

Nemaline Myopathy 5 (Amish Nemaline Myopathy) Slow Skeletal Muscle Troponin T (*TNNT1*) Gene Sequencing (Test #332)

Brief Description of Clinical Features: Mutations in the troponin T1 gene (*TNNT1*; OMIM #191041) are one cause of autosomal recessive nemaline myopathy (NEM5; OMIM #605355). NEM is a genetically and clinically heterogeneous disorder characterized by muscle weakness, hypotonia and the presence of nemaline bodies in skeletal muscle fibers. Muscle weakness is typically observed in affected neonates or infants, although later onset cases are reported (Ryan et al. *Ann Neurol* 50:312-320, 2001). The most severely affected muscle groups are proximal limb, facial, bulbar, and respiratory muscles. Deep tendon reflexes are absent or depressed. Histologically, NEM is characterized by type 1 fiber predominance and the presence of rod-like structures called nemaline bodies upon Gomori trichrome staining of skeletal muscle (Ryan et al. *Neurol* 60:665-673, 2003). Six clinical types of NEM have been delineated based on age of onset, severity and distribution of weakness, and respiratory function (Ryan et al. 2001; North and Ryan, *GeneReviews*, 2009). Troponin T1 associated NEM is a lethal form of nemaline myopathy described only in the Old Order Amish community of Pennsylvania (Johnston et al. *Am J Hum Genet* 67:814-821, 2000). Newborns affected with *TNNT1*-associated nemaline myopathy are hypotonic and have shoulder and hip contractures along with tremors. Contractures and muscle weakness progressively worsen and patients develop pectus carinatum before life-threatening respiratory symptoms develop in the second year of life (Johnston et al. 2000).

Genetics: To date, mutations in six genes have been shown to cause nemaline myopathy. Mutations in *ACTA1* (NEM3) and *NEB* (NEM2) are the only relatively common causes (Ryan et al. 2001). Among Old Order Amish of Lancaster County, Pennsylvania, a p.Glu180Stop founder mutation in exon 11 of the *TNNT1* gene was found to account for the autosomal recessive nemaline myopathy in this community (Johnston et al. 2000; Jin et al. *J Biol Chem* 278:26159-26165, 2003). The incidence of NEM5 among this population is ~1/500 (Johnston et al. 2000).

Description of This Particular Test: Testing is accomplished by amplifying all coding exons contained in mRNA isoforms A and B (exons 2-14) and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument.

Reference Sequences:

	Isoform A	Isoform B
Genomic:	NC_000019.8	NC_000019.8
mRNA:	NM_003283.4	NM_001126132.1
Protein:	NP_003274.3	NP_001119604.1

Indication for Testing: Individuals, particularly of the Old Order Amish, with symptoms consistent with the lethal form of nemaline myopathy.

Sensitivity of test: Clinical and analytical sensitivity for testing symptomatic individuals of the Old Order Amish is expected to be high. Clinical sensitivity among other populations is not known.

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: **Sequencing of *TNNT1*:** **exon 11 only: \$190** **exons 2-14: \$690**

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x12	83898 \$ 210	Sequencing x12	83904 \$ 310
Separation x1	83894 \$ 30	Interpretation/Report x1	83912 \$ 70

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

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