

Classic lissencephaly via *DCX* Gene Sequencing (Test #503)

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). *DCX*-related lissencephaly, also known as X-linked Lissencephaly type 1 (LISX1, OMIM# 300076), is a neuronal migration disorder caused by mutations in the *DCX* gene (des Portes et al. *Cell* 92: 51-61, 1998). *DCX*-related lissencephaly includes classic lissencephaly in males and subcortical band heterotopia (SBH)/double cortex syndrome in females (Dobyns et al. *Neurology* 53: 270-277, 1999; Guerrini et al *Am J Med Genet* 106:160-173, 2001). Males with classic lissencephaly typically have developmental delay, severe mental retardation and infantile-onset seizures (Dobyns et al. 1999). SBH is a milder form of lissencephaly, in which the severity of symptoms correlates with the degree of the underlying brain malformation. In individuals with SBH, cognitive abilities range from normal to learning disabilities and/or severe mental retardation with or without seizures (Guerrini et al. 2001).

Genetics: *DCX*-related lissencephaly is inherited in an X-linked manner. Approximately 10% of unaffected mothers of children with a *DCX* mutation may have somatic mosaicism or germline mosaicism (Mei et al. *Neurology* 68: 446–450, 2007). *DCX* gene encodes the DCX protein, which contains two tandem doublecortin domains that bind tubulin (Taylor et al. *J Biol Chem* 275:34442-34450, 2000). It has also been reported that DCX interacts with LIS1 protein. These proteins have important roles in proper microtubule function in the developing cerebral cortex, which could explain the role of DCX in neuronal migration and early embryonic development (Hirotsune et al. *Nat Genet* 19: 333-339, 1998; Gleeson et al. *Neuron* 23:257-271, 1999; Caspi et al. *Hum Molec Genet* 9:2205-2213, 2000). A mix of missense, nonsense, splice site and small deletion mutations as well as whole and intragenic deletion and duplication mutations have been reported in the *DCX* gene (Pilz et al. *Hum Mol Genet* 7:2029-37; Gleeson et al. *Cell* 92:63-72, 1998; Gleeson et al. *Ann Neurol* 45:146-153, 1999; Matsumoto et al. *Eur J Hum Genet* 9:5-12, 2001; Mei et al. 2007).

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of the 6 coding exon (exons 4-9) of the *DCX* 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_000023.9** mRNA: **NM_178153.1** Protein: **NP_835366.1 (CCDS 14557.1)**

Indications for Test: Candidates for this test are patients with symptoms consistent with X-linked lissencephaly 1 and family members of patients who have known *DCX* mutations.

Sensitivity of Test: Mutations in *DCX* are estimated to cause ~20% 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.

Prices:	Sequencing of <i>DCX</i> gene	\$ 590	
CPT Codes:			
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x8	83898 \$ 180	Sequencing x8	83904 \$ 220
Separation x1	83894 \$ 40	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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