

## Nephronophthisis: *NPHP1* Gene Sequencing

**Test Code:** WY

**Turnaround time:** 4 weeks

**CPT Codes:** 81479 x1

### Condition Description

Nephronophthisis, an autosomal recessive cystic kidney disease, is the most frequent monogenic cause of renal failure in childhood. There are four forms of nephronophthisis caused by mutations in four different genes. Clinically, there is a statistically different age at onset at end-stage renal disease: terminal renal failure develops at median ages of 13 years, 1 year, 19 years, and 11-34 years in *NPHP1*, *NPHP2*, *NPHP3*, and *NPHP4*. Hallmarks of familial nephronophthisis are tubular basement membrane disruption, interstitial lymphohistiocytic cell infiltration, and development of cysts at the corticomedullary border of the kidneys. The histology in later stages of NPH always merges into a chronic sclerosing tubulointerstitial nephropathy, which is found in chronic renal failure of all origins.

#### *Nephronophthisis 1*

Clinical features of familial juvenile nephronophthisis (*NPHP1*) include anemia, polyuria, polydipsia, isosthenuria, and death in uremia. Hypertension and proteinuria are conspicuous in their absence. Excessive urinary loss of sodium accounts for the rarity of hypertension. Symmetrical destruction of the kidneys involving both tubules and glomeruli (which were hyalinized) is observed. The age at death ranges from about 4 to 15 years. This is the second most common cause of childhood chronic renal failure. 65 to 75% of *NPHP1* patients exhibit large homozygous deletions in the 2q13 region that includes the *NPHP1* gene.

Joubert syndrome is an autosomal recessive multisystem disease characterized by cerebellar vermis hypoplasia with prominent superior cerebellar peduncles (resulting in the 'molar tooth sign', or MTS, on axial MRI), mental retardation, hypotonia, irregular breathing pattern, and eye movement abnormalities. Some individuals with JS have retinal dystrophy and/or progressive renal failure characterized as nephronophthisis. The disorder in such patients is referred to as cerebellooculorenal syndrome, or CORS. Individuals with a mild form of JS have been shown to have a homozygous deletion of the *NPHP1* gene identical, by mapping, to that in subjects with nephronophthisis alone. Senior-Loken syndrome, the association of nephronophthisis with autosomal recessive retinitis pigmentosa, has been observed in patients with homozygous deletion of the *NPHP1* gene.

For patients with suspected familial juvenile nephronophthisis, deletion/duplication analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by deletion/duplication analysis, sequence analysis is appropriate.

[Click here](#) for the OMIM summary on this condition.

### Genes

[NPHP1](#)

### Indications

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of familial juvenile nephronophthisis in an individual in whom deletion/duplication analysis was negative
- Carrier testing in adults with a family history of familial juvenile nephronophthisis in whom deletion/duplication analysis was negative

### Methodology

**Next Generation Sequencing:** In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

### Detection

Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Analytical Sensitivity: ~99%

### Specimen Requirements

**Submit only 1 of the following specimen types**

**Type: Saliva**

**Specimen Requirements:**

Oragene™ Saliva Collection Kit

Oragene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot

provide a blood sample.

**Specimen Collection and Shipping:**

Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

**Type: Whole Blood (EDTA)****Specimen Requirements:**

EDTA (Purple Top)

Infants and Young Children ( 2 years of age to 10 years old: 3-5 ml

Older Children & Adults: 5-10 ml

Autopsy: 2-3 ml unclotted cord or cardiac blood

**Specimen Collection and Shipping:**

Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

**Type: DNA, Isolated****Specimen Requirements:**

Microtainer

8µg

Isolation using the Perkin Elmer™ Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

**Specimen Collection and Shipping:**

Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

**Related Tests**

- Deletion/duplication analysis of the *NPHP1* gene by CGH array is available and is recommended before sequence analysis.
- [Custom diagnostic mutation analysis](#) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.