Congenital Myasthenic Syndromes: Sequencing Panel

**Condition Description**

Congenital myasthenic syndromes (CMS) are a highly variable group of diseases characterized by fatigable weakness of skeletal muscle. Symptoms range from mild to progressive disabling weakness. The age of onset is also variable ranging from birth to early childhood. Infections, fever, or excitement may precipitate severe exacerbations of weakness or episodes of respiratory insufficiency. Additional features of the neonatal onset subtypes include feeding difficulties, choking spells, poor suck and cry, eyelid ptosis, and weakness. Additional features of the childhood onset subtypes include delayed motor milestones, fluctuating eyelid ptosis, and fluctuating extraocular muscle weakness. CMS can be inherited in an autosomal recessive or an autosomal dominant manner; however, the autosomal recessive manner is more common.

**References:**
- GeneReviews
- OMIM

**Genes**

ALG2, CHAT, CHRNA1, CHRNB1, CHRND, CHRNE, COLQ, DOK7, MUSK, RAPSN, SCN4A

**Indications**

This test is indicated for:
- Confirmation of a clinical diagnosis of congenital myasthenic syndromes (CMS).
- Carrier testing in adults with a family history of congenital myasthenic syndromes (CMS).

**Methodology**

**Next Generation Sequencing:** In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

**Detection**

**Next Generation Sequencing:** Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions/duplications will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical/biochemical phenotype.

Analytical Sensitivity: ~99%.

**Specimen Requirements**

Submit only 1 of the following specimen types

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml.

Specimen Collection and Shipping: Ship sample at room temperature with overnight delivery.

**Type: Isolated DNA**

Specimen Requirements:
In microtainer: 60 ug

Isolation using the Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping: Refrigerate until time of shipment in 100 ng/ul of TE buffer. Ship sample at room temperature with overnight delivery.

**Related Tests**

- Congenital Myasthenic Syndromes: Deletion/Duplication Panel