



**Next Generation Sequencing Panel for Nephronophthisis**

**Clinical Features:**

Nephronophthisis (NPHP), an autosomal recessive cystic kidney disease, is the most frequent genetic cause of renal failure in childhood or adolescence. NPHP is characterized by renal tubular atrophy and progressive interstitial fibrosis with the development of corticomedullary cysts. The onset is typically marked by polydipsia and polyuria as a result of a defect in urine concentration. NPHP eventually progresses to end stage renal disease (ESRD), though the age of onset of ESRD varies. NPHP is generally classified based on the age of onset of ESRD: infantile (around age 1), juvenile (around age 13), or adolescent (around age 19). Additional findings include small-to-normal-sized hyperechogenic kidneys with reduced corticomedullary differentiation on abdominal ultrasonography and histopathological alterations characterized by thickened or disrupted tubular basement membranes, tubular atrophy and dilation, interstitial fibrosis and occasional renal cysts. In approximately 10-15% of cases, NPHP presents with extrarenal manifestations, including retinitis pigmentosa (Senior-Loken syndrome, Bardet-Biedl syndrome, Alstrom syndrome), liver fibrosis, cerebellar vermis hypoplasia (Joubert syndrome), and multiple developmental and neurologic abnormalities (Meckel Gruber syndrome) [1].

**Molecular Genetics:**

Mutations in *NPHP1* through *NPHP12* account for approximately 30-40% of clinically diagnosed NPHP patients, with the vast majority of mutations being detected in *NPHP1* (approximately 30%) [2]. The genes responsible for NPHP13, 14, 15, 16, 18 and 19 are more recently described and prevalence of mutations in these genes in NPHP patients is not yet known. Some genotype/phenotype correlations have been elucidated. Mutations in *NPHP2* typically cause infantile NPHP and affected patients may have slightly enlarged kidneys that resemble kidneys from PKD patients [2]. Mutations in *NPHP3*, 4 and 5 have been seen in patients with juvenile and adolescent NPHP. It is also important to note that mutations in a specific NPHP gene do not always correlate with a specific genotype/phenotype. Mutations in an NPHP gene can give rise to a broad spectrum of phenotypes from NPHP with no extrarenal abnormalities through to Joubert syndrome or Meckel Gruber syndrome [2]. The severity of phenotype may be linked to the type of mutation detected (i.e truncating mutations associated with a more severe disease, where missense mutations are associated with more mild disease) [2]. Additional studies are necessary to confirm this hypothesis.

A homozygous frameshift and splicing mutation in *XPNPEP3* was identified in two unrelated consanguineous families with nephronophthisis-like nephropathy [3]. Affected individuals had renal imaging consistent with NPHP, in addition to other extra-renal manifestations.

Biallelic mutations in *IFT172* were identified in 14 individuals in 12 families who shared a asphyxiating thoracic dystrophy, Mainzer-Saldino syndrome, or Joubert syndrome phenotype including skeletal abnormalities, nephronophthisis and liver and eye involvement. Most affected individuals had progressive nephronophthisis with progressive renal insufficiency in childhood and end stage renal disease by age 20 [4].

**Inheritance:**

Generally speaking NPHP is considered to be an autosomal recessive condition. There are several reported cases of a oligogenic mode of inheritance where mutations in more than one NPHP gene have been identified in patients with NPHP [5].

*Our Nephronophthisis Sequencing Panel and Nephronophthisis Deletion/Duplication Panel include analysis of the 20 genes listed below.*

<b>Nephronophthisis Sequencing Panel</b>				
<i>NPHP1</i>	<i>NPHP4</i>	<i>RPGRIP1L</i> (NPHP8)	<i>TTC21B</i> (NPHP12)	<i>ANKS6</i> (NPHP16)
<i>IFT172</i>	<i>IQCB1</i> (NPHP5)	<i>NEK8</i> (NPHP9)	<i>WDR19</i> (NPHP13)	<i>CEP83</i> (NPHP18)
<i>INVS</i> (NPHP2)	<i>CEP290</i> (NPHP6)	<i>SDCCAG8</i> (NPHP10)	<i>ZNF423</i> (NPHP14)	<i>DCDC2</i> (NPHP19)
<i>NPHP3</i>	<i>GLIS2</i> (NPHP7)	<i>TMEM67</i> (NPHP11)	<i>CEP164</i> (NPHP15)	<i>XPNPEP3</i> (NPHP11)

**Test methods:**

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp.

**Nephronophthisis Sequencing Panel (20 genes sequencing)**

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$2000
CPT codes:	81407
Turn-around time:	8 weeks

**Note: We cannot bill insurance for the above test.**

**Nephronophthisis Deletion/Duplication Panel (20 genes deletion/duplication)**

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$1545
CPT codes:	81407
Turn-around time:	6 weeks

**Results:**

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

**For more information about our testing options, please visit our website at [dnatesting.uchicago.edu](http://dnatesting.uchicago.edu) or contact us at 773-834-0555**

**References:**

1. Hoff, S., et al., *ANKS6 is a central component of a nephronophthisis module linking NEK8 to INVS and NPHP3*. Nat Genet, 2013. **45**(8): p. 951-6.
2. Hurd, T.W. and F. Hildebrandt, *Mechanisms of nephronophthisis and related ciliopathies*. Nephron Exp Nephrol, 2011. **118**(1): p. e9-14.
3. O'Toole, J.F., et al., *Individuals with mutations in XPNPEP3, which encodes a mitochondrial protein, develop a nephronophthisis-like nephropathy*. J Clin Invest, 2010. **120**(3): p. 791-802.
4. Halbritter, J., et al., *Defects in the IFT-B component IFT172 cause Jeune and Mainzer-Saldino syndromes in humans*. Am J Hum Genet, 2013. **93**(5): p. 915-25.
5. Hoefele, J., et al., *Evidence of oligogenic inheritance in nephronophthisis*. J Am Soc Nephrol, 2007. **18**(10): p. 2789-95.

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