

Infantile-Onset Ascending Hereditary Spastic Paralysis via *ALS2* Gene Sequencing (Test #108)

Brief Description of Clinical Features: Infantile-Onset Ascending Hereditary Spastic Paralysis (IAHSP, OMIM 607225) is a motor neuron disease characterized by a degeneration of the upper motor neurons of the corticospinal tract. The clinical hallmark of IAHSP is a slow, progressive, ascending spastic paralysis. Spasticity usually begins in the lower limbs, extending to the upper limbs and bulbar muscles and, eventually, to a severe spastic paralysis. The onset of symptoms typically occurs during the first two years of life, with most patients being wheelchair-bound by the age of ten. The disease progresses to tetraplegia (complete paralysis of both upper and lower limbs), anarthria (total or partial loss of articulate speech), dysphagia (difficulty in swallowing) and slow eye movements in the second decade of life. Despite the progressive nature of the disease, life expectancy is not affected (Eymard-Pierre et al. Am J Hum Genet 71: 518-527, 2002; Lesca et al. Neurology 60: 674-882, 2003). See also the Spastic Paraplegia Foundation at <http://www.sp-foundation.org>.

Genetics: IAHSP is transmitted with an autosomal recessive pattern and is genetically heterogeneous. Mutations in the *ALS2* gene cause IAHSP in a subset of patients (Eymard-Pierre et al. Am J Hum Genet 71:518-527, 2002). At least eight *ALS2* mutations have been reported in patients with IAHSP (Devon et al. Clin Genet 64:210-215, 2003; Verschuuren-Bemelmans et al. Eur J Hum Genet 16: 1407-1411, 2008; Bertini et al. GeneReviews, www.genetests.org, 2005). Except for one case of compound heterozygote mutation (Sztriha et al. Clin Genet 73: 591-593, 2008), all mutations were homozygous and resulted in a predicted truncated protein. In some cases parents were closely related, while history of consanguinity was absent in others. These mutations occurred in patients of North African and European origins. In addition to IAHSP, mutations in the *ALS2* gene were reported in patients with Juvenile Amyotrophic Lateral Sclerosis (JALS, OMIM 205100), Juvenile Primary Lateral Sclerosis (JPLS, OMIM 606353), and complicated Hereditary Spastic Paraplegia in a large consanguineous Pakistani family (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 mutation and to confirm results.

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

Indications for Test: Patients with symptoms suggestive of IAHSP as described above. The *ALS2* gene is also a candidate for patients with JALS (OMIM 205100), JPLS (OMIM 606353), and patients of Pakistani origin presenting with the complicated form of Hereditary Spastic Paralysis (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 12/20/12)

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