial/temporal expression pattern differences, functional redundancies and variations in genetic background. Moreover, cell-based and gene-based therapies can be evaluated for toxicity and therapeutic value before moving to larger animal (dog, primate) and human studies. A large number of ciliopathy mouse models with retinal degeneration have been reported and are summarized in Table 2. Here, we focus on two ciliopathy genes involved in retinal dystrophy: CEP290, mutations in which cause up to 15 to 25% of LCA [127]; and RPGR, the most common cause of X-linked RP and one of the most frequent causes of all forms of RP [128,129].

CEP290 mutations lead to a range of ciliopathy syndromes with variable clinical manifestations in humans [121,166-168] (Figure 1). Many patients present with full-spectrum ciliopathy yet select alleles cause only rapid photoreceptor degeneration (LCA) [89,127,169]. A hypomorphic allele of *Cep290*, *rd16*, has been described in mice [30]; $Cep290^{rd16/rd16}$ mice show rapid degeneration of rod photoreceptors beginning around postnatal day 14 and leaving only residual cones by postnatal day 28 [89]. Slower cone loss and preservation of central pathways in $Cep290^{rd16}$ mice provide opportunities for therapy [137]. Aside from the vision loss, the $Cep290^{rd16/rd16}$ mice reveal defective olfactory transport of G proteins leading to anosmia [90] and deafness caused by cochlear hair cell dysfunction [31]. A possible mechanism of photoreceptor cell death in $Cep290^{rd16}$ mice may involve abnormal accumulation of RKIP, the Raf-1 kinase inhibitor, which inhibits cilia formation [91]. Examination of the retinal phenotype of *Rkip*-knockout mice should shed further light on this question [170]. The $Cep290^{rd16}$ allele is probably hypomorphic, given the expression of the protein with an in-frame deletion and a milder phenotype. Based on the human data, a null allele of *Cep290* is expected to have a severe, full-spectrum ciliopathy phenotype, which has recently been confirmed in mice (Rachel RA, Yamamoto EA, Dong L, Swaroop A, unpublished data).

In contrast to *CEP290*, *RPGR* mutations primarily cause retinal degeneration (with a few leading to syndromic phenotypes) [171-173]. The *RPGR* gene produces multiple alternatively spliced transcripts [174-176], all of which encode an N-terminal RCC1-like domain that is structurally similar to the RCC1 protein [177]. One major constitutive isoform spans exons 1 through 19 ($RPGR^{ex1-19}$) and carries a C-terminal isoprenylation site [178]. The other major variant contains exons 1 to 14 and terminates with a large, alternative ORF15 exon ($RPGR^{orf15}$) [128]. The RPGR-ORF15 isoform is expressed predominantly in photoreceptors [92] with some exceptions [179], concentrated in the connecting cilia [95], and appears to be the functionally important in the retina as all disease-causing mutations are present in this variant [129,172,180]. Conventional gene targeting that disrupted the RCC1-like domain abolished the expression of both types of variants in *Rpgr*-knockout mice [95]; however, unlike human patients, the retinal degeneration in this mutant is slow despite defective localization of opsins to photoreceptor outer segments. An abbreviated form of *Rpgr-orf15* transgene seems to reverse the disease phenotype in this line [94]. A naturally occurring mutant mouse (*rd9*) was shown to affect only the orf15 exon of the *Rpgr* gene [149], mimicking a majority of human patients. The retinal degeneration in the *rd9* mutation is also somewhat slow. Interestingly, a recently reported mouse conditional knockout (cko) mutant exhibited relatively earlier onset of retinal disease compared to *Rpgr*-ko and *rd9* [150]. The phenotypes in these mouse mutants are closer to what is expected in patients with $RPGR^{orf15}$ mutations [150,172,180].

Mouse models have been generated for RPGR and CEP290 interactors and related ciliary proteins such as RPGRIP1, NPHP and BBS proteins (Figure 3). Retinal degeneration has been demonstrated in all of these models (Table 2). The retina in these mice reveal ultrastructural defects and provide insights into how cilia proteins contribute to ciliogenesis, the sequence of events in ciliogenesis, and functional interactions among specific proteins. Moreover, we can evaluate the effects of an individual allele on a uniform genetic background in mice. Such a feature allows the engineering of triple and quadruple mutants on a less variable genetic background to enable examination of the contribution of each allele to the phenotype [31,181]. Unexpectedly, such studies have begun to reveal surprising results. Rather than combinations of ciliopathy alleles necessarily resulting in a more severe phenotype, genetic findings reveal more complex relationships among different ciliary proteins. For example, loss of *Dync2h1*, involved in retrograde cilia trafficking, disrupts Sonic hedgehog signaling and cilia formation, yet combining this mutation with heterozygous loss of *Ift172*, an

Table 2 Mouse models of ciliopathies with retinal degeneration[a]

Gene symbol	References for mouse model	Retinal phenotype	Interactors[b]	PR domain expressed
MAK	[79]	60% ONL left at 1 month, 30% at 6 months		Axoneme
KIF3A	[130,131]	Intermediate rate of degeneration; 20% of wild-type ONL thickness by 10 to 12 weeks	DISC1, MAP3K11, PLEKHA5, USP7, PPP1R15A, **RPGR**	Axoneme
RP1	[132-136]	Slow retinal degeneration; ~40% left at 6 months	APC, MAPRE2, MAPRE3, NIF3L1, POLE	Axoneme
CEP290	[30,89,137]	Rapid retinal degeneration; ciliogenesis defects depending on strain	**RPGR**, **IFT88**, PCM1, DCTN1, **BBS4**, MAPK10, GNG13	CC/TZ
AHI1/Jouberin	[83,138,139]	Rapid – starting to go by P12; only 2 to 3 ONL rows by P24. Very few if any OS/IS	SMYD2	CC/TZ
TMEM67/MKS3	[140]	Early and rapid retinal degeneration	**MKS1**	CC/TZ
IFT88/TTC10 Tg737	[106,141]	Similar to *Cep290*^{rd16} – failure of outer segments to elongate	**RPGR**, PRRC2A, SMNDC1, PAN3, SLC9A8	CC/TZ
KIF7	[110,142]	Retina not examined; mice die perinatally	USP22	CC/TZ
LCA5 lebercilin	[85]	Rapid degeneration; between P12 and P28, reduced to 2 to 3 ONL rows. CC develops but little if any OS material.	GRIN2B, OFD1/JBTS10, IFTs	CC/TZ
RP2	[84,143-145]	Only information on function of the protein in transport within cells	UNC119, ARL3, YWHAB, APLP2	CC/TZ
RPGRIP1	[146,147]	Only three rows of ONL nuclei by 3 months of age. Overproduction of outer segments	**RPGR**, NPHP4, TFE3, SRPX, CEBPA	CC/TZ
TCTN1	[148]	Retina not examined; mice die prenatally	MKS1, TMEM216, TMEM67, **CEP290**, B9D1, TCTN2 AND CC2D2A.	CC/TZ
RPGR	[93,95,149,150]	Slow retinal degeneration	**CEP290**, **RPGRIP1**, **IFT88**, **KIF3A**, **RAB8A**	CC/TZ, BB
ALMS1	[151-154]	Slow degeneration – slight reduction in ONL thickness at 24 weeks; loss of OS over time; still some left at 24 weeks by rhodopsin staining	MEGF1, OFD1, TUBGCP2, TUBGCP3, TUBGCP4, **CEP290**(MS)	BB
ARL6/BBS3	[155]	Medium-slow retinal degeneration; hydrocephalus	**BBS1**, ARL6IP1, ARL6IP5, ARL6IP4, ARL6IP6	BB
BBS1	[87,156]	Slow degeneration (3 to 4 rows of ONL nuclei at 6 months); CC present but disrupted OS	BBS9, EEF1A1, ALDOB, ARL6/BBS3, PCM1	BB
BBS2	[157,158]	Slow degeneration – half ONL at 5 months; almost no ONL nuclei by 10 months. OS have typical indistinct, wavy pattern	EEF1A1, ALDOB, BBS7, BBS9	BB
BBS4	[156,159-161]	Intermediate rate of retinal degeneration; 2/3 of ONL remaining at 6 weeks; all PR lost by an unspecified adult age	PCM1, ALDOB, DCTN1, EEF1A1, EPAS1	BB
TTC8/BBS8	[162]	Slow degeneration – ONL half-thickness in the 'adult'. OS maybe longer than wild-type	BBS9, PCM1, **BBS4**, **BBS1**, **BBS2**	BB
MKKS/BBS6	[74,163]	Medium-slow degeneration; bulging, disorganized OS	**CEP290**, PTN, STK16, TGIF1, ICA1	BB and proximal rootlet
RAB8A	[164]	Retinal phenotype has not been examined or published	**RPGR**, RABIF, BAG6, OCRL, RAB10, PQBP1	BB
TRIM32/BBS11	[165]	Retinal phenotype has not been examined or published	ATXN1, UBE2N, SFN, UBQLN4, UBE2V1	N/A

BB, basal body; CC/TZ, connecting cilium/transition zone; ONL, outer nuclear layer; OS/IS, outer segments/inner segments; P, postnatal day; PR, photoreceptors. [a]Selection criteria for inclusion in Table 2: ciliopathy-related (even if no human disease has yet been described); and interaction with Rpgr or Cep290; and/or associated with retinal degeneration.
[b]Data in this column are taken primarily from entries in genecards.org. Genes in bold are CEP290 and/or RPGR interactors.

anterograde motor, results in a milder phenotype. *A priori* this would suggest that neutralizing two opposite forces restores equilibrium; however, reduction of the *Ift122* retrograde motor also represses the *Dync2h1* phenotype [181]. Another indication of complexity in the biogenesis and function of cilia comes from the interaction of Cep290 and Mkks, a *BBS* chaperonin protein. In this scenario, loss of *Mkks* ameliorates the sensory cilia defects in $Cep290^{rd16}$ mutant mice, and *vice versa* [31]. Together these findings suggest a dynamic and delicate equilibrium among opposing forces in cilia function.

Mouse models with long-term photoreceptor survival and intermediate rates of disease progression should provide optimal opportunities for designing and evaluating therapies. Those with extremely rapid degeneration may not allow sufficient time for gene-based or cell-based therapy to show benefit (see, however, results on $Aipl1^{ko/ko}$ [29]), whereas those with very slow degeneration are impractical because of the required time and resource commitment. The *Rpgr*-cko and $Nrl^{ko/ko}/Cep290^{rd16/rd16}$ double mutants display appropriate characteristics for designing treatments of retinal disease caused by *RPGR* and *CEP290* mutations. $Nrl^{ko/ko}/Cep290^{rd16/rd16}$ mice have the $Cep290^{rd16}$ mutation on the background of an all-cone photoreceptor retina due to the loss of *Nrl*; in this model, the cones survive longer than rapidly degenerating rods, allowing a longer window for treatment [89]. The *Rpgr*-cko model displays retinal degeneration that begins during the first months of life, allowing time for treatment options to be tested and evaluated [150].

For most ciliopathies, mouse models fail to completely recapitulate the human phenotype. For example, mouse *Rpgr* mutants exhibit a milder phenotype. At least nine genes have been identified as underlying Usher syndrome; yet most mouse mutants (except whirlin and usherin that cause type II Usher syndrome) bearing one of these mutations develop hearing deficits but not visual dysfunction [182]. In addition, many BBS mouse models do not, in general, develop polydactyly, unlike their human counterparts.

Sources of complexity in ciliopathy classification

Confusion in the nomenclature of ciliopathies originates from pleiotropy of phenotypes and from variations introduced at multiple levels, including transcriptional/translational regulation, protein–protein interactions, and cellular function. Tissue-specific expression of different splice variants or protein isoforms and their subcellular localization contribute to this complexity (see Figure 2), as in the case of RPGR [99,183]. If a gene is required for cilia formation or function in all tissues, one would expect a full-spectrum ciliopathy or prenatal lethality. However, functional redundancy and tissue/cell type selectivity (for example, of $RPGR^{orf15}$ transcript primarily in photoreceptors) would result in a more restricted phenotypic spectrum that is also susceptible to modifier effects. In the sense that a complete disruption of ciliogenesis is incompatible with life, many ciliopathy genes would appear to be only partially required for ciliogenesis or function. Different alleles of the same gene (null vs. hypomorph vs. dominant negative) might exhibit varying severity because of the specific functional modules that are impacted [168,169,184]. Functional redundancy in genes causing a specific syndrome and phenotypic overlap among syndromes contribute greatly to complexity (Figure 1 and Table 2) [185]. Modifier genetic variants that do not cause disease on their own could modulate phenotypic spectrum of a disease-causing allele in a genetically diverse (outbred) population (such as humans) by combining alleles of different genes [103,138,169,186]. This phenomenon seems to occur in particular with BBS [187-190].

Basing diagnosis on a combination of molecular definition and clinical symptoms can help as it would clear up some of the confusion resulting from diagnosis based strictly on phenotypic manifestations. Some ciliopathies are caused by mutations in genes that are primarily associated with non-ciliopathy syndromes (for example, TRIM32/BBS11, NPHP3, and KIF7). These genes are specifically associated with pathology in certain organs; for example, NPHP3 is associated with renal–hepatic–pancreatic dysplasia, BBS11/TRIM32 causes limb girdle muscular dystrophy, and KIF7 causes acrocallosal syndrome – none of these is considered a ciliopathy. Additionally, different signaling pathways and mechanisms may operate in distinct tissues. Exceptions also exist to the rule of motile cilia having a 9 + 2 microtubule configuration and sensory cilia having a 9 + 0 structure [191]. Identifying these various sources and levels of complexity are essential. NPHP and SLSN both have kidney disease, but SLSN includes retinal degeneration; however, some patients with NPHP also have retinal disease. Mutations in only two proteins causing NPHP are so far known to also cause SLSN – that is, only mutations in those two proteins, SDCCAG8 and NPHP4, can cause RP/LCA symptoms in addition to isolated renal pathology (Figure 1). Examining whether these two proteins have retina-specific isoforms would be of interest.

Perspectives and future directions

In this review we have discussed differences between human ciliopathies and their respective mouse models, focusing on CEP290, RPGR and their interactors. We have highlighted the importance of distinct compartments within cilia showing unique patterns of protein expression and their frequent interactions with proteins in the same or adjacent compartments. Given the complexity of these interactions, precise localization and function of each protein should provide valuable insights and testable

hypotheses related to disease mechanisms. We believe that uniform analysis of tissue expression patterns is critical for elucidating the role for each gene in the retina and other relevant cell types. Expression of each isoform should be determined relative to a distinct ciliary compartment. At this stage, it is unclear for most cilia proteins whether a specific isoform is expressed in the same ciliary compartment in each tissue/cell type and whether similar mechanisms and signaling pathways are involved. Standard identifiers should thus be used to illustrate various ciliary components in colocalization studies. Commonly used markers are acetylated α-tubulin and RP1 for the distal cilium and more proximal structures, γ-tubulin for the basal body, Ush2 for the periciliary ridge complex, and rootletin (Crocc) for striated rootlets. Standardizing the data collected for each mutant and in every affected tissue/cell type will allow comparative functional analysis of specific genes. Documenting the histology of the retina with emphasis on the photoreceptor layer is required at distinct stages of degeneration. Electron microscopy in longitudinal sections and cross-sections of the junction between inner and outer segments would be helpful in determining the defects caused by mutations in a specific protein or isoform (see Figure 2). Moreover, a detailed expression pattern with respect to previously defined proteins of specific ciliary compartments will allow more precise localization.

As awareness has grown of the pivotal role of cilia in sensory signaling, various questions persist. Are activated signaling pathways specific for each ciliated tissue or cell type? Do similar multiprotein complexes play similar roles in various tissues? For example, does the composition of BBSome and NPHP–JBTS–MKS complexes [192,193] change in response to microenvironment or required cellular functions in cultured cells versus different tissues? What causes variability in genotype–phenotype correlations? For example, why do only some BBS gene mutations cause both BBS and isolated retinal dystrophy (Figure 1)? Why do only selected NPHP genes additionally cause retinal dystrophy? Do such mutations provide information about which domains of each protein may have tissue-specific functions? CEP290 and RPGR co-localize and both cause LCA/RP. Why then is only CEP290 associated with other syndromic ciliopathies even though RPGR is ubiquitously expressed?

Next-generation sequencing and new proteomics-based approaches are likely to have a major impact on the progress in this field. First, detailed analysis of ciliary localization for each protein in cultured cells and in specific tissues with relevant markers of distinct compartments will refine our understanding of cilia structure and function. Ultrastructural evaluation of photoreceptor basal bodies and connecting cilia and in other ciliated cells in mouse models will provide key information about the role of each protein. With the identification of clusters of interacting proteins [193,194], these interaction networks can be used to define relevant signaling cascades and final common pathways using biochemical and genomic techniques. A better elucidation of ciliary protein networks, their precise functional interactions and downstream signaling events would be relevant for designing therapeutic approaches that are applicable to multiple ciliopathies and pertinent for more than one specific mutation.

Conclusions

Linking clinical diagnosis and nomenclature of ciliopathies with molecular identification depends on understanding how mutations in individual cilia genes contribute to distinct clinical phenotypes. This remains an important area of investigation. Using CEP290 and RPGR as examples of central proteins in the connecting cilium of the photoreceptor, we discuss the clinical phenotypes of mutations in these genes and in those of their interactors to illustrate this principle. We draw attention to the important conclusion that the cilium is comprised of four distinct compartments, each with discrete localization of proteins. By mapping the known interacting partners for CEP290 and RPGR, we find that hubs and disease networks, such as NPHP, BBS, and others, are concentrated in a single ciliary compartment, yet interact with members of other networks in adjacent compartments. A remaining mystery is to understand the significance of discrete localization of proteins (such as intraflagellar transport proteins) that are known to function across compartments, and the manner in which discrete networks (such as BBS and NPHP) interact with each other. These insights provide clues to the sources of complexity and confusion in the study of ciliopathies. We summarize by suggesting avenues of future pursuit that will clarify and expand the current knowledge in the field.

Abbreviations

BB: Basal body; BBS: Bardet–Biedl syndrome; CEP290: Centrosomal protein 290 kDa; Cko: Conditional knockout; COACH: Joubert syndrome with congenital hepatic fibrosis; IFT: Intraflagellar transport; JBTS: Joubert syndrome; LCA: Leber congenital amaurosis; NPHP: Nephronophthisis; RPGR: Retinitis pigmentosa G-protein regulator; SLSN: Senior–Løken syndrome.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors wrote the paper and designed the figures. All authors read and approved the final version of the manuscript.

Acknowledgements

The authors thank colleagues in the Neurobiology-Neurodegeneration & Repair Laboratory for helpful discussions. This research is supported by the intramural research program of the National Eye Institute.

Received: 25 July 2012 Accepted: 19 September 2012
Published: 3 December 2012

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doi:10.1186/2046-2530-1-22
Cite this article as: Rachel *et al.*: Photoreceptor sensory cilia and ciliopathies: focus on CEP290, RPGR and their interacting proteins. *Cilia* 2012 **1**:22.