Nephronophthisis (NPHP) is an autosomal recessive cystic kidney disease that constitutes the most frequent genetic cause for ESRD in the first three decades of life. Renal failure manifests at a median age of 13 yr. Initial symptoms are relatively mild, start at approximately age 6 yr, and consist of polyuria, polydipsia, secondary enuresis, and anemia. Regular fluid intake at nighttime is a characteristic feature of the patients’ history. Renal ultrasound reveals normal kidney size, increased echogenicity, and cortical medullary cysts (Figure 1A). Renal histology exhibits a characteristic triad of cortico-medullary cysts, tubular basement membrane disruption, and tubulointerstitial nephropathy (Figure 1B). Disease recurrence has never been reported in kidneys transplanted into patients with NPHP. NPHP is inherited in an autosomal recessive mode. It was first described by Smith and Graham in 1945 and by Fanconi et al., who introduced the term “familial juvenile nephronophthisis.” In juvenile NPHP, renal failure develops within the first three decades of life. In contrast, infantile NPHP, which is characterized by mutations in NPHP2/inversin, leads to renal failure between birth and age 3 yr. In more than 10% of cases, NPHP is associated with extrarenal involvement, primarily including retinal degeneration (Senior-Loken syndrome), cerebellar vermis aplasia (Joubert syndrome), liver fibrosis, and cone-shaped epiphyses. These clinical features are discussed here in light of the cilia/centrosome theory of NPHP. More than 300 cases of NPHP have been published in the literature. It has been reported from virtually all regions of the world. The incidence of the disease is estimated at nine patients per 8.3 million in the United States or one in 50,000 live births in Canada. In the North American pediatric population with ESRD, pooled data indicate a prevalence of approximately 5% of all children with renal failure.

Positional cloning has identified nine genes causing nephronophthisis when mutated. These are monogenic recessive genes, suggesting that mutations in each single one is sufficient by itself to cause NPHP in a patient bearing mutations and indicating their gene products are necessary for normal kidney function. Positional cloning generated new insights into disease mechanisms of NPHP by revealing the mechanism is related to the signaling pathways of primary cilia, centrosomes, and planar cell polarity. The demonstration that nephrocystin-1 and inversin/NPHP2 localize to primary cilia of renal tubular cells was among the first findings to support a new unifying theory of renal...
This theory states that the cystoproteins mutated in renal cystic disease in humans, mice, or zebrafish are expressed in primary cilia, basal bodies, or centrosomes. Basal bodies are the foundations from which cilia are assembled (Figure 2). After mitosis and cell division are completed, basal bodies derive from the mother centriole of the centriole pair that had organized the mitotic spindle during cell division. As 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. The structure and function of primary cilia and basal bodies are delineated in Figure 2.

Primary cilia are highly conserved structures that sense a wide variety of extracellular cues in a wide spectrum of epithelial tissues. There is a broad range of cues that can be received by specific ciliary receptors, including photosensation, mechanosensation, osmosensation, and olfactory sensation. In general, the pathogenesis of ciliopathies is based on an inability of epithelial cells to sense or process extracellular cues.

By positional cloning, we and others identified recessive mutations in nine novel genes as causing NPHP: NPHP1, NPHP2/inversin, NPHP3, NPHP4, NPHP5, NPHP6/CEP290, NPHP7/GLIS2, NPHP8/RPGRIP1L, and NPHP9/NEK8, defining NPHP types 1 through 9, respectively. This collection of genes has made diagnostic testing possible (http://www.renalgenes.org). Homozygous deletions in the NPHP1 gene account for approximately 21% of all NPHP cases, whereas the other genes contribute less than 3% each (Figure 3). As determined in more than 1000 families with NPHP, the causative genes are

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**Figure 1.** Morphology of nephronophthisis. (A) Renal ultrasound demonstrates increased echogenicity, loss of corticomedullary differentiation, and the presence of corticomedullary cysts. In contrast to PKD, kidneys are not enlarged. (B) Renal histology in NPHP shows the characteristic triad of renal tubular cysts, tubular membrane disruption, and tubulointerstitial cell infiltrates with interstitial fibrosis and periglomerular fibrosis (B is courtesy of D. Bockenhauer, London).

**Figure 2.** 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 versus 9 + 0 axoneme). 9 + 2 cilia usually have dynein arms that link the microtubule doublets and are motile, whereas most 9 + 0 cilia lack dynein arms and are nonmotile (“primary cilia”) with a few exceptions. The ciliary axoneme is anchored in the basal body, a microtubule-organizing center derived from the mother cilentro. 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. 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. Anterograde transport toward the tip is driven by heterotrimeric kinesin 2, which contains motor subunits Kif3a and Kif3b and a nonmotor subunit. Mutations of Kif3a cause renal cysts and cerebellar vermis aplasia in mice. Retrograde transport back to the cell body occurs via the motor protein cytoplasmic dynein 1B. Adapted from Bisgrove and Yost.

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still unknown in approximately 70% of patients, indicating that additional genes are involved in the pathogenesis of NPHP (Figure 3). Evidence has been generated that more than one recessive gene may be mutated in individual patients with NPHP, as has been proposed for the related disorder Bardet-Biedl syndrome (BBS). In this situation, mutations in an additional NPHP gene may modify the clinical picture of NPHP in the direction of a more severe extrarenal involvement. Here, disease mechanisms of NPHP are discussed in the context of the discovery of each of the genes encoding NPHP. We describe how resulting insights into the function of their gene products, the nephrocystins, helped refine the cilia/centrosome theory of renal cystic diseases.

**NPHP1 Locates to Cell Contacts and the Cilia Transition Zone**

Mutations in *NPHP1* were identified as causing juvenile nephronophthisis type 1,20 NPHP1 encodes nephrocystin-1, a protein that interacts with components of cell–cell and cell–matrix signaling, including p130Cas, focal adhesion kinase 2, tensin, and filamin A and B. Nephrocystin-1 is located at adherens junctions and focal adhesions of renal epithelial cells, which are involved in cell–cell and cell–basement membrane contacts, respectively (Figure 4). It also interacts with the product of other nephronophthisis genes such as nephrocystin-2/inversin, nephrocystin-3, and nephrocystin-4.

More recently, it was shown that nephrocystin-1 is targeted to the transition zone of motile and primary cilia by the protein phosphofurin acidic cluster sorting protein 1 (PACS-1). 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 co-localization of nephrocystin with PACS-1 at the base of cilia.

When NPHP1 was first identified, we proposed a pathogenic hypothesis that tied nephrocystin-1 in with defects of cell–cell and cell–matrix signaling, based on the finding that nephrocystin-1 contains an SH3 domain, localizes to adherens junctions and focal adhesions of renal epithelial cells, and interacts with integral components of these structures, such as p130Cas. “adherens junction/focal adhesion hypothesis” is partially reconciled with the “cilia/centrosome” hypothesis in an integrative hypothesis by showing that nephrocystin-4 in polarized epithelial cells co-localizes with β-catenin at cell–cell contact sites and to primary cilia, whereas, in dividing cells, it localizes to centrosomes (Figure 4).

**NPHP2/Inversin Implicates Cilia and Planar Cell Polarity in Cystogenesis**

On the basis of positional cloning and candidate gene data, we identified mutations in human inversin (*INVS*) as the cause of infantile NPHP (type 2) with and without *situs inversus*. The renal cystic changes of infantile nephronophthisis (NPHP type 2) combine clinical features of NPHP and of polycystic kidney disease (PKD). We demonstrated that nephrocystin-1 and NPHP2/inversin interact with β-tubulin, which constitutes the microtubule axoneme of primary cilia, and that they localize at primary cilia of renal tubular cells. This was one of the first findings to support a unifying theory of renal cystogenesis, which states that cytoproteins, which are mutated in renal cystic disease in humans, mice, or zebrafish, are expressed in primary cilia, basal bodies, or centrosomes. The interaction and co-localization to cilia and basal bodies of nephrocystin-1, inversin, and β-tubulin provide a functional link between the pathogenesis of NPHP, the pathogenesis of PKD, primary cilia function, and left–right axis determination. Okada et al. previously demonstrated that inversin is needed to position cilia in cells of the ventral node. Inversin was then shown to localize to different subcellular locations, in a cell cycle–dependent manner (Figure 5). Specifically, it is found at the mitotic spindle in mitosis, at the mid-body in cytokinesis, and in cilia at the basal body and centrosome in interphase (Figure 5). All of these subcellular organelles are involved in regulation of planar cell polarity or the cell cycle (Figure 4).

A major breakthrough was also made in the understanding of the pathogenesis of renal cystic diseases when Simons et al. demonstrated a role for inversin/NPHP2 in signaling mechanisms of planar cell polarity necessary to maintain normal tubular development and morphology, as outlined in Figure 6. As a consequence of this model, when inversin is defective (as in NPHP type 2), canonical Wnt pathway will prevail and disrupt the apical-basolateral polarity of renal epithelium. Because planar cell polarity signaling is important for oriented cell division, it seems logical that Fisher et al. were able to demonstrate...
abnormal orientation of mitotic spindles in two different rodent models of cystic kidney disease.

**NPHP3: A Doorstep to Treatment?**

By positional cloning, we identified mutations in *NPHP3* as responsible for adolescent nephronophthisis in a large Venezuelan kindred.\(^{11,22}\) We demonstrated that mutations in the murine ortholog *Nphp3* cause the renal cystic mouse mutant *pcy*,\(^{23}\) which was demonstrated to be responsive to treatment with a vasopressin receptor antagonist.\(^{58}\) Recently, it was shown that complete loss of *Nphp3* function results in *situs inversus*, congenital heart defects, and embryonic lethality in mice.\(^{59}\) In addition, truncating mutations of *NPHP3* in humans causes a broad clinical spectrum of early embryonic patterning defects that resembles Meckel syndrome. This includes *situs inversus*, polydactyly, central nervous system malformations, structural heart defects, preauricular fistulae, and a wide range of congenital anomalies of the kidney and urinary tract.\(^{59}\)

**NPHP4 Is Conserved in *Caenorhabditis elegans***

Mutations in the novel gene *NPHP4* were identified by homoyozosity mapping and total genome search for linkage.\(^{21,60,61}\) Nephrocystin-4, like inversin, localizes to primary cilia, basal bodies, centrosomes, and the cortical actin cytoskeleton\(^{46}\) (Figure 4). Nephrocystin-4 is conserved in *Caenorhabditis elegans* and expressed in ciliated head and tail neurons of the nematode.\(^{62}\) Upon knockdown, it exhibits a male mating phenotype, similar to the phenotype found upon knockdown of the polycystin-1 and polycystin-2 orthologs.\(^{62}\) 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 BBS proteins,\(^{62,63}\) similar to what has been described for *lov-1* and *pkd-2* mutants.\(^{64}\) These data were refined for specific neuronal cell types,\(^{65,66}\) and the necessity of *nphp-1* and *nphp-4* for morphologic integrity of ciliated neurons in *C. elegans* was observed.\(^{67,68}\) *Nphp-4* has an additional role in determining the life span of the worm.\(^{59}\)

Evolutionary conservation of 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. Striking, nephrocystin-4 and at least six proteins mutated in BBS are conserved in *Ch. reinhardtii*, where they are part of its basal body proteome.\(^{63,70}\) Defects of cystoprotein orthologs in *Ch. reinhardtii* have deficient intraflagellar transport and flagellar propulsion.\(^{71}\)
NPHP5: The Senior-Løken Syndrome Gene

When the novel gene NPHP5 was identified as mutated in nephronophthisis type 5,23 all mutations detected were truncations of the encoded protein nephrocystin-5, and all patients had early-onset retinitis pigmentosa (Senior-Løken syndrome). Nephrocystin-5 contains an IQ domain, which directly interacts with calmodulin,23 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 cells23 (Figure 4). That connecting cilia of photoreceptors are the structural equivalents of primary cilia of renal epithelial cells renders an explanation for retinal involvement in the retinal-renal syndrome Senior-Løken syndrome.

Cystogenesis: Defective Regulation of Planar Cell Polarity?

NPHP6/CEP290: Centrosomes as a Central Hub for Planar Cell Polarity Regulation

We identified by positional cloning recessive, truncating mutations in a novel gene NPHP6/CEP290 as the cause of NPHP type 6 and Joubert syndrome type 5.24 Its gene product nephrocystin-6/CEP29024 is part of the centrosomal proteome.24 Like NPHP2/inversin (Figure 5) and NPHP4, NPHP6/CEP290 is expressed in centrosomes and the mitotic spindle in a cell cycle–dependent manner. Abrogation of NPHP6 function in zebrafish causes planar cell polarity defects and recapitulates the human phenotype of NPHP type 6, including renal cysts, retinal degeneration, and cerebellar defects.24 Nephrocystin-6 modulates the activity of ATF4/CREB2, a transcription factor implicated in cAMP-depen-

Figure 5. Inversin/NPHP2 localizes to cilia, centrosomes, and the mitotic spindle in a cell cycle–dependent manner. (A) Inversin/NPHP2 is found in interphase in the cilial axoneme (data not shown), close to the centrioles of the basal body complex (arrow), and at the centrosome (arrow head). (B through D) In metaphase (B) and anaphase (C), it is at the mitotic spindle (arrows) and in telophase (D) at the midbody (arrow) of the separating cells and in the nucleus. This reflects a centriole-associated function of inversions/NPHP2 throughout the cell cycle. Reprinted from Morgan et al.,134 with permission.

Figure 6. Inversin/NPHP2 mediates a switch from the canonical to the noncanonical Wnt signaling pathway, which plays a role in planar cell polarity maintenance.59 (A) This illustration 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 noncanonical 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.125 Adapted from Germino.31
dent renal cyst formation.28 Interestingly, a 300–amino acid in-frame deletion of NPHP6/CEP290 causes retinal degeneration only, without renal or cerebellar involvement in the rds16 mouse model.24 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.24 Mutations in NPHP6/CEP290 have been confirmed as causing Joubert syndrome with and without renal involvement.35 Furthermore, truncating mutations in NPHP6 were shown to cause Meckel-Gruber syndrome.72

Correct orientation of the mitotic spindle and centrosomes with respect to the longitudinal axis of the tubule is critical for proper apical-basolateral polarity (Figure 7). Noncanonical Wnt signaling (see Figure 6) is involved in these processes during renal tubular morphogenesis, when in rodent renal tubules still elongate postnatally. The structure that would result from disruption of the longitudinal growth would be a dilated tubule or cyst. Recently, evidence for a role of planar cell polarity in renal cystic diseases57 was advanced by measuring orientation of the mitotic spindle through three-dimensional imaging of renal tubules. Comparison of the distribution of the mitotic angles in wild-type animals and rodent cystic kidney disease models suggest that mitotic angles of two rodent models of cystic kidneys, the HNF1β-deficient mouse model and the pck rat model, were clearly different from wild-type littermates.57

NPHP7/GLIS2: The Link to Hedgehog Signaling

Recently, we identified mutations in the gene NPHP7/GLIS2 in a Cree Indian kindred encoding the transcription factor Gli-similar protein 2 as the cause of NPHP type 7 (Figure 4). Starting at 8 wk of age, Glis2 mutant mice show severe renal atrophy and fibrosis resembling human nephronophthisis.28 Differential gene expression studies on Glis2 mutant kidneys demonstrated that genes promoting epithelial-to-mesenchymal transition and fibrosis are upregulated in the absence of Glis2.28 Strikingly, there was also prominent apoptosis present in distal tubular segments of the kidney, which might provide an explanation for why PKD kidneys are enlarged with hyperproliferation prevailing, whereas in NPHP, kidney size is reduced. GLIS2 is related to the GLI transcription factor, and these findings implicate the hedgehog pathway in the pathogenesis of cystic kidney diseases (Figure 8). It is a signaling pathway that controls cell determination and tissue patterning during embryogenesis. The other known role of hedgehog is the maintenance of stem cell pools in postembryonic tissues.

NPHP8: A Clinical Spectrum from Meckel Syndrome to Joubert Syndrome

Recently, missense and truncating mutations in the RPGRIP1L gene were identified by positional cloning as the cause of a Joubert syndrome-like phenotype (cerebro-oculo-renal syndrome [CORS]) and Meckel syndrome (Figure 4).29,36 It was
shown that defects in the mouse ortholog Rpgrip1l (Ftm) recapitulate the cerebral, renal, and hepatic defects of CORS and Meckel syndrome. RPGRIP1L co-localizes at the basal body and centrosomes with the protein products of both NPHP6 and NPHP4. RPGRIP1L missense mutations found in individuals with CORS diminish the interaction between RPGRIP1L and nephrocystin-4. Missense mutations were seen in patients with Joubert syndrome. These findings confirmed there is a continuum for the multiorgan phenotypic abnormalities found in Meckel syndrome, Joubert syndrome/CORS, and nephronophthisis on the basis of distinct mutations of identical genes (multiple allelism).

NPHP9: The Link From Cilia to Cell-Cycle Control

We recently identified three different highly conserved amino acid changes in the gene NEK8 (never in mitosis kinase 8) as causing NPHP type 9. One of the mutations identified is positioned in the same RCC1 domain in which a missense mutation causes renal cystic disease in jck mice. Upon expression in medullary collecting duct cells, all three mutant forms of NEK8 showed defects in ciliary and centrosomal localization to varying degrees, supporting the notion that mutations in NEK8 cause NPHP type 9 (Figure 4). As NEK8 plays a major role in cell-cycle regulation, these findings provide a direct link between a protein defective in renal cystic disease and the role of centrosomes for cell-cycle regulation (Figure 4). In this context it is interesting that also for polycystin-1 and -2 signaling, the renal cystic phenotype has been linked to cell growth regulation. Polycystin-1 expression activates the JAK-STAT pathway, thereby upregulating p21(waf1) and inducing cell-cycle arrest in G0/G1. Cell-cycle arrest required polycystin-2. Involvement of polycystin-1 and -2 signaling in the JAK/STAT pathway might explain how mutations of either gene can result in dysregulated growth. Involvement of cell-cycle regulation in renal cystic disease was confirmed by demonstration that two mouse models of PKD (jck and cpk) can be efficiently treated with the cyclin-dependent kinase inhibitor roscovitine.

Figure 9. Ciliopathies feature a broad spectrum of organ involvement, shown here for the nephronophthisis-related ciliopathies. There is overlap between different syndromes: Exclusive kidney involvement is called nephronophthisis. Associated retinal degeneration in known as Senior-Løken syndrome. Involvement of the cerebellum represents Joubert syndrome. In the most severe form, Meckel syndrome, brain malformations, liver fibrosis, heart defects, polydactyly, and perinatal mortality are associated. It has recently become evident that the spectrum can vary by at least two mechanisms: First, multiple allelism, in which a hypomorphic mutation may cause a milder phenotype. For example, a splice site mutation of NPHP6 may cause Leber congenital optic atrophy (LCA) only. In another example, the presence of one nontruncating mutation in NPHP8 can rescue the phenotype from Meckel syndrome to Joubert syndrome. Second, NPHP genes can modify each other. For instance, NPHP6 and AH11 modify recessive NPHP1 mutations to express a more severe phenotype.

The Ciliary Theory Explains Extrarenal Involvement of Eye, Brain, and Liver in NPHP

A prominent feature of NPHP is involvement of multiple organs (pleiotropy) outside the kidney. Defects in other organs are usually of a degenerative or developmental nature (Figure 9). Specifically, NPHP may be associated with tapetoretinal degeneration (Senior-Løken syndrome), cerebellar vermis aplasia (Joubert syndrome), oculomotor apraxia type Cogan, mental retardation, liver fibrosis, or cone-shaped epiphyses of the phalanges (Mainzer-Saldino syndrome). Infantile NPHP type 2 can be associated with situs inversus, retinitis pigmentosa, or cardiac ventricular septal defect. In some instances, there seems 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. The pleiotropy of NPHP has now found a potential explanation in the ciliary hypothesis of cystic kidney diseases (Figure 9). The extrarenal organ involvement in NPHP is discussed by organ system as follows (Figure 9).
fact that the primary cilium of renal epithelial cells is a structural equivalent of the connecting cilium of photoreceptor cells in the retina. We have shown that nephrocystin-5 and nephrocystin-6 are expressed in the connecting cilia of photoreceptors.

Cerebellar Vermis Aplasia (Joubert Syndrome)
In Joubert syndrome, 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 tachypnea/dyspnea (Figure 9). The radiographic feature of Joubert syndrome on axial magnetic resonance brain imaging is the so-called “molar tooth sign” of the midbrain-hindbrain junction. It is due to abnormal axonal decussation (nerve tract crossing) in the corticospinal tract and the superior cerebellar peduncles as the basis of the motor and behavioral abnormalities of Joubert syndrome. 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 Joubert syndrome (JBTS). This symptom has been described in patients with mutations in the NPHP1, NPHP4, NPHP5, NPHP6, ATR, and NPHP6 genes. Three additional recessive genes, NPHP1, NPHP4, and NPHP6, have been found mutated in JBTS. Three additional loci for JBTS have been identified: JBTS1 on chromosome 9q34.395 and JBTS2/CORS2 on chromosome 11p12-q13.3. In addition, mutations of NPHP8/RPGRIP1L can cause Joubert syndrome if at least one mutation is not truncating.

Liver Fibrosis
NPHP and the related disorder BBS can be associated with periductal liver fibrosis, as has been described for a patient with NPHP3 mutation. Patients develop hepatomegaly and moderate portal fibrosis with mild bile duct proliferation. This pattern differs from that of classical congenital hepatic fibrosis, where biliary dysgenesis is prominent, and from hepatic involvement in autosomal recessive PKD, Arima syndrome (cerebro-oculo-hepatorenal syndrome), and Meckel syndrome, which appears as bile duct proliferation. Bile duct involvement in these cystic kidney diseases may be explained by the ciliary theory because the epithelial cells lining bile ducts (cholangiocytes) possess primary cilia.

Brain Malformations (Meckel Syndrome)
Meckel syndrome (MKS) features the association of renal cystic dysplasia with occipital encephalocoele, polydactyly, and biliary digenesis (Figure 9). Two recessive genes have been identified, NPHP3 and NPHP6/CEP290, and NPHP8/RPGRIP1L. Within the spectrum of NPHP-associated ciliopathies, MKS is the most severe, leading to perinatal mortality. Consequently, MKS represents the ciliopathy of the group that encompasses defects in most organs, and involvement is most severe and 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, and occipital encephalocoele in the brain, and bones are involved by postaxial polydactyly. The notion that MKS is at the most pronounced end of the clinical spectrum is supported by 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 Joubert syndrome. In addition, the presence of two truncating mutations in NPHP6/CEP290 may cause an MKS-like phenotype (MKS4).

Cardiac Defects and Situs Inversus
In a patient with mutation of NPHP2, we observed a ventricular septal defect as a congenital cardiac malformation. Thus, the role of inversin for left–right orientation phenotype caused by the same mechanism that lead to situs inversus in this patient. We confirmed the phenotypic combination of cystic kidney disease, situs inversus, and cardiac septal defect on the basis of mutations is observed in humans, mice, and zebrafish. The patient with situs inversus also had a cardiac ventricular septal defect, which may be viewed as a “heterotaxy” (left–right orientation) phenotype caused by the same mechanism that lead to situs inversus in this patient. We confirmed the phenotypic combination of cystic kidney disease, situs inversus, and cardiac septal defect on the basis of mutations is observed in humans, mice, and zebrafish.

Skeletal Defects
Multiple disease variants that are associated with NPHP include skeletal defects, strongly suggesting a role of primary cilia function in skeletal development. These include Jeune syndrome (asphyxiating thoracic dysplasia), Ellis van Creveld syndrome, RHYNS syndrome (retinitis pigmentosa, hypopituitarism, NPHP, skeletal dysplasia), Meckel-Gruber syndrome, and Sensenbrenner syndrome (cranioectodermal dysplasia). The association of NPHP with cone-shaped epiphyses of the phalanges (types 28 and 28A) is known as Mainzer-Saldino syndrome and occurs in patients who also have retinal degeneration and cerebellar ataxia. Interestingly, mutations in the ortholog of the intraflagellar transport protein in this patient. We confirmed the phenotypic combination of cystic kidney disease, situs inversus, and cardiac septal defect on the basis of mutations is observed in humans, mice, and zebrafish. The patient with situs inversus also had a cardiac ventricular septal defect, which may be viewed as a “heterotaxy” (left–right orientation) phenotype caused by the same mechanism that lead to situs inversus in this patient. We confirmed the phenotypic combination of cystic kidney disease, situs inversus, and cardiac septal defect on the basis of mutations is observed in humans, mice, and zebrafish.

BBS and Alstrom Syndrome
BBS exhibits renal histology similar to NPHP118,119 (Figure 4). Positional cloning of recessive genes mutated in BBS reveals the molecular relationship between NPHP and BBS may lie in coexpression of the respective gene products in primary cilia, basal bodies, or centrosomes of renal epithelial cells. Alstrom syndrome exhibits some phenotypic overlap with BBS (NPHP, retinitis pigmentosa, deafness, obesity, and diabetes without mental defect, polydactyly, or hypoglycemia).
The single underlying recessive gene, ALMS1, encodes a novel protein that is a molecular component of the centrosome. This finding, together with the finding that BBS proteins localize to centrosomes, confirms the role of centrosomal proteins in cystic kidney diseases that are associated with diabetes, obesity, and retinitis pigmentosa.

Obesity is also a part of the clinical spectrum of the ciliopathies BBS and Alstrom syndrome. Interestingly, in the Bbs6 knockout mouse model, obesity is associated with hyperphagia and decreased activity of the mice.

**THEERAPEUTIC APPROACHES TO NPHP**

No effective prophylaxis or treatment is available for NPHP other than supportive care once chronic renal failure develops and dialysis and transplantation for terminal renal failure.Gattone et al. showed the renal cystic phenotype of pcy mice, which is the equivalent of human NPHP type 3, can be strongly mitigated or even reversed by treatment with the vasopressin V2 receptor antagonist OPC31260. Similar results were obtained using a pkd2 mouse model. This effect is thought to be mediated by a reduction in intracellular cAMP levels. An important future challenge will be the development of therapies that capitalize on what we have learned about the biology of NPHP and other cystic diseases of the kidney.

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