

Nephronophthisis and Joubert Syndrome via *NPHP1* Gene Sequencing (Test #651)

Brief Description of Clinical Features: Juvenile or Type 1 Nephronophthisis (NPH1) (OMIM 256100) is the most common inherited cause of chronic renal failure in children. NPH1 is characterized by polyuria, growth retardation and progressive deterioration of renal function during childhood or adolescence (Hildebrandt et al., Nat Genet 17:149-153, 1997; Hildebrandt et al., J Am Soc Nephrol 20:23-35, 2009).

Joubert Syndrome (JS) (OMIM 213300, 609583) is marked by: ataxia, hypotonia, abnormal eye movements, apraxia, neonatal respiratory anomalies, mental retardation, agenesis/hypoplasia of the cerebellar vermis and a brain malformation known as the "molar tooth sign" (MTS) on cranial MRI. MTS is considered to be the most characteristic diagnostic feature. Some JS patients develop retinal dystrophy and/or progressive renal failure. For more information, see Parisi and Glass (Gene Reviews, www.genetests.org, 2007).

Genetics: NPH1 and JS are both inherited in an autosomal recessive manner. It has been documented that mutations in the *NPHP1* gene may cause both NPH1 and JS (Hildebrandt et al., Nat Genet 17:149-53, 1997; Saunier et al. Am J Hum Genet 66:778-789, 2000; Heninger et al. Am J Kidney Dis 37:1131-1139, 2001; Parisi et al. Am J Hum Genet 75:82-91, 2004). Nephronophthisis (NPH) exhibits locus heterogeneity; nine NPH genes have been identified (*NPHP1*, *INV/NPHP2*, *NPHP3*, *NPHP4*, *NPHP5/IQCB1*, *CEP260/NPHP6*, *NPHP7/GLIS2*, *RPGRIP1L/NPHP8* and *NEK8/NPHP9*) (Hildebrandt et al., J Am Soc Nephrol 20:23-35, 2009). JS likewise have also been linked to mutations in the *AH11*, *CEP290*, *TMEM67/MKS3*, *RPGRIP1L*, *CC2D2A*, *INPP5E*, *ARL13B* and *NPHP1* genes. PreventionGenetics performs tests for all of these genes.

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of all the 20 coding exons (exons 1-20) of the *NPHP1* 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_000002.10 mRNA: NM_000272. Protein: NP_000263.2 (CCDS 2086.1)

Indications for Test: Candidates for this test are patients with symptoms consistent with NPH1 or JS 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: Approximately 2/3rds of NPH1 patients have homozygous deletions of *NPHP1* (Heninger et al. 2001), and roughly 2% of JS patients have homozygous deletions of *NPHP1* (Parisi and Glass 2007). Other mutations in *NPHP1* gene contribute approximately 3% of the NPH1 cases. PreventionGenetics offers a separate PCR test for homozygous *NPHP1* deletions (Test #275).

Turn Around Time: Maximum of 40 calendar days.

SPECIMEN REQUIREMENTS: See page 4 of the Requisition Form.

Prices:	Sequencing of the <i>NPHP1</i> gene	\$ 1,090
CPT Codes:		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x20	83898 \$330	Sequencing x20 83904 \$ 510
Separation x1	83894 \$ 70	Interpretation/Report x1 83912 \$ 110

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

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