

Caveolinopathy Testing via *CAV3* Gene Sequencing (Test #467)

Limb Girdle Muscular Dystrophy Type 1C * Rippling Muscle Disease Hypertrophic Cardiomyopathy * Long QT Syndrome 9

Brief Description of Clinical Features: The caveolinopathies are disorders of skeletal and cardiac muscle that include limb girdle muscular dystrophy type 1C (LGMD1C; OMIM #607801), rippling muscle disease (RMD; OMIM #606072), hypertrophic cardiomyopathy (OMIM #192600), and long QT syndrome 9 (LQT9; OMIM #611818). Remarkable variability in expression is known and any of the phenotypes may occur in different members of the same family (Bruno et al. *GeneReviews*, genetests.org). LGMD1C is characterized by mild-to-moderate proximal muscle weakness, calf hypertrophy, and positive Gower sign with onset in the first decade of life (Minetti et al. *Nat Genet* 18: 365–368, 1998). Serum CK levels are elevated up to 25-fold above normal and muscle biopsies reveal a dystrophic pattern with increased numbers of central nuclei and increased connective tissue (eg., Fulizio et al. *Hum Mutat* 25:82-89, 2005). RMD is a non-dystrophic muscle disorder characterized by mechanically-induced muscle contractions (Betz et al. *Nat Genet* 28:218-219, 2001). Onset of symptoms occurs in childhood and include painful muscle stiffness, weakness, and cramping, percussion-induced muscle mounding, and muscle hypertrophy. Muscle biopsies reveal increases in fiber size variability, centrally located nuclei, and mild type-1 fiber predominance (Betz et al. 2001). A single case report of hypertrophic cardiomyopathy due to a *CAV3* mutation is known (Hayashi et al. *Biochem Biophys Res Comm* 313:178-184, 2004). *CAV3* mutations are also causative for long QT syndrome via a gain of function increase in late sodium current (Vatta et al. *Circulation* 114:2104-2112, 2006). Other associations with *CAV3* mutations include hyperCKemia (Carbone et al. *Neurology* 54:1373–1376, 2000), sudden infant death syndrome (Cronk et al. *Heart Rhythm* 4:161-166, 2007), and distal myopathy (Tateyama et al. *Neurology* 58:323–325, 2002).

Genetics: The caveolinopathies are most often inherited in an autosomal dominant mode with one parent of an affected child being affected. However, reports of recessive inheritance are also known (McNally et al. *Hum Molec Genet* 7:871-877, 1998; Kubisch et al. *Ann Neurol* 57:303-304, 2005; Muller et al. *Neuromuscul Disord* 16:432-436, 2006); although the health status of the carrier parents in these cases has not been well established. The same *CAV3* mutation can cause varied clinical and histological consequences between and within families.

Description of This Particular Test: The muscle specific caveolin is encoded by exons 1-2 of the *CAV3* gene located on chr 3p25. 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: **Genomic: NC_000003.10** **mRNA and Protein: CCDS 2569.1**

Indication for Testing: Individuals with clinical signs consistent with one of the associated phenotypes. Individuals with reduced to absent caveolin-3 immunoreactivity at the plasma membrane and abnormal dysferlin staining.

Sensitivity of Test: Analytical sensitivity should be high as nearly all reported *CAV3* mutations are the type expected to be detected by sequencing of genomic DNA. Clinical sensitivity is difficult to predict because caveolinopathies are rare. Among a cohort of 663 patients seen at an Italian neuromuscular disorders center who had a range of clinical phenotypes, seven probands with caveolin deficient muscle biopsies and *CAV3* mutations were found (Fulizio et al. *Hum Mutat* 25:82-89, 2005). Among 905 unrelated long QT syndrome patients, four were found to have *CAV3* mutations (Vatta et al. *Circulation* 114:2104-2112, 2006).

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: **Sequencing of *CAV3*** **\$ 390**

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x3	83898 \$ 90	Sequencing x3	83904 \$ 130
Separation x1	83894 \$ 20	Interpretation/Report x1	83912 \$ 80

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

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