

Familial Limb Girdle Myasthenic Syndrome via *AGRN* Gene Sequencing (Test #408)

Brief Description of Clinical Features: Congenital myasthenic syndromes (CMS) are disorders of the neuromuscular junction resulting from defects in presynaptic, synaptic, or post synaptic proteins. Agrin is produced by the presynaptic neuron and released into the synaptic space and functions by activating MuSK. Clinically, a limb girdle pattern of muscle involvement makes *DOK7* and *AGRN*-related CMS unique from other CMS. Age at onset typically ranges from the birth to age 5 years (Selcen et al. *Ann Neurol* 64:71-78, 2008; Beeson et al. *Science* 313:1975-1978, 2006). Thus far, one family has been reported with *AGRN*-associated familial limb girdle myasthenic syndrome (Huzé et al. *Am J Hum Genet* 85:155-167, 2009). The affected siblings reported having difficulty running beginning in childhood, mild facial weakness, unilateral ptosis, and thin thorax and pelvis. In adulthood, muscle function was stable although weakness worsened in one sibling during pregnancy and menstruation. Disorganization of the neuromuscular junction was evident in a muscle biopsy from an affected individual. Treatment with ephedrine was found to cause sustained improvement in muscle performance and endurance.

Genetics: Abnormalities of proteins involved with neuromuscular transmission underlie familial limb girdle myasthenia syndrome, congenital myasthenia syndromes, 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. Familial limb girdle myasthenic syndrome due to *AGRN* (OMIM #103320) mutations is inherited as an autosomal recessive disorder. Affected members of the family with *AGRN*-associated CMS were homozygous for a c.5125G>C (p.Gly1709Arg) mutation (Huzé et al. 2009).

Description of This Particular Test: Argin, an extracellular matrix protein, is encoded by exons 1 – 36 of the *AGRN* gene (OMIM #103320) located on chr 1pter. 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_000001.10 mRNA: NM_198576.2
 Protein: NP_940978.2 mRNA and Protein: CCDS 3055.1

Indication for Testing: Patients with a limb girdle pattern of muscle weakness and other typical CMS muscle involvement.

Sensitivity of Test: *DOK7* and *AGRN* mutations are the only known cause of familial limb girdle myasthenic syndrome. Clinical sensitivity should be high for patients meeting rigorous clinical and electrophysiological criteria. *AGRN* mutations are probably a rare cause of familial limb girdle myasthenic syndrome.

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 <i>AGRN</i>, Exons 1-36:	\$ 1,780
CPT Codes:		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x40	83898 \$ 600	Sequencing x40 83904 \$ 890
Separation x1	83894 \$ 100	Interpretation/Report x1 83912 \$ 120

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

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