

Photoreceptor Cilia and Retinal Ciliopathies

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Photoreceptors are sensory neurons designed to convert light stimuli into neurological responses. This process, called phototransduction, takes place in the outer segments (OS) of rod and cone photoreceptors. OS are specialized sensory cilia, with analogous structures to those present in other nonmotile cilia. Deficient morphogenesis and/or dysfunction of photoreceptor sensory cilia (PSC) caused by mutations in a variety of photoreceptor-specific and common cilia genes can lead to inherited retinal degenerations (IRDs). IRDs can manifest as isolated retinal diseases or syndromic diseases. In this review, we describe the structure and composition of PSC and different forms of ciliopathies with retinal involvement. We review the genetics of the IRDs, which are monogenic disorders but genetically diverse with regard to causality.

Photoreceptors are sensory neurons designed to convert light stimuli into electrical responses, a process called phototransduction. Phototransduction takes place in the highly specialized compartment of photoreceptors, the outer segment (OS) (Pearring et al. 2013; Molday and Moritz 2015). The OS of the rod and cone photoreceptors differ in structure and protein composition, related to their functional adaptation, in which rods have high sensitivity necessary in dim light and cones are responsible for the high-resolution color vision working in bright light (Lamb and Pugh 2006; Lamb et al. 2007). Research over the past decade on the genetic and molecular components of photoreceptors in vertebrate retinae has led to the clear recognition that photoreceptor OS are specialized sensory cilia (Liu et al. 2007a; Ramamurthy and Cayouette 2009; Khanna 2015). Deficient

morphogenesis and/or dysfunction of photoreceptor sensory cilia (PSC) caused by mutations in a variety of photoreceptor-specific and common cilia genes can lead to a group of clinical manifestations, called inherited retinal degenerations (IRDs). In this review, we will discuss the structure and composition of PSC and different forms of ciliopathies with retinal involvement.

SPECIALIZED PHOTORECEPTOR SENSORY CILIA

In vertebrate retina, the visual function depends on the formation of complex sensory cilia of rod and cone photoreceptors. Photoreceptors are highly polarized neurons, composed of four distinct compartments: the OS, the inner segment (IS), the nucleus and a short axon extending to second order neurons (bipolar and hor-

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horizontal cells) (Fig. 1) (Kennedy and Malicki 2009; Pearing et al. 2013; Molday and Moritz 2015). OS are ciliary organelles with analogous structure to the primary sensory cilia in other cell types (Rosenbaum and Witman 2002; Liu

et al. 2007a; Ramamurthy and Cayouette 2009; Khanna 2015). The recognition of PSCs as distinct morphological structures is valuable for the study of photoreceptor cell biology and disease pathogenesis. Studies of genes involved in IRDs and other ciliopathies have identified dozens of novel components of the PSCs. A comprehensive proteomic study of mouse PSCs has identified ~2000 proteins in this organelle, out of which hundreds are present in other cilia (Liu et al. 2007a). These findings have greatly improved our understanding of how photoreceptor cilia are built and maintained, and how these processes are disrupted in disease.

Ciliary Backbone of PSC

The structure of the PSC is analogous to other cilia, where the axoneme arises from the basal body through the transition zone (also called the “connecting cilium”) and extends up to two-thirds of the OS (Fig. 1) (De Robertis 1956; Kaplan et al. 1987). The basal body also nucleates the ciliary rootlet, which extends into the IS, and which is covalently linked to the PSC structure (Yang et al. 2005; Liu et al. 2007a). The basal body contains nine triplet microtubules, two of which extend further to form the axoneme and the third anchors transition fibers linking the basal body to the plasma membrane. The nine doublet microtubules in the transition zone are cross-linked to the surrounding plasma membrane by Y-link structures (Besharse et al. 1985; Horst et al. 1990). These Y-link structures are absent in the rest of the axoneme. The transition zone of rods and cones measures ~0.3 μm in diameter and 1–1.5 μm in length, which is fairly consistent throughout the species (Besharse et al. 1985). This structure was originally called the “connecting cilium” by De Robertis in 1956, when he was studying some of the first electron micrographs of photoreceptor cells (De Robertis 1956). However, as an analogy with other primary sensory cilia, we refer to this region as a transition zone. Above the transition zone, disc morphogenesis takes place where the surrounding plasma membrane transforms into the disc precursors through membrane evagina-

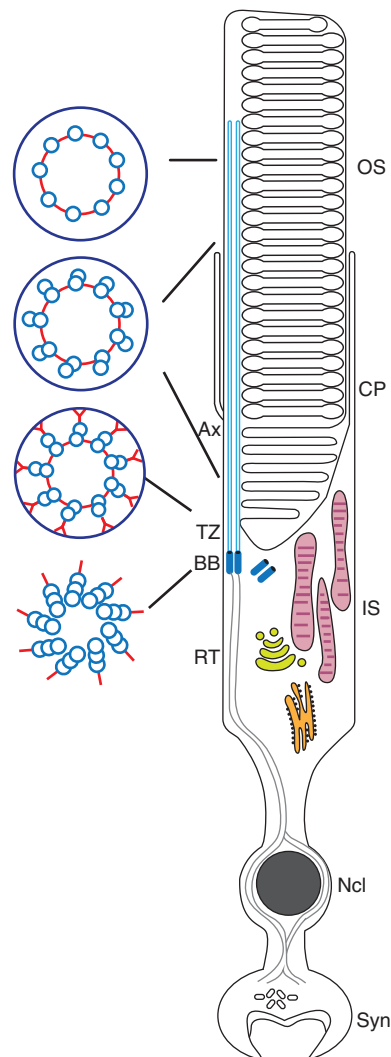


Figure 1. Photoreceptor structure. Schematic representation of the rod photoreceptor with sensory cilia components indicated. The drawings to the left of the photoreceptor represent the cross-sectional view of the microtubule structure of the distal axoneme (Ax), proximal Ax, transition zone (TZ), and basal body (BB). RT, rootlet; OS, outer segment; CP, calyceal process; IS, inner segment; Ncl, nucleus; Syn, synapse.

tion (Steinberg et al. 1980; Ding et al. 2015; Pugh 2015). At the distal part of the PSC axoneme, the double microtubules are reduced to singlets (Fig. 1) (Rosenbaum and Witman 2002; Pearing et al. 2013).

Other Structural Components of Outer Segments

PSCs are highly specialized sensory cilia, adapted for light detection by the presence of tightly packed membranous discs containing visual pigments and other phototransduction proteins (Sjostrand 1953; Nickell et al. 2007; Gilliam et al. 2012). PSCs are among the largest of mammalian cilia (Pan et al. 2005) and, like other cilia, they are comprised of a cytoskeleton backbone and a membrane domain, which is distinct from the surrounding plasma membrane (Steinberg et al. 1980; Molday and Molday 1987). In murine rods, the numerous membranous discs in the PSC compartment are stacked at a density of ~ 30 discs per micrometer, which is thought to be constant throughout species (Nickell et al. 2007; Gilliam et al. 2012). Such OS organization provides a large surface area for optimized photon capture and rapid signal transduction reactions to occur. Rhodopsin is the most abundant disc membrane protein, organized as rows of dimers with a density of $\sim 48,000$ monomers per μm^2 (Fotiadis et al. 2003). With this high density in the disc membranes, rhodopsin plays an important structural role apart from being the main visual pigment in the retina (Wang and Deretic 2014). The rim of the photoreceptor discs contains two tetraspanins: Rds/peripherin-2 (PRPH2) and retinal OS membrane protein 1 (ROM1), which facilitate the folding of the OS discs and are crucial for rim formation and sorting of the OS proteins during the OS biogenesis (Molday et al. 1987; Goldberg and Molday 1996; Arikawa et al. 2011). PRPH2 and its homolog ROM1 both form homodimers and then associate together to form tetrameric complexes, exclusively present at the disc rims (Molday et al. 1987; Goldberg and Molday 1996; Arikawa et al. 2011). Two other membrane proteins prominin 1 (PROM1) and cadherin-related family mem-

ber 1 (CDHR1) were associated with the open lamellar evaginations in rod and cone discs in *Xenopus laevis* and mice, respectively (Rattner et al. 2001; Han et al. 2012). PSC are responsible for mediating the sensory transduction of the visual system with a number of proteins involved in this process, including the above-mentioned rhodopsin. Most of these proteins are expressed specifically in PSC and, when mutated, cause nonsyndromic IRDs (Table 1) (Dryja et al. 1990; Farrar et al. 1990; Kajiwara et al. 1991, 1994; Travis et al. 1991; Bascom et al. 1992; Rosenfeld et al. 1992; Dryja et al. 1993; Maw et al. 2000; Yang et al. 2008). Studies of mutant animals have shown that the above-mentioned proteins are essential for OS disc morphogenesis and maintenance (Sanyal et al. 1980; Clarke et al. 2000; Rattner et al. 2001; Dellett et al. 2015).

PROTEIN TRANSPORT TO PSC

A unique feature of the photoreceptor OS is the high level of its renewal. Each day $\sim 10\%$ of the OS is shed from the distal tip, which is replaced by new disc formation at the base of the PSC (Young 1967). This necessitates a robust system of protein synthesis in the IS and efficient trafficking of selected proteins to the photoreceptor OS.

Intraflagellar Transport in PSC

The axoneme, initiated at the mother centriole, is built and maintained by extending its distal (+) end (Pedersen and Rosenbaum 2008). Because protein synthesis occurs in the IS, the axoneme building blocks need to be transported to the distal end via intraflagellar transport (IFT) (Rosenbaum and Witman 2002; Pedersen and Rosenbaum 2008; Taschner et al. 2012). The anterograde transport from the base to the tip of the axoneme is mediated by IFT complex B (IFT-B), where kinesin-2 is the motor protein (Rosenbaum and Witman 2002). Kinesin-2 is a heterotrimeric protein composed of Kif3A, Kif3B, and KAP, which is further associated with 14 other IFT proteins that bind cargo molecules (Taschner et al. 2012). Once the axoneme

Table 1. Genes associated with nonsyndromic retinal degeneration

Gene	Inheritance pattern	Nonsyndromic form	Syndromic form	Notes and references
Genes coding axoneme-associated proteins				
<i>ARL6</i>	AR	RP	BBS	New retina-specific exon present (Chiang et al. 2004; Fan et al. 2004; Aldahmesh et al. 2009; Pretorius et al. 2010)
<i>BBS1</i>	AR	RP	BBS	Nishimura et al. 2001; Mykytyn et al. 2002; Estrada-Cuzcano et al. 2012a
<i>BBS2</i>	AR	RP	BBS	Consugar et al. 2014; Shevach et al. 2015
<i>BBS9</i>	AR	RP	BBS	Nishimura et al. 2005; Abu-Safieh et al. 2012
<i>C2orf71</i>	AR	RP	-	Putative cilia function, exclusive eye expression (Collin et al. 2010; Nishimura et al. 2010; Kevany et al. 2015)
<i>C8orf37</i>	AR	RP	BBS	Estrada-Cuzcano et al. 2012b; Heon et al. 2016; Khan et al. 2016
<i>CEP164</i>	AR	LCA	SLS	Chaki et al. 2012
<i>CEP290</i>	AR	LCA	BBS, JBS, MKS, SLS	den Hollander et al. 2006; Sayer et al. 2006; Valente et al. 2006; Baala et al. 2007a; Helou et al. 2007; Frank et al. 2008; Leitch et al. 2008
<i>CLRN1</i>	AR	RP	USH	Joensuu et al. 2001; Khan et al. 2011
<i>FAM161A</i>	AR	RP	-	Bandah-Rozenfeld et al. 2010; Langmann et al. 2010
<i>IFT140</i>	AR	RP, LCA	JATD, MZSDS	Perrault et al. 2012; Schmidts et al. 2013a; Bifari et al. 2015; Xu et al. 2015
<i>IFT172</i>	AR	RP	BBS, JATD, MZSDS	Halbritter et al. 2013; Bujakowska et al. 2014
<i>IQCB1</i>	AR	LCA	SLS	Otto et al. 2005; Estrada-Cuzcano et al. 2011; Stone et al. 2011
<i>KIZ</i>	AR	RP	-	El Shamieh et al. 2014
<i>LAC5</i>	AR	LCA	-	den Hollander et al. 2007
<i>MAK</i>	AR	RP	-	Ozgül et al. 2011; Tucker et al. 2011
<i>NEK2</i>	AR	RP	-	Nishiguchi et al. 2013
<i>OFD1</i>	XL	RP	OFD, JBS	Ferrante et al. 2001; Coene et al. 2009; Webb et al. 2012
<i>RAB28</i>	AR	CRD	-	Roosing et al. 2013
<i>RP1</i>	AR, AD	RP	-	Guillonnet et al. 1999; Pierce et al. 1999
<i>RP1L1</i>	AR, AD	RP, OMD	-	There are some doubts about this gene being truly associated with IRD, because this gene is highly polymorphic and some mutations were seen in the

Continued

Table 1. Continued

Gene	Inheritance pattern	Nonsyndromic form	Syndromic form	Notes and references
				controls (Bowne et al. 2003; Yamashita et al. 2009; Akahori et al. 2010; Davidson et al. 2013)
<i>RP2</i>	XL	RP	-	Hardcastle et al. 1999; Mears et al. 1999
<i>RPGR</i>	XL	RP, CD, MD	RP with hearing loss and sinorespiratory infections	Extraocular phenotypes may not be related to <i>RPGR</i> , because it mapped to a 43.6-Mb interval with 215 genes including <i>OFD1</i> (Meindl et al. 1996; Roepman et al. 1996; Ayyagari et al. 2002; Yang et al. 2002; Zito et al. 2003)
<i>RPGRIP1</i>	AR	LCA, CRD	-	Dryja et al. 2001; Hameed et al. 2003
<i>SPATA7</i>	AR	LCA, RP	-	Wang et al. 2009
<i>TOPORS</i>	AD	RP	-	Chakarova et al. 2007, 2011
<i>TTC8</i>	AR	RP	BBS	Ansley et al. 2003; Riazuddin et al. 2010
<i>USH2A</i>	AR	RP	USH	Eudy et al. 1998; Rivolta et al. 2000
<i>WDR19</i>	AR	RP	SLS, CED, JATD	Bredrup et al. 2011; Coussa et al. 2013
Other structural OS proteins				
<i>CDHR1</i>	AR	CRD		Henderson et al. 2010; Ostergaard et al. 2010
<i>EYS</i>	AR	RP		Abd El-Aziz et al. 2008; Collin et al. 2008
<i>FSCN2</i>	AD	RP, MD		There are some doubts about this gene being truly associated with IRD, because a frameshift c.208delG is a common polymorphism in the Asian population (Wada et al. 2001, 2003; Zhang et al. 2007; Shin et al. 2010)
<i>PROM1</i>	AR, AD	RP, MD		Maw et al. 2000; Yang et al. 2008
<i>PRPH2</i>	AD, digenic with ROM1	RP, MD		Kajiwara et al. 1991, 1994; Travis et al. 1991
<i>ROM1</i>	AD, digenic with ROM1	RP		Bascom et al. 1992; Kajiwara et al. 1994
<i>TULP1</i>	AR	RP		Banerjee et al. 1998; Hagstrom et al. 1998; Larsson et al. 1998
Genes involved with the POS sensory function (phototransduction cascade and retinoid cycle in the photoreceptors)				
<i>ABCA4</i>	AR	STGD, RP, CRD		Allikmets et al. 1997; Sun and Nathans 1997; Cremers et al. 1998; Martínez-Mir et al. 1998
<i>CNGA1</i>	AR	RP		Dryja et al. 1995
<i>CNGA3</i>	AR	ACHR		Kohl et al. 1998

Continued

Table 1. *Continued*

Gene	Inheritance pattern	Nonsyndromic form	Syndromic form	Notes and references
<i>CNGB1</i>	AR	RP		Bareil et al. 2001
<i>CNGB3</i>	AR	ACHM, CD		Kohl et al. 2000
<i>GNAT1</i>	AD, AR	CSNB		Dryja et al. 1996
<i>GNAT2</i>	AR	ACHM		Aligianis et al. 2002; Kohl et al. 2002
<i>GRK</i>	AR	CSNB		Yamamoto et al. 1997
<i>GUCA1A</i>	AD	CD, CRD		Payne et al. 1998; Sokal et al. 1998
<i>GUCA1B</i>	AD	RP, MD		Sato et al. 2005
<i>GUCY2D</i>	AR, AD	LCA, CRD		Perrault et al. 1996; Kelsell et al. 1998
<i>OPN1LW</i>	XL	Deuteranopia, blue cone monochromacy		Nathans et al. 1986; Winderickx et al. 1992; Ayyagari et al. 1999
<i>OPN1MW</i>	XL	Protanopia, blue cone monochromacy		Nathans et al. 1986; Ayyagari et al. 1999
<i>OPN1SW</i>	AD	Tritanopia		Nathans et al. 1992; Weitz et al. 1992a,b
<i>PDE6A</i>	AR	RP		Huang et al. 1995
<i>PDE6B</i>	AR, AD	RP, CSNB		McLaughlin et al. 1993; Gal et al. 1994
<i>PDE6C</i>	AR	CD, ACHM		Thiadens et al. 2009
<i>PDE6G</i>	AR	RP		Dvir et al. 2010
<i>RDH12</i>	AR, AD	LCA, RP		Janecke et al. 2004; Perrault et al. 2004; Fingert et al. 2008
<i>RGS9</i>	AR	Delayed cone adaptation		Nishiguchi et al. 2004
<i>RGS9BP</i>	AR	Delayed cone adaptation		Nishiguchi et al. 2004
<i>RHO</i>	AD, AR	RP, CSNB		Dryja et al. 1990; Farrar et al. 1990; Rosenfeld et al. 1992; Dryja et al. 1993
<i>SAG</i>	AR	RP, CSNB		Fuchs et al. 1995; Nakazawa et al. 1998

ACHM, Achromatopsia; BBS, Bardet–Biedl syndrome; CD, cone dystrophy; CED, cranioectodermal dysplasia, also known as Sensenbrenner syndrome; CRD, cone–rod dystrophy; CSNB, congenital stationary night blindness; JBS, Joubert syndrome; JATD, Jeune asphyxiating thoracic dystrophy; LCA, Leber congenital amaurosis; MKS, Meckel–Gruber syndrome; MZSDS, Mainzer–Saldino syndrome; OFD, oral–facial–digital syndrome; OMD, occult macular dystrophy; RP, retinitis pigmentosa; SLS, Senior–Løken syndrome; STGD, Stargardt disease; USH, Usher syndrome.

and other PSC components have been delivered to the tip of the cilium, the IFT-B components are recycled back to the base of the cilium by retrograde transport mediated by IFT complex A (IFT-A) (Rosenbaum and Witman 2002). Dynein-2 is the motor protein of IFT-A and it is associated with six other IFT proteins (Taschner et al. 2012). Apart from the IFT complexes, Bardet–Biedl syndrome proteins (BBSome) are

also involved in the transport of membrane proteins to the cilium (Taschner et al. 2012; Williams et al. 2014).

Because 10% of the PSC is shed and renewed every day, the necessity for the retrograde transport in this cell type was not clear. However, identification of IRD patients with mutations in genes coding for retrograde transport proteins (e.g., *TTC21B*) and pro-

teins involved in switching from anterograde to retrograde IFT direction (e.g., *IFT172*) underlines the importance of transport in both directions for the development and maintenance of PSC (Liu et al. 2010; Davis et al. 2011; Halbritter et al. 2013; Bujakowska et al. 2014).

Transport of Membrane Proteins to PSC

Even though the plasma membrane surrounding the photoreceptor cilium is continuous with the plasma membrane of the cell body, its protein composition is different. In addition, the membranous discs in the rod photoreceptors are distinct from the surrounding plasma membrane (Steinberg et al. 1980; Molday and Molday 1987). This selective protein content in PSC membranes is established by diffusional barriers present at the base of the cilium and within the transition zone (Pearing et al. 2013; Wang and Deretic 2014; Khanna 2015). The molecular composition of the diffusional barrier is not fully understood, although certain proteins like Septin 2 and CEP290 are thought to play an important role (Pearing et al. 2013; Wang and Deretic 2014).

Because rhodopsin is the most abundant protein in the PSC, its photoreceptor OS transport has been studied in detail. After synthesis in the IS endoplasmic reticulum and transport through the Golgi and *trans*-Golgi network, rhodopsin is sorted into vesicles destined for the OS. This is achieved thanks to the presence of specific sequence signatures (e.g., VXPX and FR motifs), which facilitate interaction with a ciliary targeting molecules Arf4 and ASAP1 (Deretic et al. 2005; Wang and Deretic 2014). Further interaction with FIP3 and small GTPases Rab6, Rab8, and Rab11 directs the vesicle to the base of the OS for fusion with the membrane (Deretic et al. 2005; Pearing et al. 2013; Wang and Deretic 2014). Further, rhodopsin molecules are transported through the transition zone to the site of the disc morphogenesis by two motor proteins, kinesin II and myosin VIIa, as shown in *Kif3a* and *Myo7a* knockout mice (Liu et al. 1999; Williams 2002). As mentioned before, kinesin II mediates

a microtubule-dependent anterograde IFT (Rosenbaum and Witman 2002). Myosin VIIa is an actin-dependent motor molecule and, in mouse photoreceptors, it locates to the periciliary membrane complex; however, in primates, it locates to the calyceal processes (Sahly et al. 2012). It is, therefore, unclear whether mutations in *Myosin VIIa* in humans also lead to the aberrant opsin trafficking as shown in mice (Liu et al. 1999). Immunoelectron microscope studies of *Rana pipiens* frog photoreceptors, revealed that actin is present not only in calyceal processes but also at the sites of disc morphogenesis, suggesting involvement of actin-mediated transport in protein delivery to the forming discs (Chaitin et al. 1984). Little is known about OS targeting of other OS-specific transmembrane proteins, apart from retinol dehydrogenase (RDH8), which also contains the VXPX motif and PRPH2, which has its own OS-targeting sequence (Pearing et al. 2013).

Photoactivated Protein Diffusion

The base of the OS does not contain a selective barrier for the soluble proteins as shown in mice by the light-activated translocation of phototransduction proteins: transducin, arrestin, and recoverin (Sokolov et al. 2002; Calvert et al. 2006). Furthermore, this translocation is thought to be energy-independent, implying that the protein movement occurs by simple diffusion (Nair et al. 2005; Calvert et al. 2010). The diffusion of the proteins is dependent, however, on the steric interactions between the molecules and cell structures, termed steric volume exclusion, which reduces the entry of larger molecular weight proteins to the OS (Najafi and Calvert 2012). Light-mediated translocation of these proteins is thought to play a role in adaptation to different light conditions, in which for instance concentrating transducin in the rod OS in the darkness amplifies the phototransduction signal, and translocation of arrestin to OS in light conditions terminates transducin activation and accelerates photopigment recovery (Pearing et al. 2013). A neuroprotective role for the light-induced protein translocation has also been suggested (Pearing et al. 2013).



RETINAL CILIOPATHIES

Mutations in genes coding for ciliary proteins lead to ciliopathies, rare genetic disorders that may affect one or more organs, including the retina, central nervous system, olfactory epithelium, cardiovascular system, liver, kidney, skeletal system, gonads, and adipose tissue (Goetz and Anderson 2010; Patel and Honoré 2010; Mockel et al. 2011; Waters and Beales 2011). In this review, we will focus on ciliopathies that involve the retina, manifesting most commonly as retinitis pigmentosa (RP) (Hamel 2006; Hartong et al. 2006; Berger et al. 2010) or Leber congenital amaurosis (LCA) (Weleber 2002; Chung and Traboulsi 2009). RP is a condition that primarily affects rod photoreceptors and retinal pigment epithelium. It is the most frequent cause of the IRDs, with a prevalence of $\sim 1/3500$ and accounting for roughly 25% of vision loss in adults (Hamel 2006; Hartong et al. 2006; Berger et al. 2010). It may start in the first or second decade of life, often with nyctalopia and peripheral vision loss as early symptoms, because of the dysfunction of PSCs and photoreceptor cell death in the peripheral retina. In many cases, the disease progresses to include central vision loss as well, because of eventual dysfunction of PSCs and death of photoreceptor cells in the macula (central retina) (Fig. 2) (Hamel 2006; Hartong et al. 2006; Berger et al. 2010). LCA affects rods and cones and leads to vision loss in infancy or early childhood (Weleber 2002; den Hollander et al. 2008; Chung and Traboulsi 2009). LCA is rare, with a population frequency of $\sim 1/50,000$, yet affecting $\sim 20\%$ of children attending schools for the blind (Weleber 2002; Koenekoop 2004; Berger et al. 2010). Other subtypes of IRD are present in ciliopathy patients and often involve cone photoreceptors and the macula (Michaelides et al. 2006; Estrada-Cuzcano et al. 2012c).

Nonsyndromic Retinal Ciliopathies

As mentioned above, photoreceptor OS can be regarded as specialized cilia designed to detect light and to convert this information into a biochemical signal. Therefore, we consider that all

proteins that participate in this sensory function, as well as proteins that build the PSC structure, are in effect cilia proteins. Consequently, we can distinguish two groups of retinal ciliopathies: (1) affecting the structure, and (2) the sensory function of photoreceptor OS.

Mutations in Genes Disrupting POS Structure

There are currently 36 known genes that have been identified to harbor mutations that disrupt PSC structure and can lead to an isolated or syndromic retinal degeneration (Table 1). Thirteen genes that encode axoneme or basal body-associated proteins (*C2ORF71*, *FAM161A*, *KIZ*, *LCA5*, *MAK*, *NEK2*, *RAB28*, *RPGRIP1*, *RP1*, *RP1L1*, *RP2*, *SPATA7*, *TOPORS*) and seven genes coding for other structural PSC components (*CDHR1*, *EYS*, *FSCN2*, *PROM1*, *PRPH2*, *ROM1*, *TULP1*) have been exclusively associated with nonsyndromic retinal degeneration (Kajiwara et al. 1991, 1994; Bascom et al. 1992; Banerjee et al. 1998; Hagstrom et al. 1998; Guillonneau et al. 1999; Hardcastle et al. 1999; Mears et al. 1999; Pierce et al. 1999; Maw et al. 2000; Dryja et al. 2001; Wada et al. 2001, 2003; Chakarova et al. 2007; den Hollander et al. 2007; Abd El-Aziz et al. 2008; Collin et al. 2008; Wang et al. 2009; Akahori et al. 2010; Bandah-Rozenfeld et al. 2010; Collin et al. 2010; Henderson et al. 2010; Langmann et al. 2010; Nishimura et al. 2010; Ostergaard et al. 2010; Ozgöl et al. 2011; Tucker et al. 2011; Estrada-Cuzcano et al. 2012b; Davidson et al. 2013; Nishiguchi et al. 2013; Roosing et al. 2013; El Shamieh et al. 2014). A query of the human proteome map (Kim et al. 2014) shows that nine of these genes (*CDHR1*, *FSCN2*, *MAK*, *PROM1*, *PRPH2*, *ROM1*, *RP1*, *RP1L1*, *TULP1*) are predominantly expressed in the human retina, which corroborates with the retina-specific phenotype. With the exception of *LCA5*, which shows no significant expression in any of the assayed tissues, the remaining genes are also significantly expressed in other human tissues, and it remains unclear why mutations in these genes affect specifically the retina.

Two genes stand apart in IRD ciliopathies, *USH2A* and *CLRN1*. Mutations in these genes

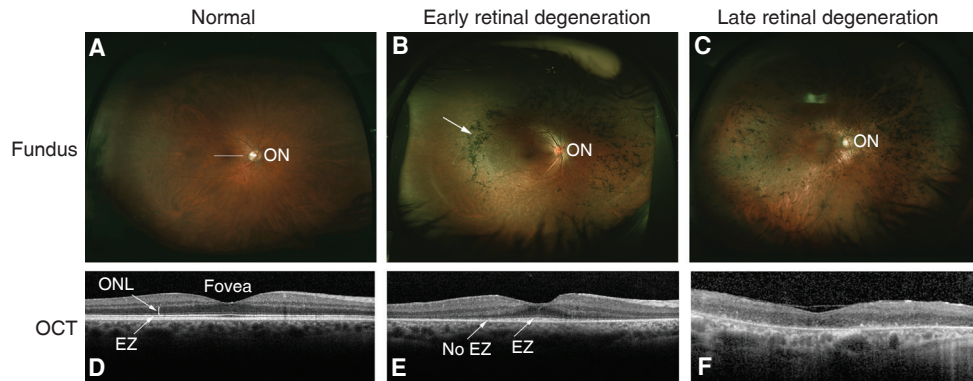


Figure 2. Clinical features of inherited retinal degeneration (IRD). Fundus photos and optical coherence tomography (OCT) images of normal and diseased retinas are shown. (A) Wide-field fundus photo shows the appearance of a normal retina; the optic nerve (ON) is visible. (B) Fundus image from a patient with early retinal degeneration because of retinitis pigmentosa (RP). The arrow shows the pigment changes, which are characteristic of this disorder. (C) Fundus image from a patient with advanced retinal degeneration because of RP. (D) A cross-sectional image of the center of the normal retina (macula; white line in A) obtained with OCT shows normal retinal layers, including the outer nuclear layer (ONL), where photoreceptor cell nuclei are located. The central indentation is normal, and indicates the fovea. The white band showing the ellipsoid zone (EZ, arrow) is generated from the junction of the inner and outer segments of photoreceptor cells, and its presence indicates normal photoreceptor cell and thus PSC structure. (E) The OCT image shows loss of photoreceptor cells peripherally, with the ONL visible only near the fovea. The EZ is evident centrally, but is lost more peripherally, indicating loss of PSCs by the more peripheral photoreceptor cells present. (F) The OCT image shows loss of the ONL and thus all of the photoreceptor cells in the macula of this patient consistent with greatly reduced central vision.

lead to isolated retinal degeneration (Rivolta et al. 2000; Khan et al. 2011) or to deaf-blindness, called Usher syndrome (Eudy et al. 1998; Joensuu et al. 2001). There is only one report of nonsyndromic IRD because of mutations in *CLRN1* (Khan et al. 2011); however, mutations in *USH2A* are the leading cause of the nonsyndromic autosomal recessive IRD, accounting for ~9% of RP patients (Hartong et al. 2006). These two genes will be further discussed in the section on Usher syndrome.

The remaining 12 genes code for axoneme proteins and are associated with isolated retinopathy or syndromic disease (Table 1). In certain cases, the broad spectrum of phenotypes associated with mutations in a given gene can be explained by the primary mutations in the gene, where mutations in the retina-specific transcripts or hypomorphic alleles may lead to the isolated retinal phenotype (Ansley et al. 2003; den Hollander et al. 2006; Coene et al. 2009; Riazuddin et al. 2010; Webb et al. 2012;

Xu et al. 2015). In other cases, the relationship between the primary disease-causing mutation and the phenotype is not clear and epistatic effects of other alleles have been suggested (Badano et al. 2003b, 2006; Estrada-Cuzcano et al. 2012a; Bujakowska et al. 2014). (Both cases will be discussed in detail in the section Broad Phenotypic Spectrum of Ciliopathies and Genetic Modifiers.)

Mutations in Genes Impeding POS Sensory Function

A less obvious subgroup of nonsyndromic retinal ciliopathies are IRDs in which PSC sensory function is affected. This classification is analogous to another ciliopathy, the dominant form of polycystic kidney disease, because of mutations in *PKD1* or *PKD2*, which code for membrane proteins that act as a cilia sensor and a calcium channel, respectively (Ong and Harris 2015). Similarly, genetic mutations that affect

phototransduction cascade and retinoid cycle in the photoreceptors are also considered as ciliopathies (Table 1). However, we do not consider as ciliopathies IRDs that are caused by mutations in genes that are expressed in the RPE or code for proteins that function in other compartments of the photoreceptor cell (e.g., splicing factor genes). A comprehensive list of all IRD genes can be found at the Retinal Information Network (RetNet) portal (sph.uth.edu/retnet/home.htm).

Usher Syndrome

Usher syndrome is an autosomal recessive dual impairment of vision and sensorineural hearing with a prevalence of $\sim 1/25,000$ people (Kremer et al. 2006; Millán et al. 2011; Bonnet and El-Amraoui 2012). It is phenotypically and genetically heterogeneous and most of the patients fall into one of the three clinical subtypes of decreasing severity: Usher syndrome type I (USH1), type II (USH2), and type III (USH3).

The most severe form, USH1, is not strictly a ciliopathy because the proteins coded by the six associated genes: *MYO7A* (Weil et al. 1995), *USH1C* (Verpy et al. 2000), *CDH23* (Bolz et al. 2001), *PCDH15* (Ahmed et al. 2001), *USH1G* (Weil et al. 2003), and *CIB2* (Riazuddin et al. 2012), locate to actin-based structures in the periciliary region, called the calyceal processes, and not to cilia themselves (Sahly et al. 2012). The function of these structures is unclear and they might have a structural role supporting the photoreceptor outer segments or be involved in fine tuning of the photoreceptor signaling. Calyceal processes are not present in all of the vertebrates and their absence in rodents may account for the subtle retinal phenotypes in most of the USH1 murine models, in which hearing and vestibular phenotypes are profound (Liu et al. 1999; Di Palma et al. 2001; Libby and Steel 2001; Johnson et al. 2003; Ahmed et al. 2008; Williams 2008; Miyasaka et al. 2013). In the ear, USH1 proteins are involved in the maturation of the stereocilia in the auditory hair cells of the inner-ear cochlea, where they form transient links between the kinocilium and stereocilia during development and the

tip links between the mature stereocilia (Kremer et al. 2006; Bonnet and El-Amraoui 2012; Riazuddin et al. 2012; Sahly et al. 2012).

USH2 is caused by mutations in one of three genes: *USH2A* (Eudy et al. 1998), *GPR98* (Weston et al. 2004), and *DFNB31* (Mburu et al. 2003). The products of these genes locate to the periciliary membrane complex adjacent to the transition zone of the photoreceptor cilia (Liu et al. 2007b; Sahly et al. 2012). In the cochlea, they form the transient ankle links between the developing stereocilia (reviewed in Bonnet and El-Amraoui 2012).

USH3, the least severe form of Usher, is caused by mutations in *CLRN1* or *HARS* (Joensuu et al. 2001; Puffenberger et al. 2012). In mice, *Clarín-1* locates to the base of the photoreceptors cilia and to synaptic ribbons (Zalocchi et al. 2009); however, it does not seem to be essential for the photoreceptor function in rodents, because homozygous *Clrn1* knockout mice show no retinal phenotype (Geller et al. 2009). In the cochlea, *Clarín-1* locates to the apical and basal aspects of stereocilia depending on the developmental stage (Zalocchi et al. 2009). *HARS* codes for a histidyl-tRNA synthetase and, currently, the mechanism of the disease is unknown (Puffenberger et al. 2012).

Of the three Usher types, the most frequent is USH2 (56%–57% cases), in which mutations in the *USH2A* gene are the most common (Millán et al. 2011). USH1 represents 33%–44% of all Usher cases, followed by USH3, with a prevalence of 2% (Yan and Liu 2010; Millán et al. 2011). However, in certain populations (Finland and Ashkenazi Jewish), USH3 reaches 40% of all Usher patients because of founder mutations (Yan and Liu 2010; Millán et al. 2011). Atypical Usher syndromes have also been reported in which the deaf–blindness phenotype is explained by mutations in two different genes: *USH2A* with *PDZD7* and *C2orf71* with *CEP250* (Table 2) (Ebermann et al. 2010; Khateb et al. 2014). Recently, two groups have reported another form of Usher syndrome because of mutations in *CEP78*, which manifest as a cone–rod dystrophy accompanied by sensorineural hearing loss involving mainly high frequencies (Nikopoulos et al. 2016; Sharon et al.

Table 2. Genetic modifiers of ciliopathies

Primary gene	Modifier	Phenotype	Evidence	References
<i>PRPH2/RDS</i>	Digenic inheritance	RP	Three families (11 affected in total)	Kajiwara et al. 1994
p.(Leu185Pro)				
<i>ROM1</i>				
p.(Gly80fs) and p.(Leu114fs)				
<i>BBS2</i>	Digenic inheritance	BBS	In one family, the affected sib carried three alleles, whereas the unaffected sib is the only compound heterozygous for the <i>BBS2</i> mutations; three additional families with a probable triallelic <i>BBS2/BBS6</i> inheritance	Katsanis et al. 2001
p.[Tyr24*] and p.[Gln59*]				
<i>BBS6</i>				
p.(Gln147*)				
<i>RPE65</i>	<i>GUCY2D</i>	More severe RD	One family with two sibs, targeted analysis of: <i>GUCY2D</i> , <i>RPE65</i> , <i>CRX</i> , <i>AIP1L1</i> , and <i>RPGRIP1</i>	Silva et al. 2004
p.(Glu102*)	p.(Ile539Val)			
<i>BBS1</i>	<i>ARL6</i>	More severe ciliopathy	In one family of two affected sibs, the sister carrying the additional <i>ARL6</i> allele showed a more severe phenotype	Fan et al. 2004
p.(Met390Arg)	p.(Gly169Ala)			
<i>BBS1</i> and unknown BBS genotypes	<i>CCDC28B</i> (c.330C>T, p.(=)) (originally noted as <i>C430T</i>)	Increased severity of disease, general mutational load	In three families, variant associated with more severe BBS; variant also enriched in BBS patients (14/226) over controls (4/274)	Badano et al. 2006
Mixed ciliopathy cohort	<i>RPGRIP1L</i>	Presence of RD in ciliopathies	Targetted screening of <i>RPGRIP1L</i> ; enrichment of 226Thr variant in ciliopathy patients with RD (43/487) over ciliopathy patients without RD (0/115); functional data, showing a decreased binding activity to RPGR	Khanna et al. 2009
	p.(Ala229Thr)			
BBS mixed cohort	<i>MKS1</i>	More severe ciliopathy phenotype, seizures in five of six patients	Targetted screening of <i>MKS1</i> in BBS cohort, heterozygous potentially modifying changes found in six patients from five families (5/155); functionally, variants ranged from mild hypomorphs to null	Leitch et al. 2008
	p.(Arg123Gln)			
	p.(Asp286Gly)			
	p.(Ile450Thr)			
	p.(Val339Met)			
	(specific to short isoform)			
<i>BBS9</i> and <i>CEP290</i>	<i>TMEM67</i>	General mutational load	Potentially pathogenic alleles found in two families: c.2241G>A affects the canonical splice site and is predicted to lead to exon skipping; p.(Ser320Cys) was functionally null	Leitch et al. 2008
	(c.2241G>A) and p.(Ser320Cys)			
<i>PRPH2</i>	<i>ROM1</i>	Increased macular involvement in RD	One family, eight affected; microarray mutation detection in 16 genes, full sequencing of <i>PRPH2</i> , <i>ROM1</i> , and <i>ABCA4</i>	Poloschek et al. 2010
	p.(Arg229His) and/or <i>ABCA4</i>			
	p.(Val2050Leu)			

Continued

Table 2. *Continued*

Primary gene	Modifier	Phenotype	Evidence	References
<i>USH2A</i>	<i>PDZD7</i> p.(Arg56fs)	More severe RD	One family with two sibs; targeted analysis of <i>PDZD7</i> and other Usher genes; digenic inheritance stated but insufficient genetic data to prove it	Ebermann et al. 2010
<i>CEP290</i>	<i>AHII</i> p.(Asn811Lys) and p.(His758Pro)	More severe neurological phenotype	Targeted screening of <i>AHII</i> in eight patients; variants detected in two patients	Coppieters et al. 2010
<i>NPHP1</i> and unknown NPHP genotypes	<i>AHII</i> p.(Arg830Trp)	Presence of RD	Targeted screening of <i>AHII</i> in 153 NPHP ± RD patients	Louie et al. 2010
Mixed MKS and BBS cohort	<i>C2ORF86</i> (various changes)	General mutational load	Targeted screening of <i>C2ORF86</i> ; enrichment of nonsynonymous coding changes in patients (6/192) versus controls (0/384)	Kim et al. 2010
<i>RPGR</i>	<i>RPGRIP1L</i> p.(Arg744Gln) and <i>IQCBI</i> p.(Ile393Asn)	Severity of RD	Targeted screening of <i>RPGRIP1L</i> , <i>RPGRIP1L</i> , <i>CEP290</i> , and <i>IQCBI</i> in 98 male patients; the results were marginally significant	Fahim et al. 2011
Mixed ciliopathy cohort	<i>TTC21B</i> (various changes)	General mutational load	Targeted screening of <i>TTC21B</i> ; enrichment of pathogenic changes in ciliopathy patients (28/555) over controls (4/305)	Davis et al. 2011
<i>C2orf71</i> p.(Gln1097*)	<i>CEP250</i> p.(Arg1155*)	More severe retinal degeneration + hearing loss	Homozygosity mapping in family with seven affected, subsequent WES in two affected; homozygous <i>CEP250</i> mutation leads to an early-onset severe hearing loss with a mild retinal degeneration and an additional homozygous stop mutation in <i>C2orf71</i> exacerbated the retinal phenotype in three individuals	Khateb et al. 2014
Mixed BBS cohort	<i>NPHP1</i> whole gene deletion and p.(Arg5Leu)	General mutational load in ciliopathies	Targeted analysis of <i>NPHP1</i> in a BBS cohort of 200 families, mutations enriched in the patient population compared with control (incidence of 1.5% (deletion) and 2.5% (missense); functional data for <i>NPHP1</i> -BBS genes interaction	Lindstrand et al. 2014
<i>PRPH2</i> (c.828+3A>T)	<i>PRPH2</i> p.[(Glu304;Lys310;Gly338)] haplotype in <i>trans</i> with the causal mutation	More severe retinal phenotype	p.[(Glu304;Lys310;Gly338)] haplotype in <i>trans</i> with the splice site mutation was associated with a more severe phenotype as investigated in 62 patients	Shankar et al. 2016

BBS, Bardet–Biedl syndrome; RD, retinal degeneration; RP, retinitis pigmentosa.

2016). Hearing loss can also be part of other syndromes, such as Altrom, as will be discussed later (Mockel et al. 2011).

Other Syndromic IRDs

Based on the presence of particular symptoms, ciliopathies are subdivided into different subtypes, traditionally named after clinicians who first described them. Here, we will review the major syndromes, which involve the retina. Even though these conditions are considered as distinct clinical entities, it is being increasingly recognized that there is a large phenotypic overlap between these diseases, in which characteristic features of two different syndromes are present in the same patient or distinct ciliopathies co-occur in single families (Lehman et al. 2010; Zaki et al. 2011; Valente et al. 2014). Traditional naming of these conditions is therefore often inaccurate and depends on the clinicians' training and their specialty. To overcome this bias, we believe that it is crucial to include in the syndrome naming the underlying molecular cause of the disease (e.g., *AH11*-associated ciliopathy). However, for the purpose of this review, we describe each syndrome as traditionally called and present the genes associated with them.

Senior–Løken syndrome (SLS) is an autosomal recessive disease characterized by juvenile nephronophthitis (NPHP) and early-onset retinal degeneration (Løken et al. 1961; Senior et al. 1961). NPHP is a medullary cystic kidney disease leading to the end-stage renal failure later in childhood or in adolescence (Ronquillo et al. 2012). About 10% of NPHP patients also have retinal degeneration (Otto et al. 2005; Mockel et al. 2011). So far, eight genes are associated with SLS (*CEP164*, *CEP290*, *IQCB1*, *NPHP1*, *NPHP4*, *SDCCAG8*, *TRAF3IP1*, *WDR19*), although other NPHP-associated genes are mutated in different syndromes involving the retina (Caridi et al. 1998; Otto et al. 2002, 2005, 2010; Sayer et al. 2006; Chaki et al. 2012; Coussa et al. 2013; Bizet et al. 2015). There is a considerable overlap between SLS and other ciliopathies, where almost all SLS genes are associated with other diseases (Fig. 3).

Joubert syndrome (JBS) is a neurological condition characterized by a distinctive abnormality of the midbrain–hindbrain junction and cerebellar vermis hypoplasia, presenting as the molar tooth sign (MTS) on brain imaging (Maria et al. 1997; Valente et al. 2013). These neurological defects correlate with the clinical presentation of hypotonia, ataxia, abnormal breathing, developmental delay, and abnormal ocular movements. JBS patients may also present with retinal degeneration, renal or hepatic defects, polydactyly, and orofacial dysmorphism (Mockel et al. 2011; Valente et al. 2013). The prevalence of JBS is estimated to be between 1/80,000 and 1/100,000 of live births (Valente et al. 2014). Mutations in 26 genes have been reported to cause JBS (*AH11*, *ARL13B*, *B9D1*, *C5orf42*, *CC2D2A*, *CEP104*, *CEP290*, *CEP41*, *CSPP1*, *INPP5E*, *KIAA0556*, *KIAA0586*, *KIF7*, *NPHP1*, *OFD1*, *RPGRIP1L*, *SRTD1*, *TCTN2*, *TCTN3*, *TECT1*, *TMEM67*, *TMEM138*, *TMEM216*, *TMEM231*, *TMEM237*, *ZNF423*) (Dixon-Salazar et al. 2004; Ferland et al. 2004; Parisi et al. 2004; Sayer et al. 2006; Baala et al. 2007b; Delous et al. 2007; Cantagrel et al. 2008; Gorden et al. 2008; Noor et al. 2008; Bielas et al. 2009; Coene et al. 2009; Edvardson et al. 2010; Dafinger et al. 2011; Garcia-Gonzalo et al. 2011; Huang et al. 2011; Chaki et al. 2012; Lee et al. 2012a,b; Srour et al. 2012a,b; Thomas et al. 2012; Romani et al. 2014; Shaheen et al. 2014; Thomas et al. 2014; Tuz et al. 2014; Sanders et al. 2015). All except one of the above genes cause autosomal-recessive or X-linked disease; *ZNF423* has been associated with a dominant JBS form, although this association showed limited genetic evidence (Chaki et al. 2012). *ZNF423* is also the only JBS gene, which is not associated with the cilium but with the DNA damage response pathway (Chaki et al. 2012).

Meckel–Gruber syndrome, also known as Meckel syndrome (MKS) is a neonatal lethal autosomal recessive disorder defined by the malformation of the central nervous system (occipital encephalocele), cystic kidneys, and liver fibrosis (Wright et al. 1994; Logan et al. 2011). Other features that may be present are postaxial or preaxial polydactyly, skeletal dys-

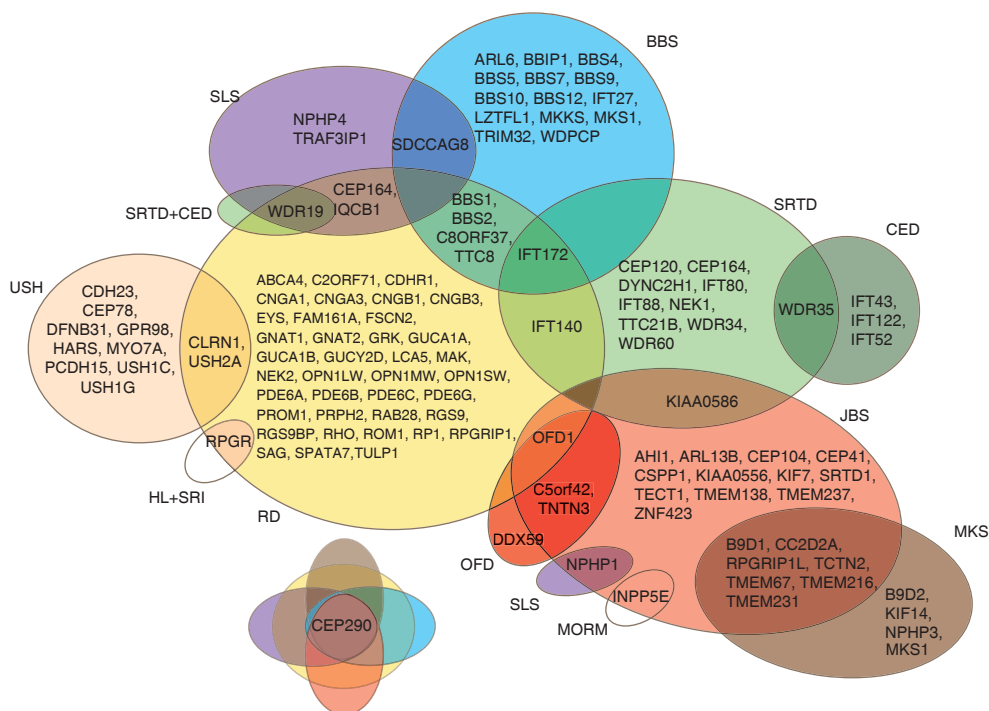


Figure 3. A Venn diagram showing a phenotypic and genetic overlap between different forms of ciliopathy. BBS, Bardet–Biedl syndrome; CED, cranioectodermal dysplasia (also known as Sensenbrenner syndrome); HL + SRI, hearing loss and sinorespiratory infections; JBS, Joubert syndrome; MKS, Meckel–Gruber syndrome; MORM, mental retardation, truncal obesity, retinal degeneration, and micropenis; OFD, oral-facial-digital syndrome; RD, retinal degeneration—nonsyndromic; SLS, Senior–Løken syndrome; SRTD, short-rib thoracic dysplasia; USH, Usher syndrome.

plasia, cleft lip/palate, microphthalmia, optic nerve coloboma, heart defects, genital anomalies, and complete or partial situs inversus (Logan et al. 2011). Mutations in 12 genes have been associated with MKS (*B9D1*, *B9D2*, *CC2D2A*, *CEP290*, *KIF14*, *MKS1*, *NPHP3*, *RPGRIP1L*, *TCTN2*, *TMEM67*, *TMEM216*, *TMEM231*) (Kyttälä et al. 2006; Smith et al. 2006; Baala et al. 2007a; Delous et al. 2007; Bergmann et al. 2008; Tallila et al. 2008; Valente et al. 2010; Dowdle et al. 2011; Hopp et al. 2011; Shaheen et al. 2011, 2013; Filges et al. 2014). There is a considerable genetic overlap between JBS and MKS, in which eight of the genes are shared between the two syndromes and co-occurrence of the two diseases was reported in the same families (Valente et al. 2014). The incidence of MKS varies among populations and it has been estimated as 1/13,250 in the United

States, 1/140,000 in the United Kingdom, and 1/9000 in Finland (Logan et al. 2011).

Bardet–Biedl syndrome (BBS) is an autosomal recessive condition defined by rod–cone degeneration, postaxial polydactyly, central obesity, mental retardation, hypogonadism, and renal dysfunction (Beales et al. 1999; Mockel et al. 2011). Other features such as hepatic fibrosis, diabetes mellitus, endocrinological disturbances, heart disease, and short stature may also be present (Beales et al. 1999). Twenty genes have been associated with BBS (*ARL6*, *BBIP1*, *BBS1*, *BBS2*, *BBS4*, *BBS5*, *BBS7*, *BBS9*, *BBS10*, *BBS12*, *CEP290*, *IFT27*, *IFT172*, *LZTFL1*, *MKKS*, *MKS1*, *SDCCAG8*, *TRIM32*, *TTC8*, *WDPCP*) (Katsanis et al. 2000; Slavotinek et al. 2000; Mykytyn et al. 2001, 2002; Nishimura et al. 2001, 2005; Ansley et al. 2003; Badano et al. 2003a; Chiang et al. 2004, 2006;

Fan et al. 2004; Li et al. 2004; Stoetzel et al. 2006, 2007; Leitch et al. 2008; Kim et al. 2010; Otto et al. 2010; Marion et al. 2012; Aldahmesh et al. 2014; Bujakowska et al. 2014; Scheidecker et al. 2014). Apart from the BBS genes associated with the nonsyndromic IRD (Table 1), a homozygous nonsense mutation (p.S701X) in *BBS12* was shown to lead to a late-onset retinal degeneration and postaxial polydactyly but no other BBS-associated clinical features (Pawlik et al. 2010).

There are two phenotypically similar diseases to BBS: Alstrom syndrome (ALMS) and MORM syndrome (mental retardation, truncal obesity, retinal degeneration, and micropenis). ALMS is characterized by cone-rod degeneration, sensorineural hearing loss, childhood obesity, and type 2 diabetes mellitus. ALMS patients often present with cardiomyopathy and other features such as renal, pulmonary, or hepatic disease may also be present. In contrast to BBS, ALMS is not associated with mental retardation, polydactyly, or hypogonadism (Mockel et al. 2011). Mutations in only one gene, *ALMS1*, have been associated with Alstrom syndrome (Collin et al. 2002). MORM has been described in only one Pakistani family of 14 individuals, in whom a homozygous truncating mutation in *INPP5E*, was found to cause the disease (Hampshire et al. 2006; Jacoby et al. 2009).

Short-rib thoracic dysplasia (SRTD) with or without polydactyly regroups syndromes formerly known as Mainzer-Saldino (MZSDS), Jeune asphyxiating thoracic dystrophy (JATD), and Ellis-van Creveld (EVC) syndromes. SRTDs are autosomal recessive skeletal ciliopathies, characterized by short ribs, constricted thoracic cage, shortened tubular bones, and a “trident” appearance of the acetabular roof (Huber and Cormier-Daire 2012). The severely constricted thoracic cage leads to respiratory insufficiency, often resulting in death in infancy. Other features that may be present are polydactyly, cleft lip/palate, retinal degeneration, and anomalies of the brain, heart, kidneys, liver, pancreas, intestines, and genitalia (Waters and Beales 2011; Huber and Cormier-Daire 2012). There is a phenotypic and genetic overlap be-

tween SRTDs and cranioectodermal dysplasia (CED), also known as Sensenbrenner syndrome. CED is characterized by sagittal craniosynostosis, narrow thorax, short limbs, brachydactyly, protuberant abdomen, and facial and ectodermal anomalies (Huber and Cormier-Daire 2012). Seventeen genes have been associated with these diseases (*CEP120*, *DYNC2H1*, *EVC*, *EVC2*, *IFT52*, *IFT122*, *IFT140*, *IFT172*, *IFT43*, *IFT80*, *KIAA0586*, *NEK1*, *TTC21B*, *WDR19*, *WDR34*, *WDR35*, *WDR60*) (Ruiz-Perez et al. 2000; Galdzicka et al. 2002; Beales et al. 2007; Dagoneau et al. 2009; Gilissen et al. 2010; Walczak-Sztulpa et al. 2010; Arts et al. 2011; Bredrup et al. 2011; Davis et al. 2011; Mill et al. 2011; Thiel et al. 2011; Perrault et al. 2012; Halbritter et al. 2013; McInerney-Leo et al. 2013; Schmidts et al. 2013b; Alby et al. 2015; Shaheen et al. 2015; Girisha et al. 2016). Interestingly, some of these genes have also been implicated with a nonsyndromic disease, for example, *TTC21B* and *WDR19* in NPHP (Bredrup et al. 2011; Davis et al. 2011) or *IFT172* and *IFT140* in RP (Fig. 3) (Bujakowska et al. 2014; Bifari et al. 2015; Xu et al. 2015).

BROAD PHENOTYPIC SPECTRUM OF CILIOPATHIES AND GENETIC MODIFIERS

One of the important aspects of the IRDs is that mutations in the same gene can lead to variable phenotypes (Ferrante et al. 2001; Ansley et al. 2003; Sayer et al. 2006; Perrault et al. 2007; Frank et al. 2008; Leitch et al. 2008; Coene et al. 2009; Riazuddin et al. 2010; Bujakowska et al. 2012; Estrada-Cuzcano et al. 2012a; Webb et al. 2012). In some cases, the severity of disease can be explained by the primary disease-causing mutation. For example, a splice site mutation of a retina-specific exon in *TTC8* leads to a nonsyndromic RP (Riazuddin et al. 2010), whereas the gene is most commonly associated with BBS (Ansley et al. 2003). The position of a mutation may also determine the phenotype as in the case of truncating mutations in *OFD1*. Nonsense mutations downstream from exon 17 lead to an X-linked dominant oral-facial-digital type 1 (OFD1) syndrome, manifesting with malformations of face, oral cavity, and digits

in affected females and lethal in males (Ferrante et al. 2001). However, truncating mutations upstream of exon 17 lead to an X-linked recessive JBS (Coene et al. 2009). In addition, hypomorphic alleles can arise by mutations activating cryptic splice sites, which leads to severely reduced levels of wild-type transcripts as in the case of *CEP290* (den Hollander et al. 2006) and *OFD1* (Webb et al. 2012).

In many cases, however, even a precise genetic diagnosis does not yield a clear genotype–phenotype correlation and the severity of disease can vary greatly even between patients with the same genetic cause of disease. Examples of this include family members that share the same 3bp deletion (c.461_463del) in the *PRPH2* gene but show phenotypes varying from RP involving the peripheral retina to macular disease involving only the central retina (Weleber et al. 1993). Similarly, individuals with mutations in the *RPI* gene show variable phenotypes, ranging from near normal to profoundly affected by retinal degeneration (Jacobson et al. 2000; Berson et al. 2001). Several genetic modifiers have already been identified in IRD disease (Table 2), in which extreme examples are cases of digenic inheritance of nonsyndromic IRD (Kajiwara et al. 1994) and BBS (Katsanis et al. 2001) or the rescuing effect of the wild-type *PRPF31* allele in the dominant *PRPF31*-associated disease (McGee et al. 1997; Vithana et al. 2003; Rose et al. 2016). Even though more than a dozen of genetic modifiers of IRD disease severity have been reported, our knowledge about these variants is still limited because the studies were conducted on a limited number of patients (sometimes single families) targeting a small number of genes and functional validation was not always performed (Table 2). In addition, no study has yet shown the validity of the previously reported modifiers and therefore they remain to be scrutinized by future research.

CONCLUSIONS

In summary, mutations in many different genes can cause retinal ciliopathies, reflecting the diversity of protein functions required for normal PSC function. As indicated, it is increasingly

clear that the phenotypes ascribed to specific genetic forms of disease overlap, and thus a revised system of disease definitions that includes the genetic etiology in the disease name would improve our understanding of these disorders, and their description for patients and clinicians. Further, as we have attempted to illustrate, studies of retinal ciliopathies have provided insights into syndromic disorders, and cilia function in general. Given the ubiquitous presence of cilia on mammalian cells, we anticipate that further study of these disorders and their pathogenesis will continue to inform us about cilia function broadly, and to be informed by the results of cilia in other contexts.

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K.M. Bujakowska et al.

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