Nemaline Myopathy, NEB-related: NEB Gene Sequencing

Test Code: SNEBX
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 extracellular 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 NEB gene (2q23.3) only, which are inherited in an autosomal recessive manner. Sequence analysis will not detect heterozygous carriers of the exon 55 deletion founder mutation seen in individuals of Ashkenazi Jewish descent. For carrier screening for the exon 55 deletion, please refer to the Ashkenazi Jewish Carrier Screening Panel or the Nemaline Myopathy, NEB-Related NEB Deletion/Duplication Assay.

For patients with suspected nemaline myopathy, NEB-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:**

- OMIM #161650: NEB gene
- OMIM #256030: Nemaline Myopathy 2

**Genes**

- NEB

**Indications**

This test is indicated for:

- Confirmation of a clinical diagnosis of nemaline myopathy, NEB-related
- Carrier testing in adults with a family history of nemaline myopathy, NEB-related

**Methodology**

**Next Generation Sequencing:** In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

**Detection**

Clinical Sensitivity: Unknown. 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 clinical and/or biochemical phenotype.

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Analytical Sensitivity: ~99%

**Specimen Requirements**

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) or ACD (yellow top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Related Tests**

- Deletion/duplication analysis of the NEB gene by CGH array is available for those individuals in whom sequence analysis is negative.
- Sequencing and deletion/duplication analysis are also available for the ACTA1, TNNT1, TPM2, and TPM3 genes.
- 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 only for known familial mutations to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.