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Nephronophthisis

Synonym: NPH

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Summary

Clinical characteristics

The nephronophthisis (NPH) phenotype is characterized by reduced renal concentrating ability, chronic tubulointerstitial nephritis, cystic renal disease, and progression to end-stage renal disease (ESRD) before age 30 years. Three age-based clinical subtypes are recognized: infantile, juvenile, and adolescent/adult.

- *Infantile NPH* can present in utero with oligohydramnios sequence (limb contractures, pulmonary hypoplasia, and facial dysmorphisms) or postnatally with renal manifestations that progress to ESRD before age 3 years.
- *Juvenile NPH*, the most prevalent subtype, typically presents with polydipsia and polyuria, growth retardation, chronic iron-resistant anemia, or other findings related to chronic kidney disease (CKD). Hypertension is typically absent due to salt wasting. ESRD develops at a median age of 13 years. Ultrasound findings are increased echogenicity, reduced corticomedullary differentiation, and renal cysts (in 50% of affected individuals). Histologic findings include tubulointerstitial fibrosis, thickened and disrupted tubular basement membrane, sporadic corticomedullary cysts, and normal or reduced kidney size.
- *Adolescent/adult NPH* is clinically similar to juvenile NPH, but ESRD develops at a median age of 19 years. Within a subtype, inter- and intrafamilial variability in rate of progression to ESRD is considerable.

Approximately 80%-90% of individuals with the NPH phenotype have no extrarenal features (i.e., they have isolated NPH); ~10%-20% have extrarenal manifestations that constitute a recognizable syndrome (e.g., Joubert syndrome, Bardet-Biedl syndrome, Jeune syndrome and related skeletal disorders, Meckel-Gruber syndrome, Senior-Løken syndrome, Leber congenital amaurosis, COACH syndrome, and oculomotor apraxia, Cogan type).

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Diagnosis/testing

Establishing the diagnosis of the NPH phenotype relies on presence of characteristic clinical findings and imaging findings on renal ultrasound examination. Establishing the genetic cause of the NPH phenotype is possible in approximately 30%-40% of individuals by identification of homozygous or compound heterozygous deletions of *NPHP1* or biallelic pathogenic variants in one of the 19 known NPH-related genes.

Genetic counseling

Isolated and syndromic nephronophthisis are both inherited in an autosomal recessive manner. At conception, each sib of an affected individual has 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. Once the NPH-related pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Management

Treatment of manifestations: Note: Treatment discussed in this *GeneReview* is limited to management of the NPH phenotype and does not include management of other findings observed in syndromic NPH. Treatment (based on international clinical practice) includes correction of water and electrolyte imbalances; treatment of anemia, hypertension, and proteinuria if present; growth hormone treatment in children who meet criteria for treatment; dialysis or renal transplantation for ESRD.

Prevention of secondary complications: Annual influenza vaccination for those with CKD; other vaccinations (e.g., pneumococcal vaccine and hepatitis B) according to local practice guidelines; standard measures to prevent secondary cardiovascular complications.

Surveillance: Monitoring of the following is recommended at least annually (and more frequently as needed for individuals with advanced CKD or at increased risk for disease progression and for therapeutic decision making): blood pressure, growth parameters, and psychomotor development; renal function; liver function; urinalysis (for evidence of proteinuria); abdominal ultrasound examination (for progression of renal disease and possible involvement of the liver, bile duct, spleen, and pancreas); and evaluations for extrarenal manifestations of syndromic NPH that can appear with time, especially retinal dystrophy.

Agents/circumstances to avoid: Nephrotoxic agents including nonsteroidal anti-inflammatory drugs (NSAIDS), aminoglycosides, and radiocontrast studies. For those with liver involvement: hepatotoxic medications.

Evaluation of relatives at risk: Presymptomatic diagnosis helps identify those who would benefit from prompt initiation of treatment and surveillance.

Clinical Description of the Nephronophthisis Phenotype

Nephronophthisis is characterized by a reduced concentrating ability of the kidney, chronic tubulointerstitial nephritis, and progression to end-stage renal disease (ESRD) before age 30 years [Hildebrandt & Zhou 2007].

On average nephronophthisis is diagnosed 3.5 years after onset of symptoms as a result of the variable and nonspecific presentations [Soliman et al 2012].

The following three clinical subtypes (based on age of onset) are recognized. Of note, within a subtype, inter- and intrafamilial variability in rate of progression to ESRD can be considerable [Caridi et al 2006].

Infantile nephronophthisis can present in utero with an oligohydramnios sequence (limb contractures, pulmonary hypoplasia, and facial dysmorphisms) or with severe renal failure in the first years of life. Hypertension can be secondary to renal failure [Haider et al 1998, Otto et al 2003].

ESRD develops before age three years [Haider et al 1998, Otto et al 2003].

Juvenile nephronophthisis, the most prevalent form of nephronophthisis, typically presents with polydipsia and polyuria, growth retardation, or chronic iron-resistant anemia [Ala-Mello et al 1996, Hildebrandt et al 2009, Soliman et al 2012].

Other findings related to chronic kidney disease (CKD) may include metabolic bone disease, metabolic acidosis, uremic symptoms (e.g., nausea, anorexia, and weakness), and proteinuria due to secondary glomerulosclerosis (late finding). Note that because of salt wasting, hypertension is typically absent [Hildebrandt et al 2009, Niaudet 2013].

ESRD develops at a median age of 13 years [Hildebrandt et al 1997, Hildebrandt et al 2009, Soliman et al 2012, Wolf 2015].

Adolescent/adult nephronophthisis. Clinical features are similar to juvenile nephronophthisis. Note that the classification of adolescent/adult NPH is historically based on a single family with biallelic pathogenic variants in *NPHP3* in which ESRD developed at a median age of 19 years [Omran et al 2000, Olbrich et al 2003].

Nomenclature

Nephronophthisis (literally "wasting of the nephrons") is a renal ciliopathy. Ciliopathies are disorders of the primary cilium, a sensory organelle present on the apical surface of nearly all cell types, including renal tubular epithelial cells. Nephronophthisis (NPH) is considered a ciliopathy because the genes associated with NPH encode proteins that localize to the primary cilium (among other localizations such as cell-cell contacts; see Molecular Genetic Pathogenesis) [Fliegauf et al 2006, Omran 2010, Novarino et al 2011, Sang et al 2011, van Reeuwijk et al 2011]. Mutation of NPH-related genes often results in defects in cilia formation or ciliary protein trafficking [Bredrup et al 2011].

The term "nephronophthisis-related ciliopathies (NPHP-RC)" is used to describe isolated nephronophthisis, nephronophthisis with extrarenal features that do not constitute a recognizable syndrome, and syndromic nephronophthisis (see Halbritter et al [2013]).

Prevalence

Juvenile nephronophthisis is the most prevalent form of nephronophthisis. The estimated incidence varies from 1:50,000 liveborns in Finland and Canada to 1:1,000,000 in the United States [Ala-Mello et al 1999, Waldherr et al 1982, Hildebrandt et al 2009]. The prevalence of nephronophthisis is likely underestimated as genetic testing in cohorts of adults with ESRD revealed individuals with undiagnosed nephronophthisis [Bollée et al 2006, Hoefele et al 2011].

Nephronophthisis, the most important monogenic cause of ESRD in children, is responsible for 2.4% to 15% of ESRD in this population [Hildebrandt et al 1993, Hamiwka et al 2008, Hildebrandt et al 2009].

Establishing the Diagnosis of the Nephronophthisis Phenotype

The diagnosis of nephronophthisis phenotype is based on the following clinical findings, renal ultrasound findings, and family history.

Clinical findings

- Polyuria and polydipsia resulting from a renal concentration defect
- Growth retardation
- Chronic anemia that is resistant to therapy
- Chronic renal failure:
  - Not resulting from congenital structural abnormalities of the kidneys and/or urinary tract
  - Without signs or symptoms of a glomerular cause

Findings on renal ultrasound examination

- **Infantile NPH.** Moderately enlarged cystic kidneys with cortical hyperechogenicity [Gagnadoux et al 1989, Salomon et al 2009, Oud et al 2014]
- **Juvenile and adolescent NPH**
  - Small to normal-sized kidneys [Gagnadoux et al 1989, Salomon et al 2009]
  - Increased echogenicity of the kidneys and reduced corticomedullary differentiation
  - Renal cyst formation on the corticomedullary border in a later stage of the disease (~ 50% of individuals with juvenile nephronophthisis)
  - In some cases, dilated bladder as a result of chronic polyuria (urinary tract is typically not dilated) [Blowey et al 1996, Hildebrandt et al 2009, Chung et al 2014]

Family history. Consistent with autosomal recessive inheritance

Note: While the characteristic histologic findings are tubulointerstitial fibrosis, thickened and disrupted tubular basement membrane, and sporadic corticomedullary cysts [Zollinger et al 1980, Hurd & Hildebrandt 2011, Soliman et al 2012], these are not required to make the diagnosis of nephronophthisis.

Disorders Not Included in the NPH Phenotype

See Table 1 for specific inherited disorders not included in the NPH phenotype.

In addition, conditions associated with a renal concentrating defect and growth retardation (e.g., nephrogenic diabetes insipidus and other tubulopathies) can mimic the NPH phenotype. For example, in 79 consanguineous and familial cases with childhood-onset CKD and NPH suspected on renal ultrasound examination, Braun et al [2016] identified pathogenic variants in NPH-related genes in 32 individuals and pathogenic variants in other monogenic kidney disease-associated genes in 18 individuals, including eight with a renal tubulopathy, four with Alport syndrome, three with a congenital anomaly of the kidney and urinary tract (CAKUT), two with autosomal recessive polycystic kidney disease (ARPKD), and one with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome (OMIM 240300).

Biallelic pathogenic variants in *XPNPEP3* [O'Toole et al 2010] and in *SLC41A1* [Hurd et al 2013] can result in a nephronophthisis-like nephropathy.

Table 1. Disorders Not Included in the NPH Phenotype

Disease Name	Gene(s)	MOI	Clinical Features	
			Overlapping w/NPH	Distinguishing from NPH
Autosomal dominant tubulointerstitial kidney disease, *MUC1*-related	*MUC1*	AD	Chronic tubulointerstitial kidney disease & minimal or absent proteinuria	• CKD is slowly progressive, → ESRD between 3rd & 7th decade. [1] • Hypertension, anemia, & gout can occur secondary to renal insufficiency.

Table 1. continued from previous page.

Disease Name	Gene(s)	MOI	Clinical Features	
			Overlapping w/NPH	Distinguishing from NPH
Autosomal dominant tubulointerstitial kidney disease, *UMOD*-related	*UMOD*	AD	• Chronic tubulointerstitial kidney disease • ↑s in serum creatinine usually between ages 5 & 40 yrs [2]	• Hyperuricemia & gout usually occur as early as the teens. [3] • ESRD usually between 4th & 7th decade [3] • Medullary cysts can be seen in advanced disease.
Autosomal dominant tubulointerstitial kidney disease, *REN*-related	*REN*	AD	Chronic tubulointerstitial kidney disease	• CKD is slowly progressive, → ESRD between 4th & 6th decade. [4] • Early-onset hypoproliferative anemia, hyperuricemia, & gout [4]
Glomerulocystic kidney disease (OMIM 609886)	*HNF1B* *UMOD*	AD	Ultrasound findings may resemble AR polycystic kidney disease or NPH.	• Incl renal cysts & diabetes syndrome • Renal disease is variable w/cortical localization of cysts (cystic dilation of Bowman's space), often detected antenatally. [5] • Kidneys are typically enlarged in childhood & become small & hypoplastic in adulthood. [5] • Presence of distinct extrarenal manifestations
Renal cysts and diabetes syndrome (OMIM 137920)	*HNF1B*	AD		Renal disease (congenital anomalies of the kidney & urinary tract incl multicystic hypo- or dysplastic kidneys)
Autosomal recessive polycystic kidney disease	*PKHD1*	AR	Enlarged hyperechogenic kidneys w/ poor corticomedullary differentiation on renal ultrasound	Differs from infantile NPH by more diffuse distribution of renal cysts & more frequent assoc w/fibrotic liver disease [6]

AD = autosomal dominant; AR = autosomal recessive; CKD= chronic kidney disease; ESRD = end-stage renal disease; MOI = mode of inheritance

1. See *ADTKD-MUC1*.

2. See *ADTKD-UMOD*.

3. Scolari & Ghiggeri [2003], Bleyer & Hart [2009], *ADTKD-UMOD*. Mutation of *UMOD* causes glomerulocystic kidney disease with hyperuricemia and isosthenuria [Rampoldi et al 2003].

4. See ADTKD-*REN*.

5. Bingham et al [2001], Lennerz et al [2010], Kojima et al [2015]

6. Waters & Beales [2011]

Genetic Causes of the Nephronophthisis Phenotype

The genetic cause of nephronophthisis (NPH) can be established by identifying biallelic pathogenic variants in one of the 19 known NPH-related genes (Table 2a and Table 2b). A genetic diagnosis can be established in approximately 30%-40% of individuals with the NPH phenotype using molecular genetic testing that includes sequence analysis and gene-targeted deletion/duplication analysis [Otto et al 2010, Halbritter et al 2013].

Of note, additional genes associated with NPH-related ciliopathies are not currently classified as NPH-related genes in OMIM (e.g., *IFT140*, associated with skeletal ciliopathies with NPH and with isolated retinitis pigmentosa; *TRAF3IP1*, associated with Senior-Løken syndrome; and *IFT81*, associated with NPH and polydactyly) [Perrault et al 2012, Schmidts et al 2013, Bizet et al 2015, Perrault et al 2015, Xu et al 2015].

In addition, many more NPH-related genes have yet to be identified [Hildebrandt et al 2009, Otto et al 2011, Wolf & Hildebrandt 2011, Arts & Knoers 2013].

See Table 2a for the most common genetic causes of NPH (i.e., >1% of NPH) and Table 2b for less common genetic causes of NPH (i.e., <1% of NPH).

Table 2a. Molecular Genetics of Nephronophthisis: Most Common Genetic Causes

Gene [1, 2]	Locus	% of NPH Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detected by Method	
			Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]
CEP290	NPHP6	2%-3% [6]	2%-3% [6]	<1% [7, 8, 9]
INVS	NPHP2	1%-2% [6]	1%-2% [6]	Unknown [7]
IQCB1	NPHP5	2%-3% [6]	2%-3% [6]	Unknown [7]
NPHP1	NPHP1	20%-25% [10]	2%-3% [11]	20%-25% [12]
NPHP3	NPHP3	1%-2% [13]	1%-2% [13]	Unknown [7]
NPHP4	NPHP4	3%-4% [13]	3%-4% [13]	Unknown [7]
TMEM67	NPHP11	2%-3% [6]	2%-3% [6]	<1% [7, 14]

Pathogenic variants of any one of the genes included in this table account for >1% of nephronophthisis.
1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on allelic variants detected.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice-site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Tory et al [2009], Halbritter et al [2013], Braun et al [2016]
7. No data on detection rate of gene-targeted deletion/duplication analysis are available.
8. A heterozygous multiexon deletion was detected in 1 of 9 individuals with a ciliopathy and a *CEP290* heterozygous pathogenic variant [Travaglini et al 2009].
9. A heterozygous 1.9-Mb deletion that included *CEP290* and a *CEP290* nonsense pathogenic variant were identified in a fetus with Meckel-Gruber syndrome [Molin et al 2013].
10. Hildebrandt et al [2009], Halbritter et al [2013]
11. Two of 79 persons with suspected NPH [Braun et al 2016]; 11 of 470 persons (5 of whom were heterozygous) [Otto et al 2008]
12. 97 of 470 persons with NPH were homozygous for the common *NPHP1* deletion (see Molecular Genetics) [Otto et al 2008, Braun et al 2016].
13. Otto et al [2008], Halbritter et al [2013], Braun et al [2016]
14. A homozygous *TMEM67* intragenic deletion was identified in 1 of 120 individuals with Meckel-Gruber syndrome [Khaddour et al [2007].

Table 2b. Molecular Genetics of Nephronophthisis: Less Common Genetic Causes

Gene [1, 2]	Locus	Comment [3]
ANKS6	NPHP16	• Pathogenic variants detected in 5 families w/infantile NPH & 1 family w/juvenile NPH [4] • Homozygosity for a pathogenic variant identified in a Turkish family w/NPH; heterozygosity for 4 variants found in 56 additional persons [5]
CEP83	NPHP18	• Homozygous or compound heterozygous pathogenic variants identified in 8 of 1,255 persons w/NPH-related ciliopathies • Early-onset NPH assoc w/ID &/or hydrocephalus in 4 persons [6]

Table 2b. continued from previous page.

Gene [1, 2]	Locus	Comment [3]
CEP164	NPHP15	• A homozygous missense pathogenic variant identified in a Saudi child w/NPH & Leber congenital amaurosis [7] • Biallelic pathogenic variants identified in 3 of 856 families w/NPH-related ciliopathies. Phenotypes ranged from severe retinal dystrophy (inactivating variants) to Senior-Løken syndrome & isolated NPH (hypomorphic variants). [7]
DCDC2	NPHP19	Biallelic truncating pathogenic variants identified in 2 unrelated persons w/NPH and early-onset severe hepatic fibrosis 8
GLIS2	NPHP7	Homozygous pathogenic variants identified in 3 affected members of a Canadian Oji-Cree family & 1 Turkish patient w/isolated NPH [9]
IFT172	NPHP17	• Biallelic pathogenic variants identified in 12 families w/short-rib thoracic dysplasia & NPH & in 4 families w/retinitis pigmentosa-assoc ciliopathies [10] • Compound heterozygous variants found in 2 persons w/Jeune asphyxiating thoracic dystrophy & Mainzer-Saldino syndrome incl renal features; & in 1 person w/renal, skeletal, & ophthalmologic findings as well as pituitary hypoplasia & an ectopic posterior pituitary gland [11]
NEK8	NPHP9	• Homozygous missense pathogenic variants identified in a Kurdish child who had ESRD by age 3 yrs • Homozygous nonsense pathogenic variants identified in a family w/a severe embryonic ciliopathy, including cystic enlargement of the kidneys [12]
RPGRIP1L	NPHP8	Pathogenic variants cause Joubert syndrome. Biallelic truncating variants generally cause the more severe Meckel-Gruber syndrome. 13
SDCCAG8	NPHP10	• Biallelic pathogenic variants found in 12 families w/NPH & retinal degeneration (Senior-Løken syndrome & Bardet-Biedl syndrome) [14] • Homozygous deletions of exons 5 to 7 have been described. [15]
TTC21B	NPHP12	• Biallelic pathogenic variants detected in 7 families w/NPH w/or w/out extrarenal features, 3 families w/ Jeune asphyxiating thoracic dystrophy, & additional families w/a NPH-related ciliopathy [16] • Biallelic missense variants also identified in persons w/familial primary focal segmental glomerulosclerosis [Huynh Cong et al 2014, Bullich et al 2017] [16] • 2 families had infantile NPH w/extrarenal features. [17]
WDR19	NPHP13	• Biallelic pathogenic variants identified in families w/cranioectodermal dysplasia, Jeune syndrome, Senior-Løken syndrome, & isolated NPH [18] • 8 persons w/biallelic pathogenic variants had NPH & dilation of the intrahepatic bile ducts. [19]

Table 2b. continued from previous page.

Gene [1, 2]	Locus	Comment [3]
ZNF423	NPHP14	• Homozygosity for a missense pathogenic variant identified in Turkish sibs w/infantile NPH, cerebellar vermis hypoplasia, & situs inversus [7] • Heterozygous pathogenic variants found in 2 persons w/Joubert syndrome demonstrated (in cellular studies) a dominant-negative effect on protein function. [7]

ESRD = end-stage renal disease; ID = intellectual disability
Biallelic pathogenic variants in any one of the genes listed in this table are reported in only a few families (i.e., <1%) with nephronophthisis).
1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. Only sequence variants have been reported thus far in all listed genes, with the exception of *SDCCAG8*, in which deletions associated with nephronophthisis have been reported.
4. Hoff et al [2013]
5. Taskiran et al [2014]
6. Failler et al [2014]
7. Chaki et al [2012]
8. Schueler et al [2015]
9. Attanasio et al [2007], Halbritter et al [2013]
10. Halbritter et al [2013], Bujakowska et al [2015]
11. Lucas-Herald et al [2015], McInerney-Leo et al [2015]
12. Otto et al [2008], [Frank et al 2013]
13. Arts et al [2007], Delous et al [2007], Wolf et al [2007], Brancati et al [2008], Otto et al [2011], Kroes et al [2016]
14. Otto et al [2010], Schaefer et al [2011], Billingsley et al [2012]
15. Otto et al [2010], Chaki et al [2011], Schaefer et al [2011]
16. Davis et al [2011], Halbritter et al [2013], Huynh Cong et al [2014], McInerney-Leo et al [2015]
17. Otto et al [2011]
18. Bredrup et al [2011], Coussa et al [2013], Halbritter et al [2013]
19. Halbritter et al [2013], Lee et al [2015]

Isolated Nephronophthisis vs Syndromic Nephronophthisis

Approximately 80%-90% of individuals with nephronophthisis have no extrarenal features (i.e., they have isolated nephronophthisis); the remaining 10%-20% of individuals with nephronophthisis have extrarenal manifestations that can constitute a recognizable syndrome [Hildebrandt et al 2009, Wolf 2015]. NPH-related genes and their associated phenotypes are summarized (Table 3a and Table 3b).

Table 3a. Phenotypes of Syndromic Nephronophthisis

Disorder [1]	Major Distinguishing Clinical Features [2]							
	Cerebellar [3]	ID [4]	Eye [5]	Skeletal dysplasia [6]	Polydactyly [7]	Hepatic fibrosis	SI	Other
Joubert syndrome	+	+	+		+	+	+	Breathing abnormalities, hypotonia, obesity
Bardet-Biedl syndrome	+	+	+		+	+	+	Structural kidney anomalies, truncal obesity
Jeune syndrome and related skeletal disorders [8]		+	+	+	+	+		

Table 3a. continued from previous page.

Disorder [1]	Major Distinguishing Clinical Features [2]							
	Cerebellar [3]	ID [4]	Eye [5]	Skeletal dysplasia [6]	Polydactyly [7]	Hepatic fibrosis	SI	Other
Meckel-Gruber syndrome [9]				+	+	+	+	Posterior fossa abnormalities (encephalocele), cleft palate
Senior-Løken syndrome			+			+	+	
Leber congenital amaurosis		+	+					
COACH syndrome	+	+	+			+		
Oculomotor apraxia, Cogan type	+	+	+					

COACH = *c*erebellar vermis hypoplasia, *o*ligophrenia, *a*taxia, *c*oloboma, and *h*epatic fibrosis; ID = intellectual disability; SI = situs inversus

1. Although all syndromes listed here are associated with NPH, the prevalence of renal disease varies. Renal disease (including nephronophthisis) has been reported in: 23%-30% of individuals with Joubert syndrome [Doherty 2009, Kroes et al 2016]; 53%-82% of individuals with Bardet-Biedl syndrome [Imhoff et al 2011, Forsythe & Beales 2013]; 21% of families and 33% of individuals with COACH syndrome [Brancati et al 2008, Doherty et al 2010]; and 19 of 31 individuals with Jeune syndrome (see Cranioectodermal Dysplasia). Nephronophthisis is an obligatory finding in Senior-Løken syndrome. The prevalence of renal disease is unknown for the other NPH-related syndromes.

2. Based on Gerdes et al [2009], Simms et al [2011], Waters & Beales [2011], Arts & Knoers [2013].

3. Cerebellar findings include molar tooth sign in Joubert syndrome, cerebellar vermis hypoplasia and ataxia in Joubert syndrome and COACH syndrome, ataxia or poor coordination in Bardet-Biedl syndrome, and oculomotor apraxia in Joubert syndrome and oculomotor apraxia, Cogan type [Forsythe & Beales 2013].

4. Cognitive ability ranges from normal to severe disabiity. Individuals with Jeune syndrome and related skeletal disorders usually have normal cognitive abilities; those with Joubert syndrome and COACH syndrome frequently have some degree of cognitive impairment [Arts & Knoers 2013].

5. Ophthalmologic features include retinitis pigmentosa in Joubert syndrome, Bardet-Biedl syndrome, cranioectodermal dysplasia (CED), Senior-Løken syndrome, and Leber congenital amaurosis; coloboma in Joubert syndrome; and oculomotor apraxia in Joubert syndrome and oculomotor apraxia, Cogan type [Waters & Beales 2011].

6. Skeletal findings include rhizomelic limb shortening, brachydactyly, and narrow thorax in Jeune syndrome and CED. Narrow thorax is more severe and often lethal in Jeune syndrome [Arts & Knoers 2013]. Skeletal findings in Meckel-Gruber syndrome comprise bowing of long bones, malformations of the cranial base, and vertebral clefting [Kjaer et al 1999].

7. Polydactyly is usually postaxial; however, other forms have been described. See Joubert Syndrome and Related Disorders.

8. Includes cranioectodermal dysplasia (CED) characterized by craniosynostosis and ectodermal involvement

9. Meckel-Gruber syndrome is a perinatally lethal ciliopathy that is associated with enlarged cystic kidneys (i.e., infantile nephronophthisis) [Wolf 2015].

Table 3b. NPH-Related Genes Associated with Syndromic Nephronophthisis

Disorder	NPH-Related Genes [1]										
	NPHP1 [2]	*NPHP3*	*NPHP4*	*CEP290*	*RPGRIP1L*	*TMEM67*	*TTC21B*	*SDCCAG8*	*WDR19*	*INVS*	*IQCB1*
Joubert syndrome [3]	1%-2%	+	+	10%	2%-4%	10%	+				
Bardet-Biedl syndrome [4]				+		+		+			

Table 3b. continued from previous page.

Disorder	NPH-Related Genes [1]										
	NPHP1 [2]	*NPHP3*	*NPHP4*	*CEP290*	*RPGRIP1L*	*TMEM67*	*TTC21B*	*SDCCAG8*	*WDR19*	*INVS*	*IQCB1*
Jeune syndrome & related skeletal disorders [5]							+		+		
Meckel-Gruber syndrome [6]		+		+	+	+					
Senior-Løken syndrome [7]	+	+	+	+				3%-4%		+	17%-18%
Leber congenital amaurosis [8]				20%							3%-4%
COACH syndrome [9]					4%-5%	74%					
Oculomotor apraxia, Cogan type [10]	+		+								

Associated genes based on OMIM

+ indicates that mutation of the gene accounts for some (unknown percentage) of the disorder. Percentages are provided where known.

1. Betz et al [2000], Gerdes et al [2009], Hildebrandt et al [2009], Simms et al [2011], Waters & Beales [2011], Arts & Knoers [2013]

2. Extrarenal manifestations (including tapetoretinal degeneration and central nervous system anomalies) in 55 out of 235 families [Chaki et al 2011]

3. Joubert syndrome: prevalence has been reported for *NPHP1* [Parisi et al 2004, Castori et al 2005], *CEP290* [Sayer et al 2006, Valente et al 2006, Helou et al 2007, Valente et al 2008, Travaglini et al 2009], *RPGRIP1L* [Arts et al 2007, Delous et al 2007, Brancati et al 2008, Parisi 2009] and *TMEM67* [Baala et al 2007b, Brancati et al 2009, Otto et al 2009, Doherty et al 2010].

4. Bardet-Biedl syndrome: biallelic pathogenic variants in *CEP290* [Leitch et al 2008] and *SDCCAG8* [Otto et al 2010, Schaefer et al 2011] have been described in a minority of affected individuals.

5. Biallelic *WDR19* pathogenic variants were identified in two families with Jeune syndrome [de Vries et al 2010] and cranioectodermal dysplasia [Bredrup et al 2011]; biallelic *TTC21B* pathogenic variants were identified in eight families with Jeune syndrome [Davis et al 2011, McInerney-Leo et al 2015].

6. Meckel-Gruber syndrome: biallelic pathogenic variants were identified in *NPHP3* [Bergmann et al 2008], *CEP290* [Baala et al 2007a, Baala et al 2007b, Frank et al 2008], *RPGRIP1L* [Delous et al 2007] and *TMEM67* [Smith et al 2006].

7. Senior-Løken syndrome: most frequently caused by biallelic pathogenic variants in *IQCB1* [Otto et al 2005] followed by *SDCCAG8* [Otto et al 2010] and *NPHP1* [Caridi et al 1998], *INVS* [O'Toole et al 2006], *NPHP3* [Omran et al 2002, Tory et al 2009], *NPHP4* [Otto et al 2002, Schuermann et al 2002] and *CEP290* [Sayer et al 2006]

8. Leber congenital amaurosis: the majority is caused by biallelic *CEP290* pathogenic variants [den Hollander et al 2006] and less frequently by biallelic *IQCB1* pathogenic variants [Stone et al 2011].

9. COACH (*c*erebellar vermis hypo/aplasia, *o*ligophrenia, *a*taxia, *c*oloboma, and *h*epatic fibrosis) syndrome: most frequently associated with compound heterozygous *TMEM67* pathogenic variants [Verloes & Lambotte 1989, Brancati et al 2008] and rarely with biallelic *RPGRIP1L* pathogenic variants [Doherty et al 2010]

10. Oculomotor apraxia, Cogan type: associated with deletions in *NPHP1* and pathogenic variants in *NPHP4* [Saunier et al 1997, Betz et al 2000, Mollet et al 2002, Hildebrandt et al 2009]

Evaluation Strategy to Establish a Genetic Cause for NPH

Diagnostic algorithms for nephronophthisis have been proposed by several groups [Chaki et al 2011, Simms et al 2011, Braun et al 2016]; however, consensus diagnostic criteria have not been established. For a genetic testing strategy, see Figure 1. The preferred strategy and techniques may differ by laboratory.

Establishing the specific genetic cause of nephronophthisis in a given individual usually involves the following.

Physical examination. It is appropriate to examine for distinguishing clinical features that may identify a specific syndrome (see Table 3a).

Family history. It is appropriate to obtain a three-generation family history with particular attention to sibs who may have nephronophthisis or one of the syndromic forms of nephronophthisis (Table 3a).

Genomic/genetic testing to confirm the molecular diagnosis of NPHP is outlined in Figure 1. Recent studies indicate that molecular testing (use of single-gene testing and/or multigene panel) can identify biallelic pathogenic variants in one of the 19 known NPH-related genes in approximately 30%-40% of affected individuals [Otto et al 2010, Halbritter et al 2013, Braun et al 2016].

1. Testing for all persons with nephronophthisis (whether nonsyndromic or syndromic) begins with *NPHP1***gene-targeted deletion/duplication analysis**, as deletions in *NPHP1* are detected in 20%-25% of individuals with isolated (i.e., nonsyndromic) nephronophthisis [Hildebrandt et al 2009, Halbritter et al 2013].
2. **If only one allele** is determined to have an *NPHP1* deletion, follow gene-targeted deletion/duplication analysis with *NPHP1***sequence analysis** [Otto et al 2008].
    a If sequence analysis does not identify a pathogenic variant on the other allele, a **multigene panel** (3.a.) and/or **more comprehensive genomic testing** (3.b.) including exome sequencing or genome sequencing can also be considered, as the individual may be a carrier of a heterozygous variant in *NPHP1* with disease caused by biallelic pathogenic variants in another NPH-related gene.
3. **If neither allele** has an *NPHP1* deletion identified on gene-targeted deletion/duplication analysis, proceed to use of a **multigene panel** (3.a.) and/or **more comprehensive genomic testing** (3.b.) including exome sequencing or genome sequencing to determine if biallelic pathogenic variants can be identified in another NPH-related gene [Braun et al 2016].
    a. The multigene panel should include the 19 NPH-related genes and other ciliopathy or renal disease-related genes of interest [Perrault et al 2012, Halbritter et al 2013, Failler et al 2014]. (For an overview of ciliopathy genes, see Braun et al [2016] or Schueler et al [2016].) 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*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (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. For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.
    b. If use of a multigene panel fails to confirm a diagnosis in an individual with features of NPH (or if use of a multigene panel is not an available or preferred next step), **more comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered.

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

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Nephronophthisis is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one NPH-related pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has 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. The offspring of an individual with nephronophthisis are obligate heterozygotes (carriers) for a nephronophthisis-related pathogenic variant.

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

Related Genetic Counseling Issues

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

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the nephronophthisis-related pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for nephronophthisis are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

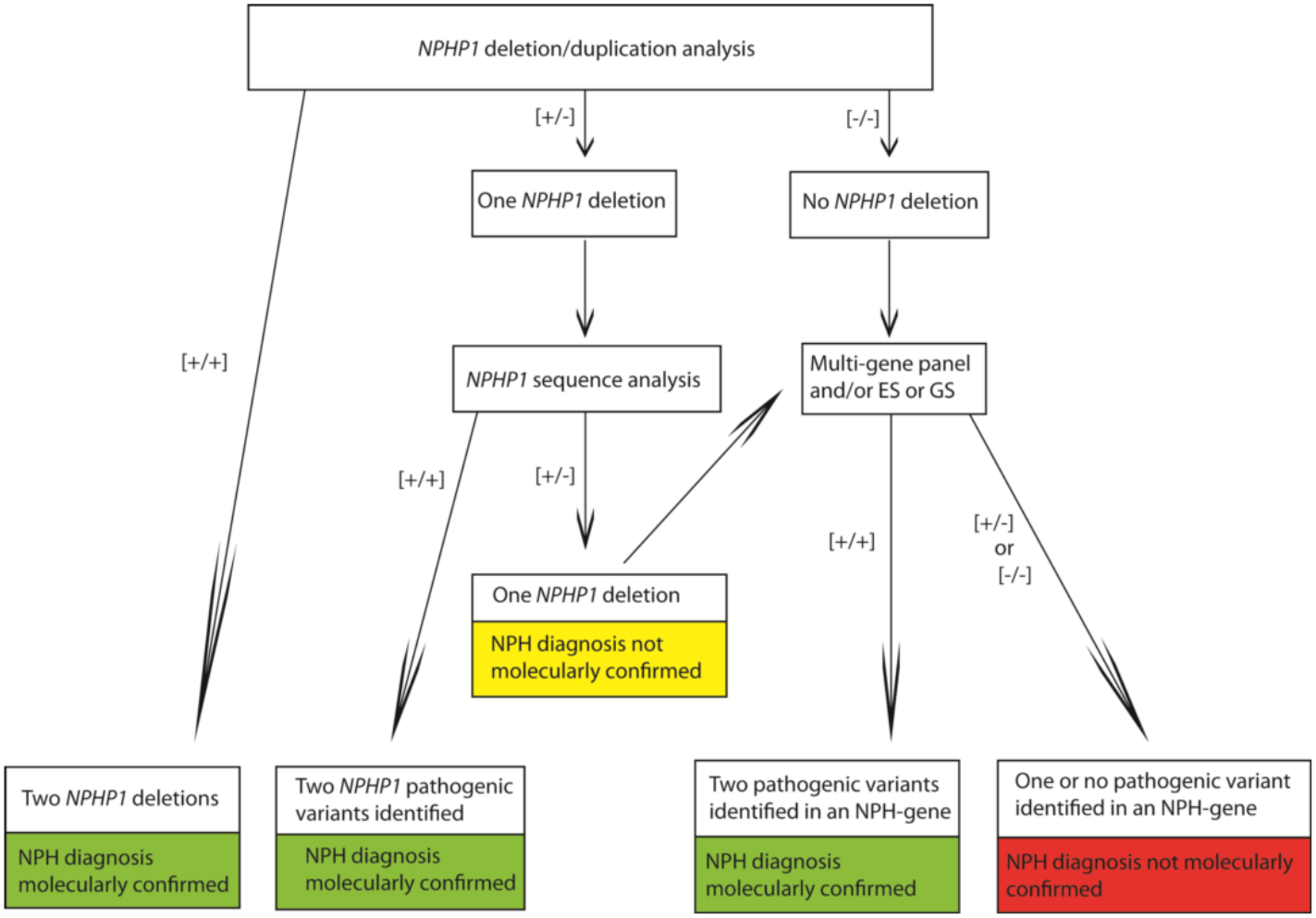

Figure 1. Strategy to identify the genetic cause of nephronophthisis. *NPHP1*-targeted deletion/duplication analysis is performed first. If only one allele is determined to have an *NPHP1* deletion, perform sequence analysis of *NPHP1*. If only one *NPHP1* pathogenic variant is found, a multigene panel of ciliary genes, ES, or GS may be considered because the *NPHP1* pathogenic variant could be acting as a genetic modifier in combination with biallelic pathogenic variants in another NPH-related gene. Of note, to date no heterozygous *NPHP1* pathogenic variant has been identified as a modifier of isolated nephronophthisis caused by biallelic pathogenic variants in another NPH-related gene.

ES = exome sequencing

GS = genome sequencing

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.

- **National Library of Medicine Genetics Home Reference**
  Nephronophthisis
- **American Kidney Fund**
  11921 Rockville Pike
  Suite 300

Rockville MD 20852
Phone: 866-300-2900
Email: helpline@kidneyfund.org
www.kidneyfund.org

- **Ciliopathy Alliance**
  United Kingdom
  Phone: 44 20 7387 0543
  www.ciliopathyalliance.org
- **Kidney Foundation of Canada**
  310-5160 Decarie Blvd.
  Montreal Ontario H3X 2H9
  Canada
  Phone: 800-361-7494 (toll-free); 514-369-4806
  Fax: 514-369-2472
  Email: info@kidney.ca
  www.kidney.ca
- **National Kidney Foundation (NKF)**
  30 East 33rd Street
  New York NY 10016
  Phone: 800-622-9010 (toll-free); 212-889-2210
  Email: info@kidney.org
  www.kidney.org
- **NephCure Kidney International**
  PA
  Phone: 866-NephCure; 866-637-4287
  Email: info@nephcure.org
  nephcure.org

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with nephronophthisis, the following evaluations are recommended [Parisi et al 2007, Simms et al 2011, KDIGO 2013]:

- Detailed family history and physical examination including blood pressure, growth parameters, developmental assessment, and dysmorphology examination to evaluate for extrarenal manifestations (Table 3a)
- Tests to evaluate the kidneys:
  - Tests of renal function including serum creatinine concentration, estimated glomerular filtration rate (eGFR), urea or blood urea nitrogen (BUN), and electrolytes

    - Complete blood count (CBC) to evaluate for anemia
    - Tests to evaluate for the metabolic bone disease of chronic kidney disease (CKD) including serum calcium, phosphate, parathyroid hormone (PTH), and alkaline phosphatase activity
    - Urinalysis from first-morning void for specific gravity to test concentrating ability (if feasible), proteinuria
- Tests of liver function including serum concentrations of transaminases, albumin, bilirubin, and prothrombin time
- Abdominal ultrasound examination to evaluate renal findings consistent with nephronophthisis and to evaluate for additional anomalies in liver, bile duct, spleen, and/or pancreas (including situs inversus)
- Referral as needed for evaluation of extrarenal manifestations, including:
    - Ophthalmologic examination
    - Brain MRI
    - Skeletal radiographs
    - Assessment of psychomotor development and/or behavior
    - Neurologic assessment
    - Endocrine assessment
    - Cardiac ultrasound examination
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

This section discusses only the management of the phenotype of nephronophthisis. Management of other findings associated with syndromic NPH (Table 3a) are beyond the scope of this *GeneReview*.

Currently no cure for nephronophthisis exists. Treatment is aimed at slowing the progression of CKD and its complications, according to international clinical practice guidelines for chronic renal failure (Kidney Disease – Improving Global Outcomes [KDIGO] 2012 Clinical Practice Guideline (CPG) for Evaluation and Management of Chronic Kidney Disease [KDIGO 2013] (full text):

- Correction of water and electrolyte imbalances, especially during intercurrent illness
- Treatment of anemia, hypertension, and proteinuria if present. Preferred therapy may differ between adult and pediatric patients [KDIGO 2013].
- Growth hormone treatment for children who have severe growth retardation as a result of chronic renal insufficiency and meet criteria for treatment [Wilson et al 2003]
- Dialysis or renal transplantation when patients reach ESRD. Renal transplantation is the preferred treatment as disease does not recur in the transplanted kidney [Pistor et al 1985].

Prevention of Secondary Complications

Annual influenza vaccination is indicated for patients with CKD. Other vaccinations (e.g., pneumococcal vaccine and hepatitis B) should follow local practice guidelines [KDIGO 2013].

For measures to prevent secondary cardiovascular complications, see KDIGO Clinical Practice Guideline for Evaluation and Management of Chronic Kidney Disease [KDIGO 2013] (full text).

Surveillance

Evaluations are recommended at least annually. More frequent monitoring is recommended for individuals with advanced-stage CKD, individuals at higher risk of disease progression, or when assessment will affect therapeutic decision making [KDIGO 2013].

- Monitoring of blood pressure, growth parameters, and development

- Renal function including serum creatinine concentration and estimated glomerular filtration rate (eGFR), urea or BUN, electrolytes, CBC, CKD metabolic bone disease including serum calcium, phosphate, PTH, and alkaline phosphatase activity
- Liver function including serum concentrations of transaminases, albumin, bilirubin, and prothrombin time
- Urinalysis to monitor proteinuria
- Abdominal ultrasound examination to evaluate progression of renal disease and possible liver, bile duct, spleen, or pancreas anomalies
- Routine evaluations for extrarenal manifestations of syndromic NPH that can appear with time, especially ophthalmologic examination for visual acuity, visual field examination, and evidence of retinal dystrophy

Agents/Circumstances to Avoid

Nephrotoxic agents – e.g., nonsteroidal anti-inflammatory drugs (NSAIDS), aminoglycosides, and radiocontrast studies – should be avoided.

Individuals with liver function impairment should avoid hepatotoxic medication.

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger sibs of a proband with NPH in order to identify as early as possible those who would benefit from initiation of treatment and surveillance measures.

Evaluations can include:

- Molecular genetic testing if the NPH-related pathogenic variants in the family are known;
- Monitoring of renal function and blood pressure if the pathogenic variants in the family are not known.

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

Pregnancy Management

For reviews of management of CKD in pregnancy see Smyth et al [2013] and Piccoli et al [2015].

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Nephronophthisis: Genes and Databases

Locus Name	Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
NPHP1	*NPHP1*	2q13	Nephrocystin-1	NPHP1 @ LOVD	NPHP1	NPHP1
NPHP2	*INVS*	9q31.1	Inversin	INVS @ LOVD	INVS	INVS

Table A. continued from previous page.

NPHP3	*NPHP3*	3q22.1	Nephrocystin-3	NPHP3 @ LOVD	NPHP3	NPHP3
NPHP4	*NPHP4*	1p36.31	Nephrocystin-4	NPHP4 @ LOVD	NPHP4	NPHP4
NPHP5	*IQCB1*	3q13.33	IQ calmodulin-binding motif-containing protein 1	IQCB1 @ LOVD	IQCB1	IQCB1
NPHP6	*CEP290*	12q21.32	Centrosomal protein of 290 kDa		CEP290	CEP290
NPHP7	*GLIS2*	16p13.3	Zinc finger protein GLIS2	GLIS2 @ LOVD	GLIS2	GLIS2
NPHP8	*RPGRIP1L*	16q12.2	Protein fantom		RPGRIP1L	RPGRIP1L
NPHP9	*NEK8*	17q11.2	Serine/threonine-protein kinase Nek8	NEK8 @ LOVD	NEK8	NEK8
NPHP10	*SDCCAG8*	1q43-q44	Serologically defined colon cancer antigen 8	SDCCAG8 @ LOVD	SDCCAG8	SDCCAG8
NPHP11	*TMEM67*	8q22.1	Meckelin	TMEM67 @ LOVD	TMEM67	TMEM67
NPHP12	*TTC21B*	2q24.3	Tetratricopeptide repeat protein 21B		TTC21B	TTC21B
NPHP13	*WDR19*	4p14	WD repeat-containing protein 19	WDR19 @ LOVD	WDR19	WDR19
NPHP15	*CEP164*	11q23.3	Centrosomal protein of 164 kDa		CEP164	CEP164
NPHP16	*ANKS6*	9q22.33	Ankyrin repeat and SAM domain-containing protein 6		ANKS6	ANKS6
NPHP17	*IFT172*	2p23.3	Intraflagellar transport protein 172 homolog		IFT172	IFT172
NPHP18	*CEP83*	12q22	Centrosomal protein of 83 kDa		CEP83	CEP83
NPHP19	*DCDC2*	6p22.3	Doublecortin domain-containing protein 2	DCDC2 database	DCDC2	DCDC2
	ZNF423	16q12.1	Zinc finger protein 423		ZNF423	ZNF423

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Nephronophthisis (View All in OMIM)

243305	INVERSIN; INVS
256100	NEPHRONOPHTHISIS 1; NPHP1
602088	NEPHRONOPHTHISIS 2; NPHP2
604387	NEPHRONOPHTHISIS 3; NPHP3
604557	ZINC FINGER PROTEIN 423; ZNF423
605755	DOUBLECORTIN DOMAIN-CONTAINING PROTEIN 2; DCDC2
606966	NEPHRONOPHTHISIS 4; NPHP4
607100	NEPHROCYSTIN 1; NPHP1

Table B. continued from previous page.

607215	NEPHROCYSTIN 4; NPHP4
607386	INTRAFLAGELLAR TRANSPORT 172; IFT172
608002	NEPHROCYSTIN 3; NPHP3
608151	WD REPEAT-CONTAINING PROTEIN 19; WDR19
608539	GLIS FAMILY ZINC FINGER PROTEIN 2; GLIS2
609237	IQ MOTIF-CONTAINING PROTEIN B1; IQCB1
609799	NEVER IN MITOSIS GENE A-RELATED KINASE 8; NEK8
609884	TRANSMEMBRANE PROTEIN 67; TMEM67
610142	CENTROSOMAL PROTEIN, 290-KD; CEP290
610937	RPGRIP1-LIKE; RPGRIP1L
611498	NEPHRONOPHTHISIS 7; NPHP7
612014	TETRATRICOPEPTIDE REPEAT DOMAIN-CONTAINING PROTEIN 21B; TTC21B
613159	NEPHRONOPHTHISIS-LIKE NEPHROPATHY 1; NPHPL1
613524	SEROLOGICALLY DEFINED COLON CANCER ANTIGEN 8; SDCCAG8
613550	NEPHRONOPHTHISIS 11; NPHP11
613553	X-PROLYL AMINOPEPTIDASE 3; XPNPEP3
613820	NEPHRONOPHTHISIS 12; NPHP12
613824	NEPHRONOPHTHISIS 9; NPHP9
614377	NEPHRONOPHTHISIS 13; NPHP13
614844	NEPHRONOPHTHISIS 14; NPHP14
614845	NEPHRONOPHTHISIS 15; NPHP15
614848	CENTROSOMAL PROTEIN, 164-KD; CEP164
615370	ANKYRIN REPEAT AND STERILE ALPHA MOTIF DOMAINS-CONTAINING PROTEIN 6; ANKS6
615382	NEPHRONOPHTHISIS 16; NPHP16
615847	CENTROSOMAL PROTEIN, 83-KD; CEP83
615862	NEPHRONOPHTHISIS 18; NPHP18
616217	NEPHRONOPHTHISIS 19; NPHP19

Molecular Pathogenesis

Almost all nephronophthisis-related genes (NPH-related genes) encode proteins localized to the cilium at the ciliary transition zone, the inversin compartment, or subunits of the IFT complexes where they are involved in ciliogenesis and regulation of ciliary protein trafficking [Fliegauf et al 2006, Omran 2010, Novarino et al 2011, Sang et al 2011, van Reeuwijk et al 2011]. In addition, the protein products of *NPHP1*, *INVS*, and *NPHP4* localize to and regulate cell-cell junctions [Donaldson et al 2002, Delous et al 2009, Hurd & Hildebrandt 2011].

The mechanism by which disruption in these NPH-related proteins leads to nephronophthisis is unknown, although recent studies have shed light on nephrocystin functions and associated pathways. Nephrocystins are implicated in important signaling pathways, such as the Wnt pathway (involved in apical-basolateral polarity of renal tubular cells in response to tubular flow) [Simons et al 2005], the Hedgehog pathway (involved in

mesenchymal-to-epithelial transition in renal tubulogenesis) [Yu et al 2002, Attanasio et al 2007], and the Hippo pathway (involved in regulation of tissue growth) [Benzing & Schermer 2012, Barker et al 2014, Wolf 2015].

In addition, the NPH-related genes *NEK8*, *CEP164*, *SDCCAG8*, *CEP290*, and *ZNF423* play a dual role in the nucleus and have been implicated in DNA damage response (DDR) signaling [Chaki et al 2012, Zalli et al 2012, Choi et al 2013, Yuan & Sun 2013, Airik et al 2014, Slaats et al 2014, Slaats & Giles 2015, Slaats et al 2015]. As pathogenic variants in *CEP164* induce epithelial-to-mesenchymal transition and a profibrotic response [Slaats et al 2014], the DDR pathway may be most closely linked to tubulointerstitial fibrosis, a hallmark feature of nephronophthisis [Slaats & Giles 2015].

Cilia are present on nearly all cell types, and pathogenic variants in NPH-related genes affect cilia function in a tissue-specific manner [Garcia-Gonzalo et al 2011, Benzing & Schermer 2012], accounting for the wide variety of extrarenal manifestations in nephronophthisis-related ciliopathies.

The considerable inter- and intrafamilial variability in the associated extrarenal manifestations and the rate of progression to ESRD may be due to the degree of protein impairment and the contribution of genetic modifiers [Caridi et al 2006, Hoefele et al 2007, Littink et al 2010, Drivas et al 2015]. Oligogenic inheritance has been described in several NPH-related ciliopathies [Katsanis et al 2001, Badano et al 2003, Baala et al 2007b, Helou et al 2007, Tory et al 2007, Leitch et al 2008, Louie et al 2010, Davis et al 2011, Lin et al 2013, Zhang et al 2014]. Note that some proposed modifier alleles occur frequently in control populations and, therefore, their own pathogenicity is debatable (e.g., see the ExAC Browser).

Examples of proposed genetic modifiers for NPH-related genes include the following:

- An *NPHP1* pathogenic variant as a modifier of an NPH-related ciliopathy phenotype, such as Bardet-Biedl syndrome [Lindstrand et al 2014]
- A heterozygous truncating variant in *CEP290* in one person and heterozygous missense variants in *AHI1* in six persons with homozygous *NPHP1* deletions [Tory et al 2007]. Variants in *CEP290* and *AHI1* were hypothesized to contribute to neurologic findings in these seven individuals who had biallelic *NPHP1* pathogenic variants.
- An enrichment of pathogenic variants in *TTC21B* in individuals with a ciliopathy, suggesting a modifier role for *TTC21B* [Davis et al 2011].

Note: To date no heterozygous *NPHP1* pathogenic variant has been identified as a modifier in isolated nephronophthisis caused by biallelic pathogenic variants in another NPH-related gene.

For a detailed summary of gene and protein information for the genes discussed in this section, see Table A, **Gene.**

NPHP1

Gene structure. *NPHP1* comprises 20 exons and is alternatively spliced in 11 variants. The largest transcript is NM_000272. It encodes a 732-amino acid product. *NPHP1* is flanked by segmental duplications that are prone to nonallelic homologous recombination [Saunier et al 2000].

Benign variants. Saunier et al [2000] demonstrated a benign rearrangement involving the two 330-kb inverted repeats surrounding the common 290-kb deletion in homozygous state in two controls (1.3%).

NPHP1 duplications have been described in persons with autism spectrum disorders and developmental delay without associated renal features [Baris et al 2006, Yasuda et al 2014].

Pathogenic variants. The common *NPHP1* 290-kb deletion (which includes the entire gene) is found in the homozygous state in 20%-25% of persons with nephronophthisis [Hildebrandt et al 2009, Halbritter et al 2013].

Other loss-of-function pathogenic variants, such as p.Leu27Ter, occur in the compound heterozygous state with the common deletion in individuals with NPH [Saunier et al 1997, Hildebrandt et al 1997].

Modifier variants. It has been proposed that heterozygous pathogenic variants act as modifier alleles in Bardet-Biedl syndrome [Lindstrand et al 2014].

Table 4. *NPHP1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
290-kb deletion including entire gene		NM_000272 NP_000263
c.80T>A	p.Leu27Ter	NM_000272.3 NP_000263.2

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *NPHP1* encodes nephrocystin 1, which localizes to the ciliary transition zone. The C-terminal region mediates NPHP1 localization to cell-cell junctions, interaction with filamins, establishment of cell polarity, and interaction of with NPHP4 [Donaldson et al 2002, Mollet et al 2005].

Abnormal gene product. Loss of NPHP1 function causes disease. For information on animal models click here.

INVS (*NPHP2*)

Gene structure. *INVS* comprises 17 exons. It has eight transcripts of which the longest is NM_014425.

Pathogenic variants. Biallelic truncating and missense pathogenic variants cause infantile and juvenile NPH [Gagnadoux et al 1989, Otto et al 2003, Tory et al 2009, Chaki et al 2011, Halbritter et al 2013].

Two individuals with compound heterozygous *INVS* truncating pathogenic variants had isolated juvenile-onset NPH (c.1417delG, c.3125delA, c.2695C>T, c.2782C>T) [Halbritter et al 2013]. There was no clear correlation between the type of pathogenic variant and the presence or severity of situs inversus or other extrarenal ophthalmologic, central nervous system, and cardiac features [Otto et al 2003, O'Toole et al 2006, Otto et al 2008, Tory et al 2009, Chaki et al 2011].

Table 5. *INVS* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.1417delG	p.Ala473GlnfsTer37	NM_014425.3
c.3125delA	p.Asn1042ThrfsTer64	NM_014425.3
c.2695C>T	p.Arg899Ter	NM_014425.3 NP_055240.2
c.2782C>T	p.Arg928Ter	NM_014425.3 NP_055240.2

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *INVS* encodes a 1,065-amino acid protein. INVS contains several domains and protein-binding motifs, including 16 ankyrin repeats, two IQ domains (including 1 calmodulin-binding domain), two D boxes (including 1 anaphase-promoting complex subunit-2 [APC2]-binding D box), and a bipartite nuclear localization signal (NLS-BP) [Morgan et al 2002a, Morgan et al 2002b, Schön et al 2002, Otto et al 2003]. INVS localizes to and defines the INVS compartment.

INVS:

- Interacts with a C-terminal region of NPHP1 [Otto et al 2003];
- Interacts with catenins and N-cadherin at membrane regions of cell-cell contact [Nürnberger et al 2002];
- Interacts in a complex with NEK8, NPHP3, and ANKS6 [Hoff et al 2013];
- Is involved in regulation of ciliary disassembly through phosphorylation and inhibition of Aurora A, a cell cycle kinase that promotes ciliary disassembly [Mergen et al 2013];
- Plays a role in the Wnt pathway [Simons et al 2005].

Abnormal gene product. See Animal Models.

NPHP3

Gene structure. *NPHP3* comprises 27 exons. It has 14 different transcripts. The longest transcript, NM_153240, encodes a protein of 1,330 amino acids.

Pathogenic variants. Homozygous pathogenic variants in *NPHP3* cause infantile-onset, juvenile-onset, and adolescent-onset NPH [Olbrich et al 2003, Simpson et al 2009, Tory et al 2009, Halbritter et al 2013].

The homozygous nonsense pathogenic variant p.Arg702Ter was identified in 12 infants from six Amish families with neonatal lethal NPH [Simpson et al 2009].

NPHP3 pathogenic variants were identified in children with infantile-onset NPH [Simpson et al 2009, Tory et al 2009, Halbritter et al 2013] and in two families with Meckel-Gruber syndrome [Bergmann et al 2008, Tory et al 2009].

Homozygous in-frame deletion of three base pairs in *NPHP3* (p.Gly1275del) was first detected in a Venezuelan family with adolescent-onset NPH [Olbrich et al 2003].

Brain and cardiac anomalies have been associated with biallelic nonsense pathogenic variants [Chaki et al 2011]. Liver fibrosis is a common extrarenal feature [Tory et al 2009, Halbritter et al 2013].

Table 6. *NPHP3* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.2104C>T	p.Arg702Ter	NM_153240.4 NP_694972.3
c.3824_3826delGAG	p.Gly1275del	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The longest *NPHP3* transcript encodes a protein of 1,330 amino acids.

NPHP3:

- Contains a coiled coil domain, a tubulin-tyrosine ligase domain, and a tetratrico peptide repeat (TPR) domain that is predicted at the site of interaction with NPHP1 [Olbrich et al 2003];
- Interacts in a complex with the proteins NEK8, INVS, and ANKS6 [Hoff et al 2013];
- Plays a role in the Wnt pathway [Bergmann et al 2008];
- Localizes at the inversin compartment [Shiba et al 2010].

Abnormal gene product. See Animal Models.

NPHP4

Gene structure. *NPHP4* comprises 30 exons. It is expressed in ten splice variants. The largest transcript is NM_015102, which encodes a protein of 1,426 amino acids.

Pathogenic variants. Numerous missense, nonsense, and splicing variants and small indels have been described. Pathogenic variants are associated with isolated juvenile-onset NPH [Mollet et al 2002, Otto et al 2002] and were associated with Senior-Løken syndrome in two families homozygous for the nonsense pathogenic variants p.Arg658Ter and p.Gln779Ter [Otto et al 2002].

While there is a correlation between the presence of extrarenal features (involving the eye, liver, and developmental delay) and mutation of *NPHP4* in general, no clear correlation between the presence of these features and a specific *NPHP4* variant type (e.g., missense, nonsense) has been found [Chaki et al 2011].

Table 7. *NPHP4* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.1972C>T	p.Arg658Ter	NM_015102.4 NP_055917.1
c.2335C>T	p.Gln779Ter	NM_015102.4 NP_055917.1

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
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Normal gene product. *NPHP4* encodes the 1,426-amino acid protein nephrocystin-4, which is part of the ciliary transition zone.

NPHP4:

- Contains a proline-rich region between positions 458 and 514 [Mollet et al 2005];
- Interacts with NPHP1, RPGRIP1, RPGRIP1L, and the tight junction-associated proteins PALS1, PATJ, and Par6 [Mollet et al 2005, Roepman et al 2005, Arts et al 2007, Delous et al 2007, Delous et al 2009];
- May be involved in actin cytoskeleton organization at sites of cell-cell and cell-matrix adhesion [Mollet et al 2005].

Abnormal gene product. See Animal Models.

IQCB1 (*NPHP5*)

Gene structure. *IQCB1* (*NPHP5*) consists of 15 exons and has seven alternatively spliced transcripts. The largest transcript is NM_001023570, which encodes a protein of 598 amino acids.

Pathogenic variants. Biallelic missense, nonsense, and splice-site pathogenic variants and small indels in *IQCB1* are associated with Senior-Løken syndrome [Otto et al 2005] and Leber congenital amaurosis [Stone et al 2011].

The phenotype of 33 individuals with biallelic nonsense or splice-site pathogenic variants in *IQCB1* comprised juvenile NPH and early-onset retinal degeneration. None had severe central nervous system or liver anomalies [Chaki et al 2011].

Modifier variant. The p.Ile393Asn variant, which is not associated with a renal phenotype, was identified as a modifier of *RPGR*-related retinitis pigmentosa [Fahim et al 2012].

Table 8. *IQCB1* Modifier Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.1178T>A	p.Ile393Asn	NM_001023570.2 NP_001018864.2

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *IQCB1* encodes a protein of 598 amino acids.

IQCB1:

- Contains two putative IQ calmodulin-binding domains that flank a coiled-coil domain;
- Interacts with calmodulin-2, the retinal protein RPGR, and CEP290 [Otto et al 2005, Schäfer et al 2008];
- Localizes along the primary cilium [Otto et al 2005].

Abnormal gene product. See Animal Models.

CEP290 (*NPHP6*)

Gene structure. *CEP290* (*NPHP6*) comprises 54 exons and eight splice variants. NM_025114 is the longest transcript.

Pathogenic variants. Pathogenic variants in *CEP290* are associated with Senior-Løken syndrome, Joubert syndrome [Sayer et al 2006, Valente et al 2006], Leber congenital amaurosis [den Hollander et al 2006], Bardet-Biedl syndrome [Leitch et al 2008], and Meckel-Gruber syndrome [Baala et al 2007b].

The majority of reported *CEP290* pathogenic variants are inactivating: in a review of 112 pathogenic variants, 88 were truncating, 20 were predicted to influence splicing, and three were missense [Coppieters et al 2010].

In 26 individuals with *CEP290* biallelic pathogenic variants, 24 developed juvenile-onset NPH and two developed infantile-onset NPH; all 26 exhibited extrarenal manifestations [Chaki et al 2011].

Table 9. Selected *CEP290* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.5707A>T	p.Glu1903Ter	NM_025114.3 NP_079390.3

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The centromere protein CEP290 is 2,479 amino acids long.

CEP290:

- Has an N-terminal domain that activates ATF4-mediated transcription. ATF4 is a transcription factor implicated in cAMP-dependent renal cyst formation [Sayer et al 2006];
- Contains an IQCB1 binding site at amino acids 696-869 [Schäfer et al 2008];
- Interacts with CC2D2A [Gorden et al 2008].

Abnormal gene product. See Animal Models.

TMEM67 (*NPHP11*)

Gene structure. *TMEM67* (*NPHP11*) comprises 28 exons and has 22 transcripts. The longest transcript, NM_153704, encodes a 995-amino acid protein.

Pathogenic variants. More than 100 pathogenic variants in *TMEM67* have been described.

Biallelic *TMEM67* pathogenic variants are associated with a variety of ciliopathies (Table 3b) ranging from NPH with hepatic fibrosis at the mild end of the spectrum (biallelic missense variants) [Otto et al 2009, Chaki et al 2011] to Joubert syndrome [Baala et al 2007b, Otto et al 2009], COACH syndrome [Verloes & Lambotte 1989, Brancati et al 2009], and Meckel-Gruber syndrome at the severe end of the spectrum (characterized by a higher prevalence of truncating variants) [Smith et al 2006, Consugar et al 2007]. Liver disease is a common feature in *TMEM67*-related disease [Otto et al 2009].

Most individuals with *TMEM67*-related NPH have juvenile NPH; the missense variants c.755T>C (p.Met252Thr) and c.1843T>C (p.Cys615Arg) were identified in an individual with infantile-onset NPH [Chaki et al 2011].

Modifier variants. Heterozygous pathogenic variants in *TMEM67* have been proposed as modifier alleles in Bardet-Biedl syndrome [Lindstrand et al 2014, Leitch et al 2008].

Table 10. *TMEM67* Variants Discussed in This *GeneReview*

Variant Classification	DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
Pathogenic	c.755T>C	p.Met252Thr	NM_153704.5 NP_714915.3
	c.1843T>C	p.Cys615Arg	
Modifier	c.958A>T	p.Ser320Cys	
	c.2241G>A	p.=	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
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Normal gene product. *TMEM67* encodes a 995-amino acid protein that localizes to the basal body [Williams et al 2011]. TMEM67 interacts with MKS1, and this interaction is required for normal ciliogenesis in mouse IMCD3 cells and patient-derived renal cells [Dawe et al 2007, Tammachote et al 2009].

Abnormal gene product. Disruption of the interaction of the C-terminus region of TMEM67 with filamin A caused defects in basal body positioning, ciliogenesis, and the Wnt signaling pathway [Adams et al 2012]. See Animal Models.

GLIS2

See Table 2b.

Table 11. Selected *GLIS2* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.523T>C	p.Cys175Arg	NM_032575.2 NP_115964.2
c.775+1G>T		

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RPGRIP1L

See Table 2b.

A common p.Ala229Thr allele in *RPGRIP1L* was enriched in individuals with ciliopathies involving retinitis pigmentosa compared to other ciliopathies and may represent a modifier of retinal degeneration [Khanna et al 2009].

Table 12. *RPGRIP1L* Modifier Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.685G>A	p.Ala229Thr	NM_015272.2 NP_056087.2

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Additional Genetic Causes of Nephronophthisis

Additional genes less commonly associated with nephronophthisis (see Table 2b):

- *ANKS6*
- *CEP83*
- *CEP164*
- *DCDC2*
- *IFT172*
- *NEK8*
- *SDCCAG8*
- *TTC21B*
- *WDR19*
- *ZNF423*

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Chapter Notes

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