Nemaline Myopathy, ACTA1-related: ACTA1 Gene Deletion/Duplication

**Test Code:** DACTA  
**Turnaround time:** 2 weeks  
**CPT Codes:** 81228 x1

### Condition Description

The term nemaline myopathy (NM) refers to a group of genetically distinct disorders linked by common morphologic features observed on muscle histology. NM is characterized by weakness, hypotonia, and depressed or absent deep tendon reflexes. Muscle weakness is usually most severe in the face, the neck flexors, and the proximal limb muscles. In some individuals with NM, the distal muscles are involved. There are six forms of NM, classified by onset and severity of motor and respiratory involvement: severe congenital (neonatal) form (16% of all individuals with NM): Amish NM, intermediate congenital form (20%); typical congenital form (46%); childhood-onset form (13%); and adult-onset (late-onset) form (4%). Considerable overlap occurs among the forms and there is variation in course and outcome even within families.

In congenital forms of NM, the face is often elongated and expressionless, with a tent-shaped mouth, high-arched palate, and retrognathia. Gross motor milestones are delayed, but most affected individuals are otherwise developmentally normal. Dysarthria and feeding difficulties are common. Respiratory problems secondary to involvement of the diaphragm and intercostal muscles are common. Many children with NM have hypermobility of joints in infancy and early childhood; contractures and deformities of the joints, including scoliosis, commonly develop with time. The extracocular muscles are usually spared. Cardiac contractility is usually normal.

Diagnosis is based on clinical findings and the observation of characteristic rod-shaped structures (nemaline bodies) on muscle biopsy stained with Gomori trichrome. Serum creatine kinase concentration is usually normal or minimally elevated. Disease-causing mutations have been identified in seven different genes, all of which encode protein components of the muscle thin filament: ACTA1, NEB, TPM3, TPM2, TNNT1, CFL2, and KBTBD13. Additional individuals with NM do not link to any of the seven identified loci, suggesting further genetic heterogeneity.

NM can be inherited in an autosomal dominant or autosomal recessive manner. In one study, approximately 20% of cases were autosomal recessive, approximately 30% autosomal dominant, and approximately 50% simplex (i.e., single occurrences in a family) representing heterozygosity for *de novo* dominant mutations or homozygosity for autosomal recessive mutations.

This testing is for mutations in the ACTA1 gene (1q42.1) only.

For patients with suspected nemaline myopathy, ACTA1-related, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

### References:

- GeneReviews: Nemaline Myopathy
- OMIM #161800 Nemaline Myopathy 3

### Genes

ACTA1

### Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of nemaline myopathy in an individual in whom sequence analysis was negative.
- Carrier testing in adults with a family history of autosomal recessive nemaline myopathy in whom sequence analysis was negative.

### Methodology

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

### Detection

Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

### Specimen Requirements

Submit only 1 of the following specimen types
**Type: DNA, Isolated**

**Specimen Requirements:**
- Microtainer
- 3μg
- Isolation using the Perkin Elmer™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

**Specimen Collection and Shipping:**
Refrigerate until time of shipment in 100 ng/μL in TE buffer. Ship sample at room temperature with overnight delivery.

**Type: Whole Blood (EDTA)**

**Specimen Requirements:**
- EDTA (Purple Top)
  - Infants and Young Children (2 years of age to 10 years old): 3-5 ml
  - Older Children & Adults: 5-10 ml
  - Autopsy: 2-3 ml unclotted cord or cardiac blood

**Specimen Collection and Shipping:**
Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

**Special Instructions**
Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Sequence analysis of the ACTA1 gene is available and is required before deletion/duplication analysis.
- Sequence and deletion/duplication analysis is also available for the NEB, TPM2, TNNT1, and TPM3 genes for nemaline myopathy.
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available for known familial mutations only. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.