

## Classic lissencephaly via *PFAH1B1/LIS1* Gene Sequencing (Test #507)

**Brief Description of Clinical Features:** Lissencephaly is defined as "smooth brain" with absent gyri (agyria) or abnormally wide gyri (pachygyria) (Brakovich 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). *LIS1*-related lissencephaly, known as Lissencephaly type 1 (*LIS1*, OMIM# 607432) is caused by cortical malformations due to deficient neuronal migration during embryogenesis. *LIS1* consists of variable grades of lissencephaly, ranging from severe complete agyria to mild subcortical band heterotopia (SBH), characterized by subcortical band of symmetric or diffused heterotopic gray matter located beneath the cortex and separated from it by a thin zone of normal white matter. Clinical features of *LIS1* include developmental delay, mental retardation and seizures (Dobyns et al. 1992). It has been reported that patients with *LIS1*-related lissencephaly have 4-layer involvement with more posterior malformation (Forman et al. J Neuropath Exp Neurol 64:847-857, 2005).

**Genetics:** *LIS1* is inherited as an autosomal dominant disorder. *LIS1* is caused by mutations in the *PFAH1B1* (also known as *LIS1*) gene (Dobyns et al. 1992). *PFAH1B1* gene encodes the *LIS1* protein, which interacts with *DCX* protein. It has been proposed that *LIS1* and *DCX* proteins are involved in proper microtubule function in the developing cerebral cortex, which could explain the role of *LIS1* in neuronal migration and early embryonic development (Hirotsume et al. Nat Genet 19:333-339, 1998; Caspi et al. Hum Molec Genet 9:2205-2213, 2000). Deletions of 17p13.3 and intragenic deletions and duplications within the *PFAH1B1* gene, as well as a mix of missense, nonsense, splice site and small deletion mutations have been reported. Most of the reported *PFAH1B1* whole gene and intragenic deletion and duplication mutations occurred *de novo* (Pilz et al. Hum Mol Genet 7:2029-37, 1998; Cardoso et al. Hum Mol Genet 9:3019-28, 2000; Uyanik et al. Neurology 69:442-447, 2007).

**Description of This Particular Test:** This test involves bidirectional sequencing using genomic DNA of the 10 coding exon (exons 2-11) of the *PFAH1B1* 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\_000017.9 mRNA: NM\_000430.3 Protein: NP\_000042.1 (CCDS 32528.1)

**Indications for Test:** Candidates for this test are patients with symptoms consistent with classical lissencephaly 1 and family members of patients who have known *PFAH1B1* mutations. Conclusive connections between clinical features and *PFAH1B1* or *TUBA1A* mutations have not been made.

**Sensitivity of Test:** *PFAH1B1* mutations are more common than mutations in the *DCX* or the *TUBA1A* genes. Mutations in the *PFAH1B1* gene are estimated to cause approximately 32% of classic lissencephaly cases (Pilz et al. 1998).

**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.

<b>Prices:</b>	<b>Sequencing of <i>PFAH1B1</i> gene</b>	<b>\$ 670</b>	
<b>CPT Codes:</b>			
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x10	83898 \$ 190	Sequencing x10	83904 \$ 260
Separation x1	83894 \$ 60	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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