

Type VI Collagenopathy Testing (Test #359):

Ullrich Congenital Muscular Dystrophy and Bethlem Myopathy

Brief Description of Clinical Features: Ullrich Congenital Muscular Dystrophy (UCMD; OMIM #254090) and Bethlem Myopathy (OMIM #158810) represent the spectrum of clinical disorders with abnormal type 6 Collagen. Bethlem Myopathy is characterized by proximal weakness and variable contractures. Most often affected by contractures are elbows, ankles and fingers. The earliest presenting signs are decreased fetal movement, neonatal hypotonia, and congenital contractures (Jobsis et al., *Brain* 122:649-655, 1999). Delayed motor milestones, muscle weakness and contractures are evident in cases of Bethlem Myopathy with early childhood onset (Lampe et al., *GeneReviews*, 2007). The clinical course in adult onset patients is typically slow but relentless; approximately two-thirds of patients over age 50 years require ambulatory support (Jobsis et al., 1999). UCMD is characterized by congenital muscle weakness, proximal joint contractures, and striking hyperlaxity of distal joints (Lampe and Bushby, *J Med Genet* 42:673-685, 2005). Affected children rarely gain the ability to walk independently and spinal rigidity and scoliosis develop. Respiratory failure in the first and second decade of life is a common cause of death (Lampe and Bushby, 2005). Serum CK levels are normal or mildly elevated in both Bethlem Myopathy and UCMD, however muscle biopsies from UCMD patients are more likely to be dystrophic and show absent or reduced immunostaining of Collagen VI (Higuchi et al., *Neuromuscul Disord.* 13:310-316, 2003). Intelligence is normal in Bethlem Myopathy and UCMD patients.

Genetics: All cases of Bethlem Myopathy reported to date have demonstrated autosomal dominant inheritance of *COL6A1*, *COL6A2* or *COL6A3* mutations (Lampe and Bushby, 2005; Jobsis et al., 1999). Once thought to be strictly a recessive condition, UCMD has been shown to be inherited in a dominant manner in numerous cases (e.g., Pan et al. *Am J Hum Genet* 73:355-369, 2003). A dominant-negative effect underlies pathogenicity of dominantly inherited UCMD (Pan et al., 2003; Baker et al., *Hum Mol Genet* 14:279-293, 2005), while most cases of recessive UCMD result from truncating mutations. Substitutions affecting the conserved Gly-X-Y motif of all three *COL6* genes and splice site mutations affecting exon 14 of *COL6A1* are common pathogenic variants.

Description of This Particular Test: Testing is accomplished by amplifying the coding exons and ~50 bp of adjacent noncoding sequence of each gene, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument. The order of testing will be: *COL6A1*, *COL6A2*, *COL6A3* unless otherwise requested. **Reference Sequences:**

Gene:	Genomic: NC_	mRNA and Protein: CCDS_
<i>COL6A1</i>	000021.7	13727.1
<i>COL6A2</i>	000021.7	13728.1
<i>COL6A3</i>	000002.10	33412.1

Indications for Testing: Individuals with clinical and pathological features consistent with Bethlem Myopathy or UCMD.

Sensitivity of test: Sequence analysis using genomic DNA from peripheral blood was found to have clinical sensitivity of 66%, 56%, and 79% among patients classified as having typical Bethlem Myopathy, severe Bethlem Myopathy, and Ulrich Congenital Muscular Dystrophy, respectively (Lampe et al., *J Med Genet* 42:108-120, 2005).

Turnaround Time: Maximum of 40 days for each gene although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of: *COL6A1*, *COL6A2*, *COL6A3*

CPT Codes	<i>COL6A1</i>	<i>COL6A2</i>	<i>COL6A3</i>	All Genes
83890	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)
83891	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)
83898	\$ 450 (x29)	\$ 370 (x23)	\$ 690 (x48)	\$ 1370 (x100)
83904	\$ 680 (x29)	\$ 560 (x23)	\$ 1030 (x48)	\$ 2060 (x100)
83894	\$ 90 (x1)	\$ 80 (x1)	\$ 120 (x1)	\$ 180 (x1)
83912	\$ 90 (x1)	\$ 80 (x1)	\$ 130 (x1)	\$ 210 (x1)
Totals:	\$ 1380	\$ 1160	\$ 2040	\$ 3890*

*When two or more of the genes on this panel are sequentially tested, a 15% discount will apply to the total cost.

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

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