

Amyotrophic Lateral Sclerosis, Autosomal Dominant or Sporadic via *ANG* Gene Sequencing --Test # 154

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 and age-dependant, but high penetrance. In rare families, the disease is transmitted with an autosomal recessive pattern (OMIM 205100). AD-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*, *VAPB*, *TARDBP*, *FUS* and *ANG*. To date, 12 different missense mutations in the *ANG* gene have been implicated in patients with ALS (Greenway et al. *Nat Genet* 38:411-413, 2006; Paubel et al. *Arch Neurol* 65:1333-1336, 2008). All *ANG* causative mutations were heterozygous; about 30 % of the mutations were found in patients with AD-ALS, while 70 % occurred in patients with the sporadic form of ALS.

Description of This Particular Test: The *ANG* gene encodes the angiogenin protein. Mutations in the *ANG* gene identified in patients with ALS were associated with functional loss of angiogenin activity (Wu et al. *Ann Neurol* 62:609-617, 2007). This test involves bidirectional DNA sequencing of the single coding exon of the *ANG* gene. The full coding sequence plus ~ 50 bp of flanking-coding DNA on either side are sequenced. We will sequence either section of the single exon in family members of patients with known mutations and to confirm results

Reference Sequences: Genomic: **NC_000014.7** mRNA and protein: **CCDS 9554.1**

Indications for Test: Patients with symptoms suggestive of AD-ALS or sporadic ALS. 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 Requisition Form.

Price:	Sequencing of the <i>ANG</i> gene		\$ 340	
CPT Codes:				
Sample Ascertainment x1	83890	\$ 30	DNA Isolation x1	83891 \$ 40
Amplification x2	83898	\$ 80	Sequencing x2	83904 \$ 110
Separation x1	83894	\$ 20	Interpretation/Report x1	83912 \$ 60

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

Contact for info: Dr. Khemissa Bejaoui, khemissa@preventiongenetics.com, www.preventiongenetics.com