

Congenital Myasthenic Syndromes via *CHRN1* Gene Sequencing (Test #402)

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. Croxen 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.

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. *CHRN1* gene mutations have been found in patients with slow channel CMS (Engel and Sine *Curr Opin in Pharmacol* 5:308-321, 2005). *CHRN1*-associated slow channel CMS (OMIM #601462) has been shown to be inherited as a recessive disorder secondary to loss-of-function mutations (Quiram et al. *J Clin Invest* 104:1403-1410, 1999), or as a dominant disorder secondary to gain-of-function mutations (Gomez et al. *Ann Neurol* 39:712-723, 1996; Engel et al. *Hum Molec Genet* 5:1217-1227, 1996). Null and low expressor *CHRN1* mutations in the homozygous or compound heterozygous state lead to CMS with end-plate AChR deficiency (Quiram et al. 1999).

Description of This Particular Test: The beta subunit of the acetylcholine receptor is encoded by exons 1 – 11 of the *CHRN1* gene (OMIM #100710) located on chr 17p12. 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_000017.10 **mRNA:** NM_000747.2
Protein: NP_000738.2 **mRNA and Protein:** CCDS 11106.1

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). *CHRN1* is a rare cause of CMS.

Turn Around Time: Maximum of 40 days although many tests are completed in 2-3 weeks.

Specimen Requirements: See bottom page 4 of the Requisition Form.

Price: **Sequencing of *CHRN1* Exons 1-11:** **\$ 680**

CPT Codes:

Sample Ascertainment x1	83890	\$ 30	DNA Isolation x1	83891	\$ 40
Amplification x10	83898	\$ 190	Sequencing x10	83904	\$ 290
Separation x1	83894	\$ 50	Interpretation/Report x1	83912	\$ 80

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

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