

Lissencephaly 3 via *TUBA1A* Gene Sequencing (Test #504)

Brief Description of Clinical Features: Lissencephaly is defined as "smooth brain" with absent gyri (agyria) or abnormally wide gyri (pachygyria) (Barkovich et al. *Ann Neurol* 1991; 30:139–46). Classic lissencephaly includes the *LIS1*-associated, *DCX*-related, and *TUBA1A*-related forms as well as the rare Baraitser-Winter syndrome (BWS) (Dobyns et al. *Neurology* 42:1375-88, 1992; Poirier et al. *Hum Mutat* 28:1055-64, 2007). *TUBA1A*-related lissencephaly, known as Lissencephaly type 3 (LIS3, OMIM# 611603) is caused by abnormal neuronal migration. LIS3 consists of variable grade of lissencephaly, ranging from severe agyria to laminar heterotopia (Poirier et al. 2007; Keays et al. *Cell* 128:45-57, 2007). Clinical features of LIS3 include congenital microcephaly, mental retardation, lack of language development, and diplegia/tetraplegia (Bahi-Buisson et al. *J Med Genet* 45:647-653, 2008). Although, the lissencephaly phenotype associated with *LIS1* and *LIS3* is similar, the *LIS3* malformation usually appears to be more severe (Poirier et al. 2007).

Genetics: LIS3 is inherited as an autosomal dominant disorder and is caused by mutations in the *TUBA1A* gene. *TUBA1A* encodes a brain specific tubulin B-alpha-1 (*TUBA1A*) protein, important for tubulin heterodimer formation. *TUBA1A* is predicted to have a role in microtubule function, which is important for neuronal migration during early embryonic development (Keays et al. 2007). Several *de novo* missense mutations have been reported in the *TUBA1A* gene (Poirier et al. 2007; Keays et al. 2007; Bahi-Buisson et al. 2008; Morris-Rosendahl et al. *Clin Genet* 74:425-433, 2008).

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of the 4 coding exons (exons 1-4) of the *TUBA1A* gene. The full coding region of each exon plus ~50 bp of flanking non-coding DNA on each side are sequenced. As indicated, we will also perform sequencing of any single exon (Test #100) for family members of patients with known mutations and to confirm previous research results (\$190 charge).

Reference Sequences: Genomic: NC_000012.10 mRNA: NM_006009.2 Protein: NP_006000.2 (CCDS 8781.1)

Indications for Test: Candidates for this test are patients with symptoms consistent with lissencephaly 3 and family members of patients who have known *TUBA1A* mutations. Conclusive connections between clinical features and *PAFH1B1* or *TUBA1A* mutations have not yet been made.

Sensitivity of Test: Mutations in the *TUBA1A* gene are estimated to cause approximately 4% of classic lissencephaly cases (Morris-Rosendahl et al. 2008).

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.

Prices: Sequencing of *TUBA1A 1* gene \$ 440

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x4	83898 \$ 100	Sequencing x4	83904 \$ 160
Separation x1	83894 \$ 30	Interpretation/Report x1	83912 \$ 80

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

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