

## Amyotrophic Lateral Sclerosis and Primary Open-Angle Glaucoma via *OPTN* Gene Sequencing --Test #156

**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.

**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. In rare families, the disease is transmitted with an autosomal recessive pattern (AR-ALS). To date, five genes have been associated with AD-ALS (*SOD1*, *SETX*, *ANG*, *VAPB*, *TARDBP* and *FUS*) and one gene with AR-ALS (*ALS2*). Recently, three different mutations in the *OPTN* gene have been reported in both AD-ALS and AR-ALS (Maruyama et al. Nature 465:223-226, 2010). A homozygous deletion of exon 5 and a homozygous nonsense mutation (Q398X) were reported in patients with AR-ALS; while one missense mutation (E478G) was reported in AD-ALS, and in patients with sporadic ALS. Prior to their involvement with ALS, *OPTN* mutations have been reported in patients with primary open-angle glaucoma (POAG OMIM 137760) (Rezaie et al. Science 295:1077-1079, 2002).

**Description of This Particular Test:** The *OPTN* gene encodes optineurin protein, which has several roles including transcription activation. This test involves bidirectional DNA sequencing of all coding exons and splice sites of the *OPTN* gene. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced. As indicated, we will also sequence one (Test #100) or two (Test #200) exons in family members of patients with known mutations or to confirm research results (\$190-340).

**Reference Sequences:** Genomic:NC\_000010.10 mRNA:NM\_001008211.1 Protein:NP\_001008212.1 (CCDS 7094.1)

**Indications for Test:** 1- Patients with symptoms suggestive of AD-ALS, AR-ALS, or sporadic ALS and no mutations in the genes most commonly associated with ALS (See ALS Panel Test # 155). 2- Patients with POAG.

**Sensitivity of Test:** Unknown at this time.

**Turnaround Time:** Maximum of 40 calendar days, although many tests are completed in 2-3 weeks.

**Specimen Requirements:** See page 4 of the Requisition Form.

<b>Price:</b>	<b>Sequencing of all coding exons of the <i>OPTN</i> gene</b>	<b>\$ 780</b>
<b>CPT Codes:</b>		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x13	83898 \$ 220	Sequencing x13 83904 \$ 330
Separation x1	83894 \$ 50	Interpretation/Report x1 83912 \$ 110

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

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