

Nemaline Myopathy, *TNNT1*-related: *TNNT1* Gene Sequencing

Test Code: STNNT

Turnaround time: 6 weeks

CPT Codes: 81479 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 extraocular 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 *KBTD13*. 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 *TNNT1* gene (19q13.4) only.

For patients with suspected nemaline myopathy, *TNNT1*-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 #605355 [Nemaline Myopathy 5](#)

Genes

[TNNT1](#)

Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of nemaline myopathy
- Carrier testing in adults with a family history of autosomal recessive nemaline myopathy

Methodology

PCR amplification of 13 exons contained in the *TNNT1* gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

Detection

Clinical Sensitivity: Disease-causing mutations have been identified in six different genes, all of which encode protein components of the muscle thin filament: *ACTA1*, *NEB*, *TPM3*, *TPM2*, *TNNT1*, and *CFL2*. Additional individuals with NM do not link to any of the five identified loci, suggesting further genetic heterogeneity. This testing is for mutations in the *TNNT1* gene (19q13.4) only. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Analytical Sensitivity: ~99%

Specimen Requirements

Submit only 1 of the following specimen types

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.

Type: Saliva

Specimen Requirements:

Oragene™ Saliva Collection Kit

Oragene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:

Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

Type: DNA, Isolated

Specimen Requirements:

Microtainer

8µg

Isolation using the Perkin Elmer™ Chemagen™ 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.

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

- Deletion/duplication analysis of the *TNNT1* gene by CGH array is available for those individuals in whom sequence analysis is negative.
- Sequence analysis and deletion/duplication analysis are also available for the *NEB*, *TPM2*, *ACTA1*, 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.