

Nephronophthisis via *NPHP4* Gene Sequencing (Test #654)

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(1):23-35, 2009). Nephronophthisis Type 4 (NPH4) (OMIM 606966) results in chronic renal failure in children after 5 years of age and in adolescents (Mollet et al. Nat Genet 32:300-305, 2002; Otto et al. Am J Hum Genet 71:1161-1169, 2002).

Genetics: NPH4 is inherited in an autosomal recessive manner, and is caused by mutations in the *NPHP4* gene (Mollet et al. 2002; Otto et al. 2002). *NPHP4* encodes the protein nephrocystin-4, which is localized to primary cilia, basal bodies, centrosomes and cortical actin cytoskeleton. It has been reported that nephrocystin-4 interacts with nephrocystin-1 and nephrocystin-3 (products of *NPHP1* and *NPHP3* genes respectively) and might have a role in cilia function and or maintenance (Mollet et al. 2002; Otto et al. 2002; Olbrich et al. Nat Genet 34:455-459, 2003; Hildebrandt et al. 2009). A mix of nonsense, frameshift, splicing and missense mutations have been reported in *NPHP4* (Mollet et al. 2002; Otto et al. 2002). Nephronophthisis exhibits locus heterogeneity. Nine NPH genes have been identified (*NPHP1*, *INVS/NPHP2*, *NPHP3*, *NPHP4*, *IQCBI/NPHP5*, *CEP260/NPHP6*, *GLIS2/NPHP7*, *RPGRIP1L/NPHP8* and *NEK8/NPHP9*) (Hildebrandt et al. 2009).

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of all the 29 coding exons (exon 2-30) of the *NPHP4* gene. The full coding region of each exon plus ~50 bp of flanking non-coding DNA on each side are sequenced. As requested, 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_000001.9 mRNA: NM_015102.2 Protein: NP_055917.1

Indications for Test: Candidates for this test are patients with symptoms consistent with juvenile or adolescent 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 *NPHP4* are estimated to cause approximately ~2% 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 *NPHP4* gene \$ 1350

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x28	83898 \$440	Sequencing x28	83904 \$ 640
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)

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