

Amyotrophic Lateral Sclerosis / Motor Neuron Disease Autosomal Dominant or Sporadic *via TARDBP* Gene Sequencing Test #153

Brief Description of Clinical Features: Amyotrophic Lateral Sclerosis (ALS, OMIM 105400), is a neurodegenerative disease characterized by a selective loss of motor neurons in the motor cortex, brain stem, and spinal cord (Tandan and Bradley, *Ann Neurol* 18:271-280, 1985). The dysfunction and loss of these neurons result in rapid progressive muscle weakness, atrophy and ultimately paralysis of limb, bulbar and respiratory muscles. The mean age of onset of symptoms is about 55 years of age; most cases begin between 40 and 70 years of age. The annual incidence of ALS is 1-2 per 100,000 (Cleveland and Rothstein, *Nat Rev Neurosci* 2:806-819, 2001). The most common symptoms include: twitching and cramping of muscles of the hands and feet, loss of motor control in the hands and arms, weakness and fatigue, tripping and falling. Symptoms usually begin with asymmetric involvement of the muscles. As the disease progresses, symptoms may include difficulty in talking, breathing, and swallowing, shortness of breath, and paralysis. See also the Amyotrophic Lateral Sclerosis Fact Sheet (www.ninds.nih.gov/disorders/amyotrophiclateralsclerosis).

Genetics: About 10 % of ALS cases are familial (Emery and Holloway, *Adv Neurol* 36:139-147, 1982). In most of these families, ALS is inherited with an autosomal dominant (AD-ALS) manner with age-dependant, but high penetrance. In rare families, the disease is transmitted with an autosomal recessive pattern (OMIM 205100). Autosomal Dominant ALS affects all ethnic groups. This form of the disease is clinically and genetically heterogeneous. At least nine genetic loci have been associated with AD-ALS, and the defective gene was identified in six of them: *SOD1*, *SETX*, *ANG*, *VAPB*, *FUS* and *TARDBP*. To date, 17 different missense mutations in the *TARDBP* gene have been implicated in patients with ALS and Motor Neuron Disease (Sreedharan et al. *Science* 319:1668-1672, 2008; Kabashi et al. *Nat Genet* 40:572-574, 2008; Gitcho et al. *Ann Neurol* 63:535-538, 2008). All *TARDBP* causative mutations were heterozygous; about half the mutations were found in patients with AD-ALS, while the other half occurred in patients with the sporadic form of ALS.

Description of This Particular Test: The *TARDBP* gene encodes the TAR DNA binding protein (TDP-43). This test involves bidirectional DNA sequencing of all 5 coding exons and splice sites of the *TARDBP* gene. The full coding sequence of each exon plus ~ 50 bp of flanking-coding 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_000001.9** mRNA and protein: **CCDS 122.1**

Indications for Test: Patients with symptoms suggestive of ALS or Motor Neuron Disease. See Dellefave and Siddique, 2007 and Harms et al. 2009 at www.genetests.org.

Sensitivity of Test: Currently unknown.

Turn Around Time: Maximum of 40 calendar days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of all coding exons of the *TARDB* gene \$ 470

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x 5	83898 \$ 120	Sequencing x 5	83904 \$ 180
Separation x1	83894 \$ 30	Interpretation/Report x1	83912 \$ 70

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

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