

Joubert Syndrome via *AH11* Gene Sequencing (Test # 266)

Brief Description of Clinical Features: Joubert Syndrome (JS) (OMIM 213300) is marked by hypotonia, abnormal ocular movements, neonatal respiratory difficulties, mental retardation, hypoplasia of the cerebellar vermis, and malformation of the brainstem. The brain malformations lead to the "molar tooth sign" on cranial MRI, which is the hallmark clinical feature of JS. Other variable JS features include cystic kidneys, nephronophthisis, retinal dystrophy, ocular coloboma, occipital encephalocele, polydactyly, ataxia, and hepatic fibrosis. For more information, see Parisi and Glass (Gene Reviews, www.genetests.org, 2007) and Parisi et al. (Eur J Hum Genet 15:511-521, 2007).

Genetics: JS is inherited in an autosomal recessive manner. Mutations in the *AH11* gene cause JS (Ferland et al. Nat Genet 36:1008-1013, 2004; Dixon-Salazar et al. Am J Hum Genet 75:979-987, 2004; Parisi et al. J Med Genet 43:334-339, 2006; Valente et al. Ann Neurol 59:527-534, 2006). The *AH11* gene encodes the AH11 protein, or jouberin, which has been predicted to have a role in cilia-associated trafficking mechanisms (Louie et al. Nat Genet 42:175-180, 2010). It has also been reported that AH11 protein is required for photoreceptor outer segment development. It modifies the retinal degeneration phenotype in nephronophthisis through direct interaction with nephrocystin-1 (NPHP1) (Louie et al. 2010; Eley et al. Kidney Int 74:1139-1149, 2008). A mix of nonsense, frameshift, splicing, deletion, insertion and missense mutations has been reported in the *AH11* gene; none are particularly frequent (Ferland et al. 2004; Dixon-Salazar et al. 2004; Parisi et al. 2006; Valente et al. 2006). Other cases of JS have also been linked to mutations in the *TMEM67/MKS3*, *CEP290*, *CC2D2A*, *RPGRIP1L*, *INPP5E*, *ARL13*, *TMEM216* and *NPHP1* genes. PreventionGenetics performs tests for all of these genes.

Description of This Particular Test: This test involves bidirectional DNA sequencing of all *AH11* gene coding exons along with ~50 bases of non coding flanking DNA on each side. As indicated, 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).

Reference Sequences: Genomic: NC_000006.11 mRNA: NM_017651.3 Protein: NP_060121.3 (CCDS 47483.1)

Indications for Test: Candidates for this test are patients with symptoms consistent with JS and 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: The prevalence of JS is about 1 in 100,000. The following are the *approximate* fractions of patients with mutations in the indicated genes for Joubert syndrome: *AH11* 10%, *TMEM67/MKS3* 10%, *CC2D2A* 10%, *CEP290* 10%, *RPGRIP1L* 2%, *ARL13B* 2%, *NPHP1* 2% (Parisi et al. 2007).

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of Requisition Form.

Prices: Sequencing of *AH11* gene \$ 1320

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x27	83898	\$ 410	Sequencing x27	83904	\$ 650
Separation	83894	\$ 80	Interpretation/Report	83912	\$ 110

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

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