

Integrin Alpha 7-Related Congenital Myopathy Testing via *ITGA7* Gene Sequencing (Test #244)

Brief Description of Clinical Features: Integrin $\alpha7\beta1$ is an integral structural component of the sarcolemma which binds laminin, thus connecting the basal lamina to the intracellular space (Muntoni and Voit, *Neuromusc Disord* 14:635-649, 2004). The integrin alpha 7 gene (*ITGA7*; OMIM #600536) encodes the $\alpha7$ subunit of the integrin $\alpha7\beta1$ heterodimer. In an *Itga7* knock out mouse model, integrin $\alpha7\beta1$ was confirmed to be essential in linking the extracellular matrix to the intracellular space of the muscle fiber independently of a similar linkage through the dystrophin-glycoprotein complex (Mayer et al. *Nat Genet* 17:318-323, 1997). The $\alpha7$ subunit, which is expressed in skeletal and cardiac muscle (Song et al. *J Cell Biol* 117:643-657, 1992), may be critical for differentiation and migration processes during myogenesis. Mutations in *ITGA7* have been found in a small set of patients with congenital myopathy (Hayashi et al. *Nat Genet* 19:94-97, 1998). Motor milestones were delayed in three reported patients; for example, one child was able to roll over at 9 months of age and walk at 2.5 years but was not able to run or jump. Another could walk independently at 2.1 years and demonstrated a waddling gait and Gower's sign. This same patient could not run or climb stairs independently. The third child was able to walk at age 5 years but only with support. Other findings in these patients included hypotonia and torticollis from birth and mildly elevated serum CK (163 IU/L, 236 IU/L, 528 IU/L). Cognitive impairment was evident in one of the three patients, although, the etiology was not known. Evaluation of muscle biopsies showed deficient integrin $\alpha7$ but normal laminin $\alpha2$, along with mild variation in fiber size, substantial fatty replacement, and little evidence of a dystrophic process.

Genetics: Congenital myopathy due to integrin $\alpha7$ deficiency is inherited as an autosomal recessive condition. Three *ITGA7* mutations consisting of two splice site mutations and one single base deletion have been reported to date (Hayashi et al. 1998). If a muscle biopsy is available, immunostaining for integrin $\alpha7$ may also be an appropriate diagnostic approach.

Description of This Particular Test: The $\alpha7$ subunit of integrin $\alpha7\beta1$ is coded by exons 1-25 of the *ITGA7* gene located on chromosome 12q13. Testing is accomplished by amplifying each coding exon 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_000012.10 **mRNA:** NM_002206.2 **Protein:** NP_002197.2

Indication for Testing: Individuals with symptoms consistent with congenital myopathy and autosomal recessive inheritance. Symptomatic individuals with mildly elevated serum CK levels and muscle biopsies demonstrating decreased immunoreactivity to integrin $\alpha7$ and normal laminin $\alpha2$ reactivity.

Sensitivity of test: Congenital myopathy due to integrin $\alpha7$ deficiency is probably a rare disorder. Hayashi et al. (1998) found three cases when they screened by immunocytochemistry 117 patients with unclassified congenital myopathy or congenital muscular dystrophy. The three patients were Japanese.

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: **Sequencing of *ITGA7* Gene** **\$ 1240**

CPT Codes:

Sample Ascertainment x1	83890	\$ 30	DNA Isolation x1	83891	\$ 40
Amplification x24	83898	\$ 400	Sequencing x24	83904	\$ 600
Separation x1	83894	\$ 80	Interpretation/Report x1	83912	\$ 90

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

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