

Joubert Syndrome Sequential Evaluation via *AHII*, *CEP290*, *MKS3* and *NPHP1* Gene Testing

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. For more information, see Parisi and Glass (Gene Reviews, www.genetests.org, 2006).

Genetics: JS is inherited in an autosomal recessive manner. To date, mutations in four genes: *AHII*, *CEP290*, *MKS3* and *NPHP1* have been identified as causative for JS. Additional JS genes will likely be identified by researchers in coming years.

Description of This Particular Test: PreventionGenetics currently offers individual tests for *AHII*, *CEP290*, *MKS3* and *NPHP1*. See the individual gene Test Descriptions from our web site for details. This particular test involves sequential, tiered, economical testing of all four genes. Tier 1 begins with sequencing of the 7 exons in *AHII* and the 12 exons in *CEP290* in which about 85% of the causative mutations in these two genes have been reported. If two likely causative mutations are found, testing stops. If one likely causative mutation is found in either gene, then testing continues with sequencing of the remaining exons in that gene. If no causative mutations are found in Tier 1, then testing continues with Tier 2 which consists of sequencing of the remaining 19 coding *AHII* exons, all 28 of the *MKS3* exons, and testing for the common deletion of the *NPHP1* gene. Tier 3 consists of sequencing of the remaining 41 *CEP290* exons and is performed only upon specific request. As with all clinical testing at PreventionGenetics, the goal here is to provide the most clinically useful information at the lowest possible cost. The 3 Tiers may be ordered separately or in any combination.

Because of the multiple JS genes, PreventionGenetics also offers linkage analysis for this disorder. Linkage analysis is appropriate if the family has multiple affected individuals or if the affected child is suspected of being the result of a consanguineous mating. Linkage analysis involves testing of 2-3 highly informative STRPs at each of the known genes. Please inquire if you would like to pursue linkage analysis prior to one or more of the individual gene tests.

Indications for Test: Candidates for this test are patients with symptoms consistent with JS. Before testing, patients should first have a baseline neurological examination and brain MRI to confirm presence of the molar tooth sign.

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.

Sensitivity of Test: From results reported in the literature, we estimate that roughly 12% of JS patients will give a positive *AHII* test, 10% a positive *CEP290* test, 10% a positive *MKS3* test, and 2% a positive *NPHP1* 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 page two of the Requisition Form.

Prices: Tier 1 Sequencing of 7 <i>AHII</i> and 12 <i>CEP290</i> Exons	\$ 940
Sequencing of the remaining <i>AHII</i> or <i>CEP290</i> Exons	\$990 or 1640
Tier 2 Sequencing of the remaining <i>AHII</i> Exons, all <i>MKS3</i> Exons and <i>NPHP1</i> deletion test	\$ 2390
Tier 3 Sequencing of the remaining 41 <i>CEP290</i> Exons	\$ 1640

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x17	83898	\$ 280	Sequencing x17	83904	\$ 460
Separation	83894	\$ 40	Interpretation/Report	83912	\$ 90

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