

Joubert Syndrome Testing via *CEP290* Gene Sequencing

Sequential (Standard) Test – Test #271; Tier 1 Only – Test #272; Tier 2 Only – Test #273

Brief Description of Disorder: Joubert syndrome (JS) (OMIM 213300) is marked by ataxia, hypotonia, abnormal ocular 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. JS patients have substantial phenotypic variation. 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, 2006).

Genetics: JS is inherited in an autosomal recessive manner. Researchers to date have identified mutations in the *CEP290*, *AH11*, *MKS3* and *NPHP1* genes as causes of JS. Additional genes are likely to be identified. *CEP290* is a large (54 exon), relatively newly characterized gene (Sayer et al. Nat Genet 38:674-681, 2006; Valente et al. Nat Genet 38:623-625, 2006). Almost all causative mutations have been either nonsense or frameshift. Patients with ocular and renal manifestations seem more likely to have mutations in *CEP290*.

Description of This Particular Test: This particular test involves bidirectional DNA sequencing of all *CEP290* gene coding exons. The test is performed in two Tiers. Tier 1 involves sequencing of the 12 exons in which about 85% of causative mutations have been reported (exons 17, 28, 31, 34, 36, 37, 40, 41, 42, 44, 46, and 54). If two likely causative mutations are found in Tier 1, testing stops. Otherwise testing continues with Tier 2 which involves sequencing of the remaining 41 coding exons. The two tiers may be ordered separately. We will also perform sequencing of any single exon or pair of exons 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 in part 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 with 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. Sayer et al. 2006 reported finding at least one likely causative mutations in *CEP290* in 8 out of 96 (8%) unrelated JS patients. In two patients only one likely causative mutation was identified. One *de novo* mutation was found.

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 will soon contain DNA testing information for patients.

SPECIMEN REQUIREMENTS: See bottom of Requisition Form.

Price: Tier 1 Sequencing of <i>CEP290</i> Exons 17, 28, 31, 34, 36, 37, 40, 41, 42, 44, 46, and 54	\$ 640
Tier 2 Sequencing of the remaining 41 <i>CEP290</i> Exons	\$ 1690
Tiers 1 and 2 Combined	\$ 2190

CPT Codes:

Codes	Description	Tier 1 Only	Tier 2 Only	Tier 1 + Tier 2
83890	Ascertainment	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)
83891	DNA Isolation	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)
83898	Amplification	\$170 (x12)	\$ 544 (x41)	\$ 744 (x53)
83904	Mutation Ident by Sequencing	\$280 (x12)	\$ 816 (x41)	\$1,116 (x53)
83894	Separation	\$ 40 (x1)	\$ 90 (x1)	\$ 90 (x1)
83912	Interpretation and Report	\$ 80 (x1)	\$ 170 (x1)	\$ 170 (x1)
Totals:		\$640	\$1,690	\$2,190

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