

Joubert Syndrome Testing via *AHII* Gene Sequencing

Brief Description of Clinical Features: Joubert syndrome (JS) (OMIM 213300) 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. JS patients have substantial phenotypic variation. Some JS patients develop retinal dystrophy and/or progressive renal failure. For more information, see Parisi and Glass (Gene Reviews, www.genetests.org, 2006).

Genetics: JS is inherited in an autosomal recessive manner. Researchers in several laboratories have identified mutations in the *AHII* gene as a cause of JS. *AHII* has 28 exons. The coding region begins in exon 3. About 40 different causative mutations have been identified in the *AHII* gene; none are particularly frequent. Causative mutations are mostly nonsense and frameshift, with some splicing and missense. Other cases of JS have also been linked to mutations in the *CEP290*, *MKS3* and *NPHP1* genes. PreventionGenetics performs tests for all of these genes.

Description of This Particular Test: This particular test involves bidirectional DNA sequencing of all *AHII* gene coding exons along with ~50 bases of non coding flanking DNA on each side. The test has two tiers. The first tier consists of the 7 exons (6, 7, 9, 11, 13, 14, 15) in which the great majority of causative mutations (~85%) have been reported in the literature. If less than two likely causative mutations are found in the first tier, then (and only then) testing continues with the second tier consisting of sequencing of the remaining 19 coding exons. We will also perform sequencing of any single exon or pair of exons in this gene for family members of patients with known mutations and to confirm research results (\$190-340 charge).

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

Indications for Test: Candidates for this test are patients with symptoms consistent with JS and the family members of patients who have known mutations. Before testing, patients should first have a baseline neurological examination and brain MRI. If the molar tooth sign is present and other symptoms of JS are present, then genetic testing is indicated.

Sensitivity of Test: The prevalence of JS is approximately 1 in 100,000. From results reported in the literature, we estimate that about 12% of JS patients with clear clinical signs will yield positive results with this test.

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 Requisition Form.

Prices:	Tier 1 Sequencing of <i>AHII</i> Exons 6, 7, 9, 11, 13, 14, 15	\$ 440
	Tier 2 Sequencing of the remaining 19 <i>AHII</i> Exons	\$ 1040
	Tiers 1 and 2 Combined	\$ 1390

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x27	83898	\$ 450	Sequencing x27	83904	\$ 720
Separation	83894	\$ 40	Interpretation/Report	83912	\$ 110

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/09) (CAP#: 7185561, AU ID: 1407125 expires 12/20/08)

Contact for info: Dr. Marwan Tayeh, marwan.tayeh@preventiongenetics.com, www.preventiongenetics.com