PREVENTION GENETICS
DISEASE PREVENTION THROUGH GENETIC TESTING

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Nemaline Myopathy 7
Skeletal Muscle Cofilin-2 (*CFL2*) Gene Sequencing (Test #249)

Brief Description of Clinical Features: Mutations in the cofilin-2 gene (*CFL2;* OMIM #601443) are one cause of autosomal recessive nemaline myopathy (NEM7; OMIM #610687). 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).
Cofilin-2 associated nemaline myopathy is apparently a rare disorder. Two siblings among a large cohort of unrelated NEM patients were found to have a homozygous *CFL2* missense mutation (Agrawal et al. *Am J Hum Genet* 80:162-167, 2007). The clinical presentation in the two affected sibs was like that of typical NEM, except facial muscles appeared to be spared and foot drop was not noted. Hypotonia was present at birth and early motor milestones were delayed. Both patients attained the ability to walk at least short distances but could not run and experienced frequent falls. Muscle biopsies from the patients showed nemaline rods, minicores, type 1 fiber predominance, and marked fiber size variability.

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). Cofilin-2, a skeletal muscle protein involved with alpha actin assembly, has been found to be mutated in one family (Argawal et al. 2007). NEM7 is inherited as an autosomal recessive disorder secondary to *CFL2* mutations.

Description of This Particular Test: The skeletal muscle form of cofilin-2 is encoded by exons 1 – 4 of the *CFL2* gene on chr 14q12. 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.

Reference Sequences: Genomic: NC_000014.8 mRNA: NM_021914.7
Protein: NP_068733.1 mRNA and Protein: CCDS 9650.1

Indication for Testing: Individuals with symptoms consistent with the nemaline myopathy and negative studies for the more common causes of this disorder.

Sensitivity of test: Cofilin-2 associated nemaline myopathy is probably a rare disorder. Argawal et al. (2007) found two sibs with *CFL2* gene mutations among a cohort of 113 unrelated patients with nemaline myopathy and 58 patients with other forms of congenital myopathy. Another report found no *CFL2* mutations among a cohort of 50 patients (Thirion et al. *Eur J Biochem* 268:3473-3482, 2001)

Turn Around 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 *CFL2*, exons 1-4:** **$ 420**

CPT Codes:

Sample Ascertainment x1	83890	$ 30	DNA Isolation x1	83891	$ 40
Amplification x4	83898	$ 100	Sequencing x4	83904	$ 150
Separation x1	83894	$ 30	Interpretation/Report x1	83912	$ 70

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

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