Nephronophthisis (NPHP), the most common monogenic cause of end-stage renal disease (ESRD) during the first three decades of life, is responsible for 2.4%–15% of ESRD in this population. The estimated incidence varies from 1:50 000 live births in Finland to 1:1 000 000 in the United States. It is caused by mutations in many genes that encode nephrocystin protein, which is involved in the function of primary cilia, basal bodies, and centrosomes. These mutations result in renal disease and extra-renal manifestations. This review provides an update about the recent advances in the field of NPHP.

CLINICAL MANIFESTATIONS OF NPHP

Nephronophthisis is characterized by reduced ability of the kidneys to concentrate solutes, chronic tubulointerstitial nephritis, cystic renal disease, and progression to ESRD before age 30. The typical clinical symptoms of NPHP include polyuria, polydipsia with regular fluid intake at night, secondary enuresis, anaemia, and growth retardation. Patients with NPHP typically have a "bland" urinalysis without evidence of proteinuria, hematuria, or cellular elements until the late stage, when proteinuria may develop into secondary glomerulosclerosis.

Clinically, three clinical subtypes of NPHP have been recognized based on the median age of onset of ESRD: infantile, juvenile, and adolescent/adult. The main characteristics of these three subtypes of NPHP are summarized in Table 1. However, there have been several case reports of patients with NPHP who progressed to ESRD between the ages of 27 and 56 years. These cases of NPHP extend the age of ESRD from birth to the sixth decade of life. Extra-renal manifestations occur in approximately 10%–20% of patients, including retinitis pigmentosa, skeletal defects, hepatic fibrosis, neurologic abnormalities, and others.
Table 1 Main features of three clinical subtypes of nephronophthisis (NPHP)

| Item                  | Infantile NPHP | Juvenile NPHP | Adolescent/ adult NPHP |
|-----------------------|----------------|---------------|------------------------|
| Onset of ESRD (median in years) | 1 year         | 13 years      | 19 years               |
| Clinical manifestations | Oligohydramnios sequence in utero (limb contractures, pulmonary hypoplasia, and facial dysmorphisms), severe renal failure in the first years of life, severe hypertension | Impaired urinary concentrating ability (polyuria and polydipsia), impaired sodium reabsorption (hypovolaemia, hyponatraemia, chronic kidney disease [severe anaemia, growth retardation], proteinuria [late stage], normal blood pressure | Similar to juvenile NPHP |
| Renal ultrasound       | Enlarged kidneys, large cortical microcysts, absent medullary cysts | Normal-sized or smaller hyperechogenic kidneys with corticomedullary cysts and poor corticomedullary differentiation | Similar to juvenile NPHP |
| Renal histology        | Tubular atrophy, usually lack tubular basement membrane change, interstitial fibrosis, collecting tubule cystic dilatation, enlarged kidneys | Tubular atrophy, tubular basement membrane disruption, cysts at the corticomedullary border, diffuse interstitial fibrosis with chronic inflammation | Similar to juvenile NPHP |
| Extra-renal association | Liver fibrosis, severe cardiac valve or septal defects, recurrent bronchial infections | Retinal degeneration, cerebellar vermis aplasia, gaze palsy, liver fibrosis, skeletal defects | Similar to juvenile NPHP |
| Typical gene           | NPHP2/INVS, NPHP3, NPHP12/ TTC21B/ BT511, NPHP14/ ZNF423, NPHP18/ CEP83 | All NPHP genes except NPHP2/ INVS | NPHP3, NPHP4, NPHP9, NEK8 |

Cardiac defects.\textsuperscript{11} NPHP is also a major clinical finding in several syndromes, including Senior-Loken, Joubert, Meckel-Gruber, Cogan, and Sensenbrenner syndromes, and asphyxiating thoracic dystrophy (ATD, also known as Jeune syndrome). A summary of the main extra-renal manifestations associated with NPHP is described in Table 2.

\textbf{GENOTYPE–PHENOTYPE CORRELATION OF NPHP}

To date, more than 25 different genes have been found to be associated with NPHP (Table 3).\textsuperscript{2,12–51} Mutations in the NPHP1 gene are the most common, being reported in approximately 20% of cases. Each of the remaining NPHP genes probably account for 1% or fewer of all cases of NPHP, and around two-thirds of cases remain genetically unknown.\textsuperscript{41}

Most nephrocystins are located in the transition zone, inversin compartment, or subunits of intraflagellar transport (IFT) complexes.\textsuperscript{6} However, genome-wide homozygosity mapping identified pathogenic mutations in NPHP1L and NPHP2L of which the protein product localizes to mitochondria.\textsuperscript{32} Currently, at least four distinct nephrocystin modules have been found: the NPHP1-4-8 module, NPHP2-3-9-ANKS6 module, NPHP5-6 module, and MKS module (Fig. 1). These nephrocystin modules are related to different signalling pathways, including the Wnt pathway, Hedgehog pathway, DNA damage response (DDR) pathway, Hippo pathway, intracellular calcium signalling pathway, cAMP signalling pathway, and mTOR pathway.

NPHP shows genetic and phenotypic heterogeneity. Mutations in single ciliary genes are often associated with multiple phenotypes (Table 1 and Table 3). Single locus allelism is insufficient to explain the variability in phenotypic heterogeneity in NPHP. Digenic and triallelic inheritance may provide an explanation. Triallelic inheritance was first demonstrated for BBS.\textsuperscript{53} To date, oligogenic inheritance has been noted in some patients with mutations in NPHP1, NPHP5, NPHP6, NPHP8, NPHP9, NPHP11, and TTC21B genes.\textsuperscript{12,54–56}

\textbf{APPROACH TO CLINICAL DIAGNOSIS OF NPHP}

The diagnosis of NPHP is suggested by clinical features and confirmed by a positive genetic test (Fig. 2). The role of renal biopsy in diagnosis is controversial. Renal biopsy should be limited to cases in which tissue diagnosis can be used to distinguish it from other differential diagnoses. Molecular genetic analysis is currently the only method available to diagnose NPHP and thus provide patients and families with an unequivocal diagnosis. Due to an increasing number of potentially causative monogenic genes and to advances in next-generation sequencing, whole-exome sequencing has mostly replaced targeted-sequencing panels in the diagnosis of NPHP.\textsuperscript{57} Using this method, a causative single-gene mutation can be detected in up to 60% of cases depending on the composition of the cohort. However, the absence of mutation is not sufficient to exclude the diagnosis of NPHP. Most importantly, genetic testing should always be combined with thorough phenotyping and genetic counseling.
Early onset autosomal dominant polycystic kidney disease and autosomal recessive polycystic kidney disease are often in the main differential diagnosis for patients with NPHP. Renal imaging may be useful in differential diagnosis. But genetic testing is required to make a definite diagnosis.

**TREATMENT OF NPHP**

There is no specific therapy for NPHP. Management is supportive, focusing on slowing the progression of CKD, controlling complications, and maintaining the promotion of growth. This disease does not recur after transplantation, so renal transplantation is the preferred renal replacement therapy.

Some potential therapeutic interventions have arisen from several lines of investigation into the pathogenesis of NPHP. Various personalized drugs include isosorbide dinitrate and tolvaptan (vasopressin V2 receptor antagonist), dimethyl fumarate, rapamycin (mTOR inhibitor), roscovitine and its analog S-CR8 (cyclin-dependent kinases inhibitor), purmorphamine (Shh signalling pathway agonist). Despite the many promising interventions that have arisen from preclinical studies, no clinical trials have
| Gene        | Chromosome | Protein                        | Location                      | Interaction partners                                                                 | Functionary mechanism                                                                 | Disorders associated with mutations                                      | Reference |
|-------------|------------|--------------------------------|-------------------------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-----------|
| NPHP1       | 2q12.3     | Nephrocystin-1                 | Adherens junction, focal adhesion, transition zone | Inversin, nephrocystin-3, nephrocystin-4, filamin A and B, tensin, β-tubulin, PTK2B, p130 Cas, focal adhesion kinase 2 | Maintains the cellular scaffolding or cytoskeleton, role in cell–cell adhesion and cell signalling | NPHP, SLSN, JBTS                                                              | 12        |
| NPHP2/INVS  | 9q21-22    | Inversin                      | Inversin compartment           | Nephrocystin-1, nephrocystin-3, calmodulin, catenins, β-tubulin, APC2                  | Acts in Wnt pathway and planar cell polarity                                        | Infantile NPHP, SLSN, Situs inversus, congenital heart defects          | 13        |
| NPHP3       | 3q22.1     | Nephrocystin-3                | Inversin compartment, axoneme  | Nephrocystin-1, inversin, NEK8, ANKS6, PTK2B, BCAR1                                   | Inhibits Wnt pathway                                                              | NPHP, liver fibrosis, RP, Situs inversus, MKS, SLSN, congenital heart defects | 14–16     |
| NPHP4       | 1p36.31    | Nephrocystin-4                | Transition zone                | Nephrocystin-1, BCAR1, PTK2B, p130Cas, filamin, tensin                               | Inhibits Wnt and Hippo pathways                                                   | Juvenile NPHP, RP, OMA, SLSN, liver fibrosis                                | 17        |
| NPHP5/IQCB1 | 3q13.33    | Nephrocystin-5/IQ motif containing B1 | Transition zone, basal body   | Calmodulin, RGR, nephrocystin-1, nephrocystin-4, nephrocystin-6                      | Forms complexes with RGR                                                          | Juvenile NPHP, early-onset RP, LCA                                        | 18        |
| NPHP6/CEP290 | 12q21.32  | Nephrocystin-6/centrosomal protein 290 | Transition zone, centrosome   | ATF4, nephrocystin-5, CC2D2A, TMEM67                                                 | Regulates activity of transcription factor ATF4/CREB2, role in cAMP-dependent renal cyst formation, cell signalling, DNA damage response (DDR), and renal cystogenesis | NPHP, RP, LCA, JBTS, MKS                                                   | 19–23     |
| NPHP7/GLI2  | 16p13.3    | Nephrocystin-7/ GLI similar 2 | Nucleus                        | N/A                                                                                    | Regulates Hedgehog signalling                                                      | NPHP                                                             | 24,25     |
| NPHP8/RPGRIP1L/MKS5 | 16q12.2 | Nephrocystin-8/RPGRIP1-like | Transition zone                | Nephrocystin-1, nephrocystin-4                                                       | Involved in Shh signalling                                                       | Juvenile NPHP, JBTS, MKS, RP, LCA, COACH                                 | 26        |
| NPHP9/NEK8  | 17q11.2    | Nephrocystin-9/NEK8            | Inversin compartment           | ANKS6                                                                                  | Regulates cell cycle, involved in Hippo and DDR signalling                         | Infantile NPHP                                                        | 27,28     |
| NPHP10/SDCCAG8/SLSN7 | 1q43-q44 | Nephrocystin-10/Serologically defined colon cancer antigen 8 | Basal body                    | Nephrocystin-5, OFD1                                                                    | Involved in DDR signalling                                                       | Juvenile NPHP, RP, SLSN, BBS                                              | 29,30     |
| NPHP11/TMEM67/MKS3 | 8q22.1 | Nephrocystin-11/Transmembrane protein 67 | Transition zone                | Nephrocystin-1, nephrocystin-4, nephrocystin-6, CEP290, MKS1, TMEM216, nesprin-2, Ciliopathy modifier | Maintains cellular structure and mitigates centrosome migration                  | NPHP, JBTS, MKS, liver fibrosis, COACH                                  | 31,32     |
| NPHP12/TTC21B/JBTS11 | 2q24.3 | Nephrocystin-12/Intraflagellar transport protein 130 | iFT-A                         | iFT-A                                                                                   | Regulates retrograde trafficking in the primary cilium,                        | Juvenile NPHP, JS, MKS, JBTS                                             | 33        |

(Continues)
yet been conducted in NPHP patients. Furthermore, large numbers of compounds which may be potential therapies are being screened in the zebrafish models of NPHP.66

The lack of a clear-cut genotype–phenotype correlation remains a major challenge for physicians treating children with NPHP, even though the development of a single

### Table 3 (Continued)

| Gene     | Chromosome | Protein                  | Location | Interaction partners                  | Functionary mechanism                                      | Disorders associated with mutations         | Reference |
|----------|------------|--------------------------|----------|---------------------------------------|------------------------------------------------------------|--------------------------------------------|-----------|
| NPHP13/  | 4p14       | Nephrocystin-13/WD repeat domain 19/IFT protein 144 | IFT-A    | N/A                                   | regulates Hedgehog signalling                               | NPHP, JS, RP, Caroli, Sensenbrenner syndrome | 34,35     |
| WDR19    |            |                          |          |                                       | Participates in retrograde IFT; acts in ciliogenesis       | Infantile NPHP, JBTS, Situs inversus       | 36        |
| NPHP14/  | 16q12.1    | Nephrocystin-14/Zinc finger protein 423 | Nucleus  | DDR protein PARP1, nephrocystin-6     | Involved in DDR signalling                                  | NPHP, liver fibrosis, RP, JBTS             | 37        |
| ZNF423   |            |                          |          |                                       |                                                            |                                            |           |
| NPHP15/  | 11q23.3    | Nephrocystin-15 centrosomal protein 164 | Basal body| Nephrocystin-3, nephrocystin-4, TTBK2, ATRIP, CCDC92, CEP83, Dvl3 | Involved in DDR signalling, regulates ciliogenesis     |                                            |           |
| CEP164   |            |                          |          |                                       |                                                            |                                            |           |
| NPHP16/  | 9q22.33    | Nephrocystin-16/ANKS6     | Axoneme  | INVS, nephrocystin-3, NEK8, ANKS3, NEK7, BICC1, HIF1AN | Connects key components of NEK8, INVS, and NPHP3 | NPHP, liver fibrosis, Situs inversus       | 38-40     |
| ANKS6    |            |                          | Inversin compartment |                                       |                                                            |                                            |           |
| NPHP17/  | 2p23.3     | Nephrocystin-17/IFT protein 172 | IFT-B    | IFT80, IFT140                         | Involved in intraflagellar transport                      | NPHP, JS, JBTS, MZSDS                      | 41        |
| IFT172   |            |                          |          |                                       |                                                            |                                            |           |
| NPHP18/  | 12q22      | Nephrocystin-18/centrosomal protein 83 | Basal body| IFT20, CEP164                         | N/A                                                       | NPHP, liver fibrosis, mental retardation, hydrocephalus | 42        |
| CEP83    |            |                          |          |                                       |                                                            |                                            |           |
| NPHP19/  | 6p22.3     | Doublecortin domain-containing protein 2 | Axoneme  | DVL                                   | Involved in Wnt signalling                                | NPHP, renal-hepatic ciliopathy            | 43        |
| DCDC2    |            |                          |          |                                       |                                                            |                                            |           |
| NPHP20/  | 15q15.1    | Mitogen-activated protein kinase binding protein 1 | Cytoplasm | N/A                                   | Involved in DDR signalling and JNK signalling              | NPHP                                        | 2         |
| MAPKBP1  |            |                          |          |                                       |                                                            |                                            |           |
| NPHP1L/  | 22q13      | X-prolyl aminopeptidase 3 | Mitochondria | Cleaves LRRC50, ALMS1, nephrocystin-6 | Interferes with cilia function by cleaving certain ciliary proteins | NPHP, myocardiosis, epilepsy              | 44,45     |
| XPNPEP3  |            |                          |          |                                       |                                                            |                                            |           |
| NPHP2L/  | 1q32.1     | Solute carrier family 41 member 1 | Tubules at the borders of the cortex and medulla | N/A                                   | Affects Mg2+ transport                                    | NPHP, bronchiectasia                      | 46        |
| /SLC41A1 |            |                          |          |                                       |                                                            |                                            |           |
| TRAF3/   | 2q37.3     | TRAF3 interacting protein 1 | Axonemes, basal bodies | N/A                                   | Affects microtubule stabilization by IFT54                 | NPHP, SLSN, RP                            | 47        |
| JBTS3    |            |                          | Basal bodies |                                       |                                                            |                                            |           |
| AH11/    | 6q23.3     | Jouberin                 |          | N/A                                   | Affects cerebellar and cortical development                | JBTS, RP                                  | 48,49     |
| JBTS5    |            |                          |          |                                       |                                                            |                                            |           |
| CC2D2A/  | 4p15.32    | Coiled coil and C2 domain containing 2A | Basal bodies | CEP290                               | Acts in ciliogenesis                                       | MKS, COACH, JBST                          | 50,51     |
| MKS5     |            |                          |          |                                       |                                                            |                                            |           |

ALMS1, Alstrom Syndrome 1; APC2, anaphase-promoting complex 2; ATF4, activating transcription factor 4; ATRIP, ATR interacting protein; BBS, Bardet-Biedl syndrome; BCA1, breast cancer anti-estrogen resistance 1; BIC1, Bicaudal-C1; CAD, cranioectodermal dysplasia; CCDC92, centrosomal protein 290; CHD, congenital heart disease; COACH, cerebellar vermis hypoplasia, oligophrenia, congenital ataxia, ocular coloboma and hepatic fibrosis; DVL3, dishevelled 3; HIF1AN, hypoxia inducible factor 1 alpha subunit inhibitor; IFT, intraflagellar transport; JATD, Jeune asphyxiating thoracic dysplasia; JBTS, Joubert syndrome; JS, Jeune syndrome; LCA, Leber congenital amaurosis; LRRC50, leucine-rich repeat containing protein 50; MKS, Meckel-Gruber syndrome; MZSDS, Mainzer-Saldino syndrome; OFD1, oral-facial-digital protein1; OMA, oculomotor apraxia; PTK2B, protein tyrosine kinase 2B; RP, retinitis pigmentosa; RPGR, retinitis pigmentosa GTPase regulator; SBS, Sensenbrenner syndrome; SLSN, Senior-Loken syndrome; TMEM67, transmembrane protein 67; TTBK2, Tau-tubulin kinase 2.

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comprehensive histopathology and the discovery of specific disease genes and molecular mechanisms have significantly improved our understanding of NPHP. Only about 30% of NPHP patients have clear genetic mutations, suggesting that more NPHP genes have yet to be discovered. Novel genes will enable us to better understand the pathogenesis and relationship between cilia and cystic diseases. It is necessary to find new therapeutic strategies and develop alternative treatments other than conservative approaches and renal replacement therapy.

**CONFLICTS OF INTEREST**

There authors declare that they have no potential or actual competing interests.
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No.

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