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Nephronophthisis

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Abstract

Nephronophthisis (NPHP) is an autosomal recessive cystic kidney disease, which represents the most frequent genetic cause for end-stage renal disease up to the third decade of life. Nephronophthisis is caused by mutations in eleven different genes called nephrocystins (*NPHP1-11*, *NPHP1L*). With an increasing number of identified genes our knowledge of nephronophthisis is changing and improving our understanding of the pathomechanisms in nephronophthisis. Recent publications described ciliary expression of nephrocystins together with other cystoproteins like polycystins 1 and 2, and fibrocystin. These findings have shifted our focus to a pathomechanism involving defects in ciliary function (ciliopathy) and planar cell polarity (PCP). In addition, discoveries of new nephrocystin genes have shown that the disease spectrum of nephronophthisis is much broader than previously anticipated. Different forms of mutations within the same *NPHP* gene can cause different disease severity. In this review we will highlighten the different hypotheses concerning the pathomechanisms for nephronophthisis and we will underline the clinical variability of nephronophthisis. The clinical spectrum has become even more complex with the possibility of oligogenicity in NPHP.

Keywords

nephronophthisis; cystic kidney disease; ciliopathy; Senior-Loken syndrome; Joubert syndrome; Meckel-Gruber syndrome; molecular genetics

INTRODUCTION

Nephronopthisis (NPHP) was first described in 1945 by Smith and Graham and 6 years later by Fanconi *et al* . [1,2]. Whereas Smith and Graham called this disease “medullary cystic kidney disease”, Fanconi *et al*. introduced later the term “familial juvenile nephronophthisis” [1,2]. The term “nephronophthisis” derives from the Greek and means “disintegration of nephrons”, which is one aspect of the histopathology. NPHP is an autosomal recessive tubulointerstitial nephropathy and is one of the most frequent genetic

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disorders causing end-stage renal disease (ESRD) in children and adolescents [3]. The most frequent form of NPHP, called NPHP type 1, is characterizied by ESRD at a mean age of 13 years [4]. Symptoms are very subtle and may start as early as 6 years of age. They consist of polyuria, polydipsia, secondary enuresis, growth retardation and anemia [5]. In addition, NPHP has a rare infantile form with age of onset of ESRD prior 4 years of age and an adolescent form with a median age of onset of ESRD of 19 years [6]. Renal ultrasound shows initially normal kidney size, increased echogenicity, poor corticomedullary differentiation and corticomedullary cysts (Figure 1) and later smaller, atrophic kidneys with increased echogenicity are found [7]. Imaging at a later stage of disease reveals small, atrophic kidneys and a more prominent cyst development. Histological findings in NPHP are tubular atrophy with thickened or thinned tubular basement membrane, cysts at the corticomedullary border and diffuse interstitial fibrosis (Figure 2) [8,9]. The histological characteristics of the infantile form of NPHP differ from the ones seen in juvenile NPHP. Infanitile NPHP combines features of NPHP (e.g. tubular cell atrophy, tubular cysts and interstitial fibrosis) with features of polycystic kidney disease (e.g. enlarged kidneys, widespread cyst development) [10,11]. Renal biopsy or mutation analysis is required for definitive diagnosis of NPHP. Over 300 cases of NPHP have been published [8]. In 10–15% of NPHP patients extrarenal symptoms are found, which include retinal degeneration (Senior-Loken syndrome), cerebellar vermis aplasia (Joubert syndrome), liver fibrosis, oculomotor apraxia (Cogan syndrome) and cone-shaped epiphysis [12]. A large variety of different syndromes have been published in association with NPHP (Table 1). One of the more prominent syndromes associated with NPHP is the severe perinatal lethal Meckel-Gruber syndrome, which includes occipital encephalocele, polydactyly, microphthalmia, and liver fibrosis among other developmental abnormalities [13]. The incidence of NPHP varies largely from 1:50,000 in Canada to approximately 1 in a million in the United States. In Finland the incidence of NPHP is reported as 1 in 61800 [5,7,14]. Finally, NPHP has also been diagnosed in adults with renal failure occurring later in life [15].

Initially, patients with NPHP were published under the term “medullary cystic kidney disease” (MCKD). Today MCKD refers to an autosomal dominant cystic kidney disease with hypertension and hyperuricemia, which shares the histology of NPHP [3]. Therefore, NPHP and MCKD have been combined to the “nephronophthisis – MCKD disesase complex” [8]. MCKD type 2 is caused by mutations in the *Uromodulin* (*UMOD*) gene [16]. Eleven different genes, that if mutated cause NPHP have been identified by positional cloning (*NPHP1-11*, *NPHP1L*) (Tab. 2). The most frequent mutation in NPHP is a homozygous deletion of *NPHP1*, which causes approximately 20% of cases with the isolated renal form of NPHP, whereas the mutations in the other genes contribute to less than three percent each [12]. In approximately 70% of all individuals with NPHP the causative gene is still unknown [12]. All eleven *NPHP* genes are sufficient to cause NPHP by two mutations in a single recessive gene. The type of gene mutated as well as the nature of mutations determine the severity of the phenotype regarding age of onset and extent of organ involvement. In addition, modifier effects have been suggested [17].

In this review we want to emphasize the changes in the understanding of the pathophysiology of NPHP. We will also outline the widening spectrum of phenotypes.

Additional phenotypes associated with nephronophthisis

Oculomotor apraxia type Cogan—Oculomotor apraxia (OMA) type Cogan [OMIM %257550] is characterized by an impaired horizontal gaze and nystagmus. As a result the affected individual has to move the head by jerky head movements in order to follow objects. OMA is a rare ocular sign found in NPHP patients with ***NPHP1*** and ***NPHP4*** mutations [12,18]. It is also encountered in Joubert syndrome. Cerebellar vermis aplasia has been published in association with OMA [19].

Nephronophthisis withretinitis pigmen tosis (Senior Loken syndrome)—About 10–15% of patients with NPHP have retinal degeneration, also called retinitis pigmentosa (RP) [20,21]. RP can result in early and severe visual impairment. Early onset of RP resembles Leber's congenital amaurosis (LCA), whereas late onset is characterized by night blindness and progressive visual loss. RP is diagnosed by fundoscopy and electroretinography. The association of retinitis pigmentosa and NPHP is called Senior-Loken syndrome (SLSN) [OMIM #266900, %606995, #606996, #609254, #610189]. The pathomechanism of the retinopathyis currently unknown but may be related to the function of the connecting cilium and centrosomes of photoreceptors, where nephrocystin proteins are expressed [12,17,22,23]. The frequency of RP with NPHP can range from 6–100%, depending on the *NPHP* mutation (e.g. 6% for *NPHP1*, 10% for *NPHP2/INV*, 100% for *NPHP5* and *NPHP6*) [12]. Retinal symptoms due to *NPHP1* deletions usually present with a milder phenotype. SLSN is also found in a few patients with *NPHP1* to *NPHP4* mutations. Several genes causing NPHP (*NPHP1*, *NPHP8/RPGRIP1L*) and NPHP-related phenotypes (*AHI1* in Joubert syndrome) are involved in photoreceptor development and act as modifiers of retinal degeneration [24–26].

Cerebellar vermis aplasia with NPHP(Joubert syndrome)—Joubert syndrome (JS) [OMIM %213300] is an autosomal recessive developmental disorder, consisting of cerebellar vermis aplasia (revealed in magnetic resonance brain imaging (MRI) as "molar tooth sign") (Fig. 3), cerebellar ataxia, hypotonia, oculomotor apraxia, neonatal tachypnea, mental retardation, and retinal degeneration [27]. NPHP is found in 17–27% of JS patients [28]. Additional associated symptoms include liver fibrosis, ocular coloboma, and polydactyly [27]. JS is also called CORS (cerebello-oculo-renal syndrome). JS is caused by mutations in *NPHP6/CEP290*, which encodes nephrocystin-6 and *NPHP8/RPGRIP1L*, which encodes nephrocystin-8 [29–31]. Additional mutations in JS were found in other genes including *AHI1, MKS3, ARL13B, CC2DA2, INPP5E,* and *TMEM216* [32–38]. Rare mutations in *NPHP1* and *NPHP4* were published in JS [39,40]. Cerebral symptoms due to *NPHP1* deletions usually present with a milder phenotype.

Meckel-Gruber syndrome—Meckel-Gruber syndrome (MKS) is characterized by renal cystic dysplasia, occipital encephalocele, microphthalmia and other central nervous system malformations, polydactyly, *situs inversus*, bile duct proliferation and pulmonary hypoplasia. Like all other forms of NPHP, MKS is inherited in an autosomal recessive mode. Newborn with MKS rarely survive longer than two weeks. Recently, a strong allelism has been described in MKS where two truncating mutations (nonsense, frame-shift or splice site mutations) in the genes *MKS1, MKS3, NPHP3, NPHP6/CEP290,* and *NPHP8/*

RPGRIP1L cause MKS, whereas the presence of at least one missense mutation causes the milder phenotype of JS or SLSN [17,30,41–43]. The defects in MKS represent developmental defects whereas in NPHP and SLSN defects of retina and kidney are degenerative in nature.

Liver fibrosis—NPHP-like ciliopathies have been described together with periportal liver fibrosis in a few cases. Hepatomegaly, portal fibrosis and bile duct proliferation were described in a patient with *NPHP3* mutation [44]. Liver fibrosis is also found in Arima syndrome (cerebro-oculo-hepato-renal syndrome) and Meckel syndrome. Very recently, mutations in *MKS3/TMEM67* was found to represent a major gene mutated in NPHP-like ciliopathies that exhibit a liver fibrosis phenotype [45]. In this context two truncating mutations caused MKS with biliary duct dysplasia, whereas the presence of at least one missense mutation among the two alleles caused only NPHP-like degenerative liver fibrosis. A similar genotype-phenotype correlation has been described for *NPHP6/CEP290*and *MKS1* [12].

Skeletal defects—Skeletal symptoms associated with NPHP are rare. The most frequent skeletal manifestation of NPHP are cone-shaped epiphyses of the phalanges, also called Mainzer-Saldino syndrome [46]. There can also be an association with cerebellar ataxia, retinal degeneration, and polydactyly [47]. Jeune syndrome (asphyxiating thoracic dysplasia) with short limbs and small thorax and Ellis van Creveld syndrome with short stature, short extremities, and polydactyly canalso occur in association with NPHP[48,49].

Cardiac defects—Rare cases of cardiac defects (e.g. ventricular septal defect) have been published in association with infantile NPHP and mutations in *NPHP2/inversin* and *NPHP3* [43,50]. Animal models (in zebrafish and mice) for *NPHP2/inversin* confirmed the association of cystic kidney disease with cardiac septal defects[50].

Diagnosing nephronophthisis: Symptoms and signs in NPHP manifest slowly and are subtle. The history may reveal polyuria, polydipsia or secondary enuresis usually starting around 6 years of age. General symptoms of renal failure may be present such as fatigue, pruritus, nausea, vomiting, uremic gastritis, anemia and growth retardation. A family history of consanguity may hint towards an autosomal recessive disease. The physical exam may reveal any of the associated extrarenal phenotypes or may be unremarkable besides pallor and short stature. Urinalysis may reveal a renal concentration defect (<400 mosm/kg in morning urine). Renal function should be evaluated as well as CBC, liver function tests and coagulation tests. Renal ultrasound may show small kidneys with poor corticomedullary differentiation and corticomedullary cysts, and if present, liver fibrosis. Renal biopsy can be done if the kidneys are not too small and atrophic at the timepoint of diagnosis. However, nowadays molecular genetic analysis is the mainstay for making a definitive diagnosis of an NPHP-like ciliopathy. If there is any indication of cerebellar involvement an MRI may be indicated to rule out the molar tooth sign, which indicates Joubert syndrome. If there is concern for NPHP an ophthalmological exam should be performed to rule out retinal degeneration. There are only two ways to obtain a definitive diagnosis of NPHP: renal

biopsy or mutation analysis (www.renalgenes.org). Mutation analysis should be initiated in the context of genetic counseling.

Genes mutated inn ephronophthisis

NPHP1 is located at cell contacts and cilary transition zone: Homozygous deletions of *NPHP1* on chromosome 2q13 cause NPHP type 1, the most frequent form of NPHP accounting for about 20% of cases [51,52]. The homozygous *NPHP1* deletion is also found in patients with additional ocular motor apraxia (OMA) [18], Senior-Loken syndrome [53] and very rarely in Joubert syndrome, which may be due to an epistatic effect by the *AHI1* gene [39,54]. In few patients a heterozygous deletion of *NPHP1* was associated with a *NPHP1*point mutation.

NPHP1 encodes nephrocystin-1, which is located at adherens junctions and focal adhesions of renal epithelial cells. In the human kidney nephrocystin-1 is expressed primarily in collecting duct cells [55]. Interaction of nephrocystin-1 was described with p130cas, focal adhesion kinase 2, tensin, filamin A and B [56–58]. Due to the expression pattern and interaction partners nephrocystin-1 was suspected to play a role in cell-cell and cell-matrix signaling. In addition, interaction was later shown with nephrocystin-2/inversin, nephrocystin-3, nephrocystin-4, and Jouberin, indicating that there is a protein complex of nephrocystins [44,50,59,60]. This complex of proteins may function in multiple intracellular compartments including the cilium, cell-cell adherens junctions and focal adhesions [50,56,57]. When ciliary localization of nephrocystin-2/inversin was discovered, nephrocystin-1 was also identified in cilia [50]. The primary ciliary localization was later refined to the transition zone (e.g. at the base of the cilium) in respiratory and renal epithelium and to the connecting cilium of the photoreceptor [61]. PACS-1 and casein kinase 2 phosphorylation are required for targeting of nephrocystin-1 to the transition zone [62].Due to the expression pattern of nephrocystin-1 in the adherens junctions and focal adhesions and the interaction with integral components of these structures (e.g. p130CAS), nephrocystin-1 was initially thought to result in a defective cell-cell and cell-matrix signaling – which resulted in the “adherens junction/focal adhesion hypothesis” [3]. This hypothesis was later linked to the “ciliary hypothesis” by the finding that nephrocystin-4, an interaction partner of nephrocystin-1, co-localizes with β-catenin at cell-cell contact sites, and to primary cilia in polarized renal epithelial cells but is found in centrosomesin dividing cells [63].

Mutations in nephrocystin-2 cause infantile NPHP, situs inversus and cardiac defects: Recessive mutations of **nephrocystin-2/inversin** were identified as the cause for NPHP2 based on a candidate gene approach and positional cloning [10,50]. Characteristics of NPHP2 are: i) age of onset of ESRD prior to 5 years of age, ii) a renal ultrasound finding ofnormal or enlarged kidneys, iii) possible antenatal presentation with oligohydramnios, iv) renal histology showingan overlap of feat ures characteristic of NPHP and ADPKD, and v)possible association with situs inversus and cardiac abnormalities (VSD) [64]. Retinitis pigmentosa is a rare finding in patients with *NPHP2/inversin* mutations [65]. Even though nephrocystin-2/inversin mutations are rare (1% of all NPHP patients), the identification of nephrocystin-2/inversin mutations as causing NPHP2 resulted in a major breakthrough

concerning our understanding of NPHP: Nephrocystin-2/inversin was found to be co-expressed in primary cilia of renal tubular cells with nephrocystin-1 and interacts with nephrocystin-1 and β-tubulin [50]. β-tubulin represents a major protein of the microtubule axoneme of primary cilia. This discovery was one of the first hints towards a unifying theory of renal cystogenesis, which implies that all genes causing cystic kidney disease are expressed in primary cilia, basal bodies or centrosomes [3,66]. Recently, nephrocystin-2/inversin was shown to function as an anchor for NPHP3 and NPHP9/Nek8 in cilia [67]. Further studies of nephrocystin-2/inversin showed a cell cycle-dependent expression of nephrocystin-2/inversin in the mitotic spindle in mitosis, the mid-body in cytokinesis and in cilia, the basal body and centrosomes in the interphase [68]. Cell-cyle-specific expression of nephrocystin-2/inversin in these organelles supported the development of the “planar cell polarity” (PCP) hypothesis of the pathogenesis of NPHP [see below “Planar cell polarity”]. This hypothesis was supported by Simons *et al*., who demonstrated a role for nephrocystin-2/inversin in the Wnt signaling pathway, which is involved in planar cell polarity [69]. If nephrocystin-2/inversin is defective, the canonical pathway of the Wnt signaling will dominate over the non-canonical form and will disrupt apical-basolateral polarity of the renal epithelial cells. Besides mutations in *NPHP2/inversin* mutations in *NPHP3* and *NPHP9/NEK8* were also identified in patients with infantile NPH [70–72].

NPHP3mutations are a rare cause of NPH Pbut maycause a wide sp ectrum of disease: ***NPHP3*** was mapped and identified in one large Venezuelan kindred with NPHP [44]. It encodes nephrocystin-3 which interacts with nephrocystin-1 and inversin [43,44]. Nephrocystin-3, like inversin, may inhibit the canonical Wnt signaling pathway [43]. Moreover, mutations in the murine ortholog *Nphp3* cause the renal cystic mouse mutant *pcy*, which generates a hypomorphic *Nphp3* allele [44]. Interestingly, the *pcy* mouse model responds very well to treatment with a vasopressin-2 receptor antagonist [73]. The *Nphp3* knockout mouse model shows *situs inversus*, congenital heart defects and embryonic lethality, a phenotype very similar to Meckel-Gruber syndrome, thus confirming that complete loss of function mutations cause the developmental phenotype of MKS, whereas missense mutations cause primarily degenerative phenotypes [43]. In humans, mutations in *NPHP3* result in a variety of phenotypes ranging from adolescent NPHP, NPHP with liver fibrosis, NPHP with RP, infantile NPHP to Meckel-Gruber syndrome (MKS), dependent on the nature of the mutated alleles [43,44,70,72]. Truncating mutations result in developmental, early-onset phenotypes resembling MKS, whereas non-truncating mutations result in milder degenerative phenotypes with later age of onset.

Nephrocystin-4: Combining the cilia and the cell junction hypothesis: NPHP4 mutations were identified by positional cloning on chromosome 1p36 [40,74]. *NPHP4* encodes nephrocystin-4, which also localizes to primary cilia, basal bodies and centrosomes [63]. Nephrocystin-4 interacts with nephrocystin-1 and nephrocystin-8/RPGRIP1L and forms complexes with α-tubulin [30,40]. Recently, nephrocystin-4 and nephrocystin-1 have been shown to associate with PALS1/PATJ and Par6, which is required for epithelial morphogenesis [75]. Mutations in *NPHP4* account for about 2% of NPHP and can result in isolated NPHP, NPHP with OMA and SLSN.

NPHP5 mutations cause a retinal-renal phenotype: Homozygous truncating mutations of ***NPHP5/IQCB1*** cause SLSN with early-onset RP in association with NPHP [76]. *NPHP5/IQCB1* encodes nephrocystin-5, which contains two IQ calmodulin binding sites and a coiled-coil domain. Nephrocystin-5 interacts directly with calmodulin via the IQ domains and forms a complex with retinitis pigmentosa GTPase regulator (RPGR) [76]. Mutations in *RPGR* result in X-linked retinitis pigmentosa. Prior to the "ciliary hypothesis" the pathologic basis for retinal involvement in SLSN was not well understood. The strong association of *NPHP5/IQCB1* mutations prompted further expression studies and nephrocystin-5 was found to be expressed in the connecting cilia of photoreceptors [76]. This finding supported the ciliary hypothesis and provided a potential pathologic basis for the retinal-renal phenotype of SLSN. The primary cilium of renal epithelial cells corresponds to the connecting cilia of the photoreceptors of the retina [77]. In addition to nephrocystin-5, expression of nephrocystin-6 was also shown in the connecting cilium of the photoreceptors and nephrocystin-5 and 6 were shown to interact with each other [29,78].

NPHP6 mutations cause Joubert syndrome: NPHP6/CEP290 were found to cause JS [29,79]. The gene product, nephrocystin-6, activates and interacts with ATF4 (activating transcription factor 4), a transcription factor which may be involved in cAMP dependent renal cyst formation [73]. Nephrocystin-6 constitutes a part of the centrosomal proteome [29,80]. Similar to the *NPHP2/INV* and *NPHP4* gene products nephrocystin-6 is localized at centrosomes and at the mitotic spindle [29]. Knockdown of the *nphp6* ortholog in zebrafish resulted in renal cysts, retinal degeneration and cerebellar malformation and a defect of planar cell polarity, thereby recapitulating the human JS phenotype [29]. *NPHP6/CEP290* mutations can also result in JS without renal involvement and in a broader variety of phenotypes ranging from isolated NPHP, SLSN, JS to MKS and BBS [29,81–84]. Interestingly, mutations of *NPHP6/CEP290* also cause isolated Leber congenital amaurosis (LCA) and amounts for 21% this disease [85]. The mouse model *rd16* has an inframe deletion of 300 amino acids in *Nphp6/Cep290*, which mimics the RP phenotype without showing brain or kidney abnormalities, resulting in a hypomorphic allele [86].

Increased apoptosis and fibrosis resultsin NPH P7: NPHP7/GLIS2 mutations were identified as causing isolated NPHP in a large Cree Indian kindred. Affected individuals developed renal failure prior to 8 years of age [87]. *NPHP7/GLIS2* encodes the Kruppel-like zinc-finger transcription factor "Gli-similar protein 2". *NPHP7/GLIS2* localizes to the primary cilia and the nucleus. A mouse knockout model of *Glis2* revealed severe renal atrophy and fibrosis [87]. The kidneys of the *Glis2* mutant mice showed upregulation of genes that promote epithelial-to-mesenchymal transition and fibrosis [87]. *NPHP7/GLIS2* is related to GLI transcription factors and thereby links the pathogenesis of NPHP to the sonic hedgehog pathway, which is involved in cell fate determination, tissue patterning and maintenance of stem cell pools in postembryonic tissues.

NPHP8/RPGRIP1L mutations cause Joubert syndromean d Meckel-Gruber syndrome: NPHP8/RPGRIP1L mutations were identified by positional cloning as causing Joubert syndrome-like phenotype (cerebro-oculo-renal syndrome [CORS]) [23]. *NPHP8/RPGRIP1L* encodes the protein RPGRIPL1 (retinitis pigmentosa GTPase regulator interacting protein 1-

like) which co-localizes with *NPHP4* and *NPHP6* at centrosomes and basal bodies [30]. Two missense mutations result in the CORS phenotype, whereas one or more truncating mutations cause the more severe phenotype of Meckel-Gruber syndrome [30,31]. RPGRIP1L was shown to interact with nephrocystin-4 and missense mutations in *NPHP8/RPGRIP1L* of affected patients reduced the RPGRIP1L interaction with nephrocystin-4 [30,88]. Additional characteristics of affected patients included polydactyly, scoliosis, pituitary agenesis and partial growth deficiency. The corresponding *Rpgrip1l* (*Ftm for fused-toes mouse*) knockout mouse exhibits cerebral, renal and hepatic defects similar to CORS and Meckel-Gruber syndrome. Recently, a genotype-phenotype correlation became evident for NPHP3, NPHP6 and NPHP8, in which the presence of two truncating mutations causes the severe, early-onset developmental dysplastic phenotype of MKS with broad organ involvement, whereas at least one missense mutation (of the two recessive mutations) causes a milder, late-onset, degenerative phenotype with more restricted organ involvement.

NPHP8/RPGRIP1L mutations were recently shown to cause retinal degeneration [89]. Missense mutations and the sequence variant (A229T) were found in patients with LCA and retinal degeneration combined with other ciliopathies as BBS, SLSN, JS and MKS.

Linking cilia and cell-cycle defects in NPHP: NPHP9/NEK8 encodes the NEK8 protein (never in mitosis A-related kinase 8), which if mutated causes NPHP type 9. Three highly conserved missense mutationswere found in three different individuals [71]. One patient with a homozygous *NPHP9/NEK8* mutation developed infantile NPHP at age of 3 years [71]. In two other patients the second recessive mutation was not identified. One of these two patients had an additional homozygous *NPHP5/IQCB1* mutation and RP in addition to NPHP [71]. One of the mutations was found in the RCC1 domain of NEK8. The corresponding *jck* mouse model, which is characterized by cystic renal disease is caused by a missense mutation (G448V) in the RCC1 domain [90]. Expression studies of all three mutated proteins in medullary collecting duct cells showed defects of centrosomal and ciliary localization of NEK8 [71]. *NPHP9/NEK8* is important in the regulation of the cell-cycle, offering a link between nephrocystins and the role of centrosomes for cell-cycle regulation. Interestingly, polycystin-1 and polycystin-2 (the two genes mutated in ADPKD, which are also expressed in primary renal cilia) signaling has also been linked to cell growth regulation involving the JAK-STAT pathway [91–93]. The *jck* and *cpk* mice, which represent models for PKD were successfully treated by the cyclin-dependent kinase inhibitor roscovitine, which underlines the involvement of cell-cycle regulation in renal cystic disease [94].

NPHP11/MKS3may cause Joubert syndrome or Meckel-Gruber syndrome: Mutations in ***NPHP11/MKS3/TMEM67*** result in a wide spectrum of NPHP-like ciliopathies ranging from NPHP with liver disease, to JS and Meckel syndrome. *NPHP11/MKS3/TMEM67* encodes the protein meckelin, which was found to be expressed in the primary cilia and the plasma membrane [95] Missense mutations in *NPHP11/MKS3/TMEM67* were discovered in a population characterized by NPHP and liver fibrosis [45,96]. Four new missense mutations were found in 5 kindreds, resulting in a hypomorphic allele and leading to a milder phenotype than the truncating mutations [45]. Doherty et al. also identified some patients

with COACH syndrome (cerebellar vermis hypoplasia, oligophrenia (developmental delay/ mental retardation), ataxia, coloboma, and hepatic fibrosis) – a JS related disorder – and found *MKS3/TMEM67* mutations in 19/23 families (83% of the cohort) [96]. Because of the strong association of *MKS3/TMEM67* mutations and the NPHP plus liver fibrosis phenotype, *MKS3/TMEM67* is now also called *NPHP11* [45].

NPHP1L – a nephronophthisis like phenotype: NPHP1L/XPNPEP3 was identified by homozygosity mapping in two consanguineous kindreds on chromosome 22. Renal histopathology was consistent with NPHP and a splice site mutation and a 4 bp deletion, causing two loss of function mutations, were discovered [97]. The phenotype included hypertension, cardiomyopathy, renal failure and seizures [97]. A complex-I-defect mitochondropathy with decreased NADH-CoQ-Oxireductase acitivity was discovered. *NPHP1L/XPNPEP3* isoform 1 has a N-terminal 79 amnio acid sequence which is responsible for mitochondrial localization and suggests a mitochondrial function of this protein [97]. Because this is the first gene not being consistent with the cilia hypothesis it may only cause a phenocopy of NPHP but may not belong to the family of ciliopathies [97].

The “ciliary hypothesis” of NPHP

Ciliary expression of nephrocystins may explain organ involvement in NPHP

—So far all proteins of genes, which cause cystic kidney disease are expressed in the primary renal cilium, basal bodies, centrosomes or the mitotic spindle in a cell-cycle dependent fashion [3,66]. Even *Uromodulin*, the gene altered in autosomal dominant medullary cystic kidney disease type 2 (MCKD2), which shares histopathology with autosomal recessive nephronophthisis, was found to be expressed in cilia [98]. The primary cilium is an organelle of almost every cell that projects like an antenna from the cell surface. The primary cilium contains an axoneme, which consists of 9+0 microtubular doublets (in contrast to motile cilia which contain 9+2 microtubular doublets) [3]. The axoneme is assembled by “intraflagellar transport” (IFT) because no protein biosynthesis occurs within the cilium [3]. Cilia are involved in photosensation, mechanosensation, osmotic, olfactory and temperature sensation [3]. The basal body from which the cilium is assembled is located at the root of the cilium and derives from the mother centriole [3].

Nephrocystin-1 and nephrocystin-4 are evolutionary conserved in the nematode *C. elegans*. Expression of the nephrocystin-1 and nephrocystin-4 orthologs was found in ciliated neurons of the head (amphids) and tail (phasmids) [99]. The expression pattern showed significant overlap with the localization of other cystoprotein orthologs in *C. elegans* like polycystin-1 (lov-1), polycystin-2 (pkd-2) or multiple orthologs of the BBS proteins [99,100]. Knockdown of the nephrocystin-1 and nephrocystin-4 orthologs resulted in a very similar phenotype compared to the knockout nematodes of the polycystin-1 and polycystin-2 orthologs (*lov-1* and *pkd-2*, respectively) [99]. Nephrocystin-1 and nephrocystin-4 orthologs were found to be required for morphologic integrity, and nephrocystin-4 contributes to the regulation of life span in the nematode [101,102]. For some nephrocystins (nephrocystin-2, -4 and -6) evolutionary conservation reaches back more than 1.5 billion years to a unicellular organism called *Chlamydomonas reinhardtii.* Nephrocystin-4 and a minimum of six other proteins of the BBS complex are part of the basal body proteome in *Ch.*

reinhardtii, which if mutated causes impaired IFT and defective flagellar propulsion [93,100] .

The function of cilia in NPHP is still not completely resolved. Renal cilia may sense tubular flow of urine [103]. For polycystin-1 and polycystin-2 it was shown that both are able to sense flow resulting in intracellular calcium signaling [103]. Other phenotypes associated with NPHP can also be explained by the ciliary hypothesis. Nephrocystin-5 and nephrocystin-6 were found to be expressed in the connecting cilium of the photoreceptor [29,76]. The connecting cilium is responsible for the daily transport of rhodopsin [3]. Impaired rhodopsin transport results in retinitis pigmentosa. Ciliary expression of nephrocystins has also been published in the central nervous system and the cholangiocytes of the liver, which could explain the association with Joubert syndrome and liver fibrosis, respectively [44,45]. Ciliary involvement was also shown for Jeune syndrome by identification of mutations in the component of intraflagellar transport*IFT80* [104].

Planar cell polarity(PCP)—The term planar cell polarity (PCP) refers to orientation of cells in a plane perpendicular to apico-basal polarity. In epithelial cells this would be the plane parallel to the basement membrane. PCP is achieved by correct orientation of the mitotic spindle and centrosomes[12, 105]. Maintenance of normal tubular development and morphology is dependent on proper planar cell polarity (PCP) [105]. The PCP hypothesis of renal cystic ciliopathies is based on the finding that the mitotic angle in cells with mutated cystoproteins is altered, which results in abnormal cell divison [105] (Fig. 4). The result of abnormal PCP is that the tubulus are not extending longitudinally but at a certain angle to the longitudinal axis resulting in a dilatation of the tubule and thereby in a cystic structure [105]. Involvement of the non-canonical Wnt pathway is important for maintenance of PCP [69]. If the elongation of tubulues is disrupted postnatally by PCP defects, aberrant morphogenesis leads to tubule cyst formation (Fig.4). Planar cell polaritydefects due to malorientation of the mitotic spindle were shown in the *pck* rat model of human ARPKD, the *Hnf1β* knockout mouse, and the *Kif3a* knockout mouse – three rodent models for cystic kidney disease [105,106].

Modifier genes in NPHP—There is evidence for modifier genes of NPHP [42,55,63,89]. Individuals with a homozygous *NPHP1* deletion and an additional heterozygous *NPHP6* mutation were identified [54,107]. Modifier genes have also been reported for Joubert syndrome and Meckel-Gruber syndrome. Tory *et al* . published a combination of mutations in either *NPHP1* and *AHI1*, *NPHP6* and *AHI1* or *NPHP1* and *NPHP6* in 28 kindreds with Joubert syndrome [54]. Both publications point out that the additional heterozygous mutation in a second gene may modulate the phenotype of the two recessive mutations in a primary gene in an epistatic way.

Possible approaches totreatment in NPH P—Currently, treatment of NPHP has to focus on the conservative approach of treating end-stage renal disease, providing dialysis and renal transplantation. Even though there is no approved specific treatment available for NPHP at this point there are some promising developments. Possible future treatment might include a vasopressin V2 receptor antagonist, because in the *pcy* mouse, a model of NPHP type 3, cystogenesis and progression of disease were altered profoundly by treatment with

OPC31260 via reduction of cAMP [73]. In addition, there is growing evidence for rapamycin (an mTOR inhibitor) to alleviate cystogenesis [108,109]. Moreover, Roscovitine has shown improvement of cyst growth in *jck* (the mouse model of NPHP type 9) and *cpk* mice, which are models for human cystic kidney disease [94].

Outlook—The understanding of NPHP has improved significantly from a solely histopathological entity to the discovery of the NPHP causing genes and molecular mechanisms. Only about 30% of patients with NPH have an identifiable mutation. This means many more *NPHP* genes are expected to be found. New genes will gives us additional insight about the pathomechanism and how cilia are linked to cyst development. New therapeutic approaches are promising and will hopefully succeed in starting alternative treatment options besides conservative treatment and renal replacement therapy.

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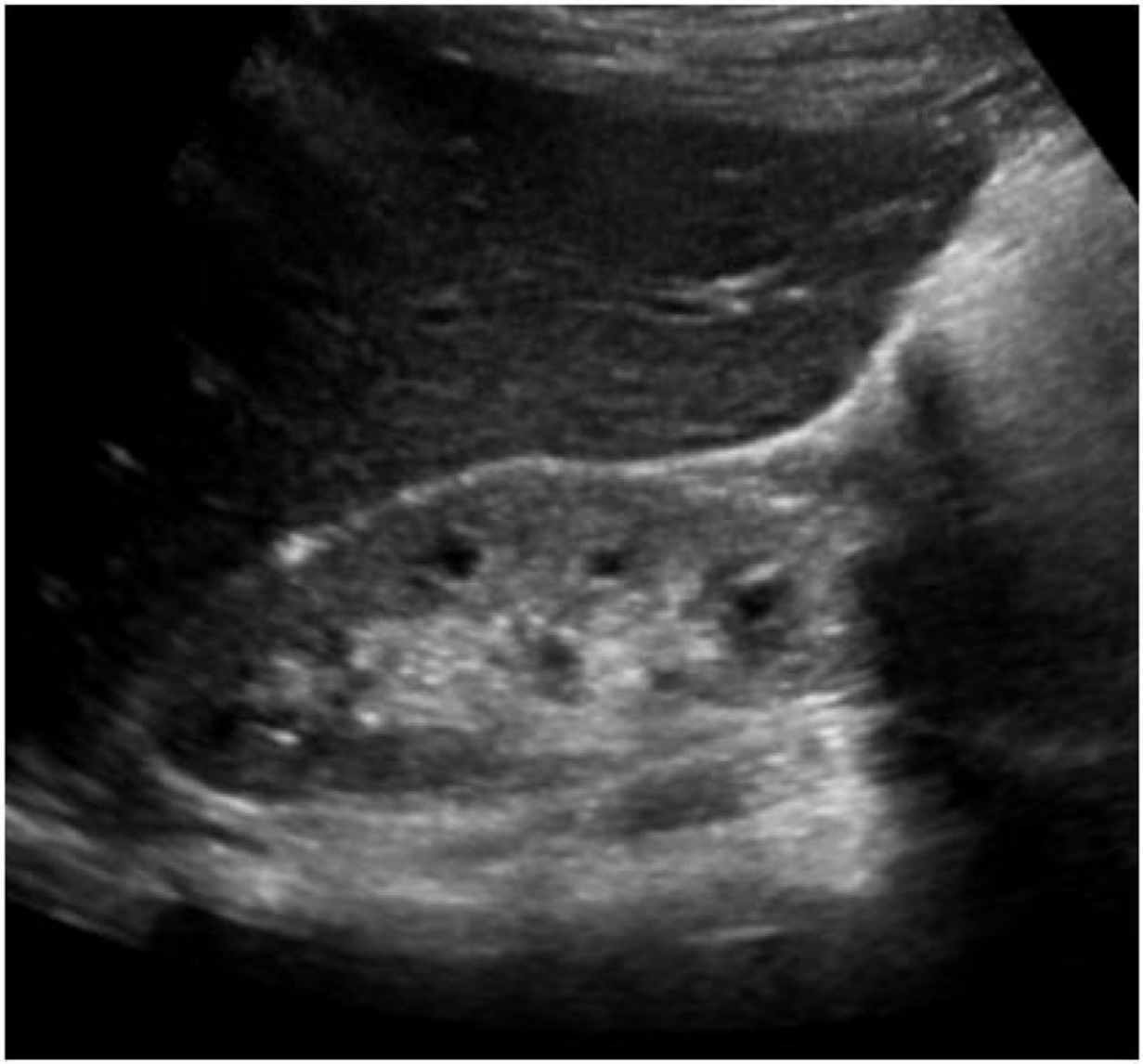

Fig 1. Renal ultrasound in NPHP

The renal ultrasound shows smaller bilateral kidneys, increased echogenicity (compare to abnormally lower echogenicity of liver), decreased cortico-medullary differentiation, and cortico-medullary cyst formation.

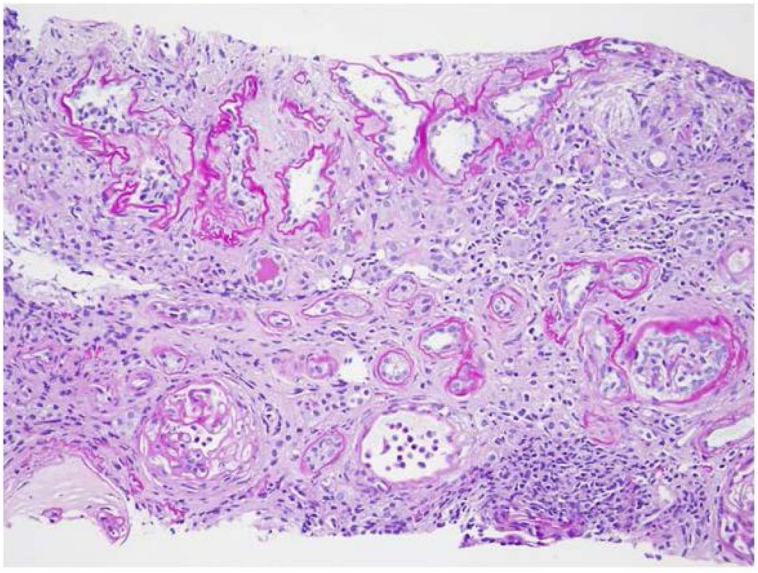

Fig 2. Renal histopathology in NPHP

Renal histopathology in NPHP is characterized by the triad of tubular cysts, tubular basement membrane disruption, and interstitial fibrosis with interstitial cell infiltration. PAS staining, magnification 20x.

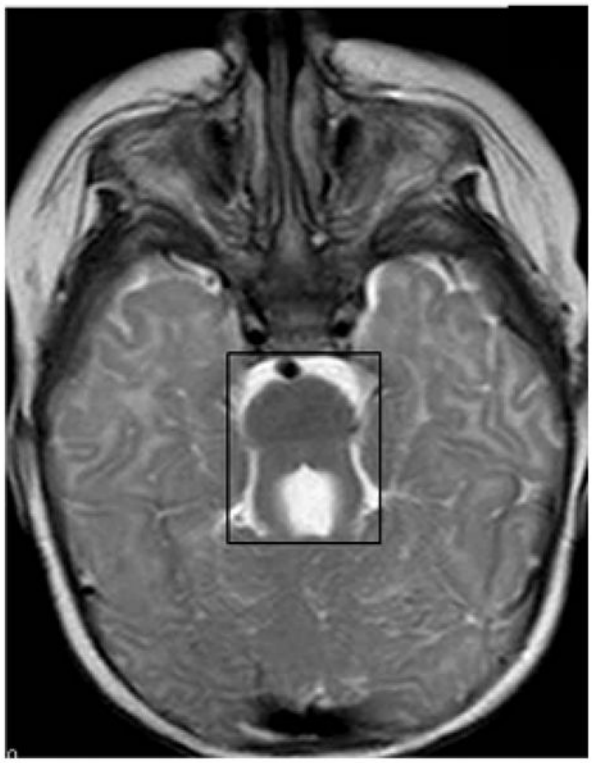

Fig 3. The "molar tooth sign" is a classical neuroradiological characteristic of JS

The "molar tooth sign" (shown in box) on a brain magnetic resonance imaging (MRI). Brain MRI axial image at the level of the superior cerebellar peduncles of a JS patient. The "molar tooth sign" is characterized by cerebellar vermis aplasia, thickened and elongated superior cerebellar peduncles, and a deepened interpeduncular fossa.

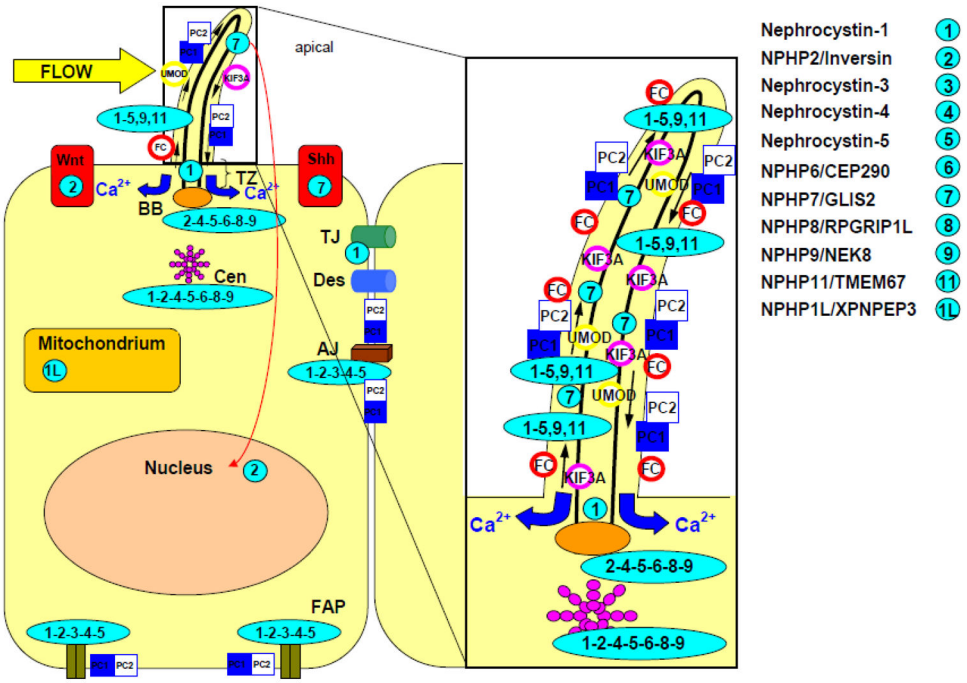

Fig 4. Subcellular localization of the nephrocystins

Nephrocystins are detected in the primary cilia, basal bodies, the mitotic spindle, focal adhesions and adherens junctions. Most nephrocystins are expressed in the primary cilium (see enlarged box), the basal body (BB) and centrosomes (Cen) in a cell cycle-dependent manner. NPHP1 is expressed in the transition zone (TZ), focal adhesion plaques (FAP), adherens junctions (AJ), and tight junctions (TJ). Arrows in the cilium show the directions of the anterograde and retrograde transport along the microtubule transport. The intraflagellar transport is mediated by kinesin 2, a heterotrimeric protein that is composed of two motor units (Kif3a and Kif3b) and one nonmotor unit (KAP3). Sensory cilia transfer external stimuli. Wnt and hedgehog (Shh) signaling interfere with planar cell polarity by orientation of centrosomes and mitotic spindles. Adapted from Watnick and Germino.[66]

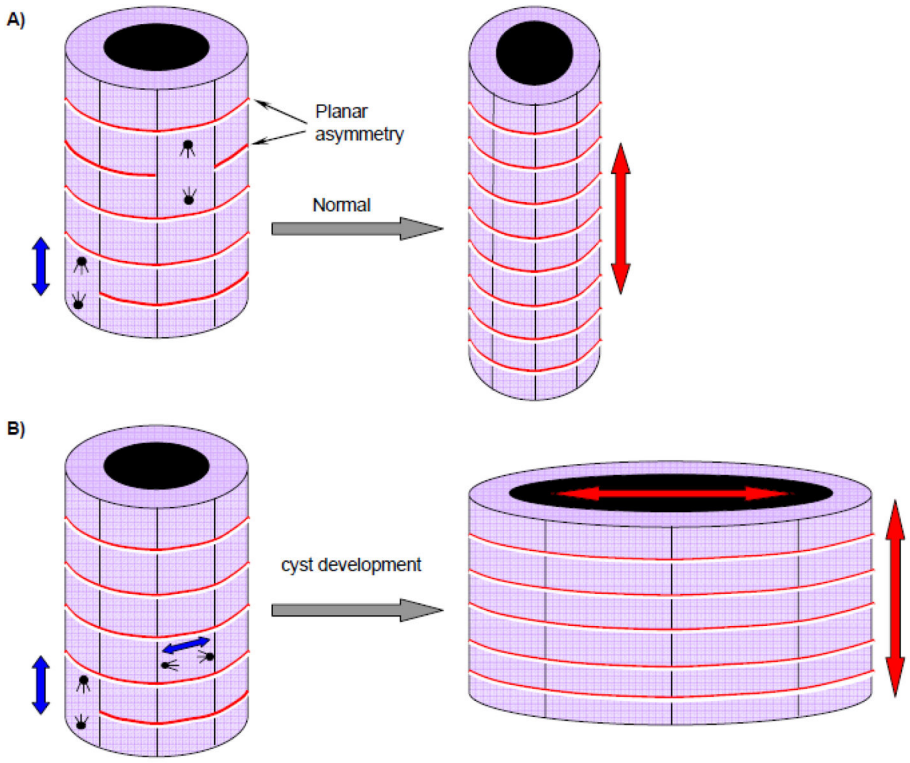

Fig 5. Altered planar cell polarity causes cyst formation

Correct orientation of the mitotic spindle and centrosomes of renal tubular epithelial cells are especially during development required for proper growth of the longitudinal axis of the tubule (A). If the apical-basolateral polarity is disrupted a dilated tubule or cyst would develop (B). Non-canonical Wnt signaling is involved in proper cell orientation. Urinary flow in the renal tubules could provide signaling via cilia about cellular orientation. Adapted from Germino 2005. [110]

Table 1

Extrarenal manifestations associated with NPHP and resulting syndromes associated with *NPHP* mutations.

Ophthalmologic disorder	**Syndrome**
Retinitis pigmentosa	Senior-Loken syndrome (SLSN)
	Arima syndrome (cerebro-oculo-hepato-renal syndrome)
	Alstrom (RP, obesity, DM type 2, hearing impairment)
	RHYNS (RP, hypopituitarism, skeletal dysplasia)
Oculomotor apraxia	Cogan syndrome
Nystagmus	Joubert syndrome/Joubert syndrome related disorders
Coloboma	Joubert syndrome/Joubert syndrome related disorders
Skeletal disorder	
Short ribs	Jeune syndrome/asphyxiating thoracic dystrophy
Cone-shaped epiphysis	Mainzer-Saldino syndrome
Postaxial polydactyly	Joubert syndrome/Joubert syndrome related disorders
	Bardet-Biedl syndrome(NPH P, RP, obesity, deafness)
	Ellis van Creveld
Skeletal dysplasia	Sensenbrenner syndrome / cranioectodermal dysplasia
	Ellis van Creveld
Neurological disorder	
Encephalocele	Meckel-Gruber syndrome (occipital encephalocele, NPHP)
Vermis aplasia	Joubert syndrome/Joubert syndrome related disorders
Hypopituitarism	RHYNS (RP, hypopituitarism, skeletal dysplasia)
Hepatic disorder	
Liver fibrosis	Boichis syndrome
	Meckel-Gruber syndrome (occipital encephaolocele, NPHP)
	Arima syndrome (cerebro-oculo-hepato-renal syndrome)
	Joubert syndrome/Joubert syndrome related disorders
Others	
Situs inversus	
Cardiac malformation	
Bronchiectasis	
Ulcerative colitis	

RP, retinitis pigmentosa/retinal degeneration; DM, diabetes mellitus; NPHP, nephronophthisis

Table 2

Summary of *NPHP1-NPHP11* genes, gene products, chromosomal localization, phenotypes, extrarenal symtoms, and mutation frequency of nephrocystins [12,53].

Gene (protein)	Chromosome	Phenotype (median age at ESRF)	Extrarenal symptoms	Mutation frequency	Interaction partners
NPHP1 (nephrocystin-1)	2q13	NPHP (13yrs)	RP (10%),OMA (2%), JS (rarely)	23.4% homozygous deletion 2.1% point mutation	Inversin, nephrocystin- 3, nephrocystin-4, filamin A and B, tensin, β-tubulin, PTK2B
NPHP2/INVS (inversin)	9q31	Infantile NPHP(<5yrs)	RP (10%), LF, *situs inversus*, VSD	1.4%	Nephrocystin-1, calmodulin, catenins, β-tubulin, APC2
NPHP3 (nephrocystin-3)	3q22	Infantile and adolescent NPHP	LF, RP (10%), situs inversus, MKS	0.7% If truncating mutation infantile form	Nephrocystin-1
NPHP4 (nephrocystin-4)	1p36	NPHP (21 yrs)	RP (10%), OMA, LF	2.6%	Nephrocystin-1, BCAR1, PTK2B
NPHP5/IQCB1 (nephrocystin-5)	3q21	NPHP (13 years)	Early-onset RP	3.6%	Calmodulin, RPGR, nephrocystin-6
NPHP6/CEP290 (nephrocystin-6/CEP290)	12q21	NPHP	JS, MKS	1%	ATF4, nephrocystin-5, CC2D2A
NPHP7/GLIS2(nephrocystin -7/GLIS2)	16p	NPHP	_	0.1%	_
NPHP8/RPGRIP1L (nephrocystin-8/RPGRIP1L)	16q	NPHP	JS, MKS	0.5%	Nephrocystin-1
NPHP9/NEK8 (nephrocystin-9/NEK8)	17q11	Infantile NPHP	_	0.1%	_
TMEM67/MKS3/NPHP11 (Meckelin/nephrocystin-11)	8q22.1	MKS, JS, NPHP+LF	JS, MKS		
NPHP1L/XPNPEP3 (nephrocystin-1L/XPNPEP3)	22q13	NPHP	Cardiomyopathy, seizures	0.1%	

ATF4, activating transcription factor 4;APC2, anap hase-promoting complex 2; BCAR1, breast cancer anti-estrogen resistance 1;CC2D2A, coiled-coil and C2 domain containing 2A;JS, Joubert syndrome; LF, liver fibrosis; MKS, Meckel-Gruber syndrome; OMA,oculomotor apraxia; PTK2B, protein tyrosine kinase 2B; RP, retinitis pigmentosa; RPGR, retinitis pigmentosa GTPase regulator; VSD, ventricular septal defect