

Nephronophthisis-Like Nephropathy-1 (NPHPL1) via *XPNPEP3* Gene Sequencing (Test #658)

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-like nephropathy-1 (NPHPL1) patients develop a renal disease reminiscent of nephronophthisis within the first three decades of life (O’Toole et al. J Clin Invest 120:791-802, 2010). Renal biopsies from NPHPL1 patients showed characteristic features of nephronophthisis, such as thickening, splitting, and attenuation of the tubular basement membrane, atrophic tubules, and mild interstitial fibrosis, while renal ultrasound revealed increased echogenicity and cysts (O’Toole et al. 2010). Extrarenal features of NPHPL1 include hypertension, essential tremor, high frequency sensorineural hearing loss, and arachnoid cysts on brain imaging. In addition, severe cases of NPHPL1 might develop a mitochondrial disorder with isolated complex I deficiency activity in muscle, seizures, mental retardation, hypertrophic dilated cardiomyopathy and chronic pancreatitis with pancreatic cysts or hepatic involvement (O’Toole et al. 2010).

Genetics: NPHPL1 is inherited in an autosomal recessive manner. Mutations in the *XPNPEP3* gene cause NPHPL1 (O’Toole et al. 2010). *XPNPEP3* gene encodes a mitochondrial protein known as X-prolyl aminopeptidase 3 (XPNPEP3), which belongs to a family of X-prolyl aminopeptidases that utilize a metal cofactor and remove the N-terminal amino acid from peptides with a proline residue in the penultimate position (Ersahin et al. Arch Biochem Biophys 435:303-310, 2005). XPNPEP3 localizes to the mitochondria of the renal cells, yet it is predicted to have a cilia-related function. Biochemical studies demonstrated that several ciliary proteins are likely XPNPEP3 substrates (Ersahin et al. 2005; O’Toole et al. 2010). A frameshift mutation and a splicing mutation within the *XPNPEP3* gene have been reported (O’Toole et al. 2010).

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of the 10 coding exons (exons 1-10) of the *XPNPEP3* gene. The full coding region of each exon plus ~50 bp of flanking non-coding DNA on each side are sequenced. As indicated, we will also perform sequencing of any single exon (Test #100) or pair of exons (Test #200) for family members of patients with known mutations and to confirm previous research results (\$190-340 charge).

Reference Sequences: Genomic: **NC_000022.10** mRNA: **NM_022098.2** Protein: **NP_071381.1 (CCDS 14007.1)**

Indications for Test: Candidates for this test are patients with symptoms consistent with nephronophthisis-like nephropathy-1 and family members of patients who have known *XPNPEP3* mutations.

Sensitivity of Test: Sensitivity of this test is currently unknown.

Turnaround 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 *XPNPEP3* gene** **\$ 690**

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x11	83898 \$ 190	Sequencing x11	83904 \$ 280
Separation x1	83894 \$ 40	Interpretation/Report x1	83912 \$ 110

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

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