Nephronophthisis: **NPHP1, INVS, NPHP3, and NPHP4** Gene Deletion/Duplication Panel

**Test Code:** WX  
**Turnaround time:** 2 weeks  
**CPT Codes:** 81228 x1, 81405 x1

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**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 respectively. 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.

**Nephronophthisis 2**

In one study, individuals with infantile nephronophthisis (NPHP2) presented within the first months of life with severe renal failure and acidosis, which could be associated with hypertension and/or polyuria and/or severe cholestasis liver disease. A renal biopsy, performed in all patients, showed similar features characterized by a diffuse chronic tubulointerstitial nephritis and particularly by the presence of microcystic dilatation of proximal tubules and Bowman space. Progression of the renal disease was extremely rapid and patients can reach end-stage renal failure before the age of 2 years (11 to 22 months).

In another study, phenotypic presentation ranged from a Potter-like syndrome to hyperechogenic kidneys, renal insufficiency, hypertension, and hyperkalemia. Affected individuals showed rapid deterioration of kidney function, leading to end-stage renal failure within 3 years. The manifestations range from prenatal fetal oliguria and oligohydramnios resulting in postnatal respiratory failure and death to postnatal onset of disease later than 30 months of age. None of the postnatally diagnosed patients had a history of either oligohydramnios or neonatal respiratory symptoms. All affected individuals developed anemia, hyperkalemic metabolic acidosis, and increased serum creatine. None of the affected subjects had polyuria, polydypsia, or associated ocular or hepatic complications. The specific clinical features of this disease are its early onset and rapid progression to end-stage renal failure. Pathologically, it differs from later-onset nephronophthisis by the absence of medullary cysts and thickened tubular basement membranes and by the presence of cortical microcysts. NPHP2 is caused by mutations in the INVS gene (also known as NPHP2) (9q31). The protein product of the INVS gene, inversion, has been shown to interact with that of the NPHP1 gene, nephrocystin.

**Nephronophthisis 3**

In one study, most individuals with adolescent nephronophthisis (NPHP3) suffered from anemia when they first came to medical attention. Onset of terminal renal failure occurred significantly later (median age, 19 years) than in juvenile nephronophthisis (median age, 13.1 years). Histologic findings in adolescent nephronophthisis are generally not distinguishable from those of juvenile nephronophthisis. Renal pathology in adolescent NPHP is characterized by alterations of tubular basement membranes, tubular atrophy and dilatation, sclerosing tubulointerstitial nephropathy, and renal cyst development predominantly at the corticomedullary junction.

Mutations in the NPHP3 gene (3q22) cause NPHP3. Mutations have been found in NPHP3 in families with isolated nephronophthisis and in families with nephronophthisis with associated hepatic fibrosis or tapetoretinal degeneration. Studies have shown that the protein product of the NPHP3 gene interacts with the protein products of NPHP1 and INVS.
Nephronophthisis 4

Mutations in the *NPHP4* gene (1p36) cause nephronophthisis 4 (NPHP4), which has also been referred to as juvenile nephronophthisis. In these families, end-stage renal disease commenced within a wide age range, 11 to 34 years. The NPHP4 protein has been shown to interact with the NPHP1 protein. Mutations in *NPHP4* have been associated with Senior-Loken syndrome-4, the association of nephronophthisis with autosomal recessive retinitis pigmentosa.

Testing is available for each gene individually or as a panel.

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

References:

- Click here for the OMIM summary on Nephronophthisis 1.
- Click here for the OMIM summary on Nephronophthisis 2.
- Click here for the OMIM summary on Nephronophthisis 3.
- Click here for the OMIM summary on Nephronophthisis 4.

**Indications**

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of nephronophthisis in individuals who have tested negative for sequence analysis
- Carrier testing in adults with a family history of nephronophthisis who have tested negative for sequence analysis

**Methodology**

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

Please note that a “backbone” of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient's phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

**Detection**

Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

**Specimen Requirements**

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

- In EDTA (purple top) tube:
  - Infants (2 years): 3-5 ml
  - Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

- OraGene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Special Instructions**
Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

Related Tests

- Sequencing analysis of the \textit{NPHP1}, \textit{INVS}, \textit{NPHP3}, and \textit{NPHP4} genes is available as a panel or individually, and is required before deletion/duplication 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.