

## Familial Limb Girdle Myasthenia Syndrome via *DOK7* Gene Sequencing (Test #465)

**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). Mutations in *DOK7* result in small neuromuscular junctions but normal acetylcholine receptor and acetylcholinesterase function (Beeson et al. *Science* 313:1975-1978, 2006). Electron microscopy studies of patients with *DOK7* mutations shows destruction and remodeling of end plates at neuromuscular junctions (Selcen et al. *Ann Neurol* 64:71-87, 2008). Clinically, a limb girdle pattern of muscle involvement makes *DOK7*-related CMS unique from other forms of CMS. Age at onset typically ranges from the birth to age 5 years (Selcen et al. 2008) with onset in a minority of patients occurring beyond 5 years (Beeson et al. 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* positive patients characterized by Selcen et al. (2008), disease severity and rate of progression was 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 had intermittent worsening of symptoms lasting from days to weeks. 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:** Familial limb girdle myasthenic syndrome due to *DOK7* gene mutations (OMIM #254300) 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 mutation. Fourteen of 16 patients reported by Selcen et al. (2008) had a least one c.1124-1127dupTGCC mutation, and four were found to have heterozygous gross alterations (intron inclusion or exon skipping) undetectable in genomic DNA.

**Description of This Particular Test:** The protein ‘downstream of tyrosine kinase 7’ is encoded by the *DOK7* gene located on chr 4p16. Testing is accomplished by amplifying the 7 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\_000004.10                      **mRNA and Protein:** CCDS 3370.2

**Indication for Testing:** Individuals with a limb girdle pattern of muscle weakness along with other typical CMS muscle involvement.

**Sensitivity of Test:** *DOK7* 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 may be limited as a consequence of gross structural changes to the mRNA not seen in gDNA (Selcen et al. 2008).

**Turn Around Time:** Maximum of 40 days.

**Specimen Requirements:** See bottom of page 2 of Requisition Form.

**Price:**                      **Sequencing of *DOK7***                      **exon 7 only: \$190**                      **exons 1-7: \$540**

**CPT Codes:**

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x8	83898 \$140	Sequencing x8	83904 \$ 210
Separation x1	83894 \$ 40	Interpretation/Report x1	83912 \$ 80

**Accreditation Info.** CLIA ID #: 52D1027685 (expires 1/18/11) (CAP#: 7185561, AU ID: 1407125 expires 12/20/10)

**Contact for info:** Thomas L. Winder, PhD, FACMG, [tom.winder@preventiongenetics.com](mailto:tom.winder@preventiongenetics.com), [www.preventiongenetics.com](http://www.preventiongenetics.com)