

Nemaline Myopathy With Cores (NEM6) via *KBTBD13* Gene Sequencing (Test #598)

Brief Description of Clinical Features: Mutations in the gene encoding Kelch repeat and BTB/POZ domains-containing protein-13 (*KBTBD13*; OMIM 613727) are one cause of autosomal dominant nemaline myopathy (NEM6; OMIM 609273). 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 upon Gomori trichrome staining of skeletal muscle (Ryan et al. *Neurology* 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*, 2009). *KBTBD13* related nemaline myopathy has been described in a small number of patients with normal early motor development followed by childhood-onset of slowly progressive proximal muscle weakness and exercise intolerance (Olive et al. *Muscle Nerve* 42:901-907, 2010; Sambuughin et al. *Am J Hum Genet* 87:842-847, 2010). Notable complaints from patients include feelings of muscle slowness or stiffness, and slow response times to falls (Gommans et al. *Neuromusc Disord* 12:13-18, 2002). Respiratory or cardiac muscles are not affected by NEM6. The disease is mildly progressive although there are no reports of wheelchair-bound patients. Histopathologic changes seen on skeletal muscle biopsy include nemaline rods, cores, loss of myofibrillar organization, and predominance of hypertrophic type 1 fibers.

Genetics: Nemaline myopathy is a genetically heterogeneous disorder and mutations in *ACTA1* (NEM3) and *NEB* (NEM2) are the only relatively common causes (Ryan et al. 2001). Heterozygous mutations in the *KBTBD13* gene have been found in a small number of patients with a relatively constant clinical phenotype (Sambuughin et al. *Am J Hum Genet* 87:842-847, 2010). NEM6 is inherited as an autosomal dominant disorder secondary to *KBTBD13* mutations.

Description of This Particular Test: The ‘Kelch repeat and BTB/POZ domains-containing protein-13’ protein is encoded by exon 1 of the *KBTBD13* gene on chromosome 15q22. Testing is accomplished by amplifying the coding exon and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument. As indicated, we will also sequence any single exon (Test #100, \$190) in family members of patients with known mutations or to confirm research results.

Reference Sequences: Genomic: NC_000015.9 mRNA: NM_001101362.2
Protein: NP_001094832.1 mRNA and Protein: CCDS 45281.1

Indication for Testing: Individuals with symptoms consistent with the childhood-onset nemaline myopathy, autosomal dominant inheritance, and negative studies for the more common causes of this disorder.

Sensitivity of test: *KBTBD13* related nemaline myopathy (NEM6) is likely a rare disorder. Thus far only a small number of patients have been reported.

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 *KBTBD13* exon 1: \$ 540

CPT Codes:

Sample Ascertainment x1	83890	\$ 30	DNA Isolation x1	83891	\$ 40
Amplification x6	83898	\$ 140	Sequencing x6	83904	\$ 225
Separation x1	83894	\$ 30	Interpretation/Report x1	83912	\$ 75

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

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