

Familial Limb Girdle Myasthenic Syndrome via *DOK7* and *AGRN* Gene Sequencing (Test #414)

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. The protein encoded by *DOK7* is essential for neuromuscular synaptogenesis due to its role in inducing autophosphorylation of the skeletal muscle receptor-like tyrosine kinase (MuSK), a key protein involved in postsynaptic differentiation (Okada et al. *Science* 312:1802-1805, 2006). 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). The latter study found that the most common clinical presentation was difficulty in walking after initially achieving normal walking milestones. In a cohort of sixteen *DOK7* patients Selcen et al. (2008), found disease severity and rate of progression to be variable; some patients exhibited mild static weakness limited to limb girdle muscles, while others had severe generalized disease with muscle atrophy. Ten of the sixteen patients with *DOK7* mutations had intermittent worsening of symptoms. All patients reported fatigue on exertion and proximal muscle weakness. Other common features among the sixteen patients included ptosis (14/16), facial weakness (13/16), bulbar symptoms (11/16), and respiratory difficulties (13/16).

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 *DOK7* (OMIM #254300) and *AGRN* (OMIM #103320) mutations is inherited as an autosomal recessive disorder. In a cohort of 21 patients, Beeson et al. (2006) found 16 to have the same exon 7 c.1124_1127dupTGCC *DOK7* mutation. Fourteen of 16 patients reported by Selcen et al. (2008) had a least one c.1124-1127dupTGCC mutation, and four were heterozygous for gross alterations (intron inclusion or exon skipping) undetectable in genomic DNA. One sibship with agrin-associated CMS has been reported (Huzé et al. *Am J Hum Genet* 85:155-167, 2009).

Description of This Particular Test: Testing of the two genes is carried out in the order specified by the client. 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:

Gene:	Genomic: NC_	mRNA: NM_	Protein: NP_	CCDS:
<i>DOK7</i>	00004.10	173660.3	775931.3	3370.2
<i>AGRN</i>	000001.10	198576.2	940978.2	30551.1

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. Analytical sensitivity of genomic DNA sequencing for *DOK7* may be limited as a consequence of gross structural changes to the mRNA not seen in genomic DNA (Selcen et al. 2008).

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: Sequential Sequencing of: *DOK7*, *AGRN*

CPT Codes

Gene	83890	83891	83898	83904	83894	83912	Totals
<i>DOK7</i>	\$ 30 x1	\$ 40 x1	\$ 140 x8	\$ 210 x8	\$ 40 x1	\$ 80 x1	\$ 540
<i>AGRN</i>	\$ 30 x1	\$ 40 x1	\$ 600 x40	\$ 890 x40	\$ 90 x1	\$ 130 x1	\$ 1,780
Panel	\$ 30 x1	\$ 40 x1	\$ 710 x48	\$ 1070 x48	\$ 120 x1	\$ 160 x1	\$ 2,130

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

Contact for info: Thomas L. Winder, PhD, FACMG, tom.winder@preventiongenetics.com, www.preventiongenetics.com