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).


**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 diagnosis 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].


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**
  ◦ 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).


**Table 1. Disorders Not Included in the NPH Phenotype**

<table>
<thead>
<tr>
<th>Disease Name</th>
<th>Gene(s)</th>
<th>MOI</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal dominant tubulointerstitial kidney disease, MUC1-related</td>
<td>MUC1</td>
<td>AD</td>
<td>Chronic tubulointerstitial kidney disease &amp; minimal or absent proteinuria</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• CKD is slowly progressive, leading to ESRD between 3rd &amp; 7th decade</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hypertension, anemia, &amp; gout can occur secondary to renal insufficiency</td>
</tr>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Disease Name</td>
<td>Gene(s)</td>
<td>MOI</td>
<td>Clinical Features</td>
</tr>
<tr>
<td>-----------------------------------------------------------</td>
<td>------------------</td>
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<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Autosomal dominant tubulointerstitial kidney disease,</td>
<td>UMOD</td>
<td>AD</td>
<td>• Chronic tubulointerstitial kidney disease</td>
</tr>
<tr>
<td>UMOD-related</td>
<td></td>
<td></td>
<td>• Elevations in serum creatinine usually occur between ages 5 &amp; 40 years</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Hyperuricemia &amp; gout usually occur as early as the teenage years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• ESRD usually occurs between 4th &amp; 7th decade</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Medullary cysts can be seen in advanced disease</td>
</tr>
<tr>
<td>Autosomal dominant tubulointerstitial kidney disease,</td>
<td>REN</td>
<td>AD</td>
<td>Chronic tubulointerstitial kidney disease</td>
</tr>
<tr>
<td>REN-related</td>
<td></td>
<td></td>
<td>CKD is slowly progressive, leading to ESRD between 4th &amp; 6th decade</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Early-onset hypoproliferative anemia, hyperuricemia, &amp; gout</td>
</tr>
<tr>
<td>Glomerulocystic kidney disease (OMIM 609886)</td>
<td>HNF1B UMOD</td>
<td>AD</td>
<td>Ultrasound findings may resemble AR polycystic kidney disease or NPH</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Includes renal cysts &amp; diabetes syndrome</td>
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<td></td>
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<td>Renal disease is variable w/ cortical localization of cysts (cystic dilation of</td>
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<td></td>
<td></td>
<td></td>
<td>Bowman’s space), often detected antenatally</td>
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<td></td>
<td></td>
<td></td>
<td>• Kidneys are typically enlarged in childhood &amp; become small &amp; hypoplastic during</td>
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<td></td>
<td></td>
<td></td>
<td>adulthood</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Presence of distinct extrarenal manifestations</td>
</tr>
<tr>
<td>Renal cysts and diabetes syndrome (OMIM 137920)</td>
<td>HNF1B</td>
<td>AD</td>
<td>Renal disease (congenital anomalies of the kidney &amp; urinary tract including</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>multi-cystic hypo- or dysplastic kidneys)</td>
</tr>
<tr>
<td>Autosomal recessive polycystic kidney disease</td>
<td>PKHD1</td>
<td>AR</td>
<td>Enlarged hyperechogenic kidneys w/ poor corticomedullary differentiation on renal</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>ultrasound</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Differs from infantile NPH by more diffuse distribution of renal cysts &amp; more</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>frequent association w/fibrotic liver disease</td>
</tr>
</tbody>
</table>

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.
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

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

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>% of NPH Attributed to Pathogenic Variants in This Gene</th>
<th>Proportion of Pathogenic Variants Detected by Test Method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sequence analysis</td>
</tr>
<tr>
<td>CEP290</td>
<td>NPHP6</td>
<td>2%-3%&lt;sup&gt;6&lt;/sup&gt;</td>
<td>2%-3%&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>INVS</td>
<td>NPHP2</td>
<td>1%-2%&lt;sup&gt;6&lt;/sup&gt;</td>
<td>1%-2%&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>IQCB1</td>
<td>NPHP5</td>
<td>2%-3%&lt;sup&gt;6&lt;/sup&gt;</td>
<td>2%-3%&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>NPHP1</td>
<td>NPHP1</td>
<td>20%-25%&lt;sup&gt;10&lt;/sup&gt;</td>
<td>2%-3%&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>NPHP3</td>
<td>NPHP3</td>
<td>1%-2%&lt;sup&gt;13&lt;/sup&gt;</td>
<td>1%-2%&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td>NPHP4</td>
<td>NPHP4</td>
<td>3%-4%&lt;sup&gt;13&lt;/sup&gt;</td>
<td>3%-4%&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td>TMEM67</td>
<td>NPHP11</td>
<td>2%-3%&lt;sup&gt;6&lt;/sup&gt;</td>
<td>2%-3%&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANKS6</td>
<td>NPHP16</td>
<td>Pathogenic variants detected in 5 families w/infantile NPH &amp; 1 family w/juvenile NPH&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homozygosity for a pathogenic variant identified in a Turkish family w/NPH; heterozygosity for 4 variants found in 56 additional patients&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gene</td>
<td>Locus</td>
<td>Comment</td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>---------</td>
</tr>
<tr>
<td>CEP83</td>
<td>NPHP18</td>
<td>Homozygous or compound heterozygous pathogenic variants identified in 8 of 1,255 individuals with NPH-related ciliopathies. Early-onset NPH associated with intellectual disability and/or hydrocephalus in 4 patients.</td>
</tr>
<tr>
<td>CEP164</td>
<td>NPHP15</td>
<td>A homozygous missense pathogenic variant identified in a Saudi child with NPH and Leber congenital amaurosis. Biallelic pathogenic variants identified in 3 of 856 families with NPH-related ciliopathies. Phenotypes ranged from severe retinal dystrophy (inactivating variants) to Senior-Løken syndrome &amp; isolated NPH (hypomorphic variants).</td>
</tr>
<tr>
<td>DCDC2</td>
<td>NPHP19</td>
<td>Biallelic truncating pathogenic variants identified in 2 unrelated individuals with NPH and early-onset severe hepatic fibrosis.</td>
</tr>
<tr>
<td>GLIS2</td>
<td>NPHP7</td>
<td>Homozygous pathogenic variants identified in 3 affected members of a Canadian Oji-Cree family &amp; 1 Turkish patient with isolated NPH.</td>
</tr>
<tr>
<td>IFT172</td>
<td>NPHP17</td>
<td>Biallelic pathogenic variants identified in 12 families with short-rib thoracic dysplasia &amp; NPH &amp; in 4 families with retinitis pigmentosa-associated ciliopathies. Compound heterozygous variants found in 2 persons with Jeune asphyxiating thoracic dystrophy &amp; Mainzer-Saldino syndrome including renal features; &amp; in 1 person with renal, skeletal, &amp; ophthalmologic findings as well as pituitary hypoplasia &amp; an ectopic posterior pituitary gland.</td>
</tr>
<tr>
<td>NEK8</td>
<td>NPHP9</td>
<td>Homozygous missense pathogenic variants identified in a Kurdish child who had ESRD by age 3 years. Homozygous nonsense pathogenic variants identified in a family with a severe embryonic ciliopathy, including cystic enlargement of the kidneys.</td>
</tr>
<tr>
<td>RPGRIP1L</td>
<td>NPHP8</td>
<td>Pathogenic variants cause Joubert syndrome. Biallelic truncating variants generally cause the more severe Meckel-Gruber syndrome.</td>
</tr>
<tr>
<td>SDCCAG8</td>
<td>NPHP10</td>
<td>Biallelic pathogenic variants found in 12 families with NPH &amp; retinal degeneration (Senior-Løken syndrome &amp; Bardet-Biedl syndrome). Homozygous deletions of exons 5 to 7 have been described.</td>
</tr>
<tr>
<td>TTC21B</td>
<td>NPHP12</td>
<td>Biallelic pathogenic variants detected in 7 families with NPH with or without extrarenal features, 3 families with Jeune asphyxiating thoracic dystrophy, &amp; additional families with a NPH-related ciliopathy. Biallelic missense variants also identified in persons with familial primary focal segmental glomerulosclerosis (Huynh Cong et al 2014, Bullich et al 2017). 2 families had infantile NPH with extrarenal features.</td>
</tr>
<tr>
<td>WDR19</td>
<td>NPHP13</td>
<td>Biallelic pathogenic variants identified in families with cranioectodermal dysplasia, Jeune syndrome, Senior-Løken syndrome, &amp; isolated NPH. 8 individuals with biallelic pathogenic variants had NPH &amp; dilation of the intrahepatic bile ducts.</td>
</tr>
</tbody>
</table>
Table 2b. continued from previous page.

<table>
<thead>
<tr>
<th>Gene 1, 2</th>
<th>Locus</th>
<th>Comment 3</th>
</tr>
</thead>
</table>
| ZNF423    | NPHP14| - Homozygosity for a missense pathogenic variant identified in Turkish sibs w/ infantile NPH, cerebellar vermis hypoplasia, & situs inversus ⁷  
- Heterozygous pathogenic variants present in 2 individuals w/Joubert syndrome demonstrated (in cellular studies) a dominant negative effect on protein function. ⁷ |

ESRD = end-stage renal disease
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], Bujaikowska et al [2015]  
11. Lucas-Herald et al [2015], McInerney-Leo et al [2015]  
12. Otto et al [2008], [Frank et al 2013]  
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

<table>
<thead>
<tr>
<th>Disorder 1</th>
<th>Major Distinguishing Clinical Features 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cerebellar 3</td>
</tr>
<tr>
<td>Joubert syndrome</td>
<td>+</td>
</tr>
<tr>
<td>Bardet-Biedl syndrome</td>
<td>+</td>
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<tr>
<td>Jeune syndrome and related skeletal disorders 8</td>
<td>+</td>
</tr>
</tbody>
</table>
Table 3a. continued from previous page.

<table>
<thead>
<tr>
<th>Disorder 1</th>
<th>Major Distinguishing Clinical Features 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cerebellar 3</td>
</tr>
<tr>
<td>Meckel-Gruber syndrome 9</td>
<td>+</td>
</tr>
<tr>
<td>Senior-Løken syndrome</td>
<td>+</td>
</tr>
<tr>
<td>Leber congenital amaurosis</td>
<td>+</td>
</tr>
<tr>
<td>COACH syndrome</td>
<td>+</td>
</tr>
<tr>
<td>Oculomotor apraxia, Cogan type</td>
<td>+</td>
</tr>
</tbody>
</table>

COACH = cerebellar vermis hypoplasia, oligophrenia, ataxia, coloboma, and hepatic 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

<table>
<thead>
<tr>
<th>Disorder 1</th>
<th>NPHP-Related Genes 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joubert syndrome 3</td>
<td>NPHP1 2</td>
</tr>
<tr>
<td>Bardet-Biedl syndrome 4</td>
<td>+</td>
</tr>
</tbody>
</table>
Table 3b. continued from previous page.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>NPH-Related Genes 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NPHP1 2</td>
</tr>
<tr>
<td>Jeune syndrome &amp; related skeletal disorders 5</td>
<td>NPHP3, NPHP4, CEP290</td>
</tr>
<tr>
<td></td>
<td>RPGRIP1L, TMEM67, TTC21B</td>
</tr>
<tr>
<td></td>
<td>+, +, +, +, +, +</td>
</tr>
<tr>
<td>Meckel-Gruber syndrome 6</td>
<td>+, +, +, +, +, +</td>
</tr>
<tr>
<td></td>
<td>3%-4%, +, 17%-18%</td>
</tr>
<tr>
<td>Senior-Løken syndrome 7</td>
<td>+, +, +, +, +, +</td>
</tr>
<tr>
<td></td>
<td>4%-5%, 74%</td>
</tr>
<tr>
<td>Leber congenital amaurosis 8</td>
<td>+, +, +, +, +</td>
</tr>
<tr>
<td></td>
<td>20%, 3%-4%</td>
</tr>
<tr>
<td>COACH syndrome 9</td>
<td>+, +, +, +, +</td>
</tr>
<tr>
<td></td>
<td>4%-5%, 74%</td>
</tr>
<tr>
<td>Oculomotor apraxia, Cogan type 10</td>
<td>+, +, +, +, +</td>
</tr>
</tbody>
</table>

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

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

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 diagnosis 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. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

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
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 www.ClinicalTrialsRegister.eu 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

<table>
<thead>
<tr>
<th>Locus Name</th>
<th>Gene</th>
<th>Chromosome Locus</th>
<th>Protein</th>
<th>Locus-Specific Databases</th>
<th>HGMD</th>
<th>ClinVar</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPHP1</td>
<td>NPHP1</td>
<td>2q13</td>
<td>Nephrocystin-1</td>
<td>NPHP1 @ LOVD</td>
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</tr>
<tr>
<td>NPHP2</td>
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<td>9q31.1</td>
<td>Inversin</td>
<td>INVS @ LOVD</td>
<td>INVS</td>
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<td>NPHP3</td>
<td>3q22.1</td>
<td>Nephrocystin-3</td>
<td>NPHP3 @ LOVD</td>
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<td>-------</td>
<td>--------</td>
<td>----------------</td>
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</tr>
<tr>
<td>NPHP4</td>
<td>NPHP4</td>
<td>1p36.31</td>
<td>Nephrocystin-4</td>
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<td>1q43-q44</td>
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<td>9q22.33</td>
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</table>

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)

<table>
<thead>
<tr>
<th>OMIM Entry</th>
<th>Description</th>
</tr>
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<tr>
<td>243305</td>
<td>INVERSIN; INVS</td>
</tr>
<tr>
<td>256100</td>
<td>NEPHRONOPHTHISIS 1; NPHP1</td>
</tr>
<tr>
<td>602088</td>
<td>NEPHRONOPHTHISIS 2; NPHP2</td>
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<tr>
<td>604387</td>
<td>NEPHRONOPHTHISIS 3; NPHP3</td>
</tr>
<tr>
<td>604557</td>
<td>ZINC FINGER PROTEIN 423; ZNF423</td>
</tr>
<tr>
<td>605755</td>
<td>DOUBLECORTIN DOMAIN-CONTAINING PROTEIN 2; DCDC2</td>
</tr>
</tbody>
</table>
### Molecular Genetic 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.


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 non-allelic 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

<table>
<thead>
<tr>
<th>DNA Nucleotide Change</th>
<th>Predicted Protein Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>290-kb deletion including entire gene</td>
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<td>NM_000272</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NP_000263</td>
</tr>
<tr>
<td>c.80T&gt;A</td>
<td>p.Leu27Ter</td>
<td>NM_000272.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NP_000263.2</td>
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</table>

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.** 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.


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

<table>
<thead>
<tr>
<th>DNA Nucleotide Change</th>
<th>Predicted Protein Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.1417delG</td>
<td>p.Ala473GlnfsTer37</td>
<td>NM_014425.3</td>
</tr>
<tr>
<td>c.3125delA</td>
<td>p.Asn1042ThrfsTer64</td>
<td>NM_014425.3</td>
</tr>
<tr>
<td>c.2695C&gt;T</td>
<td>p.Arg899Ter</td>
<td>NM_014425.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NP_055240.2</td>
</tr>
<tr>
<td>c.2782C&gt;T</td>
<td>p.Arg928Ter</td>
<td>NM_014425.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NP_055240.2</td>
</tr>
</tbody>
</table>

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.** INVS encodes a 1065-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 1330 amino acids.


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

<table>
<thead>
<tr>
<th>DNA Nucleotide Change</th>
<th>Predicted Protein Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.2104C&gt;T</td>
<td>p.Arg702Ter</td>
<td>NM_153240.4, NP_694972.3</td>
</tr>
<tr>
<td>c.3824_3826delGAG</td>
<td>p.Gly1275del</td>
<td></td>
</tr>
</tbody>
</table>

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**Normal gene product.** The longest NPHP3 transcript encodes a protein of 1330 amino acids.

NPHP3:
- Contains a coiled coil domain, a tubulin-tyrosine ligase domain, and a tetratrico peptide repeat (TPR) domain which 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 1426 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**

<table>
<thead>
<tr>
<th>DNA Nucleotide Change</th>
<th>Predicted Protein Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.1972C&gt;T</td>
<td>p.Arg658Ter</td>
<td>NM_015102.4  NP_055917.1</td>
</tr>
<tr>
<td>c.2335C&gt;T</td>
<td>p.Gln779Ter</td>
<td>NM_015102.4  NP_055917.1</td>
</tr>
</tbody>
</table>

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.

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Normal gene product. *NPHP4* encodes the 1426-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];
• 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**

<table>
<thead>
<tr>
<th>DNA Nucleotide Change</th>
<th>Predicted Protein Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.1178T&gt;A</td>
<td>p.Ile393Asn</td>
<td>NM_001023570.2</td>
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<td></td>
<td>NP_001018864.2</td>
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</table>

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.

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**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.


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**

<table>
<thead>
<tr>
<th>DNA Nucleotide Change</th>
<th>Predicted Protein Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.5707A&gt;T</td>
<td>p.Glu1903Ter</td>
<td>NM_025114.3</td>
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<td></td>
<td></td>
<td>NP_079390.3</td>
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</table>

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.

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**Normal gene product.** The centromere protein CEP290 is 2479 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.


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

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>DNA Nucleotide Change</th>
<th>Predicted Protein Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>c.755T&gt;C</td>
<td>p.Met252Thr</td>
<td>NM_153704.5</td>
</tr>
<tr>
<td></td>
<td>c.1843T&gt;C</td>
<td>p.Cys615Arg</td>
<td>NP_714915.3</td>
</tr>
<tr>
<td>Modifier</td>
<td>c.958A&gt;T</td>
<td>p.Ser320Cys</td>
<td></td>
</tr>
</tbody>
</table>

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.

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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

<table>
<thead>
<tr>
<th>DNA Nucleotide Change</th>
<th>Predicted Protein Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.523T&gt;C</td>
<td>p.Cys175Arg</td>
<td>NM_032575.2</td>
</tr>
<tr>
<td>c.775+1G&gt;T</td>
<td></td>
<td>NP_115964.2</td>
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</table>

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.

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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

<table>
<thead>
<tr>
<th>DNA Nucleotide Change</th>
<th>Predicted Protein Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.685G&gt;A</td>
<td>p.Ala229Thr</td>
<td>NM_015272.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NP_056087.2</td>
</tr>
</tbody>
</table>

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.

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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

**References**

**Literature Cited**


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**Chapter Notes**

**Author Notes**
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Website: www.kouncil.nl

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