

Nebulin Gene (*NEB*) Exon 55 Deletion Test (Test #356) Nemaline Myopathy (NEM2)

Brief Description of Clinical Features: Mutations in the nebulin gene (*NEB*; OMIM #161650) are one cause of autosomal recessive nemaline myopathy (NEM) (OMIM #256030). 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. *Neurol* 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*, 2006). Nebulin gene mutations more often cause typical neonatal onset disease, although *NEB* mutations have been found in every clinical form of NEM (Lehtokari et al. *Hum Mut* 27:946-956, 2006). Overlap among the six clinical groups is significant, and adults are sometimes diagnosed only after another family member has presented with typical signs.

Genetics: To date, mutations in six genes have been shown to cause nemaline myopathy. Mutations in *ACTA1* (NEM3) and *NEB* (NEM2) are the only relatively common causes (Ryan et al. 2001). All reported cases of *NEB*-associated NEM have demonstrated autosomal recessive inheritance (Lehtokari et al. 2006). The only common *NEB* mutation is an exon 55 deletion found at a carrier frequency of about 1% among people of Ashkenazi Jewish ancestry (Anderson et al. *Hum Genet* 115:185-190, 2004). Much rarer causes of NEM are mutations in *TPM3* (NEM1), *TPM2* (NEM4), *TNNT1* (NEM5), and *CFL2* (NEM7).

Description of This Particular Test: Testing is accomplished by amplifying patient and control DNAs with PCR primers that flank or lie within the 2,502 bp deletion, essentially as described by Anderson et al. (*Hum Genet* 115:185-190, 2004). This test permits the identification of patients with normal genotypes, patients who are homozygous for the deletion, and heterozygous carriers.

Indication for Testing: Individuals of Ashkenazi Jewish ancestry with symptoms consistent with nemaline myopathy whose muscle biopsies show predominance of type 1 fibers and nemaline bodies.

Sensitivity of test: This test is intended to detect the exon 55 *NEB* deletion mutation found in Ashkenazi Jews; it will not detect any other sequence variant. Sequencing the entire *NEB* coding region may be indicated in individuals who are clinically affected and have either one or no alleles with the exon 55 deletion. Full *NEB* gene sequencing is available from PreventionGenetics (Test #355). Because Nemaline Myopathy exhibits locus and allelic heterogeneity a negative *NEB* test does not rule out this diagnosis when classic clinical and histological findings are present.

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: *NEB* Exon 55 Deletion Test **\$ 200**

CPT Codes:

Sample Ascertainment	83890	\$	30	DNA Isolation	83891	\$	40
Amplification x1 Separation	83898	\$	40	Interpretation/Report	83912	\$	60
	83894	\$	30				

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

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