

## Bethlem Myopathy/Ullrich Congenital Muscular Dystrophy: COL6A2 Gene Sequencing

**Test Code:** SC6A2

**Turnaround time:** 4 weeks

**CPT Codes:** 81407 x1

### Condition Description

The congenital muscular dystrophies are a group of genetically and clinically heterogeneous hereditary myopathies characterized by congenital hypotonia and muscle weakness, contractures, and delayed motor development. Muscle biopsy usually reveals a nonspecific dystrophic pattern. The clinical course is broadly variable and can involve the brain and eyes. Initial testing often includes clinical evaluation, muscle imaging, electromyography, and muscle biopsy, followed by targeted genetic testing.

The collagens are a superfamily of extracellular matrix proteins that play a role in maintaining the integrity of various tissues. Collagen VI forms a microfibrillar network in close association with the basement membrane around muscle cells. Collagen VI is composed of three different peptide chains alpha1(VI), alpha2(VI), and alpha3(VI). The alpha1(VI) and alpha2(VI) chains are encoded by two genes -- *COL6A1* and *COL6A2* respectively -- situated on chromosome 21q22.3. *COL6A3*, the gene for the alpha3(VI) chain, maps to chromosome 2q37. Mutations in the type VI collagen genes are associated with Bethlem myopathy and Ullrich congenital muscular dystrophy, which are likely different ends of a clinical spectrum. Mutations are identified in approximately 66% of individuals clinically affected with Bethlem myopathy and approximately 79% of individuals clinically affected with Ullrich CMD.

#### Bethlem Myopathy

Bethlem myopathy (BM) is an autosomal dominant myopathy with contractures. BM is clinically heterogeneous, although the hallmark of this condition is early contractures of the interphalangeal joints of the fingers, elbows, and ankle joints, together with flexion contractures of the elbow and of the ankles. Other symptoms can include proximal weakness, decreased fetal movements, congenital torticollis, bilateral clubfeet, and keloid formation. IQ and brain development are usually unaffected. Onset may be in the neonatal period, childhood, or adolescence, but most children exhibit weakness or contractures during the first two years of life. Occasionally, spontaneous improvement of muscle weakness and of congenital contractures is noticed in the first decade. The course is slowly progressive, and after the fifth decade more than half of the patients need aids for ambulation, especially outdoors.

#### Ullrich Congenital Muscular Dystrophy

Ullrich congenital muscular dystrophy (UCMD) has a more severe phenotype, in general, than BM. Common symptoms include neonatal muscle weakness, proximal joint contractures, hyperlaxity of the distal joints, failure to thrive, lack of independent ambulation, and severe respiratory impairments by the end of the first decade of life. Other symptoms can include congenital hip dislocation, torticollis, prominent ears and heels, keloid formation and follicular hyperkeratosis, scoliosis, and facial weakness. IQ and brain development are usually unaffected. Respiratory failure can lead to life-threatening infections in the first or second decade of life. UCMD is autosomal recessive in about 40% of cases, and is now known to be dominant in the other 60% of cases.

Histopathological findings on muscle biopsy for both conditions are either nonspecific or show dystrophic changes and CK levels are either normal or mildly elevated. Immunofluorescent labeling of collagen VI in fibroblast cultures is a useful diagnostic tool, although double labeling is recommended to verify that the collagen VI protein that is present localizes correctly to the basement membrane. Expression of laminin alpha 2 (merosin) is normal.

For patients with suspected Bethlem myopathy or Ullrich CMD, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

#### References:

- Bertini, E and Pepe, G. Collagen type VI and related disorders: Bethlem myopathy and Ullrich scleroatonic muscular dystrophy. *Euro J Pead Neuro*. 2002; 6:193-198.
- Bonnemann, Carsten. Personal communication. July 8, 2009.
- Conti Reed, U. Congenital muscular dystrophy part I: A review of phenotypical and diagnostic aspects. *Arq Neuropsiquiatr*. 2009; 67:144-168.
- GeneTests: Collagen Type VI-Related Disorders. <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene?=bethlem>.
- GeneTests: Congenital Muscular Dystrophy Overview. <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene?=cmd-overview>
- Lampe, A and Bushby, K. Collagen VI related muscle disorders. *J Med Genet*. 2005; 42:673-685.
- Mendell, JR et al. The congenital muscular dystrophies: Recent advances and molecular insights. *Ped and Dev Pathology*. 2006; 9:427-443.

### Genes

#### COL6A2

### Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of Bethlem myopathy or Ullrich CMD.
- Carrier testing in adults with a family history of autosomal recessive Ullrich CMD.

### 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

Clinical Sensitivity: Mutations in the *COL6A1*, *COL6A2*, and *COL6A3* genes are identified approximately 66% of individuals clinically affected with Bethlem myopathy and approximately 79% of individuals clinically affected with Ullrich CMD. 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 biochemical phenotype.

Analytical Sensitivity: ~99%.

## Specimen Requirements

**Submit only 1 of the following specimen types**

### Type: Saliva

**Specimen Requirements:**

Oragene™ Saliva Collection Kit

Oragene™ 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: 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.

### 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.

## Special Instructions

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

## Related Tests

- Sequence analysis of the *COL6A1* and *COL6A3* genes is also available.
- Deletion/duplication analysis of the *COL6A1-3* genes by CGH array is available for those individuals in whom sequence analysis is negative.
- [Familial mutation testing](#) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.