Nephronophthisis: \textit{NPHP3} Gene Sequencing

\textbf{Test Code:} SNPH3  \\
\textbf{Turnaround time:} 4 weeks  \\
\textbf{CPT Codes:} 81479 x1

\section*{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 \textit{NPHP1}, \textit{NPHP2}, \textit{NPHP3}, and \textit{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 \textit{NPHP1} always 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 (\textit{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 \textit{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 \textit{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 \textit{NPHP3} gene interacts with the protein products of \textit{NPHP1} and \textit{NPHP2}.

For patients with suspected adolescent 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.

\section*{Genes}

\textit{NPHP3}

\section*{Indications}

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of adolescent nephronophthisis
- Carrier testing in adults with a family history of adolescent nephronophthisis

\section*{Methodology}

\textbf{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.

\section*{Detection}

\textbf{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.

\textbf{Analytical Sensitivity:} \textasciitilde 99%

\section*{Specimen Requirements}

\textit{Submit only 1 of the following specimen types}

\textbf{Type: DNA, Isolated}

\textbf{Specimen Requirements:}
- Microtainer
- 8\mu g
- 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.

**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: 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.

**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**
- Deletion/duplication analysis of the *NPHP3* genes by CGH array is available for those individuals in whom sequence analysis is negative.
- 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.