

Nephronophthisis via *INVS/NPHP2* Gene Sequencing (Test #652)

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. Infantile or Type 2 Nephronophthisis (NPH2) (OMIM 602088) causes chronic renal failure in infants and children before 5 year of age. NPH2 is marked by the kidney phenotype of NPH along with kidney cysts (Otto et al. Nat Genet 34:413-420, 2003; Hildebrandt et al. J Am Soc Nephrol, 20:23-35, 2009). NPH2 features may also include tubular basement membrane disruption, renal interstitial fibrosis and moderate renal enlargement with or without *situs inversus* (Okada et al. Clin Nephrol 69:135-141, 2008). Additionally, NPH2 has been reported in an adolescent patient who had renal function beyond infancy with *situs inversus* (Okada et al. 2008).

Genetics: NPH2 is inherited in an autosomal recessive manner. Mutations in the *INVS* gene (also called *NPHP2*) cause NPH2 (Otto 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). *INVS* gene encodes the inversin protein, which interacts with nephrocystin-1 (product of the *NPHP1* gene) and β -tubulin in primary cilia and basal bodies (Otto et al. 2003). Also, it has been reported that inversin protein has an important role in planar cell polarity signaling (Simons et al. Nat Genet 37:537-543, 2005). About 13 causative mutations, a mix of nonsense, frameshift, splicing and missense, have been reported (Otto et al. 2003; Tory et al. Kidney Int 75:839-847, 2009).

Description of This Particular Test: As required this test involves bidirectional sequencing using genomic DNA of all 16 coding exons (exons 2-17) of the *INVS/NPHP2* 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_000009.10** mRNA: **NM_014425.2** Protein: **NP_055240.2 (CCDS 6746.1)**

Indications for Test: Candidates for this test are patients with symptoms consistent with NPH2 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 *INVS/NPHP2* gene are estimated to cause the majority of NPH2 and approximately ~2% of all NPH cases (Hildebrandt et al. 2009).

Turn Around Time: Maximum of 40 calendar days.

Specimen Requirements: See page 4 of the Requisition Form.

Prices: **Sequencing of *INVS/NPHP2* gene** **\$ 940**

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x17	83898 \$280	Sequencing x17	83904 \$ 420
Separation x1	83894 \$ 70	Interpretation/Report x1	83912 \$ 100

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

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