

Synaptic Nuclear Envelope Protein-1 Related Disorders via SYNE1 Gene Sequencing
Autosomal Recessive Spinocerebellar Ataxia 8
Emery-Dreifuss Muscular Dystrophy
Congenital Muscular Dystrophy with Adducted Thumbs and Mental Retardation
Test #246 (exons 2 - 146) Test # 247 (French Canadian Mutation Panel)

Brief Description of Clinical Features: Autosomal recessive cerebellar ataxia 1 (ARCA1; OMIM #610743) is a phenotypically homogeneous disorder with onset from the late teens to the fifth decade of life. Patients present with cerebellar ataxia and/or dysarthria and slowly progress to significant manifestations of both (Gros-Louis et al. *Nature Genet* 39:80-85, 2007). Additional clinical signs include dysmetria, abnormal tendon reflexes in the lower extremities, and mild oculomotor involvement (Dupré et al. *Ann Neurol* 62:93-98, 2007). MRI studies show diffuse atrophy limited to the cerebellum (Dupré et al. *GeneReviews* 2007). Emery-Dreifuss muscular dystrophy (EDMD) is characterized clinically by joint contractures beginning in early childhood, slowly progressive muscle weakness and wasting, and cardiac involvement. Age of onset and severity can vary between and within affected families (Bonne et al. *GeneReviews* 2007). A phenotype consisting of congenital muscular dystrophy (CMD), adducted thumbs, mild mental retardation, and cerebellar hypoplasia has been reported in two sibs from a consanguineous family (Voit et al. *Neuromuscul Disord* 12:623-630, 2002). *SYNE1* mutations were identified in these patient's and their muscle lacked SYNE1 protein at the nuclear envelope (Voit et al. *Neuromuscul Disord*. 17:833-834, 2007).

Genetics: Spinocerebellar ataxia due to *SYNE1* mutations is inherited as an autosomal recessive disorder in families in the Beauce region of southeastern Quebec and, for this reason, it is also known as recessive ataxia of Beauce (Dupré et al. *Neurology* 58:A35, 2002). EDMD due to *SYNE1* mutations appears to be inherited in a dominant pattern as a result of disrupted binding of nesperin-1 to lamin and emerin (Zhang et al. *Hum Mol Genet* 16:2816-2833, 2007). CMD with adducted thumbs and mental retardation is inherited as an autosomal recessive disorder.

Description of This Particular Test: Synaptic nuclear envelope protein 1 is encoded by the *SYNE1* gene (OMIM #608441) located on chr 6q25. Testing is accomplished by amplifying the coding exons of transcript variants 1 and 2 and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument. A separate testing panel is offered for French Canadian-associated SCAR8. It examines the mutations p.Arg2906Stop (exon 57), c.15705-12A>G (exon 84), c.16177-2A>G (exon 87), and p.Asp5868AlafsStop13 (exon 95), which account for 76% of disease alleles in SCAR8 for that ethnic group (Dupré et al. 2007).

Reference Sequences: Genomic: NC_000006.10 mRNA and Protein: CCDS 5236.1 and 5235.1

Indication for Testing: Individuals with slowly progressive cerebellar ataxia and dysarthria with adult onset, or with presentation consistent with EDMD, or with CMD with adducted thumbs and mental retardation.

Sensitivity of Test: *SYNE1* mutations are the only known cause of autosomal recessive spinocerebellar ataxia 8. Clinical sensitivity should be high for patients with symptoms consistent with a pure cerebellar ataxia who are of French Canadian heritage. Because allelic heterogeneity exists for this homogeneous population, it is reasonable to expect this gene to be causative in other populations as well. Among 190 probands with EDMD and without lamin or emerin mutations, three were found to have heterozygous *SYNE1* mutations (Zhang et al. 2007). Too few cases of CMD caused by *SYNE1* mutations have been reported to estimate clinical sensitivity.

Turnaround Time: Maximum of 80 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: **Sequencing of SYNE1:**

Test	CPT Codes						Total
	83890	83891	83898	83904	83894	83912	
French Canadian Panel	\$ 30 x1	\$ 40 x1	\$ 150 x4	\$ 210 x4	\$ 40 x1	\$80 x1	\$ 550
Exons 2-146	\$ 30 x1	\$ 40 x1	\$ 2400 x161	\$ 3600 x161	\$ 260 x1	\$160 x1	\$ 6490

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

Contact for info: Thomas L. Winder, PhD, FACMG, tom.winder@preventiongenetics.com, www.preventiongenetics.com