

Tropomyosin 2-Related Disorders via *TPM2* Gene Sequencing (Test #331) Nemaline Myopathy (NEM3) and Distal Arthrogryposis (DA1)

Brief Description of Clinical Features: Nemaline myopathy (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 with 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*, 2006). Overlap among the six groups is significant, and adults are sometimes diagnosed only after a family member has presented with typical signs.

Distal arthrogryposis syndromes (DA) are a group of multiple congenital contracture disorders with distal joint involvement more common than proximal; variable clinical expression; and autosomal dominant inheritance (Bamshad et al. *Am J Med Genet* 65:277-281, 1996). Distal arthrogryposis type 1 (DA1) is characterized by talipes and camptodactyly, although the shoulders and hips may also be affected (Sung et al. *Am J Hum Genet* 72:681-690, 2003). The clinical phenotype of DA1 overlaps that of Freeman-Sheldon syndrome (FSS; Klemm and Hall, *Am J Med Genet* 55:414-419, 1998), and individuals with features in common to both DA1 and FSS have been found to have mutations in the *TNNI2* gene (Sung et al. 2003).

Genetics: Mutations in the gene (*TPM2*; OMIM 190990) encoding the muscle form of tropomyosin 2, also referred to as beta-tropomyosin, are a rare cause of nemaline myopathy (NEM3; OMIM 161800) and distal arthrogryposis syndrome type 1 (DA1; OMIM 108120). All cases thus far have demonstrated autosomal dominant inheritance of *TPM2* missense mutations.

Description of This Particular Test: The muscle form of beta-tropomyosin is coded by the *TPM2* gene located on chr 9p13. Testing is accomplished by amplifying the 9 coding exons and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument.

Reference Sequences: **Genomic:** NC_000009.10 **mRNA and Protein:** CCDS 6587.7

Indication for Testing: Individuals with clinical symptoms consistent with NEM and muscle biopsy studies showing nemaline bodies. Individuals with clinical symptoms consistent with distal arthrogryposis.

Sensitivity of Test: *TPM2* mutations are a rare cause of nemaline myopathy and distal arthrogryposis. In a cohort of 66 unrelated nemaline myopathy patients, two were found to have *TPM2* mutations (Donner et al. *Neuromuscul Disord* 12:151-158, 2002). One family with distal arthrogryposis has been found with a *TPM2* mutation (Sung et al. 2003).

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: **Sequencing of *TPM2*** **\$ 590**

CPT Codes:

Sample Ascertainment x1	83890	\$ 30	DNA Isolation x1	83891	\$ 40
Amplification x9	83898	\$160	Sequencing x9	83904	\$230
Separation x1	83894	\$ 50	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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