

***NPHP1* Homozygous Deletion Testing for Joubert Syndrome and Nephronophthisis (Test #275)**

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.

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: JS and NPH1 are both inherited in an autosomal recessive manner. Researchers in several laboratories have identified ~290 kb deletions of the *NPHP1* gene and surrounding DNA on chromosome 2 as a cause of both disorders (see 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). JS has also been linked to mutations in the *AH11*, *CEP290*, and *MKS3* genes (see PreventionGenetics Test Descriptions for *AH11*, *CEP290* and *MKS3* tests). NPH likewise exhibits locus heterogeneity (Hildebrandt and Otto Nat Reviews Genet 6:928-940, 2005).

Description of This Particular Test: This particular test involves amplification of 5 sequences within the commonly deleted 290 kb region that encompasses the *NPHP1* gene (Heninger et al. 2001) along with 2 sequences that flank this region and 2 control sequences on the sex chromosomes. 3 of the markers are within the *NPHP1* gene. The 9 markers are amplified in one multiplex PCR reaction. Homozygous deletions of the 290 kb region are detected by absence of expected amplified DNA products. Some smaller homozygous deletions may also be detected. Because 6 of the 7 sequences from chromosome 2 have length polymorphism (mostly microsatellites), the test will also usually rule out *carriers* of the deletion.

To support research and because development of this test was partially funded by the NIH, a completed Clinical Feature Checklist, which is available from our web site, must accompany each test requisition for JS patients. Checklists are not required for carrier testing or NPH patients.

Indications for Test: Candidates for this test are patients with symptoms consistent with NPH1 and JS and the family members of patients who have known mutations. Before testing, JS patients should first have a baseline neurological examination and brain MRI; the MTS should be present. In addition to this test for deletions, PreventionGenetics also offers sequencing tests for *AH11* and *CEP290*. These three tests may be requisitioned in any combination or order.

Sensitivity of Test: From the literature, it appears that roughly 2% of JS patients will have homozygous deletions of *NPHP1* (Parisi and Glass 2006). Approximately 2/3rds of NPH patients have homozygous deletions of *NPHP1* (Heninger et al. 2001).

Turn Around Time: Maximum of 40 days.

Joubert Syndrome Foundation: PreventionGenetics is working closely with the Joubert Syndrome Foundation (www.joubertsyndrome.org) to implement this test. The JSF web site contains DNA testing information for patients.

SPECIMEN REQUIREMENTS: See bottom of page two of the Requisition Form.

Prices: **NPHP1 Deletion Testing** **\$ 290**

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x2	83898	\$ 50	Separation	83894	\$ 90
Interpretation/Report	83912	\$ 80			

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