

Calpain 3 (CAPN3) Gene Sequencing (Test #341)

Brief Description of Clinical Features: The calpainopathies are a heterogeneous group of skeletal muscle disorders caused by mutations in the *CAPN3* gene. Limb girdle muscular dystrophy type 2A (LGMD2A; OMIM# 253600), possibly the most prevalent form of LGMD (Guglieri et al. *Hum Mut* 29:258-266, 2008), is associated with atrophy and weakness of proximal girdle muscles, scapular winging, elevated serum CK levels and, late in the course of the disease, contractures. Clinical severity, age of onset, and disease progression are highly variable (Sáenz et al., *Brain* 128:732-742, 2005). The severe phenotype (pelvofemoral LGMD) first affects the pelvic girdle followed by the shoulder girdle, and age of onset can be in childhood or adulthood. Early onset is infrequent in the scapulohumeral form and the disease course is variable. Finally, hyperCKemia is found in young asymptomatic individuals preceding disease onset. In some individuals, eosinophilic myositis (EM) is the only presenting feature (Krahn et al., *Ann Neurol* 59:905-911, 2006). These patients present in the first decade of life with idiopathic EM, elevated CK, and peripheral hypereosinophilia. It is unknown at this time if they go on to develop LGMD2A.

Genetics: *CAPN3*-related disorders are inherited in an autosomal recessive manner. Over 80% of *CAPN3* mutations are found in less than half of the 24 exons (<http://www.dmd.nl/>). Nonsense, missense, small insertions and deletions and splice site mutations have been reported. Calpain-3 protein analysis as a means to screen LGMD patients has been shown to be highly specific but of limited sensitivity (Fanin et al., *Hum Mut* 24:52-62, 2004; Groen et al., *Brain* 130:3237-3249, 2007).

Description of This Particular Test: The muscle specific calpain is coded by the *CAPN3* gene located on chromosome 15q15. Testing is accomplished by amplifying all 24 coding exons (1-24) 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_000015.8 mRNA: NM_000070.2 Protein: NP_000061.1

Indication for Testing: Individuals with clinical symptoms consistent with LGMD, absent calpain-3 on western blots, or idiopathic eosinophilic myositis. Initial clinical signs are often tiptoe walking, difficulty in running, and scapular winging.

Sensitivity of test: In large study of North American LGMD patients Moore et. al., (*J. Neuropathol. Exp. Neurol.* 65:995-1003, 2006) made a diagnosis of calpainopathy in 12% of their cohort using a combined immuno and molecular approach. In patients with a diagnosis of LGMD2A based on clinical features the likelihood of finding two *CAPN3* mutations ranges from 50% to 83% (Todorova et al., *Clin Genet* 67:356-358, 2005; Krahn et al., *Clin Genet* 69:444-449, 2006).

Turn Around Time: Maximum of 40 days.

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

Price: Sequencing of *CAPN3* \$ 1090

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x21	83898	\$ 335	Sequencing x21	83904	\$ 505
Separation	83894	\$ 70	Interpretation/Report	83912	\$ 110

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