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Nephronophthisis-Related Ciliopathies

Synonym: NPHP-RC

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Summary

The purpose of this overview is to increase the awareness of clinicians regarding genetic causes of nephronophthisis-related ciliopathies. The following are the goals of this overview.

Goal 1

Briefly describe the clinical characteristics of nephronophthisis-related ciliopathies.

Goal 2

Review the genetic causes of nephronophthisis-related ciliopathies.

Goal 3

Review the differential diagnosis of nephronophthisis-related ciliopathies with a focus on genetic conditions.

Goal 4

Provide an evaluation strategy to identify the genetic cause of a nephronophthisis-related ciliopathy in a proband (when possible).

Goal 5

Review management of nephronophthisis-related ciliopathies.

Goal 6

Inform genetic counseling of an individual with a nephronophthisis-related ciliopathy and their family members.

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1. Clinical Characteristics of Nephronophthisis-Related Ciliopathies

Nephronophthisis (NPH) is characterized by polyuria and polydipsia resulting from reduced urine-concentrating ability, chronic tubulointerstitial nephritis, and progression to end-stage kidney disease (ESKD) typically before age 30 years (although later-onset ESKD has been reported). Common associated findings are chronic anemia resistant to therapy and growth restriction. NPH is suspected in the absence of congenital anomalies of the kidneys and/or urinary tract (CAKUT) and signs or symptoms of glomerular kidney disease.

Two general age-based clinical phenotypes for NPH are recognized: an infantile-onset phenotype and a juvenile-, adolescent-, or adult-onset phenotypic continuum. However, within a phenotype, inter- and intrafamilial variability in rate of progression to ESKD can be considerable.

Infantile NPH

Infantile NPH can present in utero with oligohydramnios sequence (limb contractures, pulmonary hypoplasia, and facial dysmorphisms) or postnatally with severe hypertension and kidney manifestations that progress to ESKD before age three years. It is characterized by a rapid disease course.

Kidney ultrasound findings are moderately enlarged cystic kidneys with cortical hyperechogenicity.

Histologic findings (which might be of interest should a kidney biopsy have been obtained but are not necessary to make the diagnosis of NPH) include cortical cysts, absence of thickened tubular basement membranes, and minimal fibrosis [Oud et al 2014, Bergmann 2018].

Juvenile-, Adolescent-, or Adult-Onset NPH

Juvenile-, adolescent-, or adult-onset NPH is more common than infantile NPH. It typically presents with polydipsia and polyuria, growth restriction in children, chronic iron-resistant anemia, or other findings related to chronic kidney disease (CKD), such as metabolic bone disease, metabolic acidosis, and uremic symptoms (e.g., nausea, anorexia, and weakness) [Stokman et al 2018, Gupta et al 2021]. Proteinuria due to secondary glomerulosclerosis and hypertension are typically late findings [König et al 2017].

At the juvenile-onset end of the continuum the median age that ESKD develops is 13 years [König et al 2022]. At the adolescent- and adult-onset end of the continuum the median age that ESKD develops has yet to be determined. A recent study showed that NPH is a frequent cause (0.5%) of ESKD in adults; the oldest reported individual was age 61 years at the onset of ESKD [Snoek et al 2018].

Kidney ultrasound findings are small to normal-sized kidneys, increased echogenicity, reduced corticomedullary differentiation, and – in 50% of individuals – renal cyst formation on the corticomedullary border later in the disease course. In some instances, the bladder (but not the urinary tract) is dilated as a result of chronic polyuria.

Histologic findings (which might be of interest should a kidney biopsy have been obtained but are not necessary to make the diagnosis of NPH) include tubulointerstitial fibrosis, thickened and disrupted tubular basement membranes, and sporadic corticomedullary cysts [Braun & Hildebrandt 2017]. Focal segmental glomerulosclerosis is a nonspecific finding in advanced stages of kidney disease.

Nomenclature

The term "nephronophthisis-related ciliopathies (NPH-RC)" is used to describe isolated nephronophthisis, nephronophthisis with extrarenal features that do not constitute a recognizable syndrome, and syndromic nephronophthisis.

The term "ciliopathy" refers to the group of disorders characterized by defects in the formation or function of primary cilia, signaling organelles present on the surface of nearly all cell types.

This chapter focuses on clinical features of NPH in NPH-RC. For the purpose of this overview, the genetic causes of NPH-RC are limited to genes classified as *NPHP* genes; the more than 90 genetic causes of syndromic NPH-RC are not included [Braun & Hildebrandt 2017]. Note: *XPNPEP3* and *SLC41A1*, genes involved in an NPH-like phenotype, also fall outside the scope of this review (see Differential Diagnosis) [O'Toole et al 2010, Hurd et al 2013, Alizadeh et al 2020].

2. Genetic Causes of Nephronophthisis-Related Ciliopathies

At the time of the initial presentation, approximately 80%-90% of individuals with nephronophthisis (NPH) appear to have isolated NPH (i.e., all evident clinical findings are secondary to kidney dysfunction), and approximately 10%-20% of individuals have extrarenal manifestations that can be indicative of a syndrome (e.g., Bardet-Biedl syndrome and Joubert syndrome). With time, some individuals who originally presented with apparent isolated NPH will manifest syndromic features.

Biallelic pathogenic variants in one of the 21 genes included in Table 1 can be detected in 50%-60% of individuals with NPH [Braun & Hildebrandt 2017].

Table 1. Genes Classified as *NPHP* Genes

Gene [1, 2]	Locus	% of All NPH [3]	NPH Subtype(s) [4]	Extrarenal Features [3, 5]
Most common genes				
NPHP1	*NPHP1*	20%-25%	Juvenile, adult	RP, neurologic involvement, liver dz
NPHP4	*NPHP4*	3%-4%	Juvenile, adult	RP, neurologic involvement, liver dz, CHD (all infrequent)
CEP290	*NPHP6*	2%-3%	Infantile, juvenile, adult	RP, neurologic involvement, liver dz, Leber congenital amaurosis
IQCB1	*NPHP5*	2%-3%	Juvenile, adult	RP (in all persons), Leber congenital amaurosis, neurologic involvement
TMEM67	*NPHP11*	2%-3%	Infantile, juvenile, adult	RP, neurologic involvement, liver dz, polydactyly [6]
INVS	*NPHP2*	1%-2%	Infantile, juvenile	RP, neurologic involvement, liver dz, situs inversus, [7] CHD
NPHP3	*NPHP3*	1%-2%	Infantile, juvenile, adult	RP, neurologic involvement, liver dz, situs inversus, CHD
Less common genes				
ADAMTS9	*NPHP21*	<1%	Infantile, juvenile	Deafness, short stature, DD
ANKS6	*NPHP16*	<1%	Infantile, juvenile, adult	Neurologic involvement, liver dz, situs inversus, CHD
CEP83	*NPHP18*	<1%	Infantile, juvenile	RP, neurologic involvement, liver dz
CEP164	*NPHP15*	<1%	Juvenile	RP, neurologic involvement, liver disease, Leber congenital amaurosis, polydactyly [6]
DCDC2	*NPHP19*	<1%	Juvenile	Liver dz, deafness
GLIS2	*NPHP7*	<1%	Juvenile	
IFT172	*NPHP17*	<1%	Infantile, juvenile, adult	RP, neurologic involvement, liver dz, skeletal anomalies, [8] polydactyly
MAPKBP1	*NPHP20*	<1%	Juvenile, adult	Scoliosis, facial dysmorphisms [9]
NEK8	*NPHP9*	<1%	Infantile, juvenile	Liver dz, situs inversus, CHD, pancreas anomalies [10]
RPGRIP1L	*NPHP8*	<1%	Infantile, juvenile, adult	RP, neurologic involvement, liver dz, polydactyly
SDCCAG8	*NPHP10*	<1%	Infantile, juvenile, adult	RP, neurologic involvement, obesity, hypogenitalism [11]

Table 1. continued from previous page.

Gene [1, 2]	Locus	% of All NPH [3]	NPH Subtype(s) [4]	Extrarenal Features [3, 5]
TTC21B	*NPHP12*	<1%	Infantile, juvenile	Neurologic symptoms, liver dz, situs inversus, skeletal anomalies [8]
WDR19	*NPHP13*	<1%	Infantile, juvenile	RP, liver dz (esp Caroli disease), pancreas anomalies, skeletal anomalies
ZNF423	*NPHP14*	<1%	Infantile	Neurologic involvement, situs inversus

CHD = congenital heart disease; DD = developmental delay; dz = disease; RP = retinitis pigmentosa
1. Genes are listed first by frequency of causation of nephronophthisis-related ciliopathies, and then alphabetically.
2. OMIM Phenotypic Series (PS256100): Nephronophthisis.
3. Barroso-Gil et al [2021], Van De Weghe et al [2022]
4. Adapted from Stokman et al [2021]
5. Non-obligatory extrarenal features that may be present at the time of diagnosis or appear over time
6. Presence of supernumerary fingers and/or toes. Postaxial polydactyly is most prevalent in ciliopathies.
7. Condition in which the organs in the thorax and abdomen are positioned in a mirror image of their normal position
8. Skeletal anomalies include short stature, narrow thorax, brachydactyly, and polydactyly.
9. Tentative association in one (scoliosis) and two (facial dysmorphisms) families
10. Pancreas anomalies include cystic enlargement of the pancreas or fibrosis depending on the type of mutation.
11. Underdevelopment of genital organs, such as cryptorchidism and micropenis in males and hypoplasia of labia minora in females

Syndromic Nephronophthisis-Related Ciliopathies

Although all of the syndromes listed below are associated with nephronophthisis-related ciliopathies (NPH-RC), the prevalence of renal disease varies.

Joubert syndrome (JS). Classic JS is characterized by three primary findings: a distinctive cerebellar and brain stem malformation called the molar tooth sign, hypotonia, and developmental delay. Often these findings are accompanied by episodic tachypnea or apnea and/or atypical eye movements. In general, the breathing abnormalities improve with age, truncal ataxia develops over time, and acquisition of gross motor milestones is delayed. Cognitive abilities are variable, ranging from normal to severe intellectual disability.

Kidney disease (including NPH) has been reported in 23%-35% of individuals with JS [Doherty 2009, Kroes et al 2016, Dempsey et al 2017, Ying et al 2022]. JS with renal disease (JS-Ren) has been described traditionally in two forms (NPH and cystic dysplasia); however, these now appear to be part of a continuum, with the specific renal manifestation varying by stage of kidney disease. Juvenile NPH often presents in the first or second decade of life with polydipsia, polyuria, urine-concentrating defects, growth restriction, and/or anemia. Progression to end-stage kidney disease (ESKD) occurs on average by age 13 years.

Renal changes visible on ultrasound examination may occur late in the course and consist of small, scarred kidneys with increased echogenicity and occasional cysts at the corticomedullary junction. In early-onset kidney disease, findings may be consistent with cystic dysplasia (i.e., multiple variably sized cysts in immature kidneys with fetal lobulations).

Pathogenic variants in more than 30 genes are known to cause JS (see Tables 1a and 1b in Joubert Syndrome, Diagnosis); of these, ten genes are known to be associated with JS-Ren (see Table 2 in Joubert Syndrome, Clinical Characteristics).

COACH syndrome (*c*erebellar vermis hypoplasia, *o*ligophrenia, *a*taxia, *c*oloboma, and *h*epatic fibrosis) is a clinical subtype of Joubert syndrome (JS-H). NPH has been reported in 21%-33% of individuals with COACH syndrome [Brancati et al 2009, Doherty et al 2010]. Pathogenic variants in *CC2D2A*, *CEP290*, *INPP5E*, *RPGRIP1L*, and *TMEM67* have been associated with COACH syndrome (see Table 2 in Joubert Syndrome, Clinical Characteristics).

Bardet-Biedl syndrome (BBS) is a multisystem ciliopathy primarily characterized by retinal cone-rod dystrophy, obesity and related complications, postaxial polydactyly, cognitive impairment, hypogonadotropic hypogonadism and/or genitourinary malformations, and kidney malformations and/or renal parenchymal disease.

The renal phenotype of BBS is highly variable and can include structural anomalies, hydronephrosis and vesicoureteral reflux, and progressive renal parenchymal disease that is commonly associated with urinary concentration defects (symptoms of polyuria and polydipsia). Chronic kidney disease (CKD) is a major contributor of morbidity and mortality in individuals with BBS.

In one study, CKD was present in 31% of children and 42% of adults; 6% of children and 8% of adults developed ESKD requiring dialysis and/or transplantation. In the majority of children with BBS with advanced (Stage 4-5) CKD, the initial diagnosis of kidney disease was made within the first year of life and almost all were diagnosed by age five years [Forsythe et al 2017].

Pathogenic variants in at least 26 genes are known to be associated with BBS (see Bardet-Biedl Syndrome Overview, Causes of BBS).

Jeune syndrome and related skeletal disorders. Jeune syndrome, also called "asphyxiating thoracic dystrophy," is one of the skeletal ciliopathies, characterized by short ribs, short proximal limbs, and polydactyly. Short ribs and narrow thorax can cause severe respiratory insufficiency, a major cause of perinatal and infant mortality. After infancy, the risk of severe respiratory complications decreases. Associated features are kidney disease, liver disease, and retinitis pigmentosa [Stembalska et al 2022]. The exact prevalence of kidney disease is unknown.

Other skeletal ciliopathies include cranioectodermal dysplasia (Sensenbrenner syndrome), short-rib polydacytly syndromes, Mainzer-Saldino syndrome, and Ellis-van Creveld syndrome, collectively referred to as short-rib thoracic dysplasia (OMIM PS208500).

Meckel-Gruber syndrome is a pre- or perinatally lethal ciliopathy. Features are cystic kidney disease, central nervous system malformation (most frequently occipital encephalocele), hepatic abnormalities, and polydactyly (typically postaxial) [Hartill et al 2017]. Oligohydramnios sequence is usually present. Congenital heart defects and genital abnormalities can also occur. Pathogenic variants in approximately 16 genes are known to be associated with Meckel-Gruber syndrome (OMIM PS249000).

Senior-Løken syndrome (SLS). The main features of (SLS) are NPH and Leber congenital amaurosis or retinitis pigmentosa. Pathogenic variants in *CEP290*, *IQCB1*, *NPHP1*, *NPHP4*, *SDCCAG8*, *TRAF3IP1*, and *WDR19* are known to be associated with SLS (OMIM PS266900).

3. Differential Diagnosis of Nephronophthisis-Related Ciliopathies

Tubulointerstitial kidney diseases, cystic kidney diseases, and conditions associated with a urine-concentrating defect and growth restriction (e.g., nephrogenic diabetes insipidus and other tubulopathies) can mimic the nephronophthisis (NPH) phenotype. For example, whole-exome sequencing in 79 families (including consanguineous families) with childhood-onset chronic kidney disease (CKD) and a nephronophthisis-related ciliopathy (NPH-RC) suspected on kidney ultrasound examination identified pathogenic variants in NPH-RC-related genes in 32 individuals and pathogenic variants in other monogenic kidney disease-associated genes in 18 individuals, including genes involved in renal tubulopathies (e.g., Bartter syndrome), Alport syndrome, congenital anomalies of the kidney and urinary tract (CAKUT), and polycystic kidney disease [Braun et al 2016]. Clinical findings that differentiate NPH from autosomal dominant tubulointerstitial kidney disease (ADTKD) have been described by Devuyst et al [2019]. For monogenic kidney disorders in the differential diagnosis of NPH-RC, see Table 2.

Table 2. Monogenic Kidney Disorders in the Differential Diagnosis of Nephronophthisis-Related Ciliopathies

Gene	Disorder	MOI	Key Features
Tubulointerstitial kidney diseases			
HNF1B	ADTKD-*HNF1B*	AD	Tubulointerstitial kidney disease & variable other manifestations incl MODY, hyperuricemia & gout, hypomagnesemia, CKD, CAKUT, & unexplained liver function abnormalities
MUC1	ADTKD-*MUC1*	AD	Slowly progressive tubulointerstitial disease that leads to ESKD & need for dialysis or kidney transplantation. The rate of loss of kidney function is variable w/in & between families, w/median age of onset of 46 yrs. There are no other systemic manifestations.
REN	ADTKD-*REN*	AD	Childhood/adolescent onset, the more common presentation of ADTKD-*REN*, is characterized by ↓ estimated glomerular filtration rate, acidosis, hyperkalemia, & anemia early in life, followed by slowly progressive CKD & gout. Adult onset, the less common presentation, is characterized by gout or mild, slowly progressive CKD beginning in the 3rd decade. Anemia, hyperkalemia, & acidemia do not occur.
SEC61A1	ADTKD-*SEC61A1*	AD	Tubulointerstitial kidney disease, slowly progressive CKD, leukopenia, abscess formation, IUGR, & postnatal growth restriction (See ADTKD-*UMOD*.)
UMOD	ADTKD-*UMOD*	AD	Normal urinalysis & slowly progressive CKD, usually 1st noted in teenage yrs & progressing to ESKD between 3rd & 7th decades. Hyperuricemia is often present from an early age & gout occurs in teenage yrs in ~8% of affected persons & develops in 55% of affected persons over time.
Cystic kidney diseases			
PKHD1	ARPKD	AR	ARPKD belongs to a group of congenital hepatorenal fibrocystic syndromes & is a cause of significant kidney- & liver-related morbidity & mortality in children. It typically presents in neonatal period w/enlarged echogenic kidneys. Kidney disease is characterized by nephromegaly, hypertension, & varying degrees of kidney dysfunction. >50% of affected persons progress to ESKD w/in 1st decade of life.
ALG5	Atypical ADPKD (See ADPKD.) Note: In atypical ADPKD, kidneys are usually not as enlarged as in ADPKD.	AD	Normal-sized kidneys, characterized by multiple small kidney cysts, progressive interstitial fibrosis, & late-onset ESKD (range: age 62-91 yrs); few or no liver cysts [1]
ALG9		AD	Normal-sized to mildly enlarged kidneys, multiple kidney cysts, occasional late-onset CKD, w/or w/out liver cysts [2]
DNAJB11		AD	Normal-sized kidneys w/bilateral small cysts, occasional liver cysts, progressive tubulointerstitial fibrosis, & late-onset ESKD (range: age 59-89 yrs) [3]
GANAB		AD	Kidneys are normal-sized to mildly enlarged due to a few large cysts, mild chronic kidney disease and polycystic liver disease of variable severity. [4]
IFT140		AD	Enlarged kidneys, few large cysts, mild & late-onset CKD, few liver cysts [5]
Other			

Table 2. continued from previous page.

Gene	Disorder	MOI	Key Features
COL4A3 *COL4A4* *COL4A5*	Alport syndrome	XL AR AD	Phenotypes range from progressive kidney disease w/extrarenal abnormalities (ocular & hearing) to isolated hematuria w/non-progressive or very slowly progressive course. In XL Alport syndrome (XLAS), disease manifestations are typically more severe in affected males. In the absence of treatment, kidney disease progresses from microscopic hematuria to proteinuria, progressive renal insufficiency, & ESKD in males w/XLAS & persons w/AR Alport syndrome. However, affected females w/XLAS or persons w/AD Alport syndrome may have severe involvement as well. Progressive SNHL is usually present by late childhood / early adolescence. Ocular findings incl anterior lenticonus, maculopathy, corneal endothelial vesicles, & recurrent corneal erosion.
SLC41A1	NPH-like nephropathy 2 (OMIM 619468)	AR	Tubulointerstitial kidney disease w/histologic & ultrasound changes characteristic of NPH [6]
XPNPEP3	NPH-like nephropathy 1 (OMIM 613159)	AR	Tubulointerstitial kidney disease w/histologic & ultrasound changes characteristic of NPH. Extrarenal manifestations can incl signs of mitochondriopathy (e.g., neurologic signs, hearing loss). [7]

AD = autosomal dominant; ADTKD = autosomal dominant tubulointerstitial kidney disease; AR = autosomal recessive; ARPKD = autosomal recessive polycystic kidney; CAKUT = congenital anomalies of the kidneys and urinary tract; CKD = chronic kidney disease; ESKD = end-stage kidney disease; MODY = maturity-onset diabetes of the young; MOI = mode of inheritance; NPH = nephronophthisis; SNHL = sensorineural hearing loss; XL = X-linked

1. Lemoine et al [2022]
2. Besse et al [2019]
3. Cornec-Le Gall et al [2018]
4. Porath et al [2016]
5. Senum et al [2022]
6. Hurd et al [2013]
7. O'Toole et al [2010], Alizadeh et al [2020]

4. Evaluation Strategies to Identify the Genetic Cause of a Nephronophthisis-Related Ciliopathy in a Proband

Establishing a specific genetic cause of a nephronophthisis-related ciliopathy (NPH-RC):

- Can aid in discussions of prognosis (which are beyond the scope of this *GeneReview*) and genetic counseling;
- Usually involves a medical history, physical examination, laboratory testing, family history, and genomic/genetic testing.

Medical history. Inquire about kidney disease onset and course, environmental triggers, and extrarenal features. Medical history is nonspecific in nephronophthisis (NPH), and other causes of chronic kidney disease (CKD) should be excluded.

Physical examination. Evaluate for the presence of extrarenal features indicative of a syndromic ciliopathy (see Table 1 and Syndromic NPH-RC) and features that suggest an alternative syndromic cause of CKD.

Family history

- A three-generation family history should be taken, with attention to relatives with manifestations of NPH-RC and documentation of relevant findings through direct examination or review of medical records, including results of molecular genetic testing.
- Family history is typically consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Molecular genetic testing approaches can include a combination of gene-targeted testing (multigene panel) and comprehensive genomic testing (exome sequencing, genome sequencing). Gene-targeted testing requires the clinician to hypothesize which gene(s) are likely involved, whereas genomic testing does not.

- **A multigene panel (e.g., hereditary kidney disease or ciliopathy gene panel)** that includes some or all of the genes listed in Table 1 is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  Note: Gene-targeted deletion/duplication analysis (e.g., MLPA) or genomic testing (e.g., SNP array) is necessary to identify the common 290-kb *NPHP1* deletion, which is the most frequent cause of NPH (~25%) and results from low-copy repeats in this region [Saunier et al 2000] (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

5. Management of Nephronophthisis-Related Ciliopathies

Evaluations Following Initial Diagnosis

To establish the extent of kidney disease and screening for the presence of multisystem involvement in an individual diagnosed with a nephronophthisis-related ciliopathy (NPH-RC), the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended.

At the time of diagnosis and when indicated:

- Perform an abdominal ultrasound examination to evaluate kidney size and parenchymal aspect, and possible situs inversus and/or anomalies of the liver, bile duct, spleen, or pancreas.
- Evaluate blood pressure, growth parameters, and development.
- Perform urinalysis to measure proteinuria.
- Assess kidney function, including serum creatinine concentration and estimated glomerular filtration rate, cystatin C when indicated, electrolytes, and complete blood count.
- Assess for chronic kidney disease (CKD)-related mineral and bone disease, including serum calcium, phosphate, parathyroid hormone, and alkaline phosphatase activity.
- Assess liver function, including serum concentrations of transaminases, albumin, bilirubin, and prothrombin time.

When indicated based on genetic diagnosis or clinical signs or symptoms, evaluate extrarenal manifestations of syndromic NPH-RC (see Table 1 and Syndromic NPH-RC), including manifestations that can appear over time. Ordered by age, these include:

- Neurologic evaluation including brain MRI (e.g., for the presence of molar tooth sign, suggesting Joubert syndrome)

- Echocardiogram for congenital heart disease
- Ophthalmologic examination to assess visual acuity and visual fields, as well as evidence of retinal dystrophy
- Endocrinologic/metabolic evaluation including sex hormones and thyroid hormones, lipid spectrum, fasting glucose, and hemoglobin A1c

Consultation with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse to inform affected individuals and their families about the nature, mode of inheritance, and implications of NPH-RC in order to facilitate medical and personal decision making is recommended.

Assess need for community or online resources such as Parent to Parent.

Treatment of Manifestations

This section discusses only the management of nephronophthisis-related CKD (i.e., NPH). Note that management of extrarenal findings in nephronophthisis-related ciliopathies (NPH-RC) included in Table 1 and Syndromic NPH-RC are not addressed in this *GeneReview*.

Currently there is no cure for NPH. Treatment of NPH is aimed at slowing the progression of CKD and its complications. According to international clinical practice guidelines for CKD [KDIGO 2013] (full text), the following are the relevant issues:

- Correction of water and electrolyte imbalances, especially during intercurrent illness
- Treatment of anemia, hypertension, proteinuria, and CKD-related mineral and bone disorder if present

  Note: Preferred therapy may differ between adults and children.
- Growth hormone treatment for children who have severe growth restriction as a result of chronic renal insufficiency and meet criteria for treatment [KDIGO 2017] (full text)
- Dialysis or kidney transplantation when individuals reach end-stage kidney disease (ESKD)

  Note: Kidney transplantation is the preferred treatment, as NPH does not recur in the transplanted kidney [Kim et al 2020].
- Vaccination schedules in adults and children according to international and regional recommendations

Surveillance

The following evaluations to identify progression of NPH are recommended for all individuals at least annually (unless more frequent monitoring by the treating nephrologist is recommended for individuals with advanced CKD and individuals at higher risk of disease progression, and for therapeutic decision making) [KDIGO 2013]:

- Monitoring of blood pressure, growth parameters, and development
- Urinalysis to monitor proteinuria
- Assessment of kidney function, including serum creatinine concentration and estimated glomerular filtration rate, cystatin C when indicated, electrolytes, and complete blood count
- Assessment for CKD-related mineral and bone disease, including serum calcium, phosphate, parathyroid hormone, and alkaline phosphatase activity
- Assessment of liver function, including serum concentrations of transaminases, albumin, bilirubin, and prothrombin time
- Evaluation of extrarenal manifestations of syndromic NPH-RC when indicated (See Evaluations Following Initial Diagnosis.)

Agents/Circumstances to Avoid

Nephrotoxic agents such as nonsteroidal anti-inflammatory drugs and aminoglycosides should be avoided.

Individuals with an estimated glomerular filtration rate below 60 mL/min per 1.73 m^2 undergoing investigations involving intravascular iodinated radiocontrast media should be managed according to the KDIGO clinical practice guidelines for acute kidney injury [KDIGO 2012] (full text).

Evaluation of Relatives at Risk

For early diagnosis and treatment. It is appropriate to evaluate older and younger sibs of a proband with NPH in order to identify as early as possible those with manifestations that warrant supportive treatment and surveillance. Individuals who are diagnosed in an early disease stage can benefit from timely preparation for preemptive kidney transplantation.

If the NPH-causing pathogenic variants have been identified in an affected family member, options for family members include:

- **Predictive testing.** Targeted molecular genetic testing can – in the context of formal genetic counseling – be offered to minors with a 25% chance of being affected with NPH. Prior to predictive testing, the potential consequences of such testing (including, but not limited to, socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed.
- **Surveillance for early manifestations of NPH.** If individuals and/or parents do not choose to perform predictive genetic testing for NPH, parents/caregivers should be instructed to be aware of polydipsia, polyuria, and other signs of NPH. Annual monitoring of blood pressure and protein-to-creatinine ratio and annual or biennial monitoring of kidney and liver function should be offered.

If the NPH-causing pathogenic variants in the family are not known, it seems prudent to instruct parents/caregivers to be aware of polydipsia, polyuria, and other signs of NPH, and to offer annual monitoring of blood pressure and protein-to-creatinine ratio when this is not part of regular healthy child visits. This recommendation is experience based and not supported by literature [Authors, personal observation].

For kidney donation. If the NPH-causing pathogenic variants in the family are known, any relative who is a potential kidney donor for an individual with autosomal recessive NPH should undergo targeted molecular genetic testing. Only those family members who do not have biallelic NPH-related pathogenic variants should be evaluated further. Note: Typically, heterozygosity for an autosomal recessive NPH-related pathogenic variant does not exclude a family member from kidney donation.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

6. Genetic Counseling of Nephronophthisis-Related Ciliopathies

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Genetic counseling regarding risk to family members depends on accurate diagnosis, confirmation of the mode of inheritance in each family, and the results of molecular genetic testing.

Nephronophthisis-related ciliopathies (NPH-RC) are typically inherited in an autosomal recessive manner [Van De Weghe et al 2022].

The exception to autosomal recessive inheritance in NPH-RC is *OFD1*-related Joubert syndrome, which is inherited in an X-linked manner.

Dominant inheritance has been reported infrequently in individuals with Joubert syndrome and variants in *SLC30A7*, *SUFU*, and *ZNF423* [Chaki et al 2012, Penon-Portmann et al 2022, Serpieri et al 2022]; however, further evidence for this mode of inheritance is required.

Syndromic NPH-RC. If a proband has syndromic NPH-RC (e.g., Joubert syndrome or Bardet-Biedl syndrome), genetic counseling for the specific syndrome is appropriate.

Risk to Family Members (Autosomal Recessive Inheritance)

Parents of a proband

- The parents of an affected individual are presumed to be heterozygous for an NPH-RC-related pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an NPH-RC pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an affected individual's reproductive partner also has autosomal recessive NPH-RC or is a carrier, offspring will be obligate heterozygotes (carriers) for an NPH-RC pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an NPH-RC pathogenic variant.

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Prenatal Testing and Preimplantation Genetic Testing

Once both causative pathogenic variants have been identified in a family member with autosomal recessive NPH-RC, prenatal and preimplantation genetic testing for NPH-RC are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Nephronophthisis
- **American Kidney Fund**
  Phone: 800-638-8299
  kidneyfund.org
- **Ciliopathy Alliance**
  United Kingdom
  ciliopathyalliance.org
- **ERKNet: The European Rare Kidney Disease Reference Network**
  Phone: 49 0 6221 56-34191
  Email: contact@erknet.org
  erknet.org
- **Kidney Foundation of Canada**
  Canada
  Phone: 514-369-4806
  Email: info@kidney.ca
  kidney.ca
- **National Kidney Foundation**
  Phone: 855-NKF-CARES; 855-653-2273
  Email: nkfcares@kidney.org
  kidney.org
- **NephCure Kidney International**
  Phone: 866-NephCure; 866-637-4287
  Email: info@nephcure.org
  nephcure.org

Chapter Notes

Author Notes

Dr Marijn Stokman (marijn.stokman@radboudumc.nl) and Dr Marc Lilien (m.lilien@umcutrecht.nl) are actively involved in clinical research regarding individuals with nephronophthisis. They would be happy to communicate with individuals who have any questions regarding diagnosis of nephronophthisis-related ciliopathies (NPH-RC) or other considerations.

For more information on NPH-RC, see:

- Radboudumc Center of Expertise: Rare kidney diseases
- UMC Utrecht: Center for Hereditary and Congenital Kidney and Urinary Tract Disorders

Contact Dr Dorien Lugtenberg (dorien.lugtenberg@radboudumc.nl) to inquire about review of genetic variants of uncertain significance.

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