

α -Actin (Skeletal Muscle Form)-Related Myopathy via *ACTA1* Sequencing (Test #358) Nemaline Myopathy (NEM3) Congenital Fiber-Type Disproportion (CFTD1)

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* 2010). Overlap among the six groups is significant, and adults are sometimes diagnosed only after a family member has presented with typical signs. Congenital fiber-type disproportion (CFTD) usually presents with hypotonia and varying degrees of skeletal muscle weakness affecting the limbs. Symptoms appear at birth or within the first year of life and, in the majority of cases, remain stable over time or improve with age. The diagnosis relies on histological observation of type 1 fibers that are at least 12% smaller than the mean diameter of type 2A and/or type 2B fibers in the absence of other significant pathologic findings, most notably nemaline bodies. Actinopathies are reviewed by Goebel and Laing (*Brain Pathology* 19:516-522, 2009).

Genetics: Mutations in the skeletal muscle form of α -actin (*ACTA1*; OMIM #102610) are one cause of nemaline myopathy (NEM3; OMIM #161800) and congenital fiber-type disproportion (CFTD1; OMIM #255310). Nearly 200 unique mutations are known (Laing et al. *Hum Mutat* 30:1267-1277, 2009). NEM3 is most often inherited as an autosomal dominant condition, and most patients have *de novo* mutations (Laing et al. 2009). Parental mosaicism for *ACTA1* mutations is documented (*eg.* Nowak et al. *Nat Genet* 23:208-212, 1999). Recessive inheritance of NEM3 is rare and all such mutations manifest as null alleles. Although CFTD is a genetically heterogeneous condition that can be inherited in an autosomal recessive, autosomal dominant, or X-linked manner, the three reported cases of *ACTA1*-related CFTD have been caused by autosomal dominant mutations (Laing et al. *Ann Neurol* 56:689-694, 2004).

Description of This Particular Test: Skeletal muscle α -actin is coded by exons 2 – 7 of the *ACTA1* gene. 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_000001.10 mRNA: NM_001100.3
Protein: NP: 001091.1 mRNA and Protein: CCDS 1578.1

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 and muscle biopsy studies showing type 1 fibers that are smaller than type 2 fibers.

Sensitivity of test: *ACTA1* mutations account for 15%-25% of all cases of nemaline myopathy (*eg.* Nowak et al. 1999; Ryan et al. 2001), and possibly for up to 50% of the severe, congenital-onset form (Agrawal et al. *Ann Neurol* 56:86-96, 2004). Five other genes (*NEB*, *TPM3*, *TNNT1*, *TPM2*, *CFL2*) are associated with NEM, however, the fraction of cases attributed by them is small. Laing et al. (2004) found heterozygous *ACTA1* mutations in 6% (three unrelated individuals) of a CFTD cohort from Japan and Australia.

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

Specimen Requirements: See page 4 of Requisition Form.

Price:	Sequencing of <i>ACTA1</i>	\$ 590		
CPT Codes:				
Sample Ascertainment	83890 \$ 30	DNA Isolation	83891 \$ 40	
Amplification x11	83898 \$ 160	Sequencing x11	83904 \$ 230	
Separation	83894 \$ 40	Interpretation/Report	83912 \$ 90	

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

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