Ciliopathies

Daniela A. Braun and Friedhelm Hildebrandt

Division of Nephrology, Harvard Medical School, Boston Children's Hospital,
Boston, Massachusetts 02115

Correspondence: Friedhelm.hildebrandt@childrens.harvard.edu

Nephronophthisis-related ciliopathies (NPHP-RC) are a group of inherited diseases that affect genes encoding proteins that localize to primary cilia or centrosomes. With few exceptions, ciliopathies are inherited in an autosomal recessive manner, and affected individuals manifest early during childhood or adolescence. NPHP-RC are genetically very heterogeneous, and, currently, mutations in more than 90 genes have been described as single-gene causes. The phenotypes of NPHP-RC are very diverse, and include cystic-fibrotic kidney disease, brain developmental defects, retinal degeneration, skeletal deformities, facial dimorphism, and, in some cases, laterality defects, and congenital heart disease. Mutations in the same gene can give rise to diverse phenotypes depending on the mutated allele. At the same time, there is broad phenotypic overlap between different monogenic genes. The identification of monogenic causes of ciliopathies has furthered the understanding of molecular mechanism and cellular pathways involved in the pathogenesis.

Cilia are organelles that are present on the apical surface of almost every cell type in various tissues and organs. They are involved in a variety of cellular functions such as planar cell polarity, cell-cycle regulation and mechanosensation. Furthermore, cilia integrate multiple signaling pathways that are of critical importance for vertebrate development and organ differentiation. Hence, ciliary dysfunction gives rise to a wide spectrum of human disease phenotypes involving various organ systems. Cilia can be categorized as motile cilia and immotile cilia, also known as primary cilia. Motile cilia are present on respiratory epithelial cells, ependymal cells of cerebrospinal fluid spaces, sperm cells, and cells of the embryonic node during development. Dysfunction of motile cilia results in the human phenotype of primary ciliary

dyskinesia and Kartagener syndrome (OMIM #244400), which is characterized by impaired mucociliary clearance resulting in recurrent infections of the upper respiratory tract, recurrent pneumonia, and progressive destruction of functional respiratory tissue. Additional disease symptoms include heterotaxy, congenital heart disease, asplenia, infertility, and *situs inversus* in 50% of patients (Leigh et al. 2009). Disruption of primary cilia has first been linked to autosomal-recessive and autosomal-dominant polycystic kidney diseases, which are discussed in more detail in Ma et al. (2016). In contrast to polycystic kidney disease that typically presents with enlarged kidneys and massive cysts, the second group of cilia-related cystic kidney diseases, the group of nephronophthisis-related ciliopathies (NPHP-RC), rather presents with

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shrunk or normal-sized fibrotic kidneys and small cysts at the corticomedullary junction. The renal phenotype of NPHP frequently occurs in a syndromic manner and is accompanied by anomalies in other organ systems, specifically retinal degeneration, cerebellar vermis hypoplasia, hepatic fibrosis, skeletal anomalies, ectodermal dysplasia, brain malformations, and neurological impairment. Frequently, a broad phenotypic spectrum is caused by mutations in the same monogenic gene on an allelic basis (Table 1; Fig. 1).

NEPHRONOPHTHISIS AND RELATED DISORDERS

Nephronophthisis (NPHP) is an inherited disease that represents one of the most frequent monogenic causes of end-stage renal failure in children and young adults. NPHP is inherited in an autosomal-recessive manner, and currently mutations in up to 90 genes have been identified as disease causing. Depending on the composition of the examined cohort, mutations in these known monogenic genes account for up to 63% of cases (Braun et al. 2015). The first genetic cause of NPHP, the gene *NPHP1*, which encodes the protein nephrocystin was described in 1997 (Hildebrandt et al. 1997a; Sautner et al. 1997). It later became apparent that homozygous deletions in the *NPHP1* gene are the most frequent cause of NPHP and that mutations in this gene alone account for 20%–25% of all cases (Halbritter et al. 2013b). Each of the subsequently identified monogenic genes accounts only for a small fraction of affected individuals (Halbritter et al. 2013b). The initial clinical presentation of NPHP is typically mild, and an increase in serum-creatinine, as an indicator of impaired renal function, is typically not noted before an average age of 9 years (Gretz 1989). Clinical symptoms are polyuria with secondary enuresis, polydipsia with regular fluid intake at night, anemia, and growth retardation (Kleinknecht 1989). Based on the age of onset, NPHP is further categorized into infantile (Gagnadoux et al. 1989), juvenile (Hildebrandt et al. 1992), and adolescent (Omran et al. 2000) NPHP, in which the median onset

of clinical symptoms is at an age of 1, 13, and 15 years, respectively. In contrast to other renal diseases, patients usually do not develop arterial hypertension until the renal function is severely impaired. The clinical diagnosis of NPHP is typically based on renal ultrasound presentation with normal or small-sized kidneys, increased renal echogenicity, and loss of corticomedullary differentiation. Renal cysts in NPHP are not a necessary diagnostic criterion, and, if present, are rare, remain small, and are typically located in the corticomedullary junction region. This is in contrast to autosomal-dominant or -recessive polycystic kidney disease in which cysts are large and arise from all regions of the kidney. Hallmarks of NPHP in renal histology are thickening and disintegration of the tubular basement membrane, atrophy of renal tubular structure, and tubulointerstitial fibrosis. The prevalence of NPHP does not show regional clustering or gender predisposition (Kleinknecht 1989). Patients with NPHP have been described worldwide and in all ethnicities (Kleinknecht 1989). The incidence of NPHP has been reported as nine patients/8.3 million in the United States (Potter et al. 1980) or as one in 50,000 live births in Canada (Waldherr et al. 1982; Pistor et al. 1985). A North American study assessing causes of end-stage renal failure in pediatric patients estimated that NPHP-related ciliopathies account for ~5% of all cases (Avner 1994; Warady et al. 1997).

Because of shared features in renal histology, namely, cysts that primarily arise from the corticomedullary region and tubulointerstitial fibrosis, NPHP was previously grouped with medullary–cystic kidney disease (MCKD) under the term “NPHP–MCKD complex.” However, they are now considered distinct disease entities because of differences in mode of inheritance, age of onset, extrarenal involvement, and molecular disease cause. MCKD is an autosomal-dominant disease that presents with adult-onset chronic kidney disease and renal salt wasting. In contrast to NPHP, end-stage renal failure typically occurs around the sixth decade of life (Wolf et al. 2004). MCKD does not present as a syndromic disease; the only described extrarenal associations are hyperuricemia and

Table 1. Phenotypic spectrum of 92 monogenic genes of NPHP-RC

OMIM disease	Gene symbol (first description)	Alias	Mode of inheritance	Human disease phenotype								Subcellular localization	
				Kidney	Eye	Brain	Liver	Skeletal anomalies	Laterality defects	Congenital heart disease	Other/syndromic		
Nephronophthisis (NPHP), Senior – Loken syndrome (SLS), Joubert syndrome (JBTS), Meckel –Gruber syndrome (MKS)													
NPHP1/ SLS1/ JBTS4	NPHP1 (Hildebrandt et al. 1997a; Saunier et al. 1997)	Nephrocystin	AR	NPHP; juvenile	RP, OMA	CVH, rare							TZ
NPHP2	INVS (Otto et al. 2003b)	Inversin	AR	NPHP; infantile	RP		LF, BDP		SI		PH, OH		TZ
NPHP3/ MKS7/ RHPD1	NPHP3 (Olbrich et al. 2003)	NPHP3	AR	NPHP	RP		LF, LC		SI	CHD	MPD, MKS		TZ
NPHP4/ SLS4	NPHP4 (Mollet et al. 2002; Otto et al. 2002)	NPHP4, nephroretinin	AR	NPHP	RP, OMA		LF, BDP		HTX	CHD			BB, CA
SLS5	IQCB1 (Otto et al. 2005)	NPHP5, IQCB1	AR	NPHP	RP (all cases)								TZ, BB
NPHP6/ SLS6/ JBTS5/ MKS4/ BBS14	CEP290 (Sayer et al. 2006; Valente et al. 2006)	CEP290, NPHP6, BBS14	AR	NPHP	RP	CVH, CBD	LF, BDP	PD		VSD, rare	MKS, BBS		BB
NPHP7	GLIS2 (Attanasio et al. 2007)	NPHP7, GLIS2	AR	NPHP									CA
NPHP8/ JBTS7/ MKS5/ COACH	RPGRIP1L (Delouis et al. 2007)	NPHP8, RPGRIP1L	AR	NPHP	RP, OMA, CB	CVH, CBD	LF, BDP	PD			MKS, BBS		TZ
NPHP9	NEK8 (Otto et al. 2008)	NPHP9, NEK8	AR	NPHP			LF			CHD	MKS		TZ
SLS7/BBS16	SDCCAG8 (Otto et al. 2010)	SDCCAG8, NPHP10	AR	NPHP	RP	ID					BBS		BB
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Table 1. Continued

OMIM disease	Gene symbol (first description)	Alias	Mode of inheritance	Kidney	Eye	Brain	Liver	Skeletal anomalies	Laterality defects	Human disease phenotype		
										Congenital heart disease	Other/syndromic	Subcellular localization
NPHP11/JBTS6/MKS3/COACH	TMEM67 (Smith et al. 2006)	Meckelin, TMEM67	AR	NPHP	RP, OMA, CB	CVH	LF, BDP	PD			MKS	TZ
NPHP12/JBTS11/SRTD4	TTC21B (Davis et al. 2011)	TTC21B, NPHP12	AR	NPHP		CVH		JATD			MKS	CA
NPHP13/SLS8/CED4/SRTD5	WDR19 (Bredrup et al. 2011)	WDR19, IFT144	AR	NPHP	RP		LF	JATD, CED			CED	CA
NPHP14/JBTS19	ZNF423 (Chaki et al. 2012)	NPHP14, ZNF423	AR/AD	NPHP	RP	CVH			SI			
NPHP15	CEP164 (Chaki et al. 2012)	NPHP15, CEP164	AR	NPHP	RP	CVH, ID	LF	PD			OB	BB
NPHP16	ANKS6 (Hoff et al. 2013)	NPHP16, ANKS6	AR	NPHP			LF		SI	CHD		TZ
NPHP17/SRTD10	IFT172 (Halbritter et al. 2013a)	IFT172	AR	NPHP	RP	CVH, ID	LF	SRTD, PD, CSE		VSD	OB	CA
NPHP18	CEP83 (Failler et al. 2014)	CEP83/CCDC41	AR	NPHP	RP	ID, HC	LF					BB
NPHP19	DCDC2 (Schueler et al. 2015)	DCDC2	AR	NPHP			LF					CA
IFT81	IFT81 (Perrault et al. 2015)	IFT81	AR	NPHP	RP	CVH		PD				CA
SLS9	IFT54 (Bizet et al. 2015)	TRAF3IP1	AR	NPHP	RP	ID		BD			OB	CA, BB
JBTS1	INPP5E (Bielas et al. 2009)	INPP5E	AR	NPHP, rare	RP, OMA, CB	CVH, ID, CBD, HC	LF	PD, rare			MORM	CA
JBTS2/MKS2	TMEM216 (Valente et al. 2010)	TMEM216	AR	NPHP	RP, OMA, CB	CVH, ID, CBD, HC		PD			MKS	TZ

Continued

Table 1. Continued

OMIM disease	Gene symbol (first description)	Alias	Mode of inheritance	Human disease phenotype								Subcellular localization
				Kidney	Eye	Brain	Liver	Skeletal anomalies	Laterality defects	Congenital heart disease	Other/syndromic	
JBTS3	<i>AHI1</i> (Ferland et al. 2004)	AHI1, Joubertin	AR	NPHP, rare	RP, OMA	CVH, ID						CA
JBTS8	<i>ARL13B</i> (Cantagrel et al. 2008)	ARL13B	AR			CVH, ID						
JBTS9/ MKS6	<i>CC2D2A</i> (Gorden et al. 2008)	CC2D2A	AR	RP		CVH, ID	LF				MKS	TZ
JBTS12	<i>KIF7</i> (Putoux et al. 2011)	KIF7	AR			CBD, ID, CVH		PD, FD		VSD	ACS, BBS, HLS	CA
JBTS13	<i>TECT1</i> (Garcia-Gonzalo et al. 2011)	TECTONIC1	AR			CVH		Abnormal limbs				TZ
JBTS14	<i>TMEM237</i> (Huang et al. 2011)	TMEM237	AR	NPHP	OpA, CB, Nys	CVH, HC						TZ
JBTS15	<i>CEP41</i> (Lee et al. 2012a)	CEP41	AR		OMA, RP	CVH, ID		PD				BB
JBTS16	<i>TMEM138</i> (Lee et al. 2012b)	TMEM138	AR	NPHP, rare	OMA, CB	CVH		PD				TZ
JBTS17/ OFD6	<i>C5ORF42</i> (Srouf et al. 2012b)	C5orf42	AR	RC	OMA, RP	CVH, ID		PD, FD				-
JBTS18/ OFD4	<i>TCTN3</i> (Thomas et al. 2012)	TCTN3, C10orf61	AR	RC	OMA	CVH, OE, ID	LF, BDP	PD, FD, Abnormal limbs		VSD		TZ
JBTS20/ OFD3/ MKS11	<i>TMEM231</i> (Srouf et al. 2012a)	TMEM231	AR	RC	OMA, RP	CVH, ID, OE		FD, PD			MKS	BB
JBTS21	<i>CSPP1</i> (Akizu et al. 2014)	CSPP1	AR	NPHP	OMA, RP	CVH, ID	LF	JATD			SD, PH	BB
JBTS22	<i>PDE6D</i> (Thomas et al. 2014)	PDE6D	AR	DK	CB, MO, RP	CVH, ID		FD, PD				BB

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Table 1. Continued

OMIM disease	Gene symbol (first description)	Alias	Mode of inheritance	Kidney	Eye	Brain	Liver	Skeletal anomalies	Laterality defects	Human disease phenotype		
										Congenital heart disease	Other/syndromic	Subcellular localization
JBTS23/ SKTD14	<i>KIAA0586</i> (Alby et al. 2015; Bachmann-Gagescu et al. 2015)	<i>KIAA0586</i> , <i>TALPID3</i>	AR		OMA, CB	CVH, HC, CBD		PD, FD, SRTD		ASD	HLS, PH	BB
JBTS24/ MKS8	<i>TECTONIC2</i> (Sang et al. 2011)	<i>TECTONIC2</i>	AR	DK	Nys, MO	CVH, ID, CBD	LE, BDP	PD			MKS	TZ
JBTS25	<i>CEP104</i> (Strout et al. 2015)	<i>CEP104</i>	AR	NPHP	OMA, RP	CVH, ID, CBD		Abnormal limbs, PD				BB, ciliary tip
JBTS26	<i>KIAA0556</i> (Sanders et al. 2015)	<i>KIAA0556</i> , <i>KATNIP</i>	AR			CVH, ID		FD				Ciliary base
MKS9	<i>B9D1</i> (Hopp et al. 2011)	<i>B9D1</i>	AR	RC, DK		OE		Abnormal limbs				TZ
MKS10	<i>B9D2</i> (Dowdle et al. 2011)	<i>B9D2</i>	AR	RC		OE, AE	DPM, LF	PD				BB, TZ
MKS12	<i>KIF14</i> (Filges et al. 2014)	<i>KIF14</i>	AR	DK, RA		MC, CVH, CBD		Abnormal limbs, FD				CA
n/a	<i>TMEM107</i> (Shaheen et al. 2015a; Lambacher et al. 2016; Shylo et al. 2016)			DK	RP	CVH, ID, OE		FD, PD			JBTS, OFD, MKS	TZ
Bardet–Biedl syndrome (BBS)												
BBS1	<i>BBS1</i> (Myktyyn et al. 2002)	<i>BBS1</i>	AR/DR	RC, DK	RP	ID	LE, rare	PD, BD, FD			OB	BBSome
BBS2	<i>BBS2</i> (Katsanis et al. 2001a; Nishimura et al. 2001)	<i>BBS2</i>	AR	RC, DK	RP	ID	LE, rare	PD, BD, FD			OB	BBSome

Continued

Table 1. Continued

OMIM disease	Gene symbol (first description)	Alias	Mode of inheritance	Human disease phenotype								Congenital heart disease	Other/ syndromic	Subcellular localization
				Kidney	Eye	Brain	Liver	Skeletal anomalies	Laterality defects					
BBS3	ARL6 (Fan et al. 2004)	ARL6/BBS3	AR/DR	RC, DK	RP	ID	LF, rare	PD, BD, FD				OB	BBSome	
BBS4	BBS4 (Katsanis et al. 2002)	BBS4	AR	RC, DK	RP	ID	LF, rare	PD, BD, FD				OB	BBSome	
BBS5	BBS5 (Li et al. 2004)	BBS5	AR	RC, DK	RP	ID	LF, rare	PD, BD, FD				OB	BBSome	
BBS6/ MKKS	MKKS (Katsanis et al. 2000; Slavotinek et al. 2000)	BBS6/MKKS	AR	RC, CAKUT	RP	ID	LF, rare	PD, BD, FD, congenital dislocation of hips		CHD	MKKS, OB, HL		BBSome	
	BBS7 (Badano et al. 2003)	BBS7	AR	RC, DK	RP	ID	LF, rare	PD, BD, FD			OB		BBSome	
BBS8	TTC8 (Ansley et al. 2003)	BBS8/TTC8	AR	RC, DK	RP	ID	LF, rare	PD, BD, FD			OB		BBSome	
BBS9	PTHB1 (Nishimura et al. 2005)	PTHB1/BBS9	AR	RC, DK	RP	ID	LF, rare	PD, BD, FD			OB		BBSome	
BBS10	BBS10 (Stoetzel et al. 2006)	BBS10/C12orf58	AR	RC, DK	RP	ID	LF, rare	PD, BD, FD			OB		BBSome	
BBS11	TRIM32 (Chiang et al. 2006)	BBS11/TRIM32	AR	RC, DK	RP	ID	LF, rare	PD, BD, FD			LGMD2H, OB	-		
BBS12	BBS12 (Stoetzel et al. 2007)	C4orf24	AR	RC, DK	RP	ID	LF, rare	PD, BD, FD			OB		BBSome	
BBS13/ MKS1	MKS1 (Kytälä et al. 2006; Leitch et al. 2008)	MKS1/BBS13	AR	RC, DK, RA	RP, CB, MO	ID, MiC, OE, AA	LF, BDP	PD, BD, FD		CHD	OB, MKS, PH		BBSome	
BBS15	WDPCP (Kim et al. 2010)	WDPCP, BBS15	AR	RC, DK	RP	ID	LF, rare	PD, BD, FD		CHD	OB		BBSome	
BBS17	LZTFL1 (Marion et al. 2012)	LZTFL1/BBS17	AR	RC, DK	RP	ID	LF, rare	PD, BD, FD	SI, HTX		OB		BBSome	
BBS18	BBIP1 (Scheidecker et al. 2014)	BBIP1/BBS18	AR	RC, DK	RP	ID	LF, rare	PD, BD, FD			OB		BBSome	
BBS19	IFT27 (Aldahmesh et al. 2014)	IFT27/RABL4	AR	RC, DK	RP	ID	LF, rare	PD, BD, FD			OB		BBSome	

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Table 1. Continued

OMIM disease	Gene symbol (first description)	Alias	Mode of inheritance	Human disease phenotype									
				Kidney	Eye	Brain	Liver	Skeletal anomalies	Laterality defects	Congenital heart disease	Other/syndromic	Subcellular localization	
Skeletal ciliopathies: oral-facial-digital syndrome (OFD), cranioectodermal dysplasia (CED), short-rib thoracic dysplasia (SRTD)													
OFD1/ JBTS10/ SGBS2	OFD1 (Ferrante et al. 2001; Budny et al. 2006)	OFD1, CXorf5	XD	RC	RP	ID, CBD, SZ, CVH	LC, LF	FD, OA, PD, BD		CHD	PC	BB	
OFD5	DDX59 (Shamseldin et al. 2013)	DDX59	AR	DK, rare		ID, CBD		PD, FD, OA		CHD, rare		-	
OFD9 (VUS)	SCLT1/TBC1D32 (Adly et al. 2014)	TBC1D32/ C6orf170, SCLT1	AR		CB, MO	MC, CBD, CVH		PD, FD, OA		CHD		-	
OFD14	C2CD3 (Thauvin-Robinet et al. 2014)	C2CD3	AR		RP	ID, CBD, CVH		PD, FD, OA				BB	
CED1	IFT122 (Walczak-Szulpa et al. 2010)		AR	NPHP	RP, Nys		LE, LC	FD, OA, SRTD, BD		CHD		CA	
CED2/ SRTD7	WDR35 (Gilissen et al. 2010; Mill et al. 2011)	WDR35/IFT121	AR	NPHP	RP		LE, BDR, LC	FD, OA, SRTD, BD, PD			PH, PC	CA	
CED3	IFT43 (Arts et al. 2011)	IFT43	AR	NPHP			LF	FD, OA, BD, PD, SRTD				CA	
SRTD2	IFT80 (Beales et al. 2007)	IFT80	AR					PD, BD, SRTD, TA				CA	
SRTD3	DYN2H1 (Dagoneau et al. 2009)	DYNC2H1	AR/DR	CK, DK	RP, rare	CBD, rare	LE, rare	PD, BD, SRTD, FD		CHD, rare	JATD	CA	
SRTD6	NEK1 (Thiel et al. 2011)	NEK1	AR/DR	CK		HC, rare	LE, rare	PD, SRTD, FD, OA, Dw		CHD, rare	HE, PH	Ncl	
SRTD8	WDR60 (McInerney-Leo et al. 2013)	WDR60	AR	CK		MaC,	DPM, LF	PD, SRTD		VSD	PH, PF	BB	

Continued

Table 1. Continued

OMIM disease	Gene symbol (first description)	Alias	Mode of inheritance	Human disease phenotype								Other/ syndromic	Subcellular localization
				Kidney	Eye	Brain	Liver	Skeletal anomalies	Laterality defects	Congenital heart disease			
SRTD9 / MZSDS	IFT140 (Perrault et al. 2012; Schmidts et al. 2013b)	IFT140	AR	NPHP	RP, Nys	MiC, ID, DD	LF	SRTD, CSE, cranosynostosis				CA	
SRTD11	WDR34 (Huber et al. 2013; Schmidts et al. 2013c)	WDR34	AR					BD, PD, SRTD, TA		PH		CA	
SRTD13	CEP120 (Shaheen et al. 2015b)	CEP120, CCDC100	AR	NPHP		CVH		SRTD, PD, FD, OA		PH		BB	
EVC	EVC (Ruiz-Perez et al. 2000)						ID, DWM	PD, SRTD, CED, Dw, OA	CHD		CA + BB		
EVC	EVC2 (Galdzicka et al. 2002)						ID, DWM	PD, SRTD, CED, Dw, OA	CHD		CA + BB		
-	IFT57 (Thevenon et al. 2016)	IFT57	AR					FD, PD			CA		
-	IFT52 (Girisha et al. 2016)	IFT52	AR		VL, Nys			PD, BD, FD, SRTD			CA		
Alstrom and Usher syndrome													
ALMS	ALMS1 (Hearn et al. 2002)	ALMS1	AR	NPHP, CAKUT	RP, Nys		LF	Skeletal anomalies	DCM	SD, OB, HT, HU, Dm	BB		
USH1B	MYO7A (Weil et al. 1995)	MYO7A	AR		RP, VL	DD				SD			
USH1C	USH1C (Verpy et al. 2000)	USH1C / HARMONIN	AR		RP, VL					SD			
USH1D	CDH23 (Bolz et al. 2001)	CDH23	AR/DR		RP, VL					SD			
USH1E	USH1E (Chaib et al. 1997)	USH1E	AR		RP, VL					SD			
USH1F	PCDH15 (Ahmed et al. 2001)	PCDH15	AR		RP, VL					SD			
USH1G	SANS (Weil et al. 2003)	SANS	AR		RP, VL					SD			
USH1J/DFNB48	C12orf65 (Riazuddin et al. 2012)		AR		RP, VL					SD			
USH2A/RP39	USH2A (Eudy et al. 1998)	USHERIN	AR		RP, VL					SD			

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Table 1. Continued

OMIM disease	Gene symbol (first description)	Alias	Mode of inheritance	Human disease phenotype						Congenital heart disease	Other/syndromic	Subcellular localization
				Kidney	Eye	Brain	Liver	Skeletal anomalies	Laterality defects			
USH2C	GPR98 (Weston et al. 2004) PDZD7, DR (Ebermann et al. 2010)	GPR98	AR/DR		RP VL						SD	
USH2D/DFNB31	WHRN (Ebermann et al. 2007)	WHRN	AR		RP VL						SD	
USH3A	CLRN1 (Joensuu et al. 2001)	CLRN1	AR		RP VL						SD	
USH3B	HARS (Puffenberger et al. 2012)	HARS	AR		RP VL						SD	

Columns represent disease name, gene symbol, encoded protein/aliases, human disease phenotype, and subcellular localization. The first description of each gene is cited in the second column. Diseases are grouped as (I) Nephronophthisis (NPHP), Senior-Loken syndrome (SLS), Joubert syndrome (JBS), Meckel-Gruber syndrome (MKS); (II) Bardet-Biedl syndrome (BBS); and (III) skeletal ciliopathies, oral-facial-digital syndrome (OFD), cranioectodermal dysplasia (CED), and short-rib thoracic dysplasia (SRTD). Grouping is in accordance with Figures 1 and 2.

ACS, acrocallosal syndrome; AE, anencephaly; AR, autosomal recessive; BB, basal body; BD, brachydactyly; BDD, bile duct proliferation; CA, ciliary axoneme; CAKUT, congenital anomalies of the kidney and urinary tract; CB, coloboma; CBD, congenital brain defects; CHD, congenital heart defect; COACH, COACH (cerebellar vermis defect, oligophrenia, ataxia, coloboma, hepatic fibrosis) syndrome; CSE, cone-shaped epiphyses; CVH, cerebellar vermis hypoplasia; DCM, dilated cardiomyopathy; DD, developmental delay; DK, dysplastic kidneys; Dm, diabetes mellitus; DPM, ductal plate malformations; DR, digenic recessive; DW, dwarfism; DWM, Dandy-Walker malformation; EVC, Ellis-van Creveld syndrome; FD, facial dysmorphism; HC, hydrocephalus; HF, hydrophalus; HFS, hydrophalus; HT, hypertension; HTX, heterotaxia; HU, hyperuricemia; ID, intellectual disability; JATD, juvenile asphyxiating thoracic dystrophy; LC, liver cysts; LF, liver fibrosis; MacC, macrocephaly; MiC, microcephaly; MKKS, McKusick-Kaufman syndrome; MO, microphthalmia; MORM, MORM (mental retardation, truncal obesity, retinal dystrophy, and micropenis) syndrome; MPD, multiorgan polycystic disease; Ncl, nuclear; Nys, nystagmus; OA, oral anomalies; OB, obesity; OE, occipital encephalocele; OH, oligohydramnios; OMA, oculomotor apraxia; OMIM, Online Mendelian Inheritance in Man, Johns Hopkins University; OpA, optic atrophy; PD, polydactyly; PF, pancreatic fibrosis; PC, pancreatic cysts; PH, pulmonary hypoplasia; RA, renal agenesis; RC, renal cysts; RF, renal failure; RHPD1, renal-hepatic-pancreatic dysplasia, type 1; RP, retinitis pigmentosa; SD, sensorineural deafness; SGBS2, SI, *situs inversus*; SZ, seizures; Simpson-Golabi-Behmel syndrome, type 2; TA, trident acetabulum; TZ, transition zone; VL, vision loss; VSD, ventricular septal defect; VUS, variant of unknown significance.

Figure 1. Monogenic genes of nephronophthisis-related ciliopathies (NPHP-RC) cause distinct but widely overlapping phenotypes. Monogenic genes of NPHP-RC are categorized into four major phenotypes, namely, JBTS (blue, Joubert syndrome [JBTS]: congenital brain malformations, cerebellar vermis hypoplasia, and intellectual disability), NPHP/SLS (red, nephronophthisis/Senior-Loken syndrome [SLS]: nephronophthisis [NPHP], retinal degeneration, coloboma), BBS (yellow, Bardet-Biedl syndrome [BBS]: obesity, intellectual disability, retinal degeneration, cystic kidney disease, polydactyly, hypogonadisms), and skeletal ciliopathies (green, oral-facial-digital syndrome [OFD], cranioectodermal dysplasia (CED), short-rib thoracic dysplasia [SRTD]). As shown in a Venn diagram, numerous genes can give rise to overlapping phenotypes if mutated. Meckel-Gruber syndrome (MKS), the most severe clinical manifestation of NPHP-RC, can be caused by mutations in 10 monogenic genes. With the exception of the genes *B9D1* and *B9D2* that have not been described in association with other phenotypes, MKS is caused by mutations in monogenic genes of nephronophthisis, Joubert syndrome, and Bardet-Biedl syndrome on an allelic basis. White text indicates genes in which liver involvement has been reported.

gout. By now, two monogenic causes of MCKD have been described, namely, the genes *MUC1* (MCKD, type 1; OMIM #174000) and *UMOD* (MCKD, type 2; OMIM #603860). Interestingly, the *UMOD* protein localizes to renal primary ciliary and colocalizes with other ciliary proteins

such as nephrocystin (Zaucke et al. 2010). Besides MCKD2, mutations of *UMOD* also give rise to the renal diseases glomerulocystic kidney disease with hyperuricemia and isosthenuria (OMIM #609886) and familial juvenile hyperuricemic nephropathy (OMIM #162000).

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Figure 2. Subcellular localization of proteins encoded by monogenic genes of nephronophthisis-related ciliopathies (NPHP-RC). Subcellular localization of proteins encoded by monogenic genes of NPHP-RC is depicted. Proteins are color-coded based on their respective disease group as shown in Table 1 (red/orange/pink: nephronophthisis [NPHP], Senior–Loken syndrome [SLS], Joubert syndrome [JBTS], Meckel–Gruber syndrome [MKS]; yellow: Bardet–Biedl syndrome [BBS]; green: skeletal ciliopathies). It becomes apparent that disease groups cluster to distinct subcellular localizations. IFT, Intraflagellar transport.

RENAL PHENOTYPE OF NPHP

Clinical Presentation of NPHP

The clinical presentation of NPHP was first described in 1951 by Guido Fanconi who introduced the term “nephronophthisis,” which

translates as disappearance of nephrons to describe the renal histology of affected children (Fanconi et al. 1951). With the exception of infantile NPHP, caused by mutations in the gene *IVSN* (NPHP type 2), clinical symptoms of NPHP typically start at an average age of 4–6

years (Kleinknecht 1989). The major pathology in this early phase is an impaired ability of the kidney to concentrate urine and retain water. This results in reduced urine osmolality and explains the hallmark symptoms of NPHP, namely, polyuria and polydipsia, which are present in ~80% of affected patients (Kleinknecht 1989). Secondary enuresis and regular fluid intake at night are characteristic features of NPHP and should be specifically investigated when taking the patient's history. In contrast to other pediatric kidney diseases edema, hypertension, and recurrent infections of the urinary tract are uncommon in patients with NPHP. Later in the course of disease progression, anemia and growth retardation occur. It has been noticed that, when adjusted to the degree of renal failure, both symptoms are pronounced in NPHP as compared to other renal diseases (Ala-Mello et al. 1996). With further deterioration of renal function, the clinical presentation is dominated by classical symptoms of end-stage renal failure, such as fatigue, weakness, pruritus, pallor, electrolyte imbalance, and fluid overload. If the diagnosis is missed at this stage of disease progression, patients are at risk for cardiac arrhythmia and sudden death because of electrolyte imbalances, particularly hyperkalemia.

Therapy and Prognosis of NPHP

Despite intensive research, a curative or targeted therapy for NPHP is currently not available. Treatment of NPHP is therefore centered on correcting the secondary consequences of chronic kidney disease, such electrolyte imbalances, fluid overload, anemia, renal osteodystrophy, secondary hyperparathyroidism, and growth retardation. Psychosocial counseling and intense patient/family education are an integral part of successful treatment strategies as these patients have to cope with a chronic condition that requires intense lifelong therapy. Once end-stage renal disease (ESRD) has occurred, renal replacement therapy with either dialysis or renal transplantation is the only remaining treatment option. Recurrence of NPHP after renal transplant has never been reported (Steel et al. 1980).

Across all subtypes of NPHP, chronic renal failure typically develops within the first three decades of life (Hildebrandt et al. 1997b; Haider et al. 1998; Omran et al. 2000). Onset of ESRD later than 30 years of age is uncommon in all types of NPHP. Therefore, the clinical diagnosis should be reevaluated and other differential diagnoses should be considered if renal failure has not occurred by age 30 years. Interestingly, a high concordance in the rate of deterioration of renal function has been noticed between monozygotic twins, suggesting that the individual genotype determines the disease course and the development of ESRD (Mongeau and Worthen 1967; Makker et al. 1973).

Renal Pathology in NPHP

Macroscopic Pathology

The renal pathology of NPHP differs considerably from other cystic kidney diseases such as autosomal-dominant and autosomal-recessive polycystic kidney disease (ARPKD/ADPKD) (Waldherr et al. 1982). The kidney size is typically normal or slightly reduced. Renal echogenicity is characteristically enhanced as a result of renal fibrosis. Cysts are present in ~70% of affected individuals, but are not a prerequisite for the diagnosis of NPHP. Furthermore, progressive intestinal fibrosis rather than cyst development represents the primary pathogenic mechanism driving disease progression (Bernstein and Gardner 1992). If cysts are present, they are typically small in size, arise from the corticomedullary border region of the kidney, (Sherman et al. 1971) and develop late in the course of disease (Sworn and Eisinger 1972). In contrast to this classical renal phenotype, mutations in some monogenic genes of NPHP, notably the genes *INVS* (Otto et al. 2003b) and *ANKS6* (Hoff et al. 2013) (NPHP types 2 and 16), can cause a phenotype that resembles ARPKD and is characterized by enlarged, multicystic kidneys (Igarashi and Somlo 2002). Cysts in other organs have not been described in isolated NPHP. However, severe forms of renal ciliopathies can present as multicystic, dysplastic developmental phenotypes affecting all organ

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systems. In NPHP, there is always bilateral renal involvement.

Microscopic Pathology

Histologic hallmark findings of NPHP are summarized in a histological triad consisting of (a) disintegration and irregular thickening of the tubular basement membrane (TBM), (b) interstitial inflammation with round-cell infiltration and consecutive fibrosis, (c) tubular atrophy and cyst formation at the corticomedullary junction (Zollinger et al. 1980; Waldherr et al. 1982). Cyst formation in NPHP is thought to be secondary to degeneration and atrophy of kidney tissue rather than being an independent, primary process triggering disease progression. Early histological changes in NPHP are most prominent in distal tubules and, in contrast to other monogenic kidney disease, cells of the renal glomerulus are characteristically unaffected in NPHP. Transmission electron microscopy (TEM) in NPHP reveals characteristic changes of the tubular membrane, namely, thickening, attenuation, splitting, and granular disintegration. The presence of these alterations is discontinuous, and shows wide variability between different sections of an affected kidney. In end-stage NPHP, the histology is dominated by severe, diffuse sclerotic tubulointerstitial nephropathy.

Diagnostics and Differential Diagnosis of NPHP

Molecular genetic analysis represents the only method to diagnose NPHP-RC with certainty and thus provide patients and families with an unequivocal diagnosis. Because of an increasing number of potentially causative monogenic genes as well as advances in next-generation sequencing, whole-exome sequencing has mostly replaced targeted-sequencing panels in the diagnosis of NPHP-RC (Halbritter et al. 2012, 2013b; Gee et al. 2014). By applying this method, a causative single-gene mutation can be detected in up to 60% of cases depending on the composition of the cohort (Braun et al. 2015). However, if no mutation is detected, the diagnosis of NPHP is not excluded. Importantly,

genetic testing should always be combined with thorough phenotyping as well as genetic counseling. Renal ultrasound imaging represents a very useful tool for the early diagnosis of otherwise asymptomatic renal ciliopathies. Characteristic findings include increased echogenicity, loss of corticomedullary differentiation and corticomedullary cysts (Blowey et al. 1996; Aguilera et al. 1997; Ala-Mello et al. 1998). Renal ultrasonography can help to distinguish NPHP from other inherited kidney diseases such as congenital anomalies of the kidney and urinary tract (CAKUT) or nephrocalcinosis. In some cases, magnetic resonance imaging (MRI) can provide additional insights. Other than molecular genetic testing, there is no laboratory test that specifically detects NPHP. However, serum chemistry analysis is very useful to monitor progressive renal impairment, as well as complications of chronic kidney disease. Unaffected siblings should be carefully examined and closely monitored to allow early diagnosis. However, it is generally not recommended to perform genetic testing in unaffected siblings to avoid stigmatization (Ross et al. 2013). In contrast to other monogenic kidney diseases, proteinuria, hematuria, or recurrent infections are characteristically absent in NPHP. Lack of hypertension, differences in kidney size, and distinct localization of cysts, can help to distinguish NPHP from other forms of cystic kidney disease. However, especially in late stages differential diagnosis can be challenging.

EXTRARENAL MANIFESTATIONS OF NPHP-RELATED CILIOPATHIES

Renal ciliopathies are frequently associated with additional clinical symptoms that affect other organ systems than the kidney. Typical extrarenal manifestations of renal ciliopathies include retina, central nervous system (CNS), liver, and bones. The association of NPHP with retinal degeneration (Senior–Loken syndrome) is most frequent and occurs in ~10% of all patients with NPHP (Loken et al. 1961; Senior et al. 1961). Furthermore, NPHP can be accompanied by oculomotor apraxia (Cogan syndrome) (Betz et al. 2000), by cerebellar vermis

hypoplasia and retinal coloboma (Joubert syndrome) (Saraiva and Baraitser 1992; Valente et al. 2006), by liver fibrosis (Boichis et al. 1973), by ectodermal dysplasia (Sensenbrenner syndrome, oral-facial-digital syndrome type I) (Bredrup et al. 2011; Fehrenbach et al. 2014), and in rare cases by congenital heart defects (Otto et al. 2003a; Rajagopalan et al. 2016). Skeletal malformations associated with renal ciliopathies include thoracic dystrophy (Jeune syndrome) (Halbritter et al. 2013a; Huber et al. 2013; Schmidts et al. 2013a), poly- and brachydactyly, and cone-shaped epiphysis (Mainzer-Saldino syndrome) (Perrault et al. 2012). In addition, patients with infantile NPHP can show heterotaxy, *situs inversus* and potentially lung involvement (Otto et al. 2003a). Because extrarenal symptoms can be discrete but result in severe complications, screening of affected patients is generally recommended. Therefore, in addition to thorough genotyping, all patients should undergo ophthalmoscopy to exclude retinal involvement, as well as liver ultrasound examination and laboratory test for liver function. Characteristic extrarenal phenotypes for monogenic genes of human ciliopathies are summarized in Table 1. As shown in Figure 1, there is broad phenotypic overlap between different monogenic disease genes. Advances in next-generation sequencing have drastically accelerated the identification of novel single-gene causes of human ciliopathies over the last years. With increasing numbers of identified disease genes, it has become apparent that the proteins encoded by genes responsible for different subtypes of ciliopathies cluster in protein complexes that localize to distinct subcellular localizations (Fig. 2).

Retinal Involvement (Senior–Løken Syndrome)

Senior–Løken syndrome (SLS) or renal–retinal dysplasia describes the syndromic association of NPHP with retinal involvement. This association was first reported by Løken et al. (1961), Senior et al. (1961), and Fairley et al. (1963). The retinal pathology in SLS has been described as retinitis pigmentosa, tapetoretinal degenera-

tion, and retinal aplasia, which likely represent a phenotypic spectrum ranging from dysplastic, developmental, to degenerative defects (Saraux et al. 1970). Similarly, early- and late-onset forms of SLS can be distinguished based on age of onset and clinical presentation. The early onset type (a form of Leber congenital amaurosis) typically manifests at birth with blindness, reduced or absent response in electroretinography, and nystagmus. If not present at birth, disease symptoms develop rapidly within the first 2 years of life (Medhioub et al. 1994). The late-onset form typically develops slowly, starting with night blindness and progressive vision loss during school age. The clinical diagnosis is based on electroretinography (ERG) that shows a constant and complete extinction of response to stimuli reflecting retinal degeneration, as well as characteristic findings on funduscopy. Typically, ophthalmoscopic alterations are present in all SLS patients by the age of 10 years. Specific findings in ophthalmoscopy in these patients include retinitis pigmentosa, characterized by increased retinal pigmentation, attenuation of retinal vessels, atrophy of retinal pigment epithelium, pallor of the optic disc, and tapetoretinal degeneration. Additional eye symptoms include atrophy of the optic nerve, nystagmus, choroidal coloboma, and ametropia (myopia, hyperopia, amblyopia, and strabismus) (Adams et al. 2007). Retinitis pigmentosa is the most common extrarenal manifestation of NPHP-related ciliopathies. It occurs in ~10% of affected individuals and affects predominantly patients with causative mutations in the genes *IQCB1/NPHP5* (Otto et al. 2005) and *CEP290/NPHP6* (Valente et al. 2006). Remarkably, to date, all described cases of mutations of *IQCB1/NPHP5* showed retinal involvement (Otto et al. 2005). However, it can be present in virtually all types of NPHP. Interestingly, the renal phenotype of patients with and without retinal involvement is indistinguishable.

Oculomotor Apraxia (Cogan Syndrome)

Oculomotor apraxia, type Cogan, is a disorder of the CNS that affects the coordination of voluntary eye movements. Affected individuals are

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unable to execute purposeful horizontal eye movement to focus on or follow an object of interest. The clinical presentation is dominated by jerking head movements or compensatory head turning for side vision, as well as optokinetic nystagmus. This symptom has been described in patients with mutations in the genes *NPHP1* (Betz et al. 2000) and *NPHP4* (Mollet et al. 2002). Frequently, the defect is transient and improves after the first years of life. In contrast to retinitis pigmentosa, in which the defect lies in the eye itself, the underlying defect in Cogan syndrome affects central nervous regions responsible for motor control of eye movements, such as the nuclei of the abducens or oculomotoric nerves as well as supranuclear control regions.

Cerebellar Vermis Hypoplasia (Joubert Syndrome)

Joubert syndrome is a developmental disorder that manifests with a complex phenotype and involves various organ systems. Most prominent are developmental defects of the CNS, particularly the brain stem region and the cerebellum (Romani et al. 2013). The hallmark symptom of Joubert syndrome on radiology imaging of the CNS, namely, the so-called molar tooth sign, is explained by agenesis or hypoplasia of the cerebellar vermis. Furthermore, occipital meningo- or meningoencephalocele can be present in some cases. Clinically affected patients present with various degrees of psychomotor retardation, intellectual disability, and disrupted motor coordination causing hypotonia, ataxia, and oculomotor apraxia. Severe cases can manifest with defects of neonatal breathing regulation and newborn tachypnea. Outside the CNS, Joubert syndrome can involve facial dysmorphism, retinal dysplasia, coloboma of the optic nerve, and, less frequently, polydactyly, renal cysts, and hepatic fibrosis. Genetically, Joubert syndrome is remarkably heterogeneous and, by now, 27 monogenic genes have been identified as causative when mutated. Among the first monogenic genes to be described in patients with Joubert syndrome were the genes *NPHP1* (Parisi et al. 2004) and

AHI (Dixon-Salazar et al. 2004), which encode for a protein called Joubertin. Joubertin interacts with *NPHP1*, *NPHP3*, and *NPHP4* and, interestingly, Joubertin as well as other proteins that are altered in Joubert syndrome localizes to a defined region of primary cilia, the so-called transition zone (Fig. 2) (Omran 2010). With increasing numbers of molecularly diagnosed patients, specific genotype–phenotype correlations have been observed for specific genes (Hildebrandt et al. 2011). For example, mutations in *NPHP1*/*JBTS4* typically cause isolated nephronophthisis with Joubert syndrome (Parisi et al. 2004), whereas mutations in *CEP290*/*JBTS5* (Sayer et al. 2006; Valente et al. 2006) and *RPGRIP1L*/*JBTS7* (Arts et al. 2007; Delous et al. 2007) frequently show retinal–renal syndrome, although mutations of *TMEM67*/*JBTS6* characteristically involve liver fibrosis (Table 1; Fig. 1) (Otto et al. 2009).

Renal Ciliopathies with Liver Involvement

In patients with mutations in the genes *NPHP3* (Olbrich et al. 2003), *TMEM67* (Otto et al. 2009), *ANKS6* (Hoff et al. 2013), and most recently *DCDC2* (Schueler et al. 2015), renal ciliopathies can be associated with liver involvement. The liver phenotype in these patients is characterized by hepatomegaly, periportal liver fibrosis, ductal plate malformations, and bile duct proliferation. The phenotype of renal–hepatic ciliopathies is characteristically different from congenital liver fibrosis, which is dominated by dysplasia and agenesis of bile ducts. The association of cerebellar vermis hypoplasia, oligophrenia, congenital ataxia, ocular coloboma, and hepatic fibrosis is known as COACH syndrome and is most frequently caused by mutations of *TMEM67* (*NPHP11*/*JBTS6*/*MKS3*) (Brancati et al. 2009) or in rare cases by mutations of *CC2D2A* or *RPGRIP1L* (Doherty et al. 2010). In patients with infantile nephronophthisis (caused by mutations of *NPHP2*), a transient elevation of liver enzymes without histopathologic changes or disturbed liver architecture has been described (Haider et al. 1998). Interestingly, in some cases, different phenotypes can be caused by mutations of the

same gene on an allelic basis. Among others, this is true for mutations of the gene *ANKS6* in which protein-truncating nonsense mutations results in a severe, syndromic phenotype that involves liver fibrosis, whereas hypomorphic mutations results in isolated nephronophthisis only (Hoff et al. 2013).

Skeletal Phenotypes and Polydactyly

Short-rib thoracic dysplasia with and without polydactyly (SRTD) describes a group of ciliopathies with skeletal involvement, including poly-/brachydactyly, shortening of the long bones, cone-shaped epiphysis, and malformations of the ribs and thoracic cage. The most severe form, which is known as Jeune syndrome or asphyxiating thoracic dystrophy (ATD), is characterized by severely shortened ribs resulting in respiratory distress after birth (Jeune et al. 1955; Donaldson et al. 1985). Other diseases summarized in this group are Ellis–van Creveld syndrome (chondroectodermal dysplasia, OMIM #225500) (Moudgil et al. 1998) and Mainzer–Saldino syndrome (Mortellaro et al. 2010). The phenotypes observed in cranioectodermal dysplasia (Sensenbrenner syndrome, OMIM #218330) partially overlap with those of SRTD (Gilissen et al. 2010). Interestingly, many of the proteins encoded by genes that are mutated in patients with skeletal ciliopathies play a role in ciliary transport, such as the components of the intraflagellar transport (IFT) modules or dynein motor components (Fig. 2) (Perrault et al. 2012; Halbritter et al. 2013a; Schmidts et al. 2013a). It has been postulated that disruption of sonic hedgehog signaling, a pathway that is particularly important for bone morphogenesis and that depends on intact primary cilia for signal transduction, represents the molecular pathogenic link between ciliary dysfunction and skeletal anomalies (Huangfu et al. 2003; Qin et al. 2011).

Laterality Defects and Congenital Heart Disease

Although laterality defects such as *situs inversus* and *situs solitus* are frequently observed in pa-

tients with defects of motile cilia, they have only been described in very limited subgroups of patients with NPHP-RC. The most prominent example for this combination of phenotypes is represented by patients with mutations in the gene *NPHP2/inversin*, in which the association between infantile nephronophthisis and *situs inversus* was first described in 2003 (Otto et al. 2003a). Similar to what had been observed in the *inv/inv* knockout mouse (Mochizuki et al. 1998; Morgan et al. 1998), patients also showed congenital heart defects, such as heterotaxy, ventricular septum defects, and vascular malformations (Otto et al. 2003a). Comparably, knockdown of the ortholog of the *inversin* gene in zebrafish results in randomization of heart looping (Otto et al. 2003a). With growing numbers of detected mutations, there is increasing evidence that also proteins encoded by other monogenic genes of NPHP-RC play a role in the determination of left–right asymmetry. For example, nonsense mutations in the gene *NPHP3* cause a severe developmental phenotype resulting in embryonic lethality, which among other features also includes *situs inversus* as well as congenital heart defects (Bergmann et al. 2008). Similarly, *situs inversus* and congenital heart defects have recently been described in patients with mutations of *ANKS6* (Hoff et al. 2013) and *NEK8* (Frank et al. 2013). Interestingly, the encoded proteins of all four genes interact and colocalize to a specific compartment of primary cilia, the so-called transition zone (Czarnecki et al. 2015). This finding underlines that specific “protein modules” may give rise to distinct clinical phenotypes.

Other Syndromic Ciliopathies

Meckel–Gruber syndrome (MKS, OMIM #249000) represents the most severe clinical manifestation of human ciliopathies. It is an autosomal-recessive developmental disorder that can affect various organ systems and shows vast phenotypic pleiotropy. Frequently, the combination of severe developmental defects results in embryonic or perinatal lethality. Characteristic symptoms include malformations of the CNS, such as hydrocephalus, microcephaly,

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occipital encephalocele, and, most severely, complete anencephaly. In addition, most patients show cystic–dysplastic kidney disease, liver involvement, congenital heart defects, dysmorphic features, and skeletal malformation, predominantly polydactyly. MKS presents with oligohydramnios caused by impaired kidney function, and can be diagnosed on perinatal ultrasound. With the exception of the genes *B9D1* (Hopp et al. 2011) and *B9D2* (Dowdle et al. 2011) that have not been described in association with other phenotypes, MKS is caused by mutations in monogenic genes of nephrophtosis, Joubert syndrome, and Bardet–Biedl syndrome on an allelic basis. Typically, truncating mutations give rise to the severe developmental phenotype of MKS, whereas hypomorphic mutations result in limited, organ specific disease that is degenerative rather than developmental (Hildebrandt et al. 2011).

Oral-facial-digital syndrome, type 1 (OFD1, OMIM #311200) is an X-linked dominant ciliopathy with prominent dysmorphic and external features. Because the disease is embryonic lethal in males, all surviving affected patients are female. The syndrome is characterized by oral anomalies (i.e., defective dentation, cleft lip and palate, lobulated tongue), facial dysmorphism, and polydactyly, as well as other malformations of fingers and toes. About 50% of affected individuals show structural defects of the CNS, including microcephaly, defective gyration, agenesis of the corpus callosum, and arachnoidal cysts. Seizures and variable degrees of intellectual disability can be present (Macca and Franco 2009). In contrast to other subtypes of oral-facial-digital syndrome, adult-onset cystic kidney disease has only been described in patients with OFD type 1 in which it is present in ~50% of cases. Furthermore, fibrocystic liver disease with elevated liver enzymes can be present (Chetty-John et al. 2010). The syndrome is caused by mutations in the gene *OFD1*, which on an allelic basis can also give rise to Joubert syndrome (JBTS10, OMIM #300804) as well as Simpson–Golabi–Behmel syndrome type 2 (GBS2, OMIM #300209). Interestingly, the gene product of *OFD1* localizes to the centrosome and ciliary basal body (Chetty-John et al. 2010).

Bardet–Biedl syndrome (BBS, OMIM #209900) is a complex, syndromic ciliopathy that affects numerous organ systems. Classical symptoms include intellectual disability and behavioral anomalies, as well obesity, cystic kidney disease, retinitis pigmentosa, hypogonadism, and polydactyly. BBS is genetically very heterogeneous and by now, mutations in 19 monogenic genes have been described as causative. Although BBS is typically inherited in an autosomal-recessive manner, recent publications have suggested that digenic inheritance may also be possible (Katsanis et al. 2001b; Fan et al. 2004; Katsanis 2004). Thus far, BBS is the only ciliopathy for which a mode of inheritance different from strictly recessive (autosomal or X-linked) has been described. Interestingly, the protein products encoded by known monogenic genes of BBS interact with each other to form a tight protein complex, the so-called BBSome, which carries important functions for ciliary trafficking (Loktev et al. 2008; Jin and Nachury 2009; Zhang et al. 2013).

Alstrom syndrome (OMIM #203800) is an autosomal-recessive disorder that involves multiple organ systems and resembles BBS in some aspects of its clinical presentation. Prominent symptoms include progressive sensorineural deafness and vision loss caused by cone-rod degeneration, as well dilated cardiomyopathy with congestive heart failure. Affected patients show childhood-onset obesity and can have endocrine disorders, predominantly diabetes mellitus type 2. In some cases, kidney involvement with progressive renal failure, recurrent pulmonary infections, and hepatomegaly have been described. To date, the gene *ALMS1* (Collin et al. 2002; Hearn et al. 2002) is the only described single-gene cause of Alstrom syndrome.

Usher syndrome (OMIM #276901) is a ciliopathy that is characterized by sensorineural deafness and progressive vision loss caused by retinal degeneration. Based on severity and age of onset, Usher syndrome is further classified in subtypes 1, 2, and 3. In the most severe type 1, children are predominantly born deaf and progressive vision loss begins in childhood. The syndrome is genetically heterogeneous and, by now, mutations in 14 genes have been identified

as causative in humans (Table 1). Although the mode of inheritance is classically autosomal-recessive, digenic inheritance has been described for some genes.

MOLECULAR GENETICS OF NEPHRONOPHTHISIS-RELATED CILIOPATHIES

Identification of monogenic causes of NPHP-RC has furthered the understanding of its pathogenesis. The observation that the protein products of most NPHP-RC genes localizes to primary cilia, basal bodies, or centrosomes has led to the term ciliopathies to classify this group of diseases (Hildebrandt et al. 2011). Mutational analysis allows an etiologic classification of different subtypes of NPHP-RC, and enables physicians to provide patients and families with an unequivocal diagnosis. For the identification of the first single-gene causes of NPHP, namely, *NPHP1-GLIS2/NPHP7*, researchers relied on linkage analysis and positional cloning. Because of recent progress in next-generation sequencing, gene discovery has exponentially increased and by now, in up to 63% of affected individuals, a causative single gene mutation can be identified (Halbritter et al. 2012, 2013b; Braun et al. 2015). The combination of whole-exome sequencing with homozygosity mapping in consanguineous kindred, or with linkage analysis in familial cases, has proven to be a powerful tool for the identification of novel ciliopathy genes (Otto et al. 2010; Chaki et al. 2012; Schueler et al. 2015). By now, 19 classical NPHP genes and more than 90 additional ciliopathy genes have been identified as mutated in affected individuals. With the exception of the gene *NPHP1*, which explains about 25% of all cases with NPHP, mutations in other subsequently identified genes each account for only small percentages of affected individuals.

Nephronophthisis Type 1 (*NPHP1*)

In 1997, using total genome search and linkage analysis, a gene locus for juvenile nephronophthisis was mapped to chromosome 2q12-q13 (Antignac et al. 1993; Hildebrandt et al. 1993).

Molecular cloning subsequently allowed the identification of the gene *NPHP1* within that region (Hildebrandt et al. 1997a; Saunier et al. 2000). Future studies showed that about 25% of all patients with NPHP harbor causative mutations in this gene. About 85% of the mutations in *NPHP1* are large homozygous deletions of the complete *NPHP1* gene (Konrad et al. 1996; Saunier et al. 2000; Hildebrandt et al. 2001). The high degree of genomic rearrangements is caused by two large inverted duplications that flank the *NPHP1* locus on both sites (Saunier et al. 2000). The *NPHP1* locus was later described as one of 24 regions within the human genome in which sequence duplications results in hot spots of genomic instability that subsequently give rise to human disease (Bailey et al. 2002). In patients with mutations of *NPHP*, end-stage renal disease is reached at a median age of 13 years. About 10% show a combined phenotype of retinitis pigmentosa and NPHP (Caridi et al. 2000). The occurrence of oculomotor apraxia (Betz et al. 2000) and cerebellar vermis hypoplasia (Parisi et al. 2004) in patients with *NPHP1* mutations has been described but is very rare. Interestingly, there is no recognizable correlation between genotype and phenotype.

EVOLUTIONARY CONSERVATION AND MODEL ORGANISMS OF NPHP-RC

Numerous ciliary proteins and their functions are highly conserved throughout evolution. Most strikingly, the ciliary intraflagellar transport system is conserved down to the green alga *Chlamydomonas reinhardtii*, and this model system has proven very useful for the identification of novel proteins and mechanisms that are part of this machinery (Pedersen et al. 2006; Engel et al. 2012; Taschner et al. 2016). Orthologs of ciliary proteins are expressed in sensory neurons of the nematode *Caenorhabditis elegans*. Expression of green fluorescent protein (GFP)-tagged fusion proteins containing the promoter regions of the orthologs of the human ciliopathy genes *NPHP1* and *NPHP4*, showed that these genes are specifically ex-

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pressed in ciliated sensory neurons in the head and tail regions (Wolf et al. 2005). Interestingly, on RNAi knockdown of *nph-1* and *nph-4* male animals showed abnormal mating behavior (Wolf et al. 2005), which was similar to the phenotype observed on knockdown of the orthologs of *PKD1* and *PKD2* (Barr et al. 2001). Mutations in *nphp-8*, the *C. elegans* ortholog of *RPGRIP1L*, resulted in reduced ciliary length and functional impairment of ciliated neuron (abnormal dye filling and reduced chemotaxis) (Liu et al. 2011). *C. elegans* ciliated neurons are a unique tool for in vivo microscopy, and, as one example, this system has helped to unravel the evolutionary conserved role of the BBSome for the assembly of intraflagellar transport particles (Wei et al. 2012). Furthermore, the strong evolutionary conservation of ciliary genes allows, using the *C. elegans* system, to study newly identified human disease genes, and test for pathogenicity of specific allelic mutations in these genes (Roberson et al. 2015). Genetic mouse and zebrafish models, as well as *Xenopus tropicalis* are established vertebrate organisms to model and study gene defects that give rise to human ciliopathies. The *inv/inv* mouse, in which the murine ortholog of *NPHP2* is mutated, shows phenotypic features compatible with the one described in affected patients, in particular, cystic kidney disease, disrupted left–right determination, congenital heart defects, and liver involvement (Phillips et al. 2004). Similarly, the *pcy* mouse, in which the ortholog of human *NPHP3* is disrupted, shows tubulointerstitial renal fibrosis and cysts. The genetic zebrafish model *scorpion*^{hi459} (Duldulao et al. 2009) carries a zygotic null allele for the ortholog of the human ciliopathy gene *ALR13b*. Mutant zebrafish show a characteristic ciliopathy phenotype including body axis curvature and pronephric renal cysts (Duldulao et al. 2009). Furthermore, a canine model of NPHP (Finco et al. 1970, 1977; Finco 1976) and a chicken with a mutation of *Talpid3* (Izpisua-Belmonte et al. 1992; Davey et al. 2006), the ortholog of the human Joubert gene *KIAA0586* (Alby et al. 2015; Bachmann-Gagescu et al. 2015; Malicdan et al. 2015; Roosing et al. 2015), have been described.

CONCLUDING REMARKS

Identification of monogenic causes of human ciliopathies has furthered the understanding of underlying pathogenic mechanisms, and has implicated numerous cellular pathways in pathogenesis and disease progression. To date, no treatment for affected children is available, and further research will be needed to better understand the molecular causes of disease, and thereby identify future therapeutic strategies and potential drug targets.

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Daniela A. Braun and Friedhelm Hildebrandt

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