Tubular Disease

35 Nephronophthisis and Medullary Cystic Kidney Disease

Friedhelm Hildebrandt

Natural History of Nephronophthisis and Medullary Cystic Kidney Disease

Nephronophthisis (NPHP) is an autosomal recessive cystic kidney disease that constitutes the most frequent genetic cause for end-stage kidney disease (ESKD) in the first 3 decades of life (1–4). Three clinical forms of NPHP have been distinguished by age of onset of ESKD: infantile (5, 6), juvenile (7), and adolescent NPHP (8), which manifest with ESKD at median ages of 1 year, 13 years, and 15 years, respectively. Initial symptoms are relatively mild with the exception of infantile NPHP type 2. They consist of polyuria, polydipsia with regular fluid intake at nighttime, secondary enuresis, and anemia (9). A slightly raised serum creatinine is noted at an average age of 9 years, before ESKD invariably develops within a few years (*Fig. 35-1*). Renal ultrasound reveals increased echogenicity (*Fig. 35-2*). Beyond the age of 9 years cysts appear at the corticomedullary junction within kidneys of normal or slightly reduced size (*Fig. 35-2*) (10). Renal histology reveals a characteristic triad of tubular basement membrane disruption, tubulointerstitial nephropathy, and cysts (*Fig. 35-3*) (11, 12). In nephronophthisis cysts arise from the corticomedullary junction of the kidneys (*Fig. 35-2*). Because kidney size is normal or slightly reduced (except in infantile NPHP type 2, where there is moderate renal enlargement), cysts seem to develop *e vacuo* through loss of normal tissue. This is in contrast to polycystic kidney disease, where cysts are distributed evenly and lead to gross enlargement of the kidneys (13).

NPHP is inherited in an autosomal recessive mode. This includes NPHP variants with extrarenal manifestations (1, 13). In more than 10% of cases NPHP can be associated with extrarenal involvement, primarily including retinal degeneration (Senior-Loken syndrome) (14, 15), cerebellar vermis aplasia (Joubert syndrome) (16, 17), liver fibrosis (18), and cone-shaped epiphyses (19). The extrarenal manifestations will be discussed below in light of the cilia/centrosome theory of NPHP. NPHP has previously been grouped together with the clinical entity of medullary cystic kidney disease (MCKD) (7, 11), due to similarities of clinical and pathologic features (20). Both, NPHP and MCKD, feature corticomedullary cysts in kidneys of normal or slightly reduced size. However, MCKD is clearly distinct from NPHP regarding multiple aspects: (1) MCKD follows autosomal dominant inheritance, (2) ESKD occurs in the fourth decade or later, and, (3) in MCKD there is no extrarenal involvement other than hyperuricemia and gout.

Nephronophthisis and dominant MCKD seem to be distributed evenly among males and females. Nephronophthisis has been reported from virtually all regions of the world (21)with an incidence of 9 patients/8.3 million (22) in the United States or 1 in 50,000 live births in Canada (23). The condition constitutes the most frequent genetic cause for ESKD in the first two decades of life, and is a major cause of end-stage renal disease in children, accounting for 10–25% of these patients (21, 24, 25). In the North American pediatric ESKD population pooled data indicate a prevalence of less than 5%. MCKD appears to be somewhat more rare.

NPHP was first described by Smith and Graham in 1945 (2) and by Fanconi et al. (3), who introduced the term "familial juvenile nephronophthisis". Since then over 300 cases have been published in the literature (11). In NPHP the earliest presenting symptoms are polyuria, polydipsia, decreased urinary concentrating ability, and secondary enuresis. They occur in over 80% of cases (21) and start at around 6 years of age. Anemia and growth retardation develop later in the course of the disease (9). Regular fluid intake at nighttime is a characteristic feature of the patients' history, and starts around age 6 years. Due to the mild nature of symptoms and the lack of edema, hypertension, and urinary tract infections there is often a delay in the diagnosis of NPHP. This may cause a risk of sudden death from fluid and electrolyte imbalances. Disease recurrence has never been reported in kidneys transplanted to NPHP patients (26). By positional cloning nine different recessive genes (*NPHP1-9*) have been identified

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to cause NPHP types 1–9 (see below). This has made definite molecular genetic diagnostics possible (www.renalgenes.org). Homozygous deletions in the *NPHP1* gene account for approximately 25% of all cases of NPHP, whereas the other genes contribute less than 3% each. As expected in a recessive disease, penetrance of the renal phenotype seems to be 100%.

In NPHP, chronic renal failure develops within the first 3 decades of life (8, 27, 28). Infantile NPHP, which is characterized by mutations in *NPHP2/inversin*, leads to ESKD between birth and 3 years of age (28, 29). In a study conducted in 46 children with juvenile NPHP type 1 caused by mutations of the *NPHP1* gene, a serum creatinine of 6 mg/dl was reached at a median age of 13 years of age, (range 4–20 years) (*Fig. 35-1*) (7, 27). Similarly, the median age of ESKD in patients with mutations in the *NPHP5* gene was 13 years (30). The median time lapse between a serum creatinine of 2 and 4 mg/dl was 32 months, and between 4 and 6 mg/dl 10 months (*Fig. 35-1*) (31). In patients with adolescent NPHP due to mutations in the *NPHP3* gene ESKD developed by 19 years of age (8). If renal failure has not developed by the age of 25 years, the diagnosis of recessive NPHP should be questioned and autosomal dominant MCKD considered as a differential diagnosis. In MCKD, which follows autosomal dominant inheritance, ESKD occurs later in life. MCKD types 1 and 2 show a median onset of ESKD at 62 years (32) and 32 years (33), respectively. MCKD type 2 can be positively diagnosed by detection of mutations in the *UMOD* gene encoding uromodulin/Tamm-Horsfall protein (34).

Figure 35-1
Progression chart representing the average course of deterioration of renal function in 19 patients of 8 families with NPHP type 1 as proven by homozygous deletion of the *NPHP1* gene. Median (solid line) and quartile (dashed lines) curves were calculated from 308 serial SCR values (Reproduced with permission from (27)).

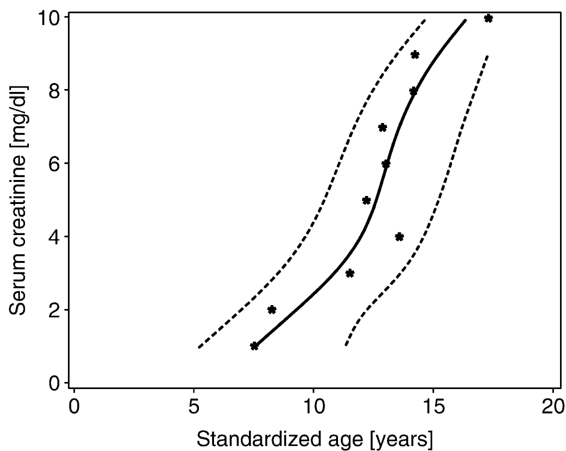


Figure 35-2
Renal ultrasound in nephronophthisis. Note kidney of normal size (12 cm between markings), loss of cortico-medullary differentiation, presence of cysts at the cortico-medullary border of the kidney, and increased echogenicity, which renders the ultrasound pattern similar to the pattern of liver (Courtesy of Dr. U. Vester, Essen).

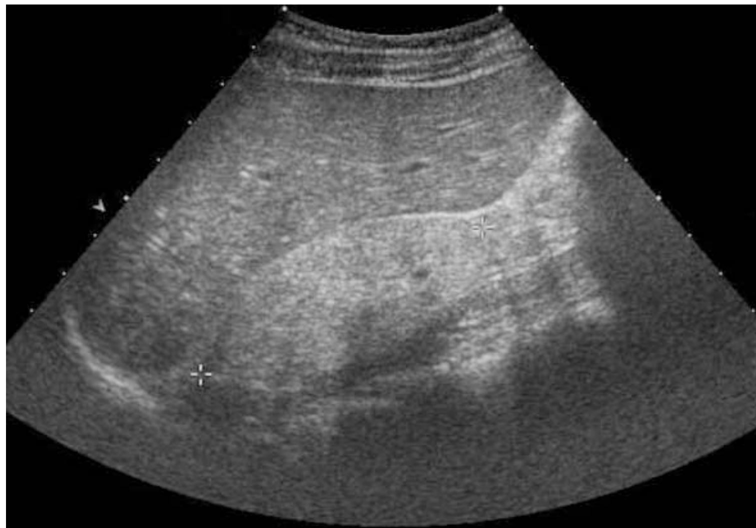
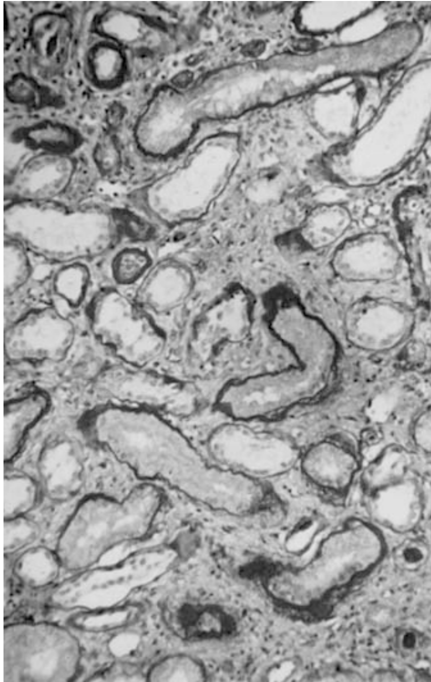


Figure 35-3
Renal histology of nephronophthisis. Note the characteristic triad of tubular basement membrane disruption, tubular cell atrophy with cysts, and interstitial infiltration with fibrosis. Hematoxylin/eosin stain (Courtesy of Prof. R Waldherr, Heidelberg).



Pathology and Histopathology

Renal histopathology is very similar in NPHP and MCKD, and has been described comprehensively in 27 patients with NPHP by Waldherr and associates (11, 12) (*Fig. 35-3*). Kidney size is normal or moderately reduced. There is always bilateral renal involvement. Macroscopically, the kidney surface has a finely granular appearance, most likely due to the protrusion of dilated cortical collecting ducts. There are between 5 to approximately 50 cysts of 1–15 mm in diameter, located preferentially at the corticomedullary border. The cysts arise primarily from the distal convoluted and medullary collecting tubules as shown by microdissection (35), but may also appear in the papilla. Cysts are observed only in about 70% of autopsy cases, and seem to arise late in the course of the disease (36). Therefore, the presence of cysts is not a prerequisite for diagnosis. No cysts are present in organs other than the kidney. The histologic changes of NPHP are characteristic but not specific for the disease and seem to develop only postnatally. Typically, there is pronounced thickening and multilayering of the tubular basement membrane (TBM), which represents the most characteristic histologic feature of NPHP and MCKD (*Fig. 35-3*). By light microscopy there appears to be a sequence of events, TBM disruption is followed by lymphocytic and histocytic peritubular infiltration. Subsequently, atrophic or dilated and tortuous tubules develop predominantly at the corticomedullary junction. In advanced stages the picture merges into a diffuse sclerosing tubulo-interstitial nephropathy. TBM changes and cyst formation are most prominent in distal tubules, where cysts are lined with a single layer of cuboidal or flattened epithelium (37–40). Glomeruli demonstrate periglomerular fibrosis with splitting and thickening of Bowman's capsule. Glomerular obsolescence is only present in nephrons that have been destroyed by tubular alterations. Leakage of Tamm-Horsfall protein from damaged collecting tubules into the interstitium has been demonstrated in patients with MCKD (41). On transmission electron microscopy there is thickening, splitting, attenuation, and granular disintegration of the tubular basement membrane without clear stages of transition (12). A marked increase of microfilaments is seen at the base of the tubular epithelial cells.

Molecular Genetics and Pathophysiology

A positional cloning approach was used to gain insight into the pathogenesis of NPHP and MCKD (*Table 35-1*). This has revealed recessive mutations in nine different novel genes as causing NPHP. These are *NPHP1* (42, 43), *NPHP2/inversin* (6), *NPHP3* (44), *NPHP4* (45, 46), *NPHP5* (30), *NPHP6/CEP290* (47, 48), *NPHP7/GLIS2* (49), *NPHP8/RPGRIP1L* (50–52), and *NPHP9/NEK8* (53), defining NPHP types 1 through 9, respectively (*Table 35-1*). These are monogenic recessive genes, implying that mutations in each single gene is sufficient in itself to cause NPHP in a patient, indicating that their gene products are necessary for normal kidney function. Gene identification thereby generated new insights into disease mechanisms of NPHP, and revealed that they are related to signaling mechanisms of primary cilia, centrosomes, and planar cell polarity (1, 6, 54, 55) (see below and *Fig. 35-4*). Gene identification has made definite molecular genetic diagnostics possible (www.renalgenes.org) for approximately 30% of cases. Homozygous deletions in the *NPHP1* gene account for approximately 21% of all NPHP cases, whereas the other genes (*Table 35-1*) contribute less than 3% each. Thus the causative genes are still unknown in about 70% of cases, indicating that

Table 35-1

Disease variants, gene loci, extrarenal manifestations, and mouse models of nephronophthisis (NPHP) and medullary cystic kidney disease (MCKD)

Disease	Gene	Onset of ESRD (Median in Years)	Chromosome	Gene (Product)	Extrarenal Association	Mouse Model
Nephronophthisis						
Type 1 (juvenile)	*NPHP1*	13	*2q12.3*	NPHP1/nephrocystin-1	SLSN, OMA, JBTS, MKS	–
Type 2 (infantile)	*NPHP2/ INVERSIN*	1–3	*9q22-q31*	NPHP2/Inversin	SLSN, ventricular septal defect, *situs inversus*	*inv/inv*[76]
Type 3 (adolescent)	*NPHP3*	19	*3q22*	NPHP3	SLSN, LF	*pcy*[82], *Nphp-/-*[83]
Type 4	*NPHP4*	20	*1p36*	NPHP4/nephroretinin	SLSN	–
Type 5	*NPHP5/ IQCB1*	13	*3q13.33*	NPHP5/IQ motif containing B1	SLSN (all patients)	–
Type 6	*NPHP6/ CEP290*	<13	*12q21.32*	NPHP6/centrosome protein Cep290	SLSN, JBTS, MKS	*rd16*[87]
Type 7	*NPHP7/ GLIS2*	~17	*16p13.3*	NPHP7/GLIS familiy zinc finger 2	–	*Glis*[2]*/-*[5]
Type 8	*NPHP8/ RPGRIP1L*	<13	*16q12.2*	NPHP8/RPGRIP1-like	JBTS, MKS	*Ftm*[51]
Type 9	*NPHP9/ NEK8*	~13	*17q11.2*	NPHP9/NIMA-related kinase 8	–	*jck*[93]
Medullary Cystic Kidney Disease						
MCKD type 1	*?*	62	*1q21*		Hyperuricemia, gout	
MCKD type 2	*UMOD*	32	*16p12*	Uromodulin/Tamm-Horsfall protein	Hyperuricemia, gout	*Umod-/-*[148]

AD autosomal dominant, *AR* autosomal recessive, *ESKD* end-stage kidney disease, *JBTS* Joubert syndrome, *LF* liver fibrosis, *MKS* Meckel syndrome, *OMA* oculomotor apraxia type Cogan, *SLSN* Senior-Loken syndrome, *UMOD* uromodulin/Tamm-Horsfall protein – = no data

further genes are involved in the pathogenesis of NPHP. Recently, evidence has been generated that more than one recessive gene may be mutated in individual patients with NPHP (56) as has been proposed for the related disorder Bardet-Biedl syndrome (BBS) (57, 58). In the following, the pathogenesis of NPHP will be discussed in the context of the discovery of each of the genes *NPHP1* – *NPHP9* (*Table 35-1*). The structure and function of primary cilia and basal bodies is delineated in *Fig. 35-2*.

NPHP1

In juvenile nephronophthisis (NPHP type 1) a gene locus has been mapped to chromosome 2q12.3 (59). This locus was further refined (60–64) and the gene (*NPHPP1*) responsible for NPHP1 was identified by positional cloning (42, 43). About 85% of patients with NPHP type 1 carry large homozygous deletions of the *NPHP1* gene (65, 66). Spontaneously occurring deletions of the *NPHP1* locus (67) as well as specific loss-of-function point mutations of *NPHP1* have been characterized (27, 68). In a subset of patients with large deletions in *NPHP1* there is an association with oculomotor apraxia type Cogan (66) (*Table 35-1*). Another subset shows an association with retinitis pigmentosa (68). Mutations in *NPHP1* were identified as causing juvenile nephronophthisis type 1 (42, 43). *NPHP1* encodes nephrocystin-1, a protein that interacts with components of cell-cell and cell-matrix signaling, including p130Cas (69), focal adhesion kinase 2 (70), tensin, filamin A and B (71, 72). It is located at adherens junctions and focal adhesions of

Figure 35-4

Cilia structure and intraflagellar transport. The cilium is a hair-like structure that extends from the cell surface into the extracellular space. Virtually all vertebrate cell types can produce cilia. Cilia consist of a microtubule-based axoneme covered by a specialized plasma membrane. The axoneme has nine peripheral microtubule doublets. There may be two central microtubules (9 + 2 vs. 9 + 0 axoneme). 9 + 2 cilia usually have dynein arms that link the microtubule doublets and are motile, while most 9 + 0 cilia lack dynein arms and are non-motile (''primary cilia'') with a few exceptions. The ciliary axoneme is anchored in the basal body, a microtubule-organizing center derived from the mother centriole. The transition zone at the junction of the basal body acts as a filter for the molecules that can pass into or out of the cilium. Nephrocystin-1 is localized at the transition zone of epithelial cells (73). During ciliogenesis, cilia elongate from the basal body by the addition of new axonemal subunits to the distal tip, the plus end of the microtubules. Axonemal and membrane components are transported in raft macromolecular particles (complex A and B) by so-called intraflagellar transport (IFT) along the axonemal doublet microtubules (159). Anterograde transport towards the tip is driven by heterotrimeric kinesin 2, which contains motor subunits Kif3a and Kif3b and a non-motor subunit. Mutations of Kif3a cause renal cysts and cerebellar vermis aplasia in mice (160). Retrograde transport back to the cell body occurs via the motor protein cytoplasmic dynein 1B (161) (modified from Bisgrove and Yost, 2006) (162).

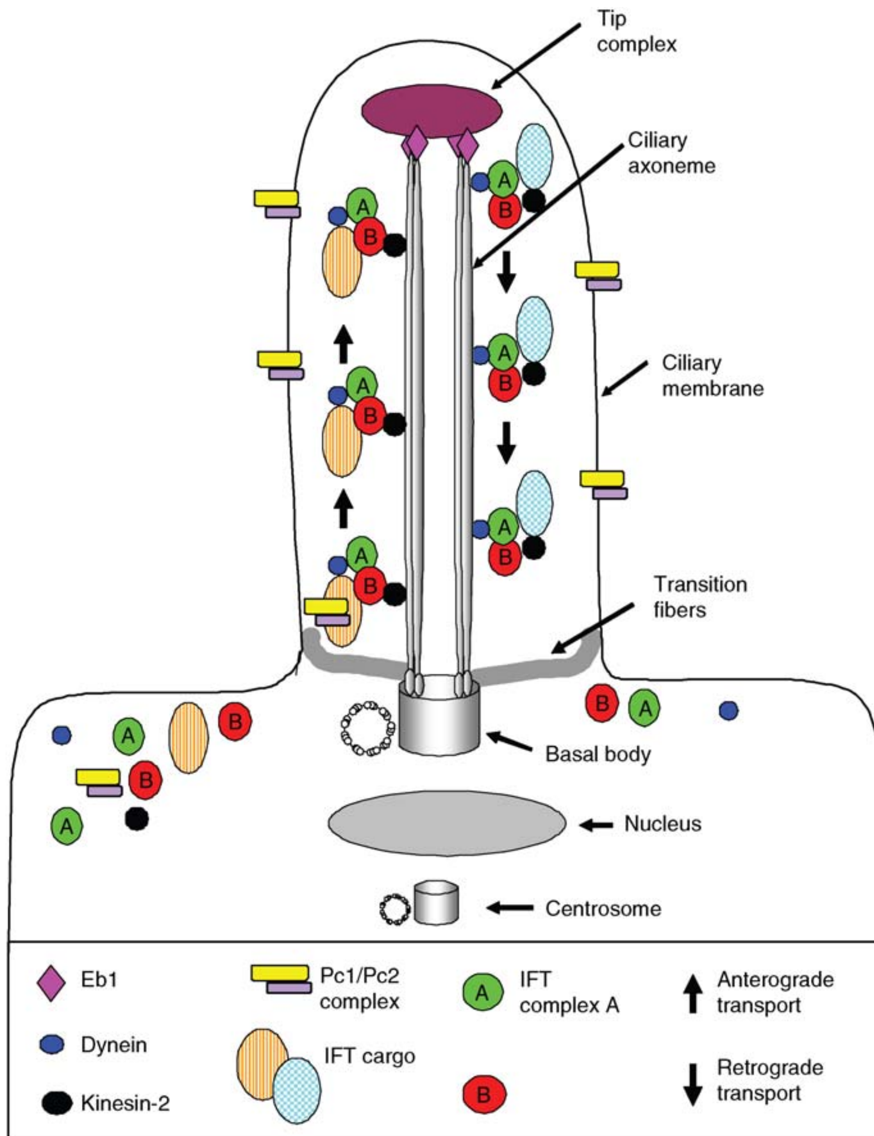
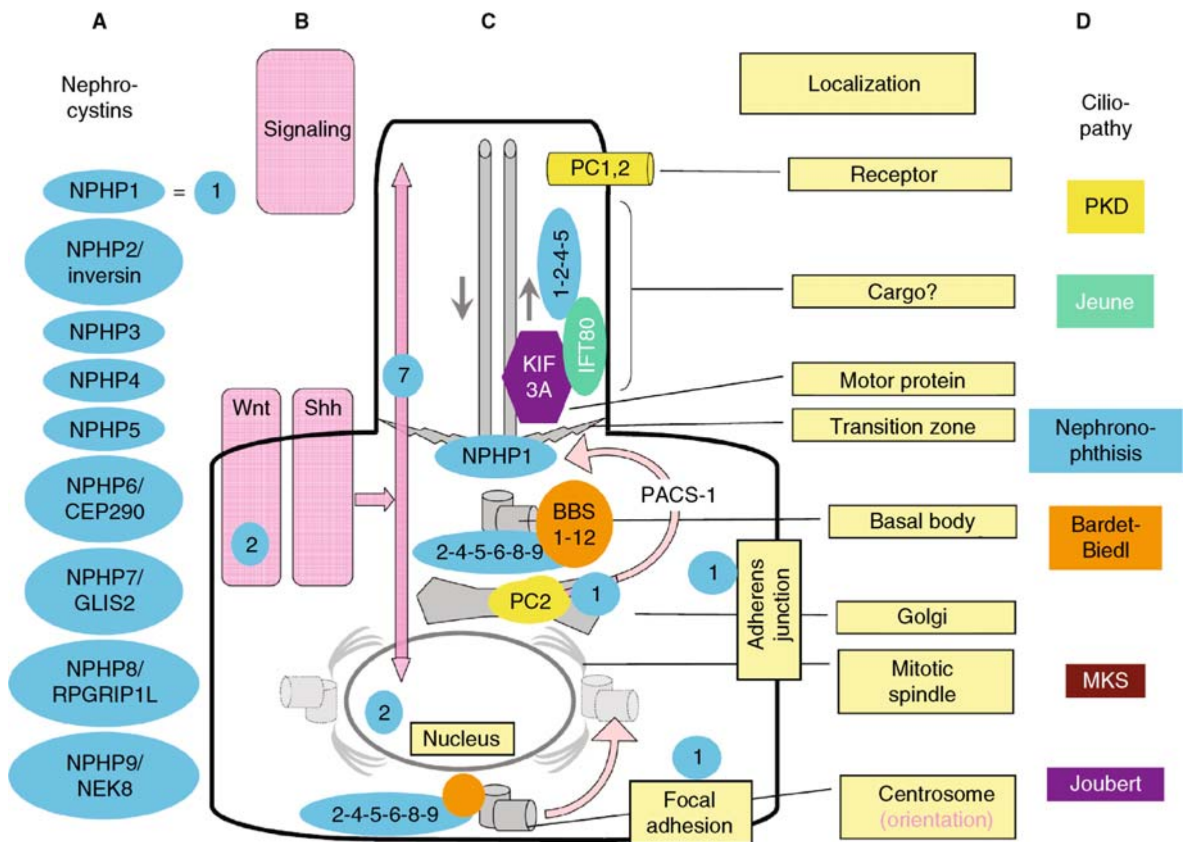


Figure 35-5

Subcellular localization of nephrocystins to primary cilia, basal bodies, the mitotic spindle, focal adhesions and adherens junctions, and functional interaction with other proteins mutated in renal ''ciliopathies''. ''Cystoproteins'' are proteins of genes mutated in cystic kidney diseases of humans, mice, or zebrafish. Depending on cell cycle stage, cystoproteins are localized at different subcellular organelles (shown in grey) (47, 163) including primary cilia, basal bodies, endoplasmic reticulum, the mitotic spindle, centrosomes, adherens junctions or focal adhesions. Arrows in the primary cilium indicate the direction of anterograde transport along the microtubule system mediated by kinesin-2 and retrograde transport by cytoplasmic dynein 1b. (A) Most nephrocystins (blue) are located at cilia, the basal body, and centrosome in a cell cycle dependent manner. NPHP1 is also at the transition zone, focal adhesions and adherens junctions. (B) Sensory cilia (*Fig. 35-4*) perceive and process cell external signals, and ''cystoproteins'' are involved in signaling mechanisms downstream of cilial signal recognition. Downstream of cilia (pink), Wnt signaling (*Fig. 35-6*) and hedgehog signaling play a role in planar cell polarity, which is mediated (C) partially through orientation of centrosomes and the mitotic spindle poles. (D) Cilia-dependent mechanisms of planar cell polarity seem to be the central to the pathogenesis of the ciliopathies, the most prominent of which are listed on the right. Wnt, the Wnt signaling pathway; Shh, the sonic hedgehog signaling pathway.



renal epithelial cells (71, 72), which are involved in cell-cell and cell-basement membrane contacts, respectively (*Fig. 35-5*). Nephrocystin-1 also interacts with the product of other nephronophthisis genes such as nephrocystin-2/inversin (6), nephrocystin-3 (44) and nephrocystin-4 (45, 46). More recently, it was shown that nephrocystin-1 is targeted to the transition zone of motile and primary cilia by the protein PACS-1 (phosphofurin acidic cluster sorting protein-1) (73, 74) (*Fig. 35-5*). This is initiated by casein kinase 2-mediated phosphorylation of three critical serine residues within a cluster of acidic amino acids in nephrocystin, leading to PACS-1 binding, and to colocalization of nephrocystin with PACS-1 at the base of cilia (74).

NPHP2/Inversin

Infantile nephronophthisis (NPHP type 2) was recognized as a distinct disease entity, in which end-stage renal failure occurs within the first 3 years of live (5, 75) (Table 35-1). Macroscopically, NPHP type 2 differs from other forms of NPHP by the presence of enlarged kidneys and cortical microcysts, and by the absence of medullary cysts. Histologically, there is no disruption of tubular basement membranes. Mutations of *NPHP2/inversin* (*INVS*) were identified as the cause of infantile NPHP (type 2) with and without situs inversus (6) by positional cloning (28) and using candidate gene data (76, 77). The renal cystic changes of infantile nephronophthisis combine clinical features of NPHP and of PKD (5). The gene products nephrocystin-1 and NPHP2/inversin interact with β-tubulin, which constitutes the microtubule axoneme of primary cilia (*Fig. 35-4*), and they are localized at primary cilia of renal tubular cells (*Fig. 35-5*) (6). These findings supported a unifying theory of renal cystogenesis (1, 54, 78, 79), which states that proteins ("cystoproteins") which are mutated in renal cystic disease in humans, mice or zebrafish, are expressed in primary cilia, basal bodies, or centrosomes (6, 54). Basal bodies are the foundations from which cilia are assembled. Once mitosis and cell division are completed, basal bodies derive from the *mother* centriole of the centriole pair that had previously organized the mitotic spindle in cell division. When cilia are formed from the basal body, the *daughter* centriole is placed on the side of the nucleus opposite to the basal body, thus specifying cell polarity (*Fig. 35-5*). It is becoming apparent that primary cilia are highly conserved structures that sense extracellular cues in a broad spectrum of epithelial tissues. There is a wide range of cues that can be received by specific ciliary receptors, including photosensation, mechanosensation, osmosensation, and olfactory sensation. In general, it seems that the pathogenesis of ciliopathies is based on an inability of epithelial cells to sense or process extracellular cues (80). Inversin was shown to localize to different subcellular locations, in a cell cycle dependent manner. Specifically, it is found at the mitotic spindle in mitosis, at the midbody in cytokinesis, and in cilia, at the basal body and centrosome in interphase (*Fig. 35-5*). All of these subcellular organelles are involved in regulation of planar cell polarity or the cell cycle (see below). In this context, a major breakthrough was made for the understanding of the pathogenesis of renal cystic diseases when Simons et al. demonstrated a role of inversin/NPHP2 in signaling mechanisms of planar cell polarity necessary to maintain normal tubular development and morphology (81) as outlined in *Fig. 35-6* (55, 81). As a consequence of this model, when inversin is defective (as in NPHP type 2) the canonical Wnt pathway will prevail (*Fig. 35-6*), which will interfere with proper apical-basolateral polarity of the renal epithelium (55) (*Fig. 35-7*).

NPHP3

In a large Venezuelan kindred we identified by positional cloning mutations in *NPHP3* as responsible for adolescent nephronophthisis (*Table 35-1*) (8, 44). The *pcy* mouse model demonstrated that mutations in the mouse ortholog *Nphp3* cause the renal cystic mouse mutant *pcy* (44), which was demonstrated to be responsive to treatment with a vasopressin receptor antagonist (82). Recently, it was shown that complete loss of *Nphp3* function results in *situs inversus*, congenital heart defects, and embryonic lethality in mice (83) and that truncating mutations of *NPHP3* in humans can cause a broad clinical pattern that resembles Meckel syndrome. This included *situs inversus*, polydactyly, central nervous system malformations, structural heart defects, preauricular fistulas, and congenital anomalies of the kidney and urinary tract (83).

NPHP4

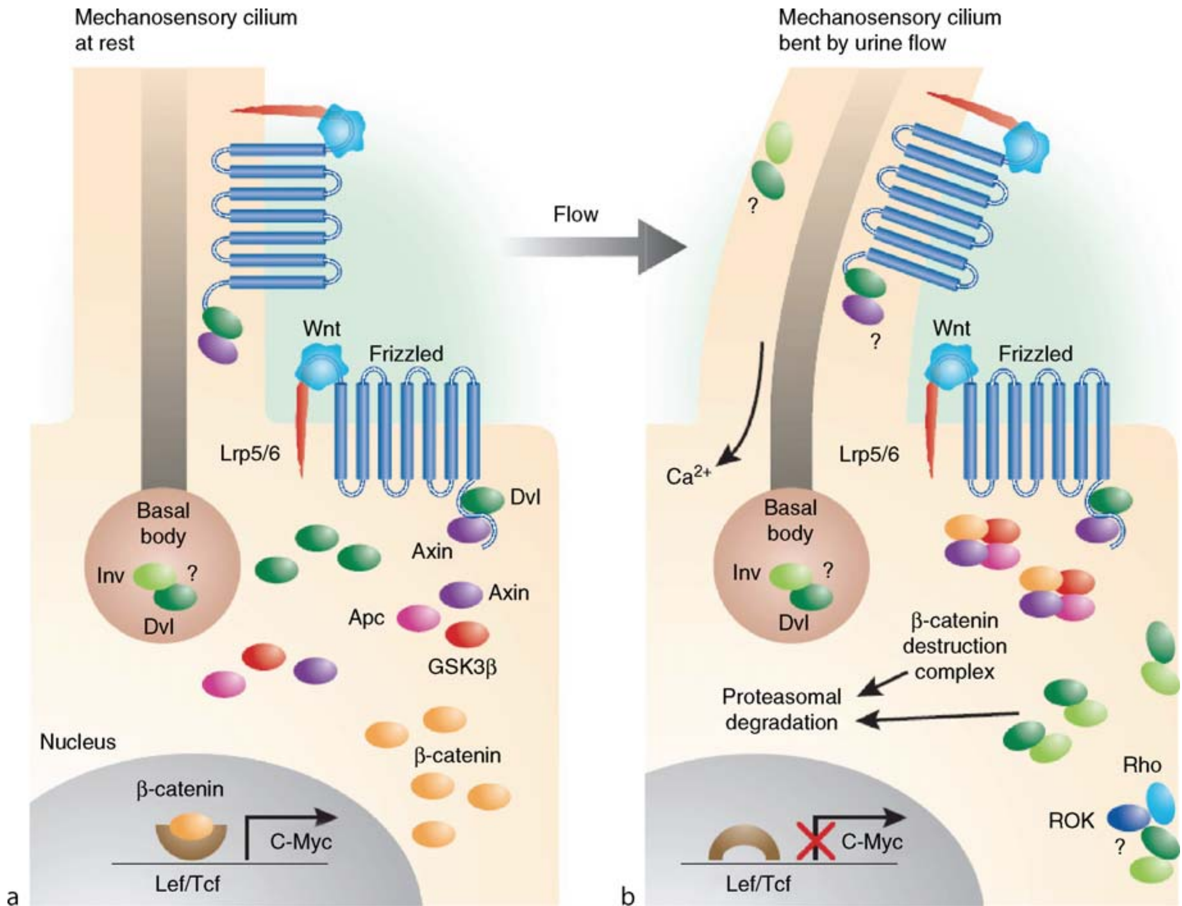
Mutations in the novel gene *NPHP4* were identified by homozygosity mapping and total genome search for linkage (45, 46, 84) (*Table 35-1*). Nephrocystin-4, like inversin, localizes to primary cilia, basal bodies, centrosomes, and the cortical actin cytoskeleton (85) (*Fig. 35-5*).

NPHP5

Recessive mutation in the novel gene *NPHP5* were identified as mutated in nephronophthisis type 5 (30). All mutations detected were truncations of the encoded protein nephrocystin-5, and all patients had an association with early-onset retinal degeneration. Thus, *NPHP5* represents the gene mutated in the typical early-onset form of Senior-Loken syndrome (SLSN) (*Table 35-1*). Nephrocystin-5 contains an IQ domain, which directly interacts with calmodulin (30), and is in a complex with the retinitis pigmentosa GTPase regulator (RPGR), which when defective causes X-linked retinitis pigmentosa. Both, nephrocystin-5 and RPGR are localized in connecting cilia of photoreceptors and in primary cilia of renal epithelial cells (30) (*Fig. 35-5*). The fact that connecting

Figure 35-6

Inversin/NPHP2 mediates a switch from the canonical the non-canonical Wnt signaling pathway, which plays a role in planar cell polarity maintenance (81). (a) This cartoon of a renal tubular epithelial cell shows how Wnt signaling occurs primarily through β-catenin–dependent pathways in the absence of urine flow. Ligand binding by the frizzled receptor results in inactivation of the β-catenin destruction complex through the presence of disheveled (Dvl), increased β-catenin levels, and upregulation of effector gene expression of the canonical Wnt signaling pathway. (b) Stimulation of the primary cilium, e.g. by urine flow, results in increased expression of inversin (Inv), which then reduces levels of cytoplasmic Dvl by increasing its proteasomal degradation. This allows reassembly and activation of the β-catenin destruction complex, thereby switching from the canonical to the non-canonical Wnt signaling pathway. The model is consistent with the finding that overexpression of β-catenin (equivalent to canonical Wnt signaling) leads to renal cysts in a mouse model (164) (from (55)).



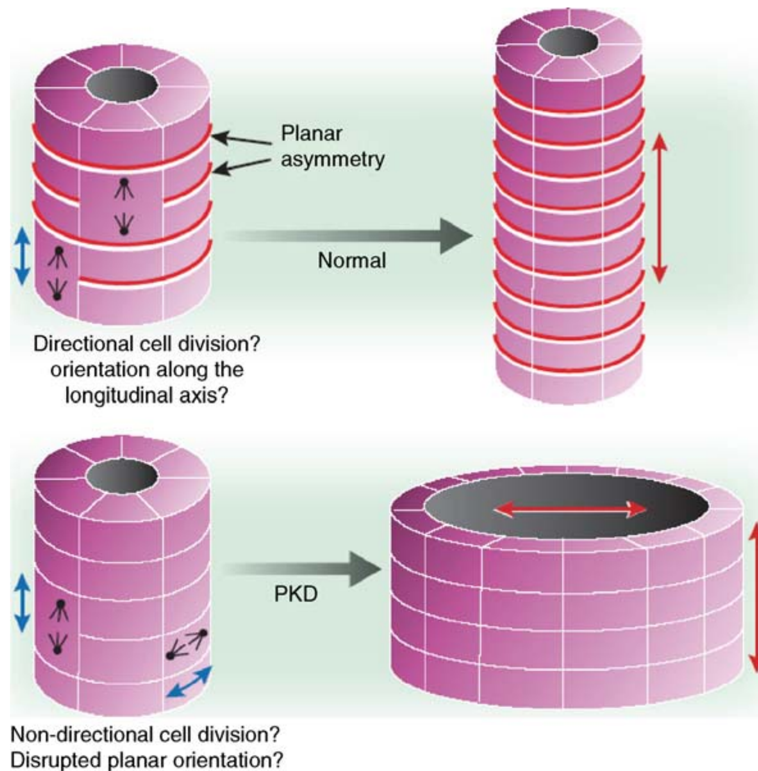
cilia of photoreceptors are the structural equivalents of primary cilia of renal epithelial cells rendered an explanation for retinal involvement in the retinal-renal syndrome Senior-Loken syndrome (*Fig. 35-8*).

NPHP6/CEP290

Recessive truncating mutations in the novel gene *NPHP6/CEP290* were identified as the cause of NPHP type 6 and Joubert syndrome type 5 by positional cloning (47). Its gene product nephrocystin-6/CEP290 is part of the centrosomal proteome (86) (*Table 35-1*). Similar to NPHP2/inversin and NPHP4, NPHP6/CEP290 is expressed in centrosomes and the mitotic spindle in a cell-cycle dependent manner. Abrogation of *NPHP6* function in zebrafish caused planar cell polarity defects and recapitulated the human phenotype of NPHP type 6, including renal cysts, retinal degeneration, and cerebellar defects (47). Nephrocystin-6 modulates the activity of ATF4/CREB2, a transcription factor that may be implicated in cAMP-dependent renal cyst formation (82).

Figure 35-7

Defects of cystoproteins lead to disruption of planar cell polarity, and thereby to renal cysts through to malorientation of the centrosome or mitotic spindle complex. Correct orientation of the mitotic spindle and centrosomes with respect to the longitudinal axis of the tubule is critical for proper planar cell polarity (i.e., the orientation of an epithelial cell layer in 3-dimensional space). Non-canonical Wnt signaling (see *Fig. 35-6*) is involved in regulation of planar cell polarity during renal tubular morphogenesis, when in rodents 2 weeks post partum the tubules still elongate. The structure that would result from disruption of this longitudinal orientation is a dilated tubule or cyst (from (55)).



Interestingly, a 300-amino acid in-frame deletion of *Nphp6/Cep290* caused retinal degeneration only, without renal or cerebellar involvement in the *rds16* mouse model (87) (*Table 35-1*). This is in accordance with the recent finding that a hypomorphic mutation of *NPHP6/CEP290* represents the most frequent cause of Leber's congenital amaurosis (88). Mutations in *NPHP6/CEP290* have been confirmed as causing JBTS with and without renal involvement (48). Furthermore, truncating mutations in *NPHP6* were shown to cause Meckel syndrome (89).

Correct orientation of the mitotic spindle and centrosomes with respect to the longitudinal axis of the renal tubule is critical for proper apical-basolateral polarity (*Fig. 35-7*). Non-canonical Wnt signaling (*Fig. 35-6*) is involved in these processes in renal tubular morphogenesis, when in rodents postnatally renal tubules still elongate. The structure resulting from disruption of the longitudinal growth would be a dilated tubule or cyst (*Fig. 35-7*). Recently, evidence was generated for a role of planar cell polarity in renal cystic diseases (90) by measuring orientation of the mitotic spindle through 3-D imaging of renal tubules. Comparison of the distribution of the mitotic angles in wild-type animals and rodent cystic kidney disease models revealed that mitotic angles of two rodent models of cystic kidneys, the HNF1β-deficient mouse model and the *pck* rat model where clearly different from wild-type littermates (90).

NPHP7/GLIS2

Recently, mutations in the *NPHP7/GLIS2* gene, encoding the transcription factor Gli-similar protein 2 were discovered as the cause of NPHP type 7 (*Fig. 35-4*) (49).

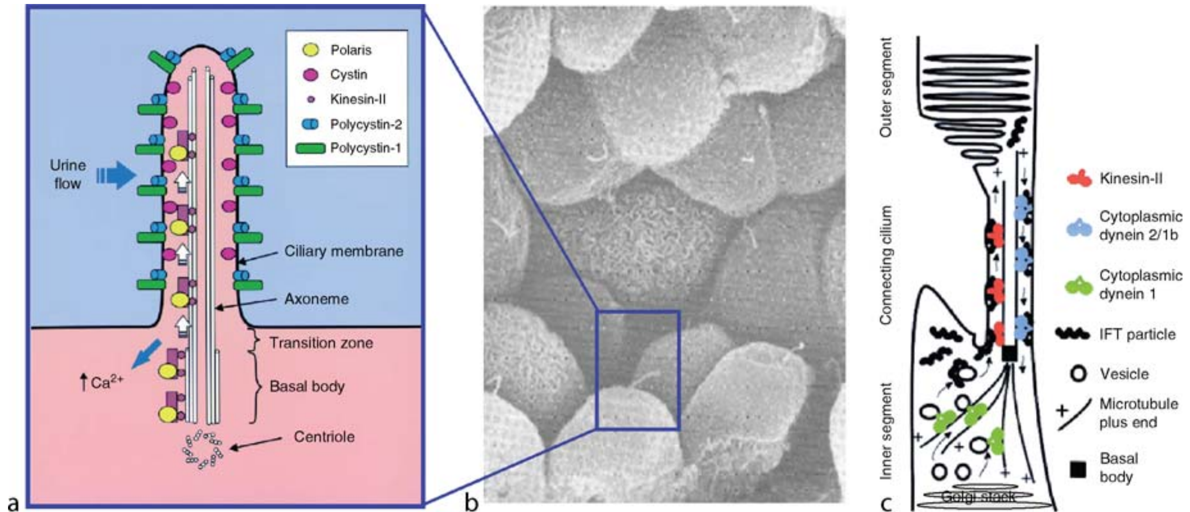


Figure 35-8

Primary (non-motile) cilia of renal epithelial cells and connecting cilia of retinal photoreceptors are analogous structures. In the primary cilium (a) of renal epithelial cells (b) "cargo" proteins are trafficked along the microtubule tracks from the region of the Golgi stack to the tip of the cilia via the motorprotein kinesin II and back down via cytoplasmic dynein 1b. (c) In an analogous fashion approximately 10^9 molecules of the visual pigment rhodopsin are transferred up and down the connecting cilia per human retina per day (modified from Somlo & Igarashi (78) and Pazour (165)).

In analogy, *Glis2* mutant mice showed severe renal atrophy and fibrosis resembling human nephronophthisis (49) (*Table 35-1*). Differential gene expression studies on *Glis2* mutant kidneys demonstrated that genes promoting epithelial-to-mesenchymal transition and fibrosis are upregulated in the absence of *Glis2* (49). There was also prominent apoptosis present in distal tubular segments of the kidney, which might provide an explanation why in PKD kidneys are enlarged with hyperproliferation prevailing, whereas in NPHP kidney size is reduced. As GLIS2 is related to the GLI transcription factor these findings implicated the hedgehog signaling pathway in the pathogenesis of cystic kidney diseases (91). It is a signaling pathway that controls, cell determination and tissue patterning during embryogenesis.

NPHP8/RPGRIP1L

Missense and truncating mutations in the *NPHP8/RPGRIP1L* gene were shown to cause Joubert syndrome and Meckel syndrome (*Table 35-1*) (51). RPGRIP1L colocalized at the basal body and centrosomes with the protein products of both *NPHP6* and *NPHP4* (51) (*Fig. 35-4*). Whereas the presence of two truncating mutations caused Meckel syndrome, missense mutations were seen in patients with Joubert syndrome (50, 51). These findings confirmed that there is a continuum for the multiorgan phenotypic abnormalities found in Meckel syndrome, Joubert syndrome, and nephronophthsisis on the basis of distinct mutations of identical genes (multiple allelism).

NPHP9/NEK8

Three different highly conserved amino acid changes were identified in the gene *NEK8* (never in mitosis kinase 8) as causing NPHP type 9 (*Table 35-1*) (53). One of the mutations identified is positioned in the same RCC1 domain, in which the missense mutation causing the renal cystic mouse model *jck* is positioned (92, 93). The notion that mutations in *NEK8* cause nephronophthisis (type 9) was supported by the finding that, upon expression in medullary collecting duct cells, all three mutant forms of *NEK8* showed defects in ciliary and centrosomal localization to varying degrees (53). As NEK8 plays a major role in cell cycle regulation, these data establish a direct link between a protein defective in renal cystic disease and the role of centrosomes for cell cycle regulation (*Fig. 35-4*). In this context it is interesting that two mouse models of polycystic kidney disease (*jck* and *cpk*) can be efficiently treated with the cyclin-dependent kinase inhibitor roscovitine (94).

Animal Models

Several spontaneously occurring mouse models of mutated genes that exhibit an NPHP-like phenotype or a phenotype of SLSN-like retinal degeneration were shown to represent orthologs of human NPHP genes. Examples are shown in *Table 35-1* for the genes *NPHP2/INVS*, *NPHP3*, *NPHP6/CEP290*, *NPHP7/GLIS2*, *NPHP8/RPGRIP1L*, and *NPHP9/NEK8*. Nephrocystin-4 is conserved in *C. elegans* and expressed in ciliated head and tail neurons of the nematode (95). Upon knockdown it exhibits a male mating phenotype, similar to the phenotype found upon knockdown of the polycystin-1 and polycystin-2 orthologs (96). Localization of nphp-1 and nphp-4 to some of these ciliated neurons also overlaps with localization of the cystoprotein orthologs polycystin-1 (*lov-1*), polycystin-2 (*pkd-2*), and with many orthologs of Bardet-Biedl syndrome (BBS) proteins (95, 97) similar to what has been described for *lov-1* and *pkd-2* mutants (96). These data have been recently refined for specific neuronal cell type (98, 99) and the necessity of *nphp-1* and *nphp-4* for morphologic integrity of ciliated neurons in *C. elegans* was demonstrated (100, 101). In addition, a role for *nphp-4* in life span of the worm has been demonstrated (102). Evolutionary conservation of nephrocystins and other cystoproteins goes even further: Some cystoproteins have been conserved over more than 1.5 billion years of evolution from the unicellular organism *Chlamydomonas Reinhardtii* to vertebrates. *Ch. Reinhardtii* uses two motor cilia (flagella) for locomotion. Strikingly, nephrocystin-4 and at least six proteins mutated in BBS are conserved in *Ch. Reinhardtii* where they are part of its basal body proteome (97, 103). Defects of cystoprotein orthologs in *Ch. Reinhardtii* have deficient intraflagellar transport and flagellar propulsion (104). This further supports the notion that cystoproteins play a role in functional modules that are conserved throughout evolution.

Extrarenal Clinical Manifestations of NPHP Occur on the Basis of Cilial Defects

A prominent feature of NPHP is involvement of multiple organs (pleiotropy) outside the kidney. Infantile NPHP type 2 (6) can be associated with *situs inversus* (29), retinitis pigmentosa (105), or cardiac ventricular septal defect (6). Defects in other organs are usually of degenerative or developmental nature. Specifically, NPHP may beassociated with tapetoretinal degeneration (Senior-Loken syndrome (14, 15), cerebellar vermis aplasia (Joubert syndrome (16, 17), ocular motor apraxia type Cogan (106), mental retardation (47), liver fibrosis (18), or cone-shaped epiphyses of the phalanges (Mainzer-Saldino syndrome (19)). In some instances there appears to be a genotype/phenotype correlation regarding pleiotropy. For instance, there is involvement of the retina in all known cases with mutations of *NPHP5* or *NPHP6*. In other instances, such as *NPHP1* mutations, the molecular basis of eye involvement is unknown.

Retinal Involvement (Senior-Loken Syndrome)

The renal-retinal involvement in Senior-Loken syndrome can be explained by the fact that the primary cilium of renal epithelial cells is a structural equivalent of the connecting cilium of photoreceptor cells in the retina (107) (*Fig. 35-8*). We have shown that nephrocystin-5 and nephrocystin-6 are expressed in the connecting cilia of photoreceptors (30, 87).

Cerebellar Vermis Aplasia (Joubert Syndrome)

In Joubert syndrome (JBTS) NPHP is associated with coloboma of the eye, with aplasia/hypoplasia of the cerebellar vermis causing ataxia, and with the inconstant symptoms of psychomotor retardation, and episodic neonatal tachy/dyspnea (16, 17, 108–110). The radiographic feature of JBTS on axial magnetic resonance brain imaging is the so-called "molar tooth sign" of the midbrain-hindbrain junction (110, 111). Ocular motor apraxia type Cogan, defined as the transient inability of horizontal eye movements in the first few years of life, may also be associated with JBTS. This symptom has been described in patients with mutations in the *NPHP1* (66, 106) ("JBTS4") and *NPHP4* (46) genes. Three different recessive genes, *NPHP1* (17, 110, 111), *AHI* (112, 113) (JBTS type 3), and *NPHP6* (48, 114), have been found mutated in JBTS. Three further loci for JBTS have been identified: *JBTS1* on chromosome 9q34.3 (115), *JBTS2/CORS2* on chromosome 11p12-q13.3 (116). In addition, mutations of *NPHP8/RPGRIP1L* can cause JBTS if at least one mutation is non-truncating (50, 51).

Liver Fibrosis

NPHP can be associated with periductal liver fibrosis (18, 117–119), as has been described for a patient with *NPHP3*

mutation, e.g. in NPHP type 3 (44). Children develop hepatomegaly and moderate portal fibrosis with mild bile duct proliferation. This pattern differs from congenital hepatic fibrosis, where biliary dysgenesis is prominent, and from hepatic involvement in ARPKD, Arima syndrome (cerebro-oculo-hepato-renal syndrome) (120–122), and Meckel syndrome, which exhibits bile duct proliferation. Bile duct involvement in these cystic kidney diseases may be explained by the ciliary theory, as the epithelial cells lining bile ducts (cholangiocytes) possess primary cilia.

Brain Malformations (Meckel Syndrome)

Within the spectrum of NPHP-associated ciliopathies Meckel syndrome (MKS) is the most severe. It leads to perinatal mortality with renal cystic dysplasia, occipital encephalocele, polydactyly, and biliary digenesis. Two recessive genes have been identified, *MKS1* (123) and *MKS3* (124), and another gene locus, *MKS2* (125), has been mapped. Recently, a Meckel-like phenotype has been described for truncating mutations of *NPHP3* (83), *NPHP6/CEP290* (89), and *NPHP8/RPGRIP1L* (50, 51). MKS represents the ciliopathy of the group that encompasses defects in most organs, and organ involvement is of developmental rather than degenerative nature. For instance, organ defects reveal cystic dysplasia rather than NPHP in the kidneys, microphthalmia of the eyes, bile duct dysgenesis in the liver, occipital encephalocele in the brain, bones involvement by postaxial polydactyly (126). The notion that MKS is at the most pronounced end of the clinical spectrum, is supported by the finding that the presence of two truncating mutations in *NPHP8/RPGRIP1L* causes MKS, whereas one "mild" mutation (missense rather than truncating) may cause the less severe phenotype of JBTS (51). In addition, the presence of 2 truncating mutations in *NPHP6/CEP290* may cause an MKS-like phenotype (MKS4) (89).

Cardiac Defects and *Situs Inversus*

In a patient with mutation of *NPHP2* a ventricular septal defect as a congenital cardiac malformation has been described (29). Thus, the role of inversin for left-right axis specification known from mouse models was confirmed in humans (76, 77). As this was associated with *situs inversus* cardiac ventricular septal defect may be viewed as a "heterotaxy" (left-right orientation) phenotype caused by the same mechanism (127). We confirmed the phenotypic combination of cystic kidney disease, *situs inversus,* and cardiac septal defect on the basis of *inversin* mutations is observed in humans, mice, and zebrafish (6).

Skeletal Defects

NPHP can be associated with skeletal defects, including Jeune syndrome (asphyxiating thoracic dysplasia) (128–131), Ellis van Creveld syndrome (132), RHYNS syndrome (retinitis pigmentosa, hypopituitarism, NPHP, skeletal dysplasia) (133), Meckel-Gruber syndrome (123, 124), and Sensenbrenner syndrome (cranioectodermal dysplasia) (134, 135). This strongly suggests a role of primary cilia function in skeletal development. The association of NPHP with cone-shaped epiphyses of the phalanges (type 28 and 28A) is known as *Mainzer-Saldino syndrome*, and occurred in patients who also had retinal degeneration and cerebellar ataxia (19). Interestingly, mutations in the ortholog of the intraflagellar transport protein IFT80 of *Ch. Reinhardtii* was found to be the cause of Jeune syndrome (136) (*Fig. 35-4*), which emphasized the strong evolutionary conservation of "ciliopathy genes".

Medullary Cystic Kidney Disease

Goldman and associates were the first to report a large kindred with dominant inheritance exhibiting an adult-onset medullary cystic kidney disease (MCKD) (137), followed by publication of two large pedigrees from the United States by Gardner et al. (138, 139). Whereas histopathology is very similar in MCKD and NPHP, MCKD differs from NPHP by its dominant mode of inheritance, and its onset of ESKD in the third decade of life, with an average at age 28.5 years (138). In MCKD penetrance appears to be very high by the age of 45 years. Another feature distinguishing NPHP from MCKD is the lack of extrarenal involvement in dominant disease, with the exception of hyperuricemia and gout (*Table 35-1*). A gene locus for MCKD type 1 has been mapped to chromosome 1q (32), but the responsible gene has not yet been identified (140–145). The locus for MCKD type 2 resides on chromosome 16 (146, 147). Recently, mutations in the *UMOD* gene encoding uromodulin/Tamm-Horsfall protein have been identified as responsible for MCKD type 2 (34, 148) and a group of "uromodulin associated kidney diseases" including familial juvenile hyperuricemic nephropathy (FJHN) and glomerulocystic kidney disease (GCKD) (149–152). Thus, MCKD type 2 can be positively diagnosed by mutation analysis of the UMOD gene.

Diagnosis

Laboratory Studies

Patients with NPHP are usually diagnosed when an increased serum creatinine value is detected fortuitously. Patient history generally reveals prolonged nocturia since school age. Specific gravity of a morning urine specimen will be low. Renal ultrasound will then corroborate the diagnosis (*Fig. 35-2*), which can be subsequently confirmed by molecular genetic diagnostics (www.renalgenes.org). A diagnostic algorithm for nephronophthisis has been suggested (153). Hematuria, proteinuria, and bacteriuria are uncommon in NPHP. In rare cases, where proteinuria is present, it is usually mild and of the tubular type. Laboratory studies are needed to assess the severity of renal failure and generally demonstrate elevation of serum creatinine, blood urea nitrogen and phosphorus, together with metabolic acidosis, hypocalcemia, and anemia. In SLS retinitis pigmentosa is diagnosed by its specific findings on ophthalmoscopy including increased retinal pigment, attenuation of retinal vessels, and pallor of the optic disc. If retinitis pigmentosa is present, electroretinography and electro-oculography can be employed to evaluate severity. Retinal degeneration is characterized by a constant and complete extinction of the electroretinogram, preceeding the development of visual and fundoscopic signs of retinitis pigmentosa. Ophthalmoscopy should be performed in any patient to evaluate for signs of retinal degeneration. Liver function test and hepatic ultrasonography are important to facilitate detection of patients with hepatic fibrosis.

Imaging

The most useful imaging technique in NPHP or MCKD is renal ultrasonography. Kidneys are of normal or moderately reduced size, show increased echogenicity, loss of cortico-medullary differentiation and, in later stages, cyst formation at the cortico-medullary border of the kidneys (10) (*Fig. 35-2*). Garel and associates have described medullary cysts in 13 of 15 children studied at the time of renal failure (mean age 9.7 years) (154). Roentgenography contributes little to the diagnosis of the disease. Medullary cysts can sometimes also be demonstrated on magnetic resonance imaging or computed tomography (155, 156). Histology is characteristic but not pathognomonic in NPHP or MCKD, because cysts may be absent and tubulointerstitial disease can be relatively unspecific. Renal biopsy can be circumvented as an initial procedure due to the availability of molecular genetic diagnostics in NPHP (www.renalgenes.org). If molecular genetic diagnostics do not detect a molecular defect, the diagnosis can be based on the combined results of typical history with polyuria, polydipsia and anemia, and the classical appearance of the kidney on ultrasound, and renal histology. A thorough pedigree analysis should be documented for each of three successive generations, to rule out autosomal dominant MCKD.

Molecular Genetic Diagnosis

Recently, molecular genetic diagnosis has become available mostly for NPHP type 1, but is theoretically possible also for the very rare forms of NPHP type 2 through 9 (see above). A diagnostic algorithm should be followed to avoid unnecessary renal biopsy (153). Molecular genetic analysis is the only diagnostic procedure, by which the diagnosis of NPHP can be made with certainty. However, due to the presence of additional loci for NPHP, the lack of detection of mutations in the *NPHPP1* gene does not exclude the diagnosis of NPHP. If renal disease with features of the NPHP or MCKD complex occurs in a person older than 25 years, its presence should be thoroughly sought in preceding generations. This may frequently result in detection of a pattern of autosomal dominant inheritance. In this case mutation analysis in the *UMOD* gene is warranted.

Genetic Counseling

Molecular genetic testing should be performed only following consent within the guidelines of the National and International Societies for Human Genetics (http://www.ashg.org/press/healthprofessional.shtml). The acceptance of molecular genetic diagnostics may be strongly enhanced in the US due to the recent passing of the Genetic Information Nondiscrimination Act (GINA) by congress (http://www.ashg.org/press/ginaupdate.shtml). Before genetic counseling, a thorough pedigree analysis to distinguish recessive (early-onset) from dominant (late-onset) disease is mandatory, and extrarenal organ involvement should be sought. Since non-symptomatic potential carriers of recessive defects should not be examined by molecular genetic diagnostics, unaffected siblings below 25 years of age should be re-evaluated yearly for maximal urinary concentrating ability and renal ultrasound. If symptoms evolve and serum creatinine increases, molecular genetic diagnostics following informed consent is

warranted, to allow early prevention of complications from electrolyte disturbances, dehydration, anemia, and growth retardation. If a transplant recipient's renal histology suggests NPHP and a living related donor is considered, molecular genetic diagnostics may help to exclude or detect renal disease within the family. Because there is genetic locus heterogeneity in diseases of the NPHP and MCKD, prenatal diagnosis can only be performed by direct genetic testing. This requires a setting, in which a specific mutation or deletion of the *NPHPP1–9* genes have already been characterized in an affected sibling.

Differential Diagnosis

On histopathology NPHP and MCKD have to be differentiated from other forms of interstitial nephropathies like chronic pyelonephritis or drug injury. In oligomeganephronic dysplasia kidney size is reduced and histology is distinct from NPHP. The paucity of urinary abnormalities, the frequent lack of hypertension, normal kidney size, and the localization of renal cysts (if present) readily differentiate variants of the NPHP and MCKD from recessive or dominant polycystic kidney disease. Finally, medullary sponge kidney (157) can easily be distinguished from NPHP or MCKD, since it does usually not lead to chronic renal failure and shows calcifications and calculi on renal ultrasound.

Prognosis and Therapy

There is no causative therapy for NPHP or MCKD. Therapy is symptomatic and is directed towards the treatment of hypertension, if present, as well as the correction of disturbances of electrolyte, acid-base and water balance. Hypokalemia may contribute to the polyuria, so that oral potassium supplementation may alleviate this symptom. Metabolic acidosis should be corrected, and osteodystrophy and secondary hyperparathyroidism treated with adequate calcium supplementation, phosphorus restriction, phosphate binders, and vitamin D therapy. Anemia will be treated with iron supplementation and erythropoetin, and growth retardation may require administration of growth hormone. Adequate nutrition should be maintained with the help of a dietician. Psychological counseling of the patients is an integral part of therapy, because of the poor self-image associated with growth retardation and to alleviate pressures resulting from the need to comply with complicated medications and dietary prescriptions. All patients will require renal replacement therapy by dialysis and renal transplantation during childhood, adolescence or, in dominant disease, in early adult life.

Gattone et al. have recently shown that the renal cystic phenotype of *pcy* mice, which is the equivalent of human NPHP type 3 (*Table 35-1*) can be strongly mitigated or even reversed by treatment with the vasopressin V2 receptor antagonist OPC31260 (82). Similar results were obtained using a *pkd2* mouse model (158). This effect is thought to be mediated by a reduction in intracellular cAMP levels (47). An important future challenge will be the development of therapies that capitalizes on what has been learnt about the pathobiology of NPHP, MCKD and other cystic diseases of the kidney.

References

1. Hildebrandt F, Otto EA. Primary cilia: a unifying pathogenic concept for cystic kidney disease? *Nat Rev Genet* 2005.
2. Smith C, Graham J. Congenital medullary cysts of the kidneys with severe refractory anemia. *Am J Dis Child* 1945;69:369–377.
3. Fanconi G, Hanhart E, Albertini A. Die familiäre juvenile Nephronophthise. *Helv Pediatr Acta* 1951;6:1–49.
4. Hildebrandt F, Zhou W. Nephronophthisis-associated ciliopathies. *J Am Soc Nephrol* 2007;18(6):1855–1871.
5. Gagnadoux Mf, Bacri Jl, Broyer M, Habib R. *Infantile chronic tubulo-interstitial nephritis with cortical microcysts: variant of nephronophthisis or new disease entity? Pediatr Nephrol* 1989;3(1):50–55.
6. Otto EA, Schermer B, Obara T et al. Mutations in *INVS* encoding inversin cause nephronophthisis type 2, linking renal cystic disease to the function of primary cilia and left-right axis determination. *Nat Genet* 2003;34(4):413–420.
7. Hildebrandt F, Waldherr R, Kutt R, Brandis M. The nephronophthisis complex: clinical and genetic aspects. *Clin Investig* 1992;70 (9):802–808.
8. Omran H, Fernandez C, Jung M et al. Identification of a new gene locus for adolescent nephronophthisis, on chromosome 3q22 in a large Venezuelan pedigree. *Am J Hum Genet* 2000;66(1):118–127.
9. Ala-Mello S, Kivivuori SM, Ronnholm KA et al. Mechanism underlying early anaemia in children with familial juvenile nephronophthisis. *Pediatr Nephrol* 1996;10(5):578–581.
10. Blowey DL, Querfeld U, Geary D et al. Ultrasound findings in juvenile nephronophthisis. *Pediatr Nephrol* 1996;10(1):22–24.
11. Waldherr R, Lennert T, Weber HP et al. The nephronophthisis complex. A clinicopathologic study in children. *Virchows Arch A Pathol Anat Histol* 1982;394(3):235–254.
12. Zollinger HU, Mihatsch MJ, Edefonti A et al. Nephronophthisis (medullary cystic disease of the kidney). A study using electron microscopy, immunofluorescence, and a review of the morphological findings. *Helv Paediatr Acta* 1980;35(6):509–530.
13. Hildebrandt F. Juvenile nephronophthisis. In Harmon WE (ed.). Pediatric nephrology, Baltimore Williams & Wilkins, 1999.
14. Senior B, Friedmann AI, Braudo JL. Juvenile familial nephropathy with tapetoretinal degeneration: a new oculorenal dystrophy. *Am J Ophthalmol* 1961;52:625–633.

15. Loken AC, Hanssen O, Halvorsen S, Jolster NJ. Hereditary renal dysplasia and blindness. *Acta Paediatr* 1961;50:177–184.
16. Saraiva JM, Baraitser M. Joubert syndrome: a review. *Am J Med Genet* 1992;43(4):726–731.
17. Valente EM, Marsh SE, Castori M et al. Distinguishing the four genetic causes of jouberts syndrome-related disorders. *Ann Neurol* 2005;57(4):513–519.
18. Boichis H, Passwell J, David R, Miller H. Congenital hepatic fibrosis and nephronophthisis. A family study. *Q J Med* 1973;42 (165):221–233.
19. Mainzer F, Saldino RM, Ozonoff MB, Minagi H. Familial nephropathy associated with retinitis pigmentosa, cerebellar ataxia and skeletal abnormalities. *Am J Med* 1970;49(4):556–562.
20. Gardner KD, Jr. Juvenile nephronophthisis and renal medullary cystic disease. *Perspect Nephrol Hypertens* 1976;4:173–185.
21. Kleinknecht C. The inheritance of nephronophthisis. Inheritance of Kidney and Urinary Tract Diseases, vol. 9, Boston: Kluwer,1989, pp. 464.
22. Potter DE, Holliday MA, Piel CF et al. Treatment of end-stage renal disease in children: a 15-year experience. *Kidney Int* 1980;18 (1):103–109.
23. Waldherr R. Der nephronophthise-komplex. *Nieren- und Hochdruckkh* 1983;12:397–406.
24. Cantani A, Bamonte G, Ceccoli D. Familial juvenile nephronophthisis. *Clinical Pediatr* 1986;25:90–95.
25. Betts PR, Forest-Hay I. Juvenile nephronophthisis. *Lancet* 1973;2:475–478.
26. Steel BT, Lirenman DS, Battie CW. Nephronophthisis. *Am J Med* 1980;68:531–538.
27. Hildebrandt F, Strahm B, Nothwang HG et al. Molecular genetic identification of families with juvenile nephronophthisis type 1: rate of progression to renal failure. APN Study Group. Arbeitsgemeinschaft fur Padiatrische Nephrologie. *Kidney Int* 1997;51 (1):261–269.
28. Haider NB, Carmi R, Shalev H et al. A Bedouin kindred with infantile nephronophthisis demonstrates linkage to chromosome 9 by homozygosity mapping. *Am J Hum Genet* 1998;63 (5):1404–1410.
29. Otto EA, Schermer B, Obara T et al. Mutations in INVS encoding inversin cause nephronophthisis type 2, linking renal cystic disease to the function of primary cilia and left-right axis determination. *Nat Genet* 2003;34(4):413–420.
30. Otto EA, Loeys B, Khanna H et al. Nephrocystin-5, a ciliary IQ domain protein, is mutated in Senior-Loken syndrome and interacts with RPGR and calmodulin. *Nat Genet* 2005;37(3):282–288.
31. Gretz N. Rate of deterioration of renal function in juvenile nephronophthisis. *Pediatr Nephrol* 1989;3:56–60.
32. Christodoulou K, Tsingis M, Stavrou C et al. Chromosome 1 localization of a gene for autosomal dominant medullary cystic kidney disease. *Hum Mol Genet* 1998;7(5):905–911.
33. Scolari F, Ghiggeri GM, Amoroso A et al. Genetic heterogeneity for autosomal dominant medullary cystic kidney disease (ADMCKD). *J Am Soc Nephrol* 1998;9:393A.
34. Bleyer AJ, Hart TC. Medullary cystic kidney disease type 2. *Am J Kidney Dis* 2004;43(6):1142;
35. Sherman FE, Studnicki FM, Fetterman GH. Renal lesions of familial juvenile nephronophthisis examined by microdissection. *Am J Clin Path* 1971;55:391.
36. Sworn MJ, Eisinger AJ. Medullary cystic disease and juvenile nephronophthisis in separate members of the same family. *Arch Dis Child* 1972;47:278.
37. Giselson N, Heinegard D, Holmberg CG et al. Renal medullary cystic disease or familial juvenile nephronophthisis: a renal tubular disease. Biochemical findings in two siblings. *Am J Med* 1970;48(2):174–184.
38. Chamberlin BC, Hagge WW, Stickler GB. Juvenile nephronophthisis and medullary cystic disease. *Mayo Clin Proc* 1977;52(8):485–491.
39. van Collenburg JJ, Thompson MW, Huber J. Clinical, pathological and genetic aspects of a form of cystic disease of the renal medulla: familial juvenile nephronophthisis (FJN). *Clin Nephrol* 1978; 9(2):55–62.
40. Ivemark BI, Ljungqvist A, Barry A. Juvenile nephronophthisis. Part 2. A histologic and microangiographic study. *Acta Paediatr* 1960;49:480–487.
41. Resnick J, Sisson S, Vernier RL. Tamm-Horsfall protein. Abnormal localization in renal disease. *Lab Invest* 1978;38:550.
42. Hildebrandt F, Otto E, Rensing C et al. A novel gene encoding an SH3 domain protein is mutated in nephronophthisis type 1. *Nat Genet* 1997;17(2):149–153.
43. Saunier S, Calado J, Heilig R et al. A novel gene that encodes a protein with a putative src homology 3 domain is a candidate gene for familial juvenile nephronophthisis. *Hum Mol Genet* 1997; 6(13):2317–2323.
44. Olbrich H, Fliegauf M, Hoefele J et al. Mutations in a novel gene, *NPHP3*, cause adolescent nephronophthisis, tapeto-retinal degeneration and hepatic fibrosis. *Nat Genet* 2003;34(4):455–459.
45. Otto E, Hoefele J, Ruf R et al. A gene mutated in nephronophthisis and retinitis pigmentosa encodes a novel protein, nephroretinin, conserved in evolution. *Am J Hum Genet* 2002;71(5):1167–1171.
46. Mollet G, Salomon R, Gribouval O et al. The gene mutated in juvenile nephronophthisis type 4 encodes a novel protein that interacts with nephrocystin. *Nat Genet* 2002;32(2):300–305.
47. Sayer JA, Otto EA, O'Toole JF et al. The centrosomal protein nephrocystin-6 is mutated in Joubert syndrome and activates transcription factor ATF4. *Nat Genet* 2006;38(6):674–681.
48. Valente EM, Silhavy JL, Brancati F et al. Mutations in CEP290, which encodes a centrosomal protein, cause pleiotropic forms of Joubert syndrome. *Nat Genet* 2006;38(6):623–625.
49. Attanasio M, Uhlenhaut NH, Sousa VH et al. Loss of GLIS2 causes nephronophthisis in humans and mice by increased apoptosis and fibrosis. *Nat Genet* 2007;39(8):1018–1024.
50. Wolf MT, Saunier S, O'Toole JF et al. Mutational analysis of the RPGRIP1L gene in patients with Joubert syndrome and nephronophthisis. *Kidney Int* 2007;72(12):1520–1526.
51. Delous M, Baala L, Salomon R et al. The ciliary gene RPGRIP1L is mutated in cerebello-oculo-renal syndrome (Joubert syndrome type B) and Meckel syndrome. *Nat Genet* 2007;39(7):875–881.
52. Roepman R, Bernoud-Hubac N, Schick DE et al. The retinitis pigmentosa gtpase regulator (RPGR) interacts with novel transport-like proteins in the outer segments of rod photoreceptors. *Hum Mol Genet* 2000;9(14):2095–2105.
53. Otto EA, Trapp ML, Schultheiss UT et al. NEK8 mutations affect ciliary and centrosomal localization and may cause nephronophthisis. *J Am Soc Nephrol* 2008;19(3):587–592.
54. Watnick T, Germino G. From cilia to cyst. *Nat Genet* 2003;34 (4):355–356.
55. Germino GG. Linking cilia to Wnts. *Nat Genet* 2005;37(5):455–457.
56. Hoefele J, Wolf MT, O'Toole JF et al. Evidence of oligogenic inheritance in nephronophthisis. *J Am Soc Nephrol* 2007;18 (10):2789–2795.
57. Beales PL, Badano JL, Ross AJ et al. Genetic interaction of BBS1 mutations with alleles at other BBS loci can result in non-Mendelian Bardet-Biedl syndrome. *Am J Hum Genet* 2003;72(5):1187–1199.

58. Badano JL, Kim JC, Hoskins BE et al. Heterozygous mutations in *BBS1*, *BBS2* and *BBS6* have a potential epistatic effect on Bardet-Biedl patients with two mutations at a second BBS locus. *Hum Mol Genet* 2003;12(14):1651–1659.
59. Antignac C, Arduy CH, Beckmann JS et al. A gene for familial juvenile nephronophthisis (recessive medullary cystic kidney disease) maps to chromosome 2p. *Nat Genet* 1993;3(4):342–345.
60. Hildebrandt F, Singh-Sawhney I, Schnieders B et al. Mapping of a gene for familial juvenile nephronophthisis: refining the map and defining flanking markers on chromosome 2. APN Study Group. *Am J Hum Genet* 1993;53(6):1256–1261.
61. Spurr NK, Barton H, Bashir R et al. Report and abstracts of the Third International Workshop on Human Chromosome 2 Mapping 1994. Aarhus, Denmark, June 24–26, 1994. *Cytogenet Cell Genet* 1994;67 (4):215–244.
62. Hildebrandt F, Cybulla M, Strahm B et al. Physical mapping of the gene for juvenile nephronophthisis (*NPH1*) by construction of a complete YAC contig of 7 Mb on chromosome 2q13. *Cytogenet Cell Genet* 1996;73(3):235–239.
63. Spurr NK, Bashir R, Bushby K et al. Report and abstracts of the Fourth International Workshop on Human Chromosome 2 Mapping 1996. *Cytogenet Cell Genet* 1996;73(4):255–273.
64. Nothwang HG, Strahm B, Denich D et al. Molecular cloning of the interleukin-1 gene cluster: construction of an integrated YAC/PAC contig and a partial transcriptional map in the region of chromosome 2q13. *Genomics* 1997;41(3):370–378.
65. Saunier S, Calado J, Benessy F et al. Characterization of the NPHP1 locus: mutational mechanism involved in deletions in familial juvenile nephronophthisis. *Am J Hum Genet* 2000;66(3):778–789.
66. Betz R, Rensing C, Otto E et al. Children with ocular motor apraxia type Cogan carry deletions in the gene (*NPHP1*) for juvenile nephronophthisis. *J Pediatr* 2000;136(6):828–831.
67. Otto E, Betz R, Rensing C et al. A deletion distinct from the classical homologous recombination of juvenile nephronophthisis type 1 (NPH1) allows exact molecular definition of deletion breakpoints. *Hum Mutat* 2000;16(3):211–223.
68. Caridi G, Murer L, Bellantuono R et al. Renal-retinal syndromes: association of retinal anomalies and recessive nephronophthisis in patients with homozygous deletion of the NPH1 locus. *Am J Kidney Dis* 1998;32(6):1059–1062.
69. Otto E, Kispert A, Schatzle S et al. Nephrocystin: gene expression and sequence conservation between human, mouse, and *Caenorhabditis elegans*. *J Am Soc Nephrol* 2000;11(2):270–282.
70. Benzing T, Gerke P, Hopker K et al. Nephrocystin interacts with Pyk2, p130(Cas), and tensin and triggers phosphorylation of Pyk2. *Proc Natl Acad Sci USA* 2001;98(17):9784–9789.
71. Donaldson JC, Dempsey PJ, Reddy S et al. Crk-associated substrate p130(Cas) interacts with nephrocystin and both proteins localize to cell-cell contacts of polarized epithelial cells. *Exp Cell Res* 2000;256 (1):168–178.
72. Donaldson JC, Dise RS, Ritchie MD, Hanks SK. Nephrocystin-conserved domains involved in targeting to epithelial cell-cell junctions, interaction with filamins, and establishing cell polarity. *J Biol Chem* 2002;277(32):29028–29035.
73. Fliegauf M, Horvath J, von Schnakenburg C et al. Nephrocystin specifically localizes to the transition zone of renal and respiratory cilia and photoreceptor connecting cilia. *J Am Soc Nephrol* 2006;17 (9):2424–2433.
74. Schermer B, Hopker K, Omran H et al. Phosphorylation by casein kinase 2 induces PACS-1 binding of nephrocystin and targeting to cilia. *Embo J* 2005;24(24):4415–4424.
75. Bodaghi E, Honarmand MT, Ahmadi M. Infantile nephronophthisis. *Int J Pediatr Nephrol* 1987;8(4):207–210.
76. Mochizuki T, Saijoh Y, Tsuchiya K et al. Cloning of inv, a gene that controls left/right asymmetry and kidney development. *Nature* 1998;395(6698):177–181.
77. Morgan D, Turnpenny L, Goodship J et al. Inversin, a novel gene in the vertebrate left-right axis pathway, is partially deleted in the inv mouse. *Nat Genet* 1998;20(2):149–156.
78. Igarashi P, Somlo S. Genetics and pathogenesis of polycystic kidney disease. *J Am Soc Nephrol* 2002;13(9):2384–2398.
79. Nauli SM, Alenghat FJ, Luo Y et al. Polycystins 1 and 2 mediate mechanosensation in the primary cilium of kidney cells. *Nat Genet* 2003;33(2):129–137.
80. Benzing T, Walz G. Cilium-generated signaling: a cellular GPS? *Curr Opin Nephrol Hypertens* 2006;15(3):245–249.
81. Simons M, Gloy J, Ganner A et al. Inversin, the gene product mutated in nephronophthisis type II, functions as a molecular switch between Wnt signaling pathways. *Nat Genet* 2005;37 (5):537–543.
82. Gattone VH, 2nd, Wang X, Harris PC, Torres VE. Inhibition of renal cystic disease development and progression by a vasopressin V2 receptor antagonist. *Nat Med* 2003;9(10):1323–1326.
83. Bergmann C, Fliegauf M, Bruchle NO et al. Loss of nephrocystin-3 function can cause embryonic lethality, Meckel-Gruber-like syndrome, situs inversus, and renal-hepatic-pancreatic dysplasia. *Am J Hum Genet* 2008;82(4):959–970.
84. Schuermann MJ, Otto E, Becker A et al. Mapping of gene loci for nephronophthisis type 4 and Senior-LÃ¸ken Syndrome, to chromosome 1p36. *Am J Hum Genet* 2002;70(5):1240–1246.
85. Mollet G, Silbermann F, Delous M et al. Characterization of the nephrocystin/nephrocystin-4 complex and subcellular localization of nephrocystin-4 to primary cilia and centrosomes. *Hum Mol Genet* 2005;14(5):645–656.
86. Andersen JS, Wilkinson CJ, Mayor T et al. Proteomic characterization of the human centrosome by protein correlation profiling. *Nature* 2003;426(6966):570–574.
87. Chang B, Khanna H, Hawes N et al. In-frame deletion in a novel centrosomal/ciliary protein CEP290/NPHP6 perturbs its interaction with RPGR and results in early-onset retinal degeneration in the rd16 mouse. *Hum Mol Genet* 2006;15 (11):1847–1857.
88. den Hollander AI, Koenekoop RK, Yzer S et al. Mutations in the CEP290 (NPHP6) gene are a frequent cause of Leber congenital amaurosis. *Am J Hum Genet* 2006;79(3):556–561.
89. Baala L, Audollent S, Martinovic J et al. Pleiotropic effects of CEP290 (NPHP6) mutations extend to Meckel syndrome. *Am J Hum Genet* 2007;81(1):170–179.
90. Fischer E, Legue E, Doyen A et al. Defective planar cell polarity in polycystic kidney disease. *Nat Genet* 2006;38(1):21–23.
91. Huangfu D, Liu A, Rakeman AS et al. Hedgehog signalling in the mouse requires intraflagellar transport proteins. *Nature* 2003;426 (6962):83–87.
92. Sohara E, Luo Y, Zhang J et al. Nek8 regulates the expression and localization of polycystin-1 and polycystin-2. *J Am Soc Nephrol* 2008;19(3):469–476.
93. Liu S, Lu W, Obara T et al. A defect in a novel Nek-family kinase causes cystic kidney disease in the mouse and in zebrafish. *Development* 2002;129(24):5839–5846.
94. Bukanov NO, Smith LA, Klinger KW et al. Long-lasting arrest of murine polycystic kidney disease with CDK inhibitor roscovitine. *Nature* 2006;444(7121):949–952.

95. Wolf MT, Lee J, Panther F et al. Expression and phenotype analysis of the nephrocystin-1 and nephrocystin-4 homologs in Caenorhabditis elegans. *J Am Soc Nephrol* 2005;16(3):676–687.
96. Barr MM, DeModena J, Braun D et al. The Caenorhabditis elegans autosomal dominant polycystic kidney disease gene homologs lov-1 and pkd-2 act in the same pathway. *Curr Biol* 2001;11 (17):1341–1346.
97. Badano JL, Teslovich TM, Katsanis N. The centrosome in human genetic disease. *Nat Rev Genet* 2005;6(3):194–205.
98. Bae YK, Qin H, Knobel KM et al. General and cell-type specific mechanisms target TRPP2/PKD-2 to cilia. *Development* 2006;133 (19):3859–3870.
99. Jauregui AR, Barr MM. Functional characterization of the C. Elegans nephrocystins NPHP-1 and NPHP-4 and their role in cilia and male sensory behaviors. *Exp Cell Res* 2005;305(2):333–342.
100. Bae YK, Lyman-Gingerich J, Barr MM, Knobel KM. Identification of genes involved in the ciliary trafficking of C. Elegans PKD-2. *Dev Dyn* 2008;273(8):2021–2029.
101. Jauregui AR, Nguyen KC, Hall DH, Barr MM. The Caenorhabditis elegans nephrocystins act as global modifiers of cilium structure. *J Cell Biol* 2008;180(5):973–988.
102. Winkelbauer ME, Schafer JC, Haycraft CJ et al. The C. Elegans homologs of nephrocystin-1 and nephrocystin-4 are cilia transition zone proteins involved in chemosensory perception. *J Cell Sci* 2005;118(Pt 23):5575–5587.
103. Mykytyn K, Sheffield VC. Establishing a connection between cilia and Bardet-Biedl Syndrome. *Trends Mol Med* 2004;10(3):106–109.
104. Efimenko E, Bubb K, Mak HY et al. Analysis of xbx genes in C. Elegans. *Development* 2005;132(8):1923–1934.
105. O'Toole JF, Otto E, Frishberg Y, Hildebrandt F. Retinitis Pigmentosa and Renal Failure in a Patient with Mutations in Inversin. *J Am Soc Nephrol* 2004;15:215A.
106. Saunier S, Morin G, Calado J et al. Large deletions of the NPH1 region in Cogan syndrome (CS) associated with familial juvenile nephronophthisis (NPH). *Am J Hum Genet* 1997;61:A346.
107. Pazour GJ, Dickert BL, Vucica Y et al. Chlamydomonas IFT88 and its mouse homologue, polycystic kidney disease gene tg737, are required for assembly of cilia and flagella. *J Cell Biol* 2000;151 (3):709–718.
108. Joubert M, Eisenring JJ, Robb JP, Andermann F. Familial agenesis of the cerebellar vermis. A syndrome of episodic hyperpnea, abnormal eye movements, ataxia, and retardation. *Neurology* 1969;19 (9):813–825.
109. Parisi MA, Dobyns WB. Human malformations of the midbrain and hindbrain: review and proposed classification scheme. *Mol Genet Metab* 2003;80(1–2):36–53.
110. Gleeson JG, Keeler LC, Parisi MA et al. Molar tooth sign of the midbrain-hindbrain junction: occurrence in multiple distinct syndromes. *Am J Med Genet* 2004;125A(2):125–134; discussion 117.
111. Castori M, Valente EM, Donati MA et al. NPHP1 gene deletion is a rare cause of Joubert syndrome related disorders. *J Med Genet* 2005;42(2):e9.
112. Utsch B, Sayer JA, Attanasio M et al. Identification of the first AHI1 gene mutations in nephronophthisis-associated Joubert syndrome. *Pediatr Nephrol* 2006;21(1):32–35.
113. Parisi MA, Doherty D, Eckert ML et al. AHI1 mutations cause both retinal dystrophy and renal cystic disease in Joubert syndrome. *J Med Genet* 2006;43(4):334–339.
114. Sayer JA, Otto EA, O'Toole JF et al. The centrosomal protein nephrocystin-6 is mutated in Joubert syndrome and activates transcription factor ATF4. *Nat Genet* 2006;38(6):674–681.
115. Saar K, Al-Gazali L, Sztriha L et al. Homozygosity mapping in families with Joubert syndrome identifies a locus on chromosome 9q34.3 and evidence for genetic heterogeneity. *Am J Hum Genet* 1999;65(6):1666–1671.
116. Keeler LC, Marsh SE, Leeflang EP et al. Linkage analysis in families with Joubert syndrome plus oculo-renal involvement identifies the CORS2 locus on chromosome 11p12-q13.3. *Am J Hum Genet* 2003;73(3):656–662.
117. Delaney V, Mullaney J, Bourke E. Juvenile nephronophthisis, congenital hepatic fibrosis and retinal hypoplasia in twins. *Q J Med* 1978;47(187):281–290.
118. Proesmans W, Van Damme B, Macken J. Nephronophthisis and tapetoretinal degeneration associated with liver fibrosis. *Clin Nephrol* 1975;3(4):160–164.
119. Rayfield EJ, McDonald FD. Red and blonde hair in renal medullary cystic disease. *Arch Intern Med* 1972;130(1):72–75.
120. Kumada S, Hayashi M, Arima K et al. Renal disease in Arima syndrome is nephronophthisis as in other Joubert-related Cerebello-oculo-renal syndromes. *Am J Med Genet A* 2004;131 (1):71–76.
121. Satran D, Pierpont ME, Dobyns WB. Cerebello-oculo-renal syndromes including Arima, Senior-Loken and COACH syndromes: more than just variants of Joubert syndrome. *Am J Med Genet* 1999;86(5):459–469.
122. Chance PF, Cavalier L, Satran D et al. Clinical nosologic and genetic aspects of Joubert and related syndromes. *J Child Neurol* 1999;14 (10):660–666; discussion 669–72.
123. Kyttala M, Tallila J, Salonen R et al. MKS1, encoding a component of the flagellar apparatus basal body proteome, is mutated in Meckel syndrome. *Nat Genet* 2006;38(2):155–157.
124. Smith UM, Consugar M, Tee LJ et al. The transmembrane protein meckelin (MKS3) is mutated in Meckel-Gruber syndrome and the wpk rat. *Nat Genet* 2006;38(2):191–196.
125. Roume J, Genin E, Cormier-Daire V et al. A gene for Meckel syndrome maps to chromosome 11q13. *Am J Hum Genet* 1998;63 (4):1095–1101.
126. Khaddour R, Smith U, Baala L et al. Spectrum of MKS1 and MKS3 mutations in Meckel syndrome: a genotype-phenotype correlation. Mutation in brief #960. Online. *Hum Mutat* 2007;28 (5):523–524.
127. McGrath J, Somlo S, Makova S et al. Two populations of node monocilia initiate left-right asymmetry in the mouse. *Cell* 2003;114 (1):61–73.
128. Donaldson MD, Warner AA, Trompeter RS et al. Familial juvenile nephronophthisis, Jeune's syndrome, and associated disorders. *Arch Dis Child* 1985;60(5):426–434.
129. Jeune M, Beraud C, Carron R. Dystrophie thoracique asphyxiante de caractere familial. [Asphyxiating thoracic dystrophy with familial characteristics.]. *Arch Fr Pediatr* 1955;12(8):886–891.
130. Amirou M, Bourdat-Michel G, Pinel N et al. Successful renal transplantation in Jeune syndrome type 2. *Pediatr Nephrol* 1998;12(4):293–294.
131. Sarimurat N, Elcioglu N, Tekant GT et al. Jeune's asphyxiating thoracic dystrophy of the newborn. *Eur J Pediatr Surg* 1998; 8(2):100–101.
132. Moudgil A, Bagga A, Kamil ES et al. Nephronophthisis associated with Ellis-van Creveld syndrome. *Pediatr Nephrol* 1998; 12(1):20–22.
133. Di Rocco M, .Picco P, .Arslanian A .et al. Retinitis pigmentosa, hypopituitarism, nephronophthisis, and mild skeletal dysplasia (RHYNS): a new syndrome? *Am J Med Genet* 1997;73(1):1–4.

134. Tsimaratos M, Sarles J, Sigaudy S, Philip N. Renal and retinal involvement in the Sensenbrenner syndrome. *Am J Med Genet* 1998;77(4):337.
135. Costet C, Betis F, Berard E et al. [Pigmentosum retinis and tubulointerstitial nephronophtisis in Sensenbrenner syndrome: a case report]. *J Fr Ophtalmol* 2000;23(2):158–160.
136. Beales PL, Bland E, Tobin JL et al. IFT80, which encodes a conserved intraflagellar transport protein, is mutated in Jeune asphyxiating thoracic dystrophy. *Nat Genet* 2007;39(6):727–729.
137. Goldman SH, Walker SR, Merigan TC, Jr. et al. Hereditary occurrence of cystic disease of the renal medulla. *N Engl J Med* 1966;274 (18):984–992.
138. Gardner KD. Evolution of clinical signs in adult-onset cystic disease of the renal medulla. *Ann Intern Med* 1971;74:47–54.
139. Burke JR, Inglis JA, Craswell PW et al. Juvenile nephronophthisis and medullary cystic disease – the same disease (report of a large family with medullary cystic disease associated with gout and epilepsy). *Clin Nephrol* 1982;18(1):1–8.
140. Wolf MT, Mucha BE, Hennies HC et al. Medullary cystic kidney disease type 1: mutational analysis in 37 genes based on haplotype sharing. *Hum Genet* 2006;119(6):649–658.
141. Kiser RL, Wolf MT, Martin JL et al. Medullary cystic kidney disease type 1 in a large Native-American kindred. *Am J Kidney Dis* 2004;44 (4):611–617.
142. Wolf MT, Karle SM, Schwarz S et al. Refinement of the critical region for MCKD1 by detection of transcontinental haplotype sharing. *Kidney Int* 2003;64(3):788–792.
143. Stavrou C, Koptides M, Tombazos C et al. Autosomal-dominant medullary cystic kidney disease type 1: clinical and molecular findings in six large Cypriot families. *Kidney Int* 2002;62(4):1385–1394.
144. Fuchshuber A, Kroiss S, Karle S et al. Refinement of the gene locus for autosomal dominant medullary cystic kidney disease type 1 (MCKD1) and construction of a physical and partial transcriptional map of the region. *Genomics* 2001;72(3):278–284.
145. Fuchshuber A, Deltas CC, Berthold S et al. Autosomal dominant medullary cystic kidney disease: evidence of gene locus heterogeneity. *Nephrol Dial Transplant* 1998;13(8):1955–1957.
146. Scolari F, Puzzer D, Amoroso A et al. Identification of a new locus for medullary cystic disease, on chromosome 16p12. *Am J Hum Genet* 1999;64(6):1655–1560.
147. Hateboer N, Gumbs C, Teare MD et al. Confirmation of a gene locus for medullary cystic kidney disease (MCKD2) on chromosome 16p12. *Kidney Int* 2001;60(4):1233–1239.
148. Hart TC, Gorry MC, Hart PS et al. Mutations of the UMOD gene are responsible for medullary cystic kidney disease 2 and familial juvenile hyperuricaemic nephropathy. *J Med Genet* 2002;39 (12):882–892.
149. Rezende-Lima W, Parreira KS, Garcia-Gonzalez M et al. Homozygosity for uromodulin disorders: FJHN and MCKD-type 2. *Kidney Int* 2004;66(2):558–563.
150. Wolf MT, Mucha BE, Attanasio M et al. Mutations of the Uromodulin gene in MCKD type 2 patients cluster in exon 4, which encodes three EGF-like domains. *Kidney Int* 2003;64(5):1580–1587.
151. Dahan K, Devuyst O, Smaers M et al. A cluster of mutations in the UMOD gene causes familial juvenile hyperuricemic nephropathy with abnormal expression of uromodulin. *J Am Soc Nephrol* 2003;14(11):2883–2893.
152. Dahan K, Fuchshuber A, Adamis S et al. Familial juvenile hyperuricemic nephropathy and autosomal dominant medullary cystic kidney disease type 2: two facets of the same disease? *J Am Soc Nephrol* 2001;12(11):2348–2357.
153. Hildebrandt F, Rensing C, Betz R et al. Establishing an algorithm for molecular genetic diagnostics in 127 families with juvenile nephronophthisis. *Kidney Int* 2001;59(2):434–445.
154. Garel LA, Habib R, Pariente D et al. Juvenile nephronophthisis: sonographic appearance in children with severe uremia. *Radiology* 1984;151(1):93–95.
155. McGregor AR, Bailey RR. Nephronophthisis-cystic renal medulla complex: diagnosis by computerized tomography. *Nephron* 1989;53 (1):70–72.
156. Fyhrquist FY, Klockars M, Gordin A et al. Hyperreninemia, lysozymuria, and erythrocytosis in Fanconi syndrome with medullary cystic kidney. *Acta Med Scand* 1980;207(5):359–365.
157. Cacchi R, Ricci V. Sopra una rara e forse ancora non descritta effezione cistica della piramidi renali ("rene a spugna"). *Atti Soc Ital Urol* 1948;5:59.
158. Torres VE, Wang X, Qian Q et al. Effective treatment of an orthologous model of autosomal dominant polycystic kidney disease. *Nat Med* 2004;10(4):363–364.
159. Kozminski KG, Johnson KA, Forscher P, Rosenbaum JL. A motility in the eukaryotic flagellum unrelated to flagellar beating. *Proc Natl Acad Sci USA* 1993;90(12):5519–5523.
160. Lin F, Hiesberger T, Cordes K et al. Kidney-specific inactivation of the KIF3A subunit of kinesin-II inhibits renal ciliogenesis and produces polycystic kidney disease. *Proc Natl Acad Sci USA* 2003;100(9):5286–5291.
161. Pazour GJ, Dickert BL, Witman GB. The DHC1b (DHC2) isoform of cytoplasmic dynein is required for flagellar assembly. *J Cell Biol* 1999;144(3):473–481.
162. Bisgrove BW, Yost HJ. The roles of cilia in developmental disorders and disease. *Development* 2006;133(21):4131–4143.
163. Nurnberger J, Bacallao RL, Phillips CL. Inversin forms a complex with catenins and N-cadherin in polarized epithelial cells. *Mol Biol Cell* 2002;13(9):3096–3106.
164. Saadi-Kheddouci S, Berrebi D, Romagnolo B et al. Early development of polycystic kidney disease in transgenic mice expressing an activated mutant of the beta-catenin gene. *Oncogene* 2001;20 (42):5972–5981.
165. Pazour GJ, Rosenbaum JL. Intraflagellar transport and cilia-dependent diseases. *Trends Cell Biol* 2002;12(12):551–555.