

Autosomal Recessive Spinocerebellar Ataxia and Amyotrophic Lateral Sclerosis Type 4 via *SETX* Gene Sequencing – Test #109

Brief Description of Disorders: Autosomal Recessive Cerebellar Ataxias (ARCAs) are a heterogeneous group of neurological disorders involving both the central and peripheral nervous systems, and in some cases additional systems and organs (Palau and Espinós Orphanet J Rare Dis 1:47, 2006). ARCAs involve a wide range of clinical features including gait imbalance, diminished tendon reflexes, involuntary movements and ophthalmological and cutaneous abnormalities. ARCAs are distinguished from other cerebellar ataxias by an autosomal recessive inheritance, onset before the age of 20 years and slow progression (Fogel and Perlman Lancet Neurol 6:245-257, 2007).

Amyotrophic Lateral Sclerosis Type 4 (ALS4, OMIM 602433) is a neurological disease characterized by juvenile onset, usually before the age of 25 years, a slow progression and a normal life span. Typical symptoms include distal muscle weakness and atrophy, brisk deep-tendon reflexes and a positive Babinski sign (Chen et al. Am J Hum Genet 74:1128-1135, 2004).

Genetics: Mutations in the *SETX* gene cause one form of ARCAs: Spinocerebellar Ataxia, Autosomal Recessive 1 (SCAR1, OMIM 606002). Because oculomotor apraxia was observed in the initial patients with *SETX* mutations, this form of the disease was also referred to as Ataxia-Oculomotor Apraxia 2 (Moreira et al. Nat Genet 36:225-227, 2004). Subsequent reports detected oculomotor apraxia in only 50% of patients with *SETX* mutations (Moreira and Koenig, GeneReviews, 2007, www.genetests.org). SCAR1 patients constitute a heterogeneous group presenting with cerebellar ataxia and a range of additional features, including oculomotor apraxia, elevated serum levels of α -fetoprotein and creatine kinase (Moreira et al. Nat Genet 36:225-227, 2004), distal amyotrophy, peripheral neuropathy (Duquette et al. Ann Neurol 57:408-414, 2005; Asaka et al. Neurology 66:1580-1581, 2006) and nystagmus, spasticity and areflexia (Nicolaou et al. BMC Med Genet 9:28, 2008). At least 27 *SETX* mutations have been reported in patients with SCAR1. These mutations are distributed throughout the gene and include missense, nonsense, splicing and small deletions/insertions.

In addition to the SCAR1-causative mutations, three dominant missense mutations in the *SETX* gene were identified in patients with ALS4 (Chen et al. Am J Hum Genet 74:1128-1135, 2004) and one dominant missense mutation was found in a Chinese patient with apparently isolated ALS (Zhao et al. Amyotroph Lateral Scler 10:118-122, 2009).

Description of this Particular Test: The *SETX* gene encodes the senataxin protein. *SETX* testing for SCAR1 or ALS4 at PreventionGenetics involves bidirectional sequencing of all 24 coding exons and splice sites of *SETX* gene. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced. We will sequence any single or double exons in family members of patients with known mutation or to confirm previous results.

Reference Sequences: Genomic: **NC_000009.10** mRNA and protein: **CCDS 6947.1**

Indications for Test: Patients with SCAR1 (OMIM 606002) and patients with ALS 4 (OMIM 602433).

Sensitivity of Test: Currently unknown.

Turn Around Time: Maximum of 40 calendar days.

Specimen Requirement: See page 4 of the Requisition Form.

Price:	Sequencing of all coding exons of the <i>SETX</i> Gene:	\$ 1690
CPT Codes:		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x 31	83898 \$ 560	Sequencing x 31 83904 \$ 850
Separation x1	83894 \$ 110	Interpretation/Report x1 83912 \$ 100

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

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