

## Lissencephaly with Cerebellar Hypoplasia via *RELN* Gene Sequencing (Test #506)

**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). Autosomal recessive lissencephaly with cerebellar hypoplasia (also known as Norman-Roberts syndrome; OMIM 257320), is characterized by severe abnormalities of the cerebellum, hippocampus, and brainstem associated with craniofacial features including low sloping forehead and a prominent nasal bridge (Norman et al. Canad J Neurol Sci 3:39-46, 1976; Dobyns et al. Am J Med Genet 18:509-526, 1984; Iannetti et al. Am J Med Genet 47:95-99, 1993; Hong et al. Nat Genet 26:93-96, 2000). Brain MRI of patients with autosomal recessive lissencephaly with cerebellar hypoplasia showed moderate lissencephaly changes consistent with lissencephaly type I, grade 2, and profound cerebellar hypoplasia (Hong et al. 2000; Hourihane et al. Neuropediatrics 24:43-46, 1993). Neurologic features associated with lissencephaly with cerebellar hypoplasia include hypertonia, hyperreflexia, seizures, and profound mental retardation (Iannetti et al. 1993).

**Genetics:** Lissencephaly with cerebellar hypoplasia is inherited as an autosomal recessive disorder and is caused by mutations in the *RELN* gene (Hong et al. 2000, Zaki et al. Am J Med Genet 143A:939-944, 2007). *RELN* gene encodes RELN, an extracellular matrix protein, which interacts with LIS1 protein, a product of the *PAFAH1B1* gene (Quattrocchi et al. J Biol Chem 277:303-309, 2002; Assadi et al. Nat Genet 35:270-276, 2003). Although the precise function of RELN protein is uncertain, it has been predicted to have a role in the regulation of neuronal migration and positioning in brain development and might be involved in signal transduction (Trommsdorf et al. Cell 97:689-701, 1999; Quattrocchi et al. 2002). A splice site mutation and large deletion have been reported in the *RELN* gene (Hong et al. 2000, Zaki et al. 2007).

**Description of This Particular Test:** This test involves bidirectional sequencing using genomic DNA of the 65 coding exons (exons 1-65) of the *RELN* 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) or pair of exons (Test #200) for family members of patients with known mutations and to confirm previous research results (\$190-340 charge).

**Reference Sequences:** Genomic: NC\_000007.13 mRNA: NM\_005045.3 Protein: NP\_005036.2 (CCDS\_47680.1)

**Indications for Test:** Candidates for this test are patients with symptoms consistent with autosomal recessive lissencephaly with cerebellar hypoplasia and family members of patients who have known *RELN* 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 *RELN* gene \$ 2,590

**CPT Codes:**

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x65	83898 \$ 870	Sequencing x65	83904 \$ 1300
Separation x1	83894 \$ 190	Interpretation/Report x1	83912 \$ 160

**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](mailto:ying.wang@preventiongenetics.com), [www.preventiongenetics.com](http://www.preventiongenetics.com)