

Joubert and Meckel-Gruber Syndromes via *CEP290* Gene Sequencing (Test #267)

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).

Meckel-Gruber Syndrome (MKS) (OMIM 249000) is characterized by occipital encephalocele, polycystic kidneys, hepatic developmental defects and postaxial polydactyly (Alexiev et al. Arch Pathol Lab Med 130:1236-1238, 2006). MKS is a common cause of prenatal echogenic kidneys (Chaumoitre et al. Ultrasound Obstet Gynecol 28:911-917, 2006). Nearly all MKS infants are stillborn or die shortly after birth. The clinical features of JS and MKS clearly overlap.

Genetics: JS and MKS both exhibit autosomal recessive inheritance. Both disorders have high levels of locus heterogeneity. Mutations in the *CEP290* gene cause both JS and MKS (Sayer et al. Nat Genet 38:674-681, 2006). The *CEP290* gene encodes the centrosomal protein-290 KD, or CEP290, which is localized to the centrosome/primary cilia (Valente et al. Nat Genet 38:623-625, 2006). Although the precise function of the CEP290 is not known, it has been proposed to have a role in cilia and centrosome structure and function (Valente et al. 2006). A mix of nonsense, frameshift, splicing, deletion, insertion and missense mutations has been reported in the *CEP290* gene (Valente et al. 2006; Sayer et al. 2006; Brancati et al. Am J Hum Genet 81:104-113, 2007). Other cases of JS have also been linked to mutations in the *AH11*, *TMEM67/MKS3*, *CC2D2A*, *RPGRIP1L*, *INPP5E*, *ARL13*, *TMEM216* and *NPHP1* genes, while other MKS cases have been linked to mutations in *MKS1*, *TMEM67/MKS3*, *CC2D2A* and *RPGRIP1L*. PreventionGenetics performs tests for all of these genes.

Description of This Particular Test: This particular test involves bidirectional DNA sequencing of all *CEP290* 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_000012.11 mRNA: NM_025114.3 Protein: NP_079390.3

Indications for Test: Candidates for this test are patients with symptoms consistent with JS or MKS 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: *CEP290* 10%, *AH11* 10%, *TMEM67/MKS3* 10%, *CC2D2A* 10%, *RPGRIP1L* 2%, *ARL13B* 2%, *NPHP1* 2% (Parisi et al. 2007). The numbers for MKS are approximately *CEP290* 10%, *MKS1* 15%, *TMEM67/MKS3* 15%, *CC2D2A* 10%, *RPGRIP1L* 2%.

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

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of *CEP290* gene \$ 2190

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x51	83898 \$ 750	Sequencing x51	83904 \$1120
Separation x1	83894 \$ 130	Interpretation/Report x1	83912 \$ 120

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

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