

Juvenile Primary Lateral Sclerosis, Autosomal Recessive via *ALS2* Gene Sequencing (Test #108)

Brief Description of Clinical Features: Primary lateral sclerosis (PLS) is characterized by neurological dysfunction limited to the upper motor neurons (UMN) of the corticospinal tract (Russo, Arch Neurol 39: 662-664, 1982). The most common features of PLS are spastic quadriparesis, hyperactive muscle-stretch reflexes and bilateral Babinski's sign. Additional features include spastic dysarthria, dysphagia and exaggerated affective responses such as weeping or loathing. PLS is typically characterized by a gradual onset, slow and steady progression and long duration (Beal and Richardson, Arch Neurol 38: 630-633, 1981). Two forms of PLS, juvenile and adult, are recognized based on the age of onset. In juvenile PLS (JPLS, OMIM 606353) symptoms begin in early childhood, sometimes before twelve months of age (Grunnet et al. Neurology 39:1530-1532, 1989); in adult PLS (PLSA1, OMIM 611637) the age of onset varies between 35 and 66 years of age (Pringle et al. Brain 115 (Pt 2): 495-520, 1992). JPLS is always inherited with an autosomal recessive manner, while adult PLS is either sporadic or autosomal dominant. See also the Spastic Paraplegia Foundation at: <http://www.sp-foundation.org>.

Genetics: JPLS is caused by mutations in the *ALS2* gene (Hadano et al. Nat Genet 29:166-173, 2001; Yang et al. Nat Genet 29: 160-165, 2001; Bertini et al. GeneReviews, www.genetests.org, 2005). To date, four homozygous mutations in the *ALS2* gene were found in patients with JPLS. These include two 2-bp deletions in families from Saudi Arabia (1867delCT) (Yang, 2001) and Kuwait (1425delAG) (Hadano, 2001), a nonsense mutation (c.1619 G>A) in an Italian family (Panzeri et al. Brain 129(Pt 7): 1710-1719, 2006) and a splice site mutation (c.2980-2A>G) in a Cypriot family (Mintchev et al. Neurology 72: 28-32, 2009). While consanguinity was documented in the families from Saudi Arabia, Kuwait and Cyprus, the Italian family did not illustrate history of consanguinity. Patients from all families showed the first symptoms before the age of two years. All four mutations resulted in a predicted truncated protein with loss of function. In addition to JPLS, mutations in the *ALS2* gene were reported in patients with juvenile amyotrophic lateral sclerosis (JALS, *ALS2*, AR-ALS OMIM 205100), infantile-onset ascending hereditary spastic paralysis (IAHSP, OMIM 607225) and complicated hereditary spastic paraplegia (cHSP, Gros-Louis et al. Ann Neurol 53: 144-145, 2003).

Description of This Particular Test: The *ALS2* gene encodes the Alsin protein. This test involves bidirectional DNA sequencing of all 33 coding exons and splice sites of the *ALS2* gene. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced. We will sequence any single exon or pair of exons in family members of patients with known mutations and to confirm results.

Reference Sequences: Genomic: **NC_000002.10** mRNA and protein: **CCDS 42800.1**

Indications for Test: Patients with symptoms suggestive of JPLS as described above. The *ALS2* gene is also a candidate for patients with JALS (*ALS2*, AR-ALS OMIM 205100), IAHSP (OMIM, 607225) and cHSP (Gros-Louis et al. Ann Neurol 53:144-145, 2003).

Sensitivity of Test: Currently unknown.

Turn Around Time: Maximum of 40 calendar days.

Specimen Requirements: See page 4 of Requisition Form.

Price: Sequencing of all coding exons of the *ALS2* Gene: \$ 1790

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x 37	83898 \$ 610	Sequencing x 37	83904 \$ 910
Separation x1	83894 \$ 90	Interpretation/Report x1	83912 \$ 110

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/11)

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