

**Amyotrophic Lateral Sclerosis, Autosomal Dominant and Sporadic
 via SOD1, FUS, TARDBP, ANG, OPTN and FIG4 Gene Sequencing Panel --Test #155**

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. In most cases, symptoms 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) and the ALS Association (www.alsa.org).

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 in an autosomal dominant (AD-ALS) manner with age-dependant, but high penetrance. Most of the remaining cases of ALS are sporadic (SALS) with no known affected relatives. It is, however, unclear how many of these cases are inherited, with low penetrance. In rare families, the disease is transmitted with an autosomal recessive pattern (AR-ALS). ALS is genetically heterogeneous, and affects all ethnic groups. To date, six genes (*SOD1*, *FUS*, *TARDBP*, *ANG*, *OPTN* and *FIG4*) have been associated with the typical form of ALS, including AD-ALS and SALS. At least 250 heterozygous causative mutations have been reported in these six genes. Although the vast majority of mutations are missense, most types of mutations have been reported. Large deletions or rearrangements are rare.

Mutations in two genes (*ALS2* and *OPTN*) have been reported in patients with AR-ALS. Individual tests for both genes are available (Tests # 108 and 156).

Description of This Particular Test: PreventionGenetics offers sequencing of each of the six genes individually, or the combined Panel described here. The Panel involves bidirectional DNA sequencing of all coding exons of the six genes listed, below. The full coding sequence of each exon plus ~50 bp of flanking-coding DNA on either side are sequenced. Testing is performed sequentially in the order listed in the following Table. The order of genes may also be specified by the client. Testing stops when a likely causative mutation is found. The Panel offers cost savings compared to individual gene sequencing (see Prices and CPT Codes, below). As indicated, we will also sequence any single exon (Test #100, \$190) in any of these genes for family members of patients with known mutations, or to confirm research results.

Reference Sequences and Sensitivity of Test:

| Gene | Genomic NC_ | mRNA NM_ | Protein NP_ | CCDS | ALS Type/Percentage |
|---------------|-------------|-------------|-------------|---------|--|
| <i>SOD1</i> | 000021.8 | 000454.4 | 000445.1 | 33536.1 | Familial (20%), Sporadic (4%) |
| <i>FUS</i> | 000016.9 | 004960.3 | 004951.1 | 10707.1 | Familial (5%), Sporadic (2%) |
| <i>TARDBP</i> | 000001.10 | 007375.3 | 031401.1 | 122.1 | Familial (5%), Sporadic (2%) |
| <i>ANG</i> | 000014.8 | 001145.4 | 001136.1 | 9554.1 | Familial (>2%), Sporadic (1%) |
| <i>FIG4</i> | 000006.11 | 014845.5 | 055660.1 | 5078.1 | Familial (Unknown), Sporadic (Unknown) |
| <i>OPTN</i> | 000010.10 | 001008211.1 | 001008212.1 | 7094.1 | Familial (Unknown), Sporadic (0%) |

Indications for Test: All patients with symptoms suggestive of ALS or Motor Neuron Disease, as defined by the El Escorial criteria (<http://www.wfnals.org/guidelines/1998elescorial/elescorial1998.htm>).

Sensitivity of Test: The sensitivity of this test appears to be different between familial and sporadic ALS. See the Table above (Donkervoort and Siddique, 2009, www.genetests.org; DeJesus-Hernandez et al. Hum Mutat 31:E1377-1389, 2010; Daoud et al. J Med Genet 46:112-114, 2010; Gellera et al. Neurogenetics 9:33-40, 2008).

Turnaround Time: Maximum of 40 calendar days for the first gene, and 70 days for the entire panel, although most tests are completed more rapidly.

Specimen Requirements: See page 4 of Requisition Form.

Prices and CPT Codes:

| CPT | Description | <i>SOD1</i> | <i>FUS</i> | <i>TARDBP</i> | <i>ANG</i> | <i>FIG4</i> | <i>OPTN</i> | <i>PANEL</i> |
|--------------|-----------------------|---------------|---------------|---------------|---------------|----------------|---------------|------------------|
| 83890 | Ascertainment | \$ 30 (x1) | \$ 30 (x1) | \$ 30 (x1) | \$ 30 (x1) | \$ 30 (x1) | \$ 30 (x1) | \$ 30 (x1) |
| 83891 | DNA Isolation | \$ 40 (x1) | \$ 40 (x1) | \$ 40 (x1) | \$ 40 (x1) | \$ 40 (x1) | \$ 40 (x1) | \$ 40 (x1) |
| 83898 | Amplification | \$ 120 (x5) | \$ 270 (x15) | \$ 120 (x5) | \$ 80 (x2) | \$ 360 (x23) | \$ 220 (x13) | \$1190 (x63) |
| 83904 | Sequencing | \$ 190 (x5) | \$ 400 (x15) | \$ 180 (x5) | \$ 110 (x2) | \$ 530 (x23) | \$ 330 (x13) | \$1790 (x63) |
| 83894 | Separation | \$ 40 (x1) | \$ 70 (x1) | \$ 30 (x1) | \$ 20 (x1) | \$ 80 (x1) | \$ 50 (x1) | \$ 180 (x1) |
| 83912 | Interpretation/Report | \$ 70 (x1) | \$ 80 (x1) | \$ 70 (x1) | \$ 60 (x1) | \$ 130 (x1) | \$ 110 (x1) | \$ 290 (x1) |
| | Totals | \$ 490 | \$ 890 | \$ 470 | \$ 340 | \$ 1170 | \$ 780 | \$ 3,520* |

*When three or more genes in the Panel are tested, the price will be 85% of the sum of the individual gene prices.

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

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