

Familial Limb-Girdle Myasthenic Syndrome With Tubular Aggregates via *GFPT1* Gene Sequencing (Test #594)

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. Clinically, a limb-girdle pattern of muscle involvement makes *DOK7*, *AGRN* and *GFPT1*-related CMS unique from other CMS. Senderek et al. (*Am J Hum Genet* 88:162-172, 2011) found mutations in the *GFPT1* gene (OMIM 138292) in 13 families with autosomal recessive limb-girdle myasthenic syndrome with tubular aggregates (OMIM 610542). *In vitro* studies showed evidence for increased turnover and/or defective translation as an underlying pathological mechanism. Reduced numbers of acetylcholine receptors and decreased protein glycosylation were also noted (Senderek et al. 2011). Clinical symptoms, with onset from during adolescence, include limb-girdle weakness and wasting with normal or slightly elevated serum CK levels (Rodolico et al. *Neuromusc Disord* 12:964-969, 2002). Muscle cramps and moderate exercise-induced fatigability are also documented (Sieb et al. *Neuromusc Disord* 6:115-119, 1996). Neither ptosis nor ophthalmoplegia are findings in *GFPT1*-related CMS. Electrophysiologic studies show decremental compound motor action potential responses in affected muscles, and single-fiber EMG show impaired neuromuscular transmission with increased jitter (Rodolico et al. 2002). Muscle biopsies demonstrate 60- to 80-nm parallel subsarcolemmal tubular aggregates located predominantly in type 2 muscle fibers (Sieb et al. 1996). In contrast to *DOK7*-related CMS, tubular aggregates may be a universal finding in *GFPT1*-related CMS (Slater et al. *Brain* 129:2061-2076, 2006). Patients with limb-girdle myasthenic syndrome with tubular aggregates respond well to treatment with acetylcholinesterase inhibitors (Rodolico et al. 2002; Beeson et al. *Science* 313: 1975-1978, 2006).

Genetics: Abnormalities of proteins involved with neuromuscular transmission underlie familial limb-girdle myasthenic syndrome, congenital myasthenic 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 with tubular aggregates due to *GFPT1* mutations is inherited as an autosomal recessive disorder (Senderek et al. 2011).

Description of This Particular Test: Glutamine fructose-6-phosphate amidotransferase is encoded by exons 1 – 19 of the *GFPT1* gene. 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. As indicated, we will also sequence one (Test #100, \$190) or two (Test #200, \$340) exons in family members of patients with known mutations or to confirm research results.

Reference Sequences: **Genomic:** NC_000002.11 **mRNA:** NM_002056.2
 Protein: NP_002047.2 **mRNA and Protein:** CCDS 33216

Indication for Testing: Patients with a slowly progressive limb-girdle pattern of muscle weakness without facial involvement and tubular aggregates in muscle. Limb-girdle CMS patients who respond to AChE inhibitors.

Sensitivity of Test: *DOK7*, *AGRN* and *GFPT1* mutations are the only known cause of familial limb-girdle myasthenic syndrome. Clinical sensitivity should be high for patients meeting rigorous clinical, histopathological, and electrophysiological criteria.

Turnaround 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 *GFPT1*, Exons 1-19:** **\$ 1090**

CPT Codes:

Sample Ascertainment x1	83890	\$ 30	DNA Isolation x1	83891	\$ 40
Amplification x21	83898	\$ 340	Sequencing x21	83904	\$ 520
Separation x1	83894	\$ 65	Interpretation/Report x1	83912	\$ 95

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

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