

Miller-Dieker Lissencephaly Syndrome via *YWHAE* Gene Sequencing (Test #505)

Brief Description of Clinical Features: Miller-Dieker lissencephaly syndrome (MDLS; OMIM 247200) is characterized by lissencephaly, microcephaly, wrinkled skin over the glabella and frontal suture, prominent occiput, narrow forehead, downward slanting palpebral fissures, small nose and chin, cardiac malformations, hypoplastic male external genitalia, growth retardation, and mental deficiency with seizures (Schinzel J Med Genet 25:454-462, 1988, Dobyns et al. Am J Hum Genet 48:584-594, 1991). Lissencephaly is defined as "smooth brain" with absent gyri (agyria) or abnormally wide gyri (pachygyria) (Brakovich et al. Ann Neurol 1991; 30:139-46). MDLS patients mostly have more severe lissencephaly (complete agyria) than *LIS1*-associated lissencephaly patients (OMIM 607432), explained by two additional genes deletion, *CRK* and *YWHAE* (also known as *14-3-3ε*), on 17p13.3 distal to *LIS1* gene (Chong et al. Hum Molc Genet 6:147-155, 1997). Subsequently, it has been documented that the deletion of *YWHAE* gene is responsible for the greater severity of Miller-Dieker syndrome compared to *LIS1*-associated lissencephaly (Toyo-oka et al. Nat Genet 34:274-285, 2003).

Genetics: Miller-Dieker lissencephaly syndrome is inherited as an autosomal dominant disorder. MDLS is caused by mutations in the *YWHAE* gene (also known as *14-3-3ε*) (Toyo-oka et al. 2003; Bi et al. Nat Genet 41:168-177, 2009). *YWHAE* gene encodes the 14-3-3-epsilon protein, which binds and protects NUDEL, a phosphorylated protein important in regulating dynein activity in M phase. It has been predicted that 14-3-3-epsilon protein is required for NEDUL localization and cytoplasmic dynein function and might be important for neuronal migration (Toyo-oka et al. 2003). Submicroscopic deletions or duplication of 17p13.3 including the *LIS1* and/or *YWHAE* have been reported in MDLS patients (Chong et al. 1997; Toyo-oka et al. 2003; Bi et al. 2009). Of note, no point mutations in the *YWHAE* gene have yet been reported in MDLS patients; therefore, aCGH analysis for deletions and duplications within the *YWHAE* gene should be performed first.

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of the 6 coding exon (exons 1-6) of the *YWHAE* 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_006761.4 Protein: NP_006752.1 (CCDS 11001.1)

Indications for Test: Candidates for this test are patients with symptoms consistent with Miller-Dieker lissencephaly syndrome and family members of patients who have known *YWHAE* mutations.

Sensitivity of Test: Sensitivity of this test is currently unknown.

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 *YWHAE* gene \$ 520

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x6	83898 \$ 130	Sequencing x10	83904 \$ 200
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).

Contact for Info: Dr. Ying Wang, ying.wang@preventiongenetics.com, www.preventiongenetics.com