

Telethoninopathy Testing via *TCAP* Gene Sequencing (Test #468)
Limb Girdle Muscular Dystrophy, Type 2G (LGMD2G)
Dilated Cardiomyopathy, Type 1N (CMD1N)
Hypertrophic Cardiomyopathy

Brief Description of Clinical Features: Mutations in the titin-CAP (*TCAP*) gene, which encodes the sarcomeric protein telethonin, cause limb girdle muscular dystrophy type 2G (LGMD2G; OMIM 601954; Moreira et al. *Nat Genet* 24:163-166, 2000), dilated cardiomyopathy type 1N (CMD1N; OMIM 607487; Knöll et al. *Cell* 111:943-955, 2002), and hypertrophic cardiomyopathy (Hayashi et al. *J Am Coll Cardiol* 44:2192-2201, 2004). Affected members from three families with the LGMD phenotype have been reported to have disease onset between 2 and 15 years of age with variability in clinical severity. Marked weakness in the distal muscles of the legs manifests itself as difficulty with walking, running, and climbing stairs (Moreira et al. *Am J Hum Genet* 61:151-159, 1997). Some, but not all, reported patients lost the ability to walk in the 2nd to 4th decade of life (Moreira et al. *Nature Genet* 24:163-166, 2000). Serum CK levels were slightly elevated in clinically mild cases, while those with earlier onset and more severe muscle weakness had 10- to 30-fold increased serum CK levels, calf hypertrophy, and dystrophic muscle biopsies (Moreira et al. 2000). Heart involvement was reported in three of six affected members of one family (Moreira et al. 2000). Foot drop and absent tendon reflexes without involvement of sensory and cranial nerves were found to be a common feature (Moreira et al. 1997). Heterozygous *TCAP* mutations have also been documented to be one cause of dilated (DCM) and hypertrophic (HCM) cardiomyopathy.

Genetics: Limb girdle muscular dystrophy due to *TCAP* mutations is inherited as an autosomal recessive condition. Telethonin associated cardiomyopathy occurs sporadically or is inherited as an autosomal dominant condition. The *TCAP* gene (OMIM 604488) encodes telethonin, a sarcomeric protein localized to the Z disc and a substrate for the protein titin. Limb girdle muscular dystrophy and cardiomyopathy are genetically heterogeneous, therefore, a negative *TCAP* sequencing test does not rule out a diagnosis of these disorders when classic clinical findings are present. If a muscle biopsy is available, immunostaining may also be an appropriate diagnostic approach.

Description of This Particular Test: Telethonin is coded by exons 1-2 of the *TCAP* gene located on chromosome 17q12. 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_000017.9** **mRNA and Protein: CCDS 11342.1**

Indication for Testing: Individuals with symptoms consistent with LGMD and autosomal recessive inheritance. Individuals with sporadic or dominantly inherited dilated or hypertrophic cardiomyopathy.

Sensitivity of test: Telethonin appear to be a rare cause of limb girdle muscular dystrophy and cardiomyopathy. Homozygous or compound heterozygous *TCAP* mutations have been found in three families with members affected with limb girdle muscular dystrophy (Moreira et al. 2000). Among a cohort of 389 HCM patients, four were found to have a *TCAP* mutation (Bos et al. *Mol Genet Metab* 88:78-85, 2006). In a study of 482 patients (346 with HCM and 136 with DCM) Hayashi et al (*J Am Coll Cardiol* 44:2192-2201, 2004) found *TCAP* mutations in two patients with HCM and one with DCM.

Turn Around Time: Maximum of 40 days, although many tests are completed in 20-30 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price:	Sequencing of <i>TCAP</i> Gene:	\$ 390		
CPT Codes:				
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40	
Amplification x 3	83898 \$ 90	Sequencing x3	83904 \$ 130	
Separation x1	83894 \$ 30	Interpretation/Report x1	83912 \$ 70	

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

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