

Joubert and Meckel-Gruber Syndromes via *TMEM67/MKS3* Gene Sequencing (Test #274)

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. JS patients have substantial phenotypic variation. Some JS patients develop retinal dystrophy and/or progressive renal failure. For more information, see Parisi and Glass (Gene Reviews, www.genetests.org, 2006).

Meckel-Gruber Syndrome (MKS) (OMIM 249000) is the most common form of syndromic neural tube defect. MKS is characterized by occipital encephalocele, polycystic kidneys, 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.

Genetics: Both JS and MKS are relatively rare autosomal recessive disorders. Both disorders are caused by mutations in multiple, unlinked genes. Mutations in the *MKS3* gene (also called *TMEM67*) were very recently identified as causes of both JS and MKS (Baala et al. Am J Hum Genet 80:186-194, 2007; Smith et al. Nat Genet 38:191-196, 2006; Dawe et al. Hum Mol Genet 16:173-186, 2007; and Consugar et al. Hum Genet 121:591-599, 2007). JS *MKS3* causative mutations were missense and splicing. MKS *MKS3* causative mutations were frameshift, splicing, nonsense and missense.

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 28 coding exons of the *MKS3* gene. 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).

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 (JS only). Checklists are not required for carrier testing.

Reference Sequences: Genomic: NC_000008.9 mRNA: NM_153704.4 Protein: NP_714915.3

Indications for Test: Candidates for this test are patients with symptoms consistent with JS or MKS, and the family members of patients with known mutations. In addition to this *MKS3* gene test, PreventionGenetics also offers sequencing of *AH11*, *CEP290*, *NPHP1*, *RPGRIP1L* and *MKS1* genes, as well as a test for homozygous deletion of *NPHP1*. Consugar et al. 2007 reported that MKS patients with polydactyly were much more likely to have *MKS1* than *MKS3* mutations.

Sensitivity of Test: Based on initial reports from the literature, we estimate that roughly 10% of JS patients (Baala et al. 2006) and roughly 30% of MKS patients will carry mutations in the *MKS3* gene (Consugar et al. 2007).

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See bottom of page 2 of Requisition Form.

Price: Sequencing of *MKS3* Exons 1-28

\$ 1290

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x25	83898	\$ 380	Sequencing x25	83904	\$ 670
Separation	83894	\$ 60	Interpretation/Report	83912	\$ 110

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