

Nemaline Myopathy Test Panel - Test #350

Brief Description of Clinical Features: Nemaline myopathy (NM) 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, NM 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. *Neurol* 60:665-673, 2003). Six clinical types of NM 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 clinical groups is significant and adults are sometimes diagnosed only after another family member has presented with typical signs. Severe, lethal congenital-onset NM is more often caused by *ACTA1* mutations (Agrawal et al. *Ann Neurol* 56:86-96, 2004). Nebulin gene mutations more often cause typical neonatal onset disease, although *NEB* mutations have been found in every clinical form of NM (Lehtokari et al. *Hum Mutat* 27:946-956, 2006). Troponin T1 associated NM is a lethal disorder described only in the Old Order Amish community of Pennsylvania (Johnston et al. *Am J Hum Genet* 67:814-821, 2000).

Genetics: Mutations in seven genes have been shown to cause NM. Mutations in *ACTA1* and *NEB* are the only relatively common causes (Ryan et al. 2001). *ACAT1* related NM can be inherited as a dominant or recessive condition while *NEB* NM is a recessive condition (North and Ryan, 2010).

Description of This Particular Test: The following genes are tested in the order specified by the client. 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. See also the individual Test Descriptions for each gene.

Reference Sequences:

Gene	NM Subtype	Genomic: NC_	mRNA: NM_	Protein: NP_	mRNA and Protein: CCDS
<i>ACTA1</i>	NEM3	000001.9	001100.3	001091.1	1578.1
<i>NEB</i>	NEM2	000002.10	004543.3	004534.2	N/A
<i>TPM2</i>	NEM4	000009.10	003289.3	003280.2	6587.7
<i>TPM3</i>	NEM1	000001.9	152263.2	689476.2	41403.1
<i>TNNT1</i>	NEM5	000019.8	003283.4	003274.3	12917.1
<i>CFL2</i>	NEM7	000014.8	021914.7	068733.1	9650.1

Indication for Testing: Individuals with clinical symptoms consistent with NM and a muscle biopsy with nemaline bodies.

Sensitivity of test: *ACTA1* mutations account for 15%-25% of all individuals with NM (eg. Nowak et al. *Nat Genet* 1999; Ryan et al. 2001), and possibly up to 50% of severe lethal congenital-onset NM (Agrawal et al. 2004). Nebulin mutations are the next most common cause of NM. Deletion of exon 55 of *NEB* occurs with a carrier frequency of about 1% among people of Ashkenazi Jewish ancestry (Anderson et al. *Hum Genet* 115:185-190, 2004). Five other genes (*TPM3*, *TNNT1*, *TPM2*, *CFL2*, *KBTBD13* [NEM6]) are associated with NM, however, the fraction of cases attributed by them is small.

Turn Around Time: Approximately 2 to 3 weeks per gene or maximum of 80 days for the panel.

Specimen Requirements: See page 4 of the Requisition Form.

Price and CPT codes: Sequencing of *ACTA1*, *NEB*, *TPM2*, *TPM3*, *TNNT1*, *CFL2* Genes and *NEB* exon 55 deletion test:

CPT	<i>ACTA1</i>	<i>NEB</i>	<i>NEB</i> x55 del	<i>TPM2</i>	<i>TPM3</i>	<i>TNNT1</i>	<i>CFL2</i>	Panel
83890	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)
83891	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)
83898	\$ 140 (x6)	\$ 1,810 (x146)	\$ 40 (x1)	\$ 160 (x9)	\$ 160 (x8)	\$ 210 (x12)	\$ 100 (x4)	\$ 2,840 (x186)
83904	\$ 210 (x6)	\$ 3,870 (x146)	N/A	\$ 230 (x9)	\$ 240 (x8)	\$ 310 (x12)	\$ 150 (x4)	\$ 4,250 (x185)
83894	\$ 40 (x1)	\$ 420 (x1)	\$ 30 (x1)	\$ 50 (x1)	\$ 40 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 560 (x1)
83912	\$ 70 (x1)	\$ 320 (x1)	\$ 60 (x1)	\$ 80 (x1)	\$ 60 (x1)	\$ 70 (x1)	\$ 70 (x1)	\$ 340 (x1)
Totals:	\$ 530	\$6,490	\$ 200	\$ 590	\$ 570	\$ 690	\$420	\$ 8,060

When 4 or more genes on this panel are sequentially tested, a 15% discount will apply to the sum of the prices of the individual tests.

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

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