Nephronophthisis: \textit{NPHP3} Gene Deletion/Duplication

\textbf{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, interstitiallymphohistiocytic cell infiltration, and development of cysts at the corticomedullary border of the kidneys. The histology in later stages of NPHalways merges into a chronic sclerosing tubulointerstitial nephropathy, which is found in chronic renal failure of all origins.

\textit{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 juvenilene nephronophthisis (median age, 13.1 years). Histologic findings in adolescent nephronophthisis are generally not distinguishable from those of juvenilene 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 \textit{NPHP3} gene (3q22) cause NPHP3. Mutations have been found in \textit{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 \textit{NPHP1} and \textit{NPHP2}.

\textbf{Genes}

\textit{NPHP3}

\textbf{Indications}

This test is indicated for:

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

\textbf{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.

\textbf{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.

\textbf{Specimen Requirements}

Submit only 1 of the following specimen types

\textbf{Type: DNA, Isolated}

\textbf{Specimen Requirements:}

- Microtainer
- 3µg

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

\textbf{Specimen Collection and Shipping:}

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

\textbf{Type: Whole Blood (EDTA)}

\textbf{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 24 hours of collection. Do not refrigerate or freeze.

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 NPHP3 gene is available and is required before deletion/duplication 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.