

Joubert and Meckel-Gruber Syndromes via *CC2D2A* Gene Sequencing (Test #278)

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, 2006) 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 with 7 JS genes (*TMEM67/MKS3*, *AH1*, *CC2D2A*, *CEP290*, *RPGRIP1L*, *ARL13B*, *NPHP1*) and 5 MKS genes (*MKS1*, *TMEM67/MKS3*, *CC2D2A*, *CEP290*, *RPGRIP1L*) identified to date. Additional genes are likely to be identified in future. Both JS and MKS are ciliopathies, meaning that they are caused by mutations in genes which encode proteins involved in cilia/centrosome structure and function (Hildebrandt and Otto Nat Rev Genet 6:928-940, 2005; www.ciliaproteome.org). *CC2D2A* has recently been reported to be mutated in both JS and MKS (Gorden et al. Am J Hum Genet 83:1-13, 2008; Noor et al. Am J Hum Genet 82:1011-1018, 2008; Noor et al. Am J Hum Genet 83:656, 2008; and Tallila et al. Am J Hum Genet 82:1361-1367, 2008). About 10 causative mutations, a mix of nonsense, splicing, frameshift and missense, have been reported.

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of all 36 coding exons (exons 3-38) of the *CC2D2A* gene (Tallila et al. 2008). The full coding region of each exon plus ~50 bp of flanking non-coding DNA on either side are sequenced. We will also perform sequencing of any single or pair of exons for family members of patients with known mutations and to confirm previous results (\$190-340).

Reference Sequences: Genomic: NC_000004.10 mRNA: NM_001080522.2 Protein: NP_001073991.2

Indications for Test: Patients with symptoms consistent with JS or MKS are candidates. Conclusive connections between clinical features and mutated genes have not yet been made. Genome Polymorphism Scans (our Test #510) may be an appropriate first step for testing affected offspring of consanguineous matings.

Sensitivity of Test: The following are the *approximate* fractions of patients with mutations in the indicated genes.

JS: *TMEM67/MKS3* 10%, *AH1* 10%, *CC2D2A* 10%, *CEP290* 10%, *RPGRIP1L* 2%, *ARL13B* 2%, *NPHP1* 2%

MKS: *MKS1* 15%, *TMEM67/MKS3* 15%, *CC2D2A* 10%, *CEP290* 10%, *RPGRIP1L* 2%

Turn Around Time: Maximum of 40 calendar days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of *CC2D2A* Gene \$ 1590

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x30	83898 \$ 530	Sequencing x30	83904 \$ 790
Separation x1	83894 \$ 80	Interpretation/Report x1	83912 \$ 120

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

Contact: Dr. Keith Nykamp, keith.nykamp@preventiongenetics.com, www.preventiongenetics.com