

## Limb Girdle Muscular Dystrophy, Type 2J and Tibial Muscular Dystrophy via *TTN* Sequence Analysis - Exons 307 to 312 (Test #385)

**Brief Description of Clinical Features:** Mutations in the six exons that encode the C-terminus of titin cause limb girdle muscular dystrophy type 2J (LGMD2J; OMIM 608807) and tibial muscular dystrophy (TMD; OMIM 600334). LGMD2J is a severe, early onset disorder characterized by weakness of all proximal muscles. In the first reported cases weakness appeared in the first decade of life and progressed over the next 20 years to wheelchair confinement (Udd et al. *Muscle and Nerve* 14:1050-1058, 1991). Patients with the other, less severe, clinical presentation showed onset of distal muscle weakness in lower limbs in the third or fourth decade of life. Progression was very slow without greater disability throughout their lifetime. Tibial muscle weakness and wasting are clinical landmarks for TMD (Udd et al. 1991). By studying segregation of the two clinical phenotypes within a large consanguineous pedigree, Udd (*J Med Genet* 29:383-389, 1992) demonstrated that both were likely caused by a mutation in the same gene. Subsequently, Hackman et al. (*Amer J Hum Genet* 71:492-500, 2002) found homozygosity for an insertion/deletion mutation in the terminal exon of *TTN* in severely affected family members, and heterozygosity for the same mutation in members affected with the milder, adult onset TMD phenotype. Homozygous mutations in other exons encoding the C-terminus have been found to result in a condition with severe, early onset myopathy and fatal cardiomyopathy (Carmignac et al. *Ann Neurol* 61:340-351, 2007).

**Genetics:** LGMD2J and TMD are inherited as autosomal recessive and autosomal dominant disorders, respectively. The *TTN* gene (OMIM 188840) encodes titin, a 3,700 kDa protein measuring 2 μm in length that stretches from the Z disk to the M band of the sarcomere. An 11 base pair insertion/deletion mutation in exon 312 of *TTN* (the terminal exon) has been shown to cause both LGMD2J and TMD in the Finnish population. Missense, and truncating mutations in exons 311 and 312 have also been found to cause LGMD2J and TMD in patients from Finland, France, and Spain (Hackman et al 2002; Hackman et al. *Neuromuscul Disord* 18:922-928, 2008). Patients with truncating mutation in exon 311, which contains a calpain-3 binding domain, have a more severe and earlier onset form of TMD (Hackman et al. 2008). Titin-related cardiomyopathy (CMD1G; OMIM 604145) is most often caused by mutations spread throughout the *TTN* gene; however, two unrelated patients with severe myopathy and fatal cardiomyopathy occurring together have been reported with homozygous truncating mutations in exons 307 and 309 (Carmignac et al. 2007).

**Description of This Particular Test:** The giant sarcomere protein titin (formerly called connectin) is encoded by exons 2-312 of the *TTN* gene at chromosome 2q31. Six exons at the C-terminus of *TTN* encode immunoglobulin and calpain-3 binding domains associated with the sarcomeric M band. These exons (307 -312) are referred to as Mex1 – Mex6 in the literature. Testing is accomplished by amplifying exons 307 through 312, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument.

**Reference Sequences:** Genomic: NC\_000002.11      mRNA: NM\_133378.3      Protein: NP\_596869

**Indication for Testing:** Individuals with symptoms consistent with LGMD2J or tibial muscular dystrophy, particularly of Finnish heritage.

**Sensitivity of test:** Mutations in six terminal exons of *TTN* have been found in a small number of patients from Finland, France, and Spain (see above).

**Turn Around Time:** Maximum of 40 days, although many tests are completed in 3-4 weeks.

**Specimen Requirements:** See page 4 of the Requisition Form.

**Price:** Sequencing of *TTN* Exons 311 and 312 (Test #200): \$ 340      Exons 307 – 312 (Test #385): \$ 1290

**CPT Codes:**

Sample Ascertainment x1	83890	\$ 30	DNA Isolation x1	83891	\$ 40
Amplification x 26	83898	\$ 410	Sequencing x 26	83904	\$ 610
Separation x1	83894	\$ 90	Interpretation/Report x1	83912	\$ 110

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

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