

Nephronophthisis and Senior-Loken syndrome via *NPHP3* Gene Sequencing (Test #653)

Brief Description of Clinical Features: Nephronophthisis (NPH) is the most common genetic cause of progressive renal failure in children and young adults. NPH is characterized by polyuria, growth retardation and progressive deterioration of renal function with normal or slightly reduced kidney size (Hildebrandt et al., Nat Genet 17:149-153, 1997; Hildebrandt et al. J Am Soc Nephrol 20:23-35, 2009). Nephronophthisis Type 3 (NPH3) (OMIM 604387) results in chronic renal failure in adolescents (Omran et al. Am. J. Hum. Genet 66:118-127, 2000; Olbrich et al. Nat Genet 34:455-459, 2003). However, NPH3 has been also reported in five infants before 5 years of age (Tory et al. Kidney Int 75:839-847, 2009). Of note, a few cases of NPH3 have been associated with tapetoretinal degeneration known as Senior-Loken syndrome (OMIM# 606995) (Bergmann et al. A J Hum Genet 82:959-970, 2008).

Genetics: NPH3 is inherited in an autosomal recessive manner. Mutations in the *NPHP3* gene cause NPH3 (Olbrich et al. 2003). *NPHP3* encodes a protein called nephrocystin-3. It has been indicated that nephrocystin-3 interacts with nephrocystin-1 and nephrocystin-4 (products of *NPHP1* and *NPHP4* genes respectively). Nephrocystin-3 may also have a role in microtubule regulation in monocilia (Olbrich et al. 2003). A mix of nonsense, frameshift, splicing and missense mutations have been reported in *NPHP3* (Tory et al. 2009; Olbrich et al. 2003). Nephronophthisis exhibits locus heterogeneity. Nine NPH genes have been identified to date (*NPHP1*, *INVS/NPHP2*, *NPHP3*, *NPHP4*, *IQCB1/NPHP5*, *CEP260/NPHP6*, *GLIS2/NPHP7*, *RPGRIP1L/NPHP8* and *NEK8/NPHP9*) (Hildebrandt et al. 2009).

Description of This Particular Test: As required, this test involves bidirectional sequencing using genomic DNA of all the 27 coding exons (exons 1-27) of the *NPHP3* gene. The full coding region of each exon plus ~50 bp of flanking non-coding DNA on each side are sequenced. We will also perform sequencing of any single exon or pair of exons for family members of patients with known mutations and to confirm previous research results (\$190-340 charge).

Reference Sequences: Genomic: NC_000003.10 mRNA: NM_153240.3 Protein: NP_694972.3 (CCDS 3078.1)

Indications for Test: Candidates for this test are patients with symptoms consistent with adolescent or juvenile NPH and the family members of patients who have known mutations. Conclusive connections between clinical features and individual mutated genes have not yet been made.

Sensitivity of Test: Mutations in *NPHP3* gene are estimated to cause approximately ~1% of the NPH cases (Hildebrandt et al. 2009).

Turn Around Time: Maximum of 40 calendar days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Prices: Sequencing of the *NPHP3* gene \$ 1320

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x27	83898 \$420	Sequencing x27	83904 \$ 630
Separation x1	83894 \$ 80	Interpretation/Report x1	83912 \$ 120

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

Contact: Dr. Keith Nykamp, keith.nykamp@preventiongenetics.com, www.preventiongenetics.com