

Ciliopathy via *INPP5E* Gene Sequencing (Test #279)

Brief Description of Clinical Features: Ciliopathies are a group of related disorders that include Joubert Syndrome (OMIM 213300), Meckel-Gruber Syndrome (OMIM 249000), Nephronophthisis (OMIM 256100) and Bardet-Biedl Syndrome (OMIM 209900). All of the Ciliopathies are caused by mutations in genes encoding proteins involved in cilia/centrosome structure and function (Hildebrandt and Otto Nat Rev Genet 6:928-940, 2005; www.ciliaproteome.org). Clinical features of the Ciliopathies overlap. Joubert Syndrome (JS) 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: The Ciliopathies exhibit autosomal recessive inheritance. All of the Ciliopathies have high levels of locus heterogeneity. The *INPP5E* gene has recently been reported to be mutated in Joubert Syndrome (the *JBTS1* locus) (Bielas et al. Nat Genet 41:1032-1036, 2009) and MORM Syndrome (Mental retardation, Obesity, Retinal dystrophy and Micropenis) (Jacoby et al. Nat Genet 41:1027-1031, 2009). MORM Syndrome is related in clinical features to Bardet-Biedl Syndrome. The Joubert families all had missense mutations, and the MORM family had a nonsense mutation near the 3' end of the gene.

Description of This Particular Test: *INPP5E* encodes the enzyme inositol polyphosphate-5-phosphatase E. As required, this test involves bidirectional sequencing using genomic DNA of all 10 coding exons (exons 1-10) of the *INPP5E* gene. 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_000009.11 mRNA: NM_019892.3 Protein: NP_063945.2 (CCDS 7000.1)

Indications for Test: Patients with symptoms consistent with Joubert Syndrome or MORM and who do not have mutations in the most commonly mutated Joubert genes are candidates. Conclusive connections between clinical features and mutated genes have not yet been made.

Sensitivity of Test: The fraction of Joubert patients with mutations in *INPP5E* is currently unknown (see also the *CC2D2A* Test Description).

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 2-3 weeks. For multiple, sequential gene tests add about 10 days per gene.

Specimen Requirements: See page 4 of the Requisition Form.

Price:	Sequencing of <i>INPP5E</i> Gene		\$ 690	
CPT Codes:				
Sample Ascertainment x1	83890	\$ 30	DNA Isolation x1	83891 \$ 40
Amplification x11	83898	\$ 190	Sequencing x11	83904 \$ 290
Separation x1	83894	\$ 50	Interpretation/Report x1	83912 \$ 90

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

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