PREVENTION GENETICS
DISEASE PREVENTION THROUGH GENETIC TESTING

CLIA #: 52D1027685 ● CAP #: 7185561
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Tropomyosin 3-Related Myopathies *via TPM3* Gene Sequencing (Test #357)
Congenital Fiber Type Disproportion (CFTD) Nemaline Myopathy (NEM1)

Brief Description of Clinical Features: Congenital fiber type disproportion (CFTD) is a genetically and clinically heterogeneous congenital myopathy usually presenting as hypotonia and delayed motor milestones before 1 year of age. Clinical findings among CFTD patients with *TPM3* mutations include proximal limb-girdle weakness, weakness of neck flexion and ankle dorsiflexion, facial weakness, ptosis, and absent or decreased deep tendon reflexes (Clarke et al. *Ann Neurol* 63:329-337, 2008; Lawlor et al. *Hum Mutat* 31:176-183, 2010). Dependence on nocturnal ventilation support was a common finding in these two studies and, except for the most severely affected individual, patients remained ambulatory. Age of onset and severity is noted to vary even within the same family (Clarke et al. 2008), however, patients diagnosed as adults through family studies were aware of symptoms of weakness and/or myalgia as children (Lawlor et al. 2010). Histologically, type 1 muscle fibers from patients were smaller that type 2 fibers by 50% to 77% in one study (Clarke et al. 2008) and 47% in another (Lawlor et al. 2010). Marked fiber size disproportion was due to hypotrophy of type 1 fibers and hypertrophy of type 2 fibers. Typical of CFTD, overall type 1 fiber predominance, absence of type 2B fibers, and absence of other histopathology was commonly observe in patient biopsies (Clarke et al. 2008). Nemaline myopathy (NEM) is a genetically and clinically heterogeneous disorder characterized by muscle weakness, hypotonia and the presence of rod-like structures called 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 also characterized by type 1 fiber predominance, however, the presence of nemaline bodies is a finding unique to NEM (Ryan et al. *Neurol* 60:665-673, 2003).

Genetics: Mutations in the gene encoding the muscle form of tropomyosin 3 (*TPM3*; OMIM #191030), also referred to as alpha-tropomyosin-$_{SLOW}$, are a rare cause of nemaline myopathy (NEM1; OMIM #609284) and the most common cause of congenital fiber type disproportion (CFTD; OMIM #255310). Myopathy due to *TPM3* mutations may be inherited as an autosomal dominant or recessive disorder (Lawlor et al. 2010; Clarke et al 2008; Ryan et al. 2001). *De novo TPM3* mutations have also been documented to be causative for CFTD (Clarke et al. 2008).

Description of This Particular Test: The muscle form of alpha-tropomyosin is coded by exons 1 – 10 of the *TPM3* gene located on chr 1q22. Testing is accomplished by amplifying the 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_000001.9** **mRNA: NM_152263.2**
Protein: NP_689476.2 **mRNA and Protein: CCDS 41403.1**

Indication for Testing: Individuals with clinical symptoms consistent with NEM and muscle biopsy studies showing nemaline bodies, and individuals with clinical symptoms consistent with CFTD with muscle biopsies demonstrating fiber type disproportion in the absence of nemaline bodies and other histological findings suggestive of another diagnosis.

Sensitivity of test: *TPM3* mutations are the most common known cause of CFTD. Clinical sensitivity should be high when type 1 fiber hypotrophy is ≥50% in the absence of other histopathological findings. Lawlor et al. (2009) found six of 13 patients with a diagnosis of CFTD based on type 1 fiber hypotrophy to have mutations in this gene. In another cohort of 23 CFTD families, six were found to have *TPM3* mutations (Clarke et al. 2008). It is estimated that *TPM3* accounts for <3% of NEM (Wattanasirichaigoon et al. *Neurol* 59:613-617, 2002).

Turnaround Time: Maximum of 40 days although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price:	**Sequencing of *TPM3***		**$ 570**	
CPT Codes:				
Sample Ascertainment	83890	$ 30	DNA Isolation	83891 $ 40
Amplification x 8	83898	$ 160	Sequencing x8	83904 $ 240
Separation	83894	$ 40	Interpretation/Report	83912 $ 60

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

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