

Congenital Myasthenic Syndrome via *MUSK* Gene Sequencing (Test #406)

Brief Description of Clinical Features: Congenital myasthenic syndromes (CMS) are disorders of the neuromuscular junction resulting from abnormalities of presynaptic, synaptic, or post synaptic proteins. CMS are characterized by fatiguable weakness affecting limb, ocular, facial, and bulbar muscles. Neonates present with feeding problems, choking, feeble cry, and muscle weakness. Patients presenting in later childhood are seen with abnormal exercise-induced fatigue and difficulty running. Most patients present prior to 2 years of age although rare exceptions are reported (eg. Croxson et al. *Neurol* 59:162-168, 2002). Symptoms are extremely variable, and are in some case induced by febrile illness, infection, or excitement (eg. Byring et al. *Neuromuscul Disord* 12:548-553, 2002). Life threatening respiratory crises may occur in affected neonates or older children. CMS may be differentiated from myasthenia gravis, an acquired autoimmune disorder, by earlier age at onset and by negative serology tests for anti-acetylcholine receptor (AChR) and anti-MuSk antibodies. One sibship with CMS and mutations in the muscle specific tyrosine kinase (*MUSK*) gene has been reported (Chevessier et al. *Hum Molec Genet* 13:3229-3240, 2004). Symptoms of hypotonia, respiratory distress, vocal cord paralysis, and ptosis were present congenitally and tracheostomies were performed. During childhood and adolescence one sibling experienced exercise-induced fatigue and ptosis but overall the course improved with no severe respiratory distress. Symptoms worsened during this patient’s pregnancy. The second patient died in early childhood (Chevessier et al. 2004). Evaluation of a muscle biopsy revealed severe deficiencies in *MUSK* and *CHRNE* gene products and remarkable structural abnormalities of the neuromuscular junction.

Genetics: Abnormalities of proteins involved with neuromuscular transmission underlie CMS, limb girdle CMS, Pena-Shokeir syndrome, and multiple pterygium syndromes. These disorders, which may represent a phenotypic continuum of a single entity, are most often inherited in an autosomal recessive manner. Post synaptic CMS with AChR deficiency (OMIM #608931) is inherited as an autosomal recessive condition and, rarely, is secondary to mutations in the *MUSK* gene (OMIM #601296). The siblings reported by Chevessier et al. (2004) had one null and one missense mutation.

Description of This Particular Test: The muscle-specific tyrosine kinase is encoded by exons 1 – 15 of the *MUSK* gene located on chr 9q31. 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_000009.1 mRNA: NM_005592.2
 Protein: NP_005583.1 mRNA and Protein: CCDS 48005.1

Indication for Testing: A comprehensive diagnostic algorithm can be found in (*GeneReviews*, Abicht and Lochmüller, 2006).

Sensitivity of Test: Sensitivity for CMS testing is at least 50% overall; 30% for *CHRNE*, 10% for *RAPSN*, and 7.5% for *COLQ* (*GeneReviews*, Abicht and Lochmüller, 2006). CMS due to *MUSK* mutations is probably a rare disease.

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 *MUSK*, Exons 1-15: \$ 920

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x16	83898 \$ 270	Sequencing x16	83904 \$ 410
Separation x1	83894 \$ 70	Interpretation/Report x1	83912 \$ 100

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

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