

TTN-related Disorders: TTN Gene Sequencing

Test Code: STTNX

Turnaround time: 6 weeks

CPT Codes: 81479 x1

Condition Description

Titan is an extremely large protein that makes up a large part of cardiac and skeletal muscle sarcomere. Titan is encoded by the *TTN* gene (2q31.2). Mutations in the *TTN* gene are associated with different disorders and modes of inheritance.

Autosomal Dominant:

- Dilated cardiomyopathy
- Hypertrophic cardiomyopathy
- Hereditary myopathy with early respiratory failure

Autosomal Recessive:

- Limb-girdle muscular dystrophy
- Tardive tibial muscular dystrophy
- Early-onset myopathy with fatal cardiomyopathy

Dilated Cardiomyopathy

Hereditary dilated cardiomyopathy (DCM) may be inherited in an autosomal dominant, autosomal recessive, or X-linked manner, depending on the gene involved. DCM is characterized by left ventricular enlargement and reduced myocardial contraction force. Typically, DCM presents with one of three features: heart failure, thromboembolic disease, or arrhythmias and/or conduction system disease. Approximately 20-50% of idiopathic dilated cardiomyopathy (those cases not due to acquired causes) are thought to have a genetic cause.

Hypertrophic Cardiomyopathy

Hereditary hypertrophic cardiomyopathy (HCM) is characterized by left ventricular hypertrophy in the absence of a predisposing cardiac or cardiovascular condition. The manifestation of HCM is extremely variable, even within the same family, and can range from asymptomatic to progressive heart failure. Other features include syncope, presyncope, shortness of breath, chest pain, orthostasis, and palpitations. The onset of HCM is usually during adolescence or young adulthood; however, it can range from infancy to much later in adult life.

Hereditary Myopathy with Early Respiratory Failure

Hereditary myopathy with early respiratory failure (HMERF) is an adult-onset myopathy with early respiratory muscle involvement. In most individuals with HMERF, the respiratory muscles, especially the diaphragm, were involved. Additionally, individuals with HMERF have proximal weakness of the upper and lower extremities, the neck flexors were involved and some had foot extensor weakness. Creatine kinase (CK) levels are normal or slightly elevated. The age of onset can range from the second to the fifth decade of life.

Limb-Girdle Muscular Dystrophy

Limb-girdle muscular dystrophy (LGMD) is a descriptive term applied to a clinically and genetically heterogeneous group of childhood- or adult-onset muscular dystrophies. LGMD is characterized by weakness and wasting restricted to the limb musculature, proximal greater than distal. Onset, progression, and distribution of the weakness and wasting vary considerably among individuals and genetic subtypes. Serum creatine kinase (CK) levels in individuals with LGMD are usually elevated, and muscle biopsy reveals dystrophic changes. LGMDs are distinct from the much more common X-linked dystrophinopathies, which include Duchenne and Becker muscular dystrophy (DMD/BMD). Currently, there are at least twelve genes that cause LGMDs. Mutations in the *TTN* gene cause autosomal recessive LGMD 2J.

Tardive Tibial Muscular Dystrophy

Tardive tibial muscular dystrophy, also known as Udd distal myopathy, is an autosomal dominant disorder that has slow disease progression. It is characterized by weakness of ankle dorsiflexion and the loss of ability to walk on ones heels after age 35.

Early-Onset Myopathy with Fatal Cardiomyopathy

Early-onset myopathy with fatal cardiomyopathy (EOMFC), also known as Salih myopathy, is an autosomal recessive disorder that is characterized by muscle weakness and delayed motor development. The muscle weakness can begin in the neonatal period or in early infancy. As the disease progresses, other systems become involved; moderate joint and neck contractures, scoliosis, and dilated cardiomyopathy. Cognitive development is normal. Two mutations within the *TTN* gene are needed to cause EOMFC.

References:

- GeneReviews
- OMIM #188840: *TTN* gene
- OMIM #604145: DCM 1G
- OMIM #613765: HCM 9
- OMIM #608807: LGMD 2J
- OMIM #611705: Early-onset myopathy with fatal cardiomyopathy
- OMIM #603689: Hereditary myopathy with early respiratory failure
- OMIM #600334: Tardive tibial muscular dystrophy
- Nicolao *et al.* (1999), *Am J Hum Genet*, 64:788-792.

Genes

TTN

Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of a *TTN*-related disorder.
- Carrier testing in adults with a family history of a *TTN*-related disorder.

Methodology

Next Generation Sequencing: In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

Detection

Dilated Cardiomyopathy – unknown; HCM – unknown; LGMD2J – unknown; Tardive tibial muscular dystrophy – 100%; Early-Onset Myopathy with Fatal Cardiomyopathy– 100%; Hereditary myopathy with early respiratory failure – unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical and/or biochemical phenotype.

Analytical Sensitivity: ~99%

Specimen Requirements

Submit only 1 of the following specimen types

Type: Saliva

Specimen Requirements:

Oragene™ Saliva Collection Kit

Orangene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:

Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

Type: DNA, Isolated

Specimen Requirements:

Microtainer

8µg

Isolation using the Perkin Elmer™ Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping:

Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

Type: Whole Blood (EDTA)

Specimen Requirements:

EDTA (Purple Top)

Infants and Young Children (2 years of age to 10 years old: 3-5 ml

Older Children & Adults: 5-10 ml

Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:

Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

Related Tests

- A cardiomyopathy next generation sequencing panel is available and includes the *TTN* gene.
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available only for known familial mutations to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.