

Amyotrophic Lateral Sclerosis-8 Spinal Muscular Atrophy, Autosomal Dominant, Adult-Onset via *VAPB* Gene Sequencing (Test #107)

Brief Description of Clinical Features: A variant of amyotrophic lateral sclerosis (ALS), termed ALS8 (OMIM #608627) and mild, late-onset spinal muscular atrophy (OMIM #182980) have been attributed to a mutation in vesicle associated protein B, coded by *VAPB* (OMIM #605704). ALS8 demonstrates earlier onset and slower clinical course than classic ALS (Nishimura et al. *J Med Genet* 41:315-320, 2004). Mean age of disease onset was 38 years in a large Brazilian kindred, and notable initial symptoms include painful cramps, fasciculation, tremor, weakness and fatigue (Nishimura et al., 2004). Postural tremor, which was stable over time, was also an early sign. Lower motor neuron involvement was a universal symptom and all four limbs were affected. Serum CK was normal or slightly elevated and muscle biopsies demonstrated a neurogenic pattern (Nishimura et al. 2004). In other family members, clinical symptoms resemble a late onset, slowly progressive spinal muscular atrophy (Nishimura et al *Am J Hum Genet* 75:822-831, 2004).

Genetics: Disorders associated with *VAPB* demonstrate autosomal dominant inheritance. A *VAPB* missense mutation in exon 2 has been found to segregate with disease in a Caucasian Brazilian family of Portuguese decent (Nishimura et al., *J Med Genet* 41:315-320, 2004; Nishimura et al. *Hum Genet* 118:499-500, 2005). The disorder is completely penetrant within the reported family; although variability in clinical symptoms suggests the effect of modifier genes.

Description of This Particular Test: Vesicle-associated membrane protein B, a member of a small family of proteins that localize to intracellular membranes, is coded by exons 1-6 of the *VAPB* gene on chromosome 20q13.3. Testing is accomplished by amplifying each coding exon and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument. Exon 2, harboring the Portuguese founder mutation, can be tested separately.

Reference Sequences: **Genomic:** NC_000020.9 **mRNA and Protein:** CCDS 33498.1

Indication for Testing: Specific clinical signs observed in affected members of the Brazilian family include lower motor neuron symptoms with involvement in all four limbs, bulbar involvement, postural tremor, and painful cramping (Nishimura et al. *J Med Genet* 41:315-320, 2004).

Sensitivity of test: Mutations in *VAPB* are a rare cause of disease. Thus far the Portuguese p.Pro56Ser mutation is the only pathogenic variant reported. Evidence suggests that *VAPB* is not significantly associated with sporadic ALS (Kirby et al. *Neurology* 68:1951-1953, 2007).

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price:	Sequencing of <i>VAPB</i> Gene	Exons 1-6	\$ 490
CPT Codes:			
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x6	83898 \$ 120	Sequencing x6	83904 \$ 180
Separation x1	83894 \$ 40	Interpretation/Report x1	83912 \$ 80

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

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