GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Collagen Type VI-Related Disorders

[*Includes: Bethlem Myopathy, Ullrich Congenital Muscular Dystrophy*]

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Initial Posting: June 25, 2004.
Last Update: April 6, 2007.

Summary

Disease characteristics. Collagen type VI-related disorders include Bethlem myopathy and Ullrich congenital muscular dystrophy (CMD). Bethlem myopathy is characterized by the combination of proximal muscle weakness and variable contractures, affecting most frequently the long finger flexors, elbows, and ankles. The onset of Bethlem myopathy may be prenatal (characterized by decreased fetal movements), neonatal (hypotonia or torticollis), in early childhood (delayed motor milestones, muscle weakness, and contractures), or in adulthood (proximal weakness and Achilles tendon or long finger flexor contractures). Because of slow but ongoing progression, more than two-thirds of affected individuals over age 50 years rely on supportive means for outdoor mobility. Respiratory involvement is rare and seems to be related to more severe muscle weakness in later life. Ullrich CMD is characterized by congenital weakness and hypotonia, proximal joint contractures, and striking hyperlaxity of distal joints. Some affected children acquire the ability to walk independently; however, progression of the disease often results in later loss of ambulation. Early and severe respiratory involvement may require artificial ventilatory support in the first or second decade of life. Although originally described as separate entities, Bethlem myopathy and Ullrich CMD represent a clinical continuum in which individuals presenting with intermediate phenotypes could be considered to have either "mild Ullrich CMD" or "severe Bethlem myopathy."

Diagnosis/testing. Diagnosis depends on typical clinical features, with the serum creatine kinase concentration usually being normal or only mildly elevated and muscle biopsy showing myopathic or dystrophic changes. In Bethlem myopathy, collagen VI immunolabeling of muscle is usually normal or shows subtle alterations only. In Ullrich CMD, collagen VI immunolabeling is absent or markedly reduced from the endomysium and basal lamina, but may be normal around capillaries. Mutations in the genes *COL6A1*, *COL6A2*, and *COL6A3* are associated with Bethlem myopathy and Ullrich CMD. Molecular genetic testing is available on a clinical basis.

Management. *Bethlem myopathy/Ullrich CMD:* Physiotherapy advice regarding stretching, splinting, and mobility aids; possible orthopedic assessment if surgery for Achilles tendon contractures is to be considered; respiratory surveillance for possible nocturnal hypoventilation. Prophylaxis of chest infections with vaccination and physiotherapy; aggressive treatment of pulmonary infections. *In addition for Ullrich CMD:* Assessment of nutritional status and growth; management of feeding difficulties. Active surveillance for development of scoliosis; therapy for scoliosis as indicated.

Genetic counseling. Bethlem myopathy is inherited in an autosomal dominant manner and Ullrich CMD classically in an autosomal recessive manner although dominant inheritance secondary to *de novo* mutations can occur. Individuals with Bethlem myopathy are heterozygous for a *COL6A1*, *COL6A2*, or *COL6A3* mutation and are symptomatic. They may have an affected parent. Parents of individuals with autosomal recessive Ullrich CMD are usually heterozygous for a *COL6A1*, *COL6A2*, or *COL6A3* mutation, but do not appear to manifest related symptoms. Each child of an individual with Bethlem myopathy has a 50% chance of inheriting the condition; no individuals with Ullrich CMD have been known to reproduce. The risk to the sibs of the proband depends upon the genetic status of the proband's parents.

For parents of a proband with proven autosomal recessive Ullrich CMD: at conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being neither affected nor a carrier. No laboratories offering direct molecular genetic testing for prenatal diagnosis for Bethlem myopathy or Ullrich CMD are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutation has been identified in an affected family member.

Diagnosis

Clinical Diagnosis

Bethlem myopathy is recognized clinically by the combination of the following [Jobsis et al 1999]:

- Proximal muscle weakness
- Variable contractures, affecting most frequently the long finger flexors, elbows, and ankles

Ullrich congenital muscular dystrophy (CMD) is recognized clinically by the combination of the following [Voit 1998, Muntoni et al 2002]:

- Congenital weakness and hypotonia
- Proximal joint contractures
- Striking hyperlaxity of distal joints

Note: (1) Although originally described as separate entities, Bethlem myopathy and Ullrich CMD represent a clinical continuum in which individuals presenting with intermediate phenotypes could be considered to have either "mild Ullrich CMD" or "severe Bethlem myopathy." (2) As Bethlem myopathy may also present at birth, it may be difficult to categorize a neonate who has no family history of muscle disease into either Bethlem myopathy or Ullrich CMD initially; however, with time the stable acquisition of ambulation allows the diagnosis of Bethlem myopathy.

In both Bethlem myopathy and Ullrich CMD:

- Intelligence is normal (in contrast to some other CMD subtypes).
- Unusual skin features may be present, including follicular hyperkeratosis, and keloid or "cigarette-paper" scarring [Pepe et al 2002].

Testing

Bethlem myopathy

- Serum creatine kinase concentration is normal or mildly elevated.
- Muscle biopsy reveals myopathic or dystrophic changes. Collagen VI immunolabeling of muscle is often normal or shows only subtle alterations. In older individuals, a secondary reduction of laminin beta-1 labeling may be observed [Merlini et al 1999].

Ullrich CMD

- Serum creatine kinase concentration is usually normal or mildly elevated.
- Muscle biopsy more commonly shows dystrophic features with degeneration and regeneration and replacement of muscle with fat and fibrous connective tissue. Collagen VI immunolabeling from the endomysium and basal lamina ranges from absent to moderately or markedly reduced, but may be normal around capillaries [Higuchi et al 2003].
- If muscle is not available for collagen immunolabeling, loss of collagen VI in dermal fibroblast cultures may be a useful adjunct to the diagnosis [Jimenez-Mallebrera et al 2006].

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Genes. Mutations in the genes *COL6A1*, *COL6A2*, and *COL6A3* are associated with Bethlem myopathy and Ullrich CMD.

Clinical uses

- Diagnostic testing
- Carrier testing for autosomal recessive forms of the disease

Clinical testing

- **Sequence analysis.** Using genomic DNA derived from blood samples, sequence analysis of the three collagen VI genes detected putative mutations in [Lampe et al 2005]:
  - 66% of individuals clinically classified as having Bethlem myopathy
  - 56% of individuals with Bethlem myopathy with an unusually severe phenotype
  - 79% of individuals with Ullrich CMD
- **Linkage analysis.** Linkage studies are based upon accurate clinical diagnosis of the affected family members and accurate understanding of the genetic relationships in

the family. Linkage analysis is dependent on the availability and willingness of both affected and unaffected family members to be tested.

- **Bethlem myopathy.** When a known disease-causing mutation is not identified in a family, linkage analysis can theoretically be considered in families with more than one affected family member who belongs to different generations.
- **Ullrich CMD.** Linkage analysis is not useful for the vast majority of families with Ullrich CMD given that Ullrich CMD can be caused by either *de novo* dominant mutations or autosomal recessive mutations. Ullrich CMD caused by *de novo* dominant mutations cannot be distinguished from recessively inherited Ullrich CMD by history, clinical examination or laboratory data.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Bethlem Myopathy and Ullrich CMD

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
gDNA sequence analysis	*COL6A1*, *COL6A2*, *COL6A3* sequence variants	56%-79% [2]	Clinical Testing

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, genetic mechanism, and/or test method
2. Mutation detection frequency varies by phenotype [Lampe et al 2005]

Interpretation of sequence analysis results

- **Types of sequence alterations that may be detected [1]**
  - Pathogenic sequence alteration reported in the literature
  - Sequence alteration predicted to be pathogenic but not reported in the literature
  - Sequence variation of unknown clinical significance [2]
  - Sequence alteration predicted to be benign but not reported in the literature
  - Benign sequence alteration reported in the literature
- **Possibilities if a sequence alteration is not detected**
  - Patient does not have a mutation in the tested gene (e.g., a sequence alteration exists in another gene at another locus)
  - Patient has a sequence alteration that cannot be detected by sequence analysis (e.g., a large deletion, a splice site deletion)
  - Patient has a sequence alteration in a region of the gene (e.g., an intron or regulatory region) not covered by the laboratory's test

1. Adapted from the ACMG Recommendations for Standards for Interpretation of Sequence Variations (2000)
2. Family studies may be used to determine if this sequence alteration is segregating with the phenotype.

Testing Strategy

- Clinical evaluation
- Measurement of serum creatine kinase concentration

- Muscle biopsy with collagen VI immunolabeling
- Skin biopsy and dermal fibroblast culture with collagen VI immunolabeling

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *COL6A1*, *COL6A2*, and *COL6A3*, but *COL6A1* has been proposed as the locus for ossification of the posterior longitudinal ligament of the spine [Tanaka et al 2003, Tsukahara et al 2005].

Clinical Description

Natural History

Bethlem myopathy. The onset of Bethlem myopathy ranges from prenatal to mid-adulthood. Prenatal onset is characterized by decreased fetal movements; neonatal onset with hypotonia or torticollis; early-childhood onset with delayed motor milestones, muscle weakness and contractures; and adult onset (4th-6th decade) with proximal weakness and Achilles tendon or long finger flexor contractures. As some adults are unaware of weakness, age of onset cannot always be established.

The contractures may come and go during childhood, but nearly all affected individuals eventually exhibit flexion contractures of the fingers, wrists, elbows, and ankles. These contractures can become disabling when combined with muscle weakness.

Individuals can have moderate weakness and atrophy of the muscles of the trunk and limbs with proximal muscles being more involved than distal muscles and extensors more than flexors.

As a result of slow but ongoing progression of the condition, more than two-thirds of affected individuals over age 50 years need supportive means (i.e., canes, crutches, or wheelchair) for outdoor mobility [Jobsis et al 1999; Pepe, Giusti et al 1999].

Respiratory muscle and especially diaphragmatic involvement necessitating artificial nocturnal respiratory support is part of the clinical spectrum but is rare and seems to be related to severe weakness that occurs in later life [Haq et al 1999]. Respiratory failure may supervene prior to loss of ambulation and may be associated with diaphragmatic weakness [Bushby & Lampe, unpublished observation].

Cardiac function is usually normal [Mohire et al 1988, de Visser et al 1992].

Ullrich congenital muscular dystrophy **(CMD).** In addition to characteristic muscle weakness of early onset, proximal joint contractures, and hyperelasticity of the wrists and ankles, other features observed are congenital hip dislocation, prominent calcanei, and a transient kyphotic deformity at birth.

With time, the distal hyperlaxity can evolve into marked finger flexion contractures and tight Achilles tendons [Furukawa & Toyokura 1977, Muntoni et al 2002].

Some affected children acquire the ability to walk independently; however, progression of the disease often results in later loss of ambulation.

Rigidity of the spine is often associated with scoliosis.

Early and severe respiratory involvement may require artificial ventilatory support in the first or second decade of life.

Failure to thrive is common.

Follicular hyperkeratosis over the extensor surfaces of upper and lower limbs and keloid and cigarette paper scar formation are common.

Cardiac involvement has not been documented to date.

Genotype-Phenotype Correlations

Specific mutations tend to be strictly associated with either the Bethlem myopathy or Ullrich CMD phenotype. Heterozygous triple helical glycine substitutions located towards the N-terminus usually appear to have a dominant-negative effect whereas virtually no Bethlem myopathy-causing mutations have been documented in the C-terminal part of the triple helix [Lampe & Bushby 2005].

Penetrance

Parents of individuals with Ullrich CMD (inherited in an autosomal recessive manner) are usually heterozygous for a *COL6A1*, *COL6A2*, or *COL6A3* mutation, but do not appear to manifest any related symptoms.

Individuals with Bethlem myopathy (inherited in an autosomal dominant manner) are heterozygous for a *COL6A1*, *COL6A2*, or *COL6A3* mutation and are symptomatic. However, careful clinical examination may be necessary to identify findings diagnostic of Bethlem myopathy in minimally symptomatic parents of individuals with Bethlem myopathy.

Anticipation

Anticipation is not observed.

Nomenclature

Bethlem myopathy was first described as "benign myopathy with autosomal dominant inheritance" [Bethlem & Wijngaarden 1976]. Other terms in use include benign congenital myopathy, benign congenital muscular dystrophy, and benign congenital myopathy with contractures.

Ullrich CMD was first described as "congenital atonic sclerotic muscular dystrophy" [Ullrich 1930]. Other terms used in the past include congenital hypotonic sclerotic muscular dystrophy and congenital muscular dystrophy with distal laxity.

Prevalence

Prevalence is estimated at 0.5:100,0000 in Bethlem myopathy and 0.1:100,000 in Ullrich CMD [personal communication, F Norwood; Bromley Hospitals NHS Trust, Orpington, UK], but the disorders are probably currently underdiagnosed.

Both conditions have been described in individuals from a variety of ethnic backgrounds.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Bethlem myopathy. When contractures are subtle or missed, the major differential diagnoses are the limb-girdle muscular dystrophies (LGMDs) [Scacheri et al 2002] (see Limb-Girdle Muscular Dystrophy Overview).

When contractures are a prominent feature, the major differential diagnoses are X-linked or autosomal dominant Emery-Dreifuss muscular dystrophy, both of which are associated with serious cardiac complications [Pepe et al 2002].

Immunohistochemical testing (i.e., western blotting and immunohistochemistry) performed on muscle biopsy and/or molecular genetic testing can help to establish the diagnosis of some LGMD subtypes such as sarcoglycanopathy, calpainopathy, and dysferlinopathy as well as X-linked or autosomal dominant Emery-Dreifuss muscular dystrophy.

Ullrich congenital muscular dystrophy **(CMD).** In the neonatal period, the differential diagnosis includes the following:

- Other forms of CMD (see Congenital Muscular Dystrophy Overview). These do not generally present with the distal hyperlaxity characteristic of Ullrich CMD and are usually associated with serum creatine kinase concentrations higher than those observed in Ullrich CMD. Biochemical testing (i.e., western blotting and immunohistochemistry) performed on the muscle biopsy and molecular genetic testing can help to establish the diagnosis of some CMD subtypes such as merosin-deficient MDC1A or MDC1C *(FKRP* mutations). In addition, brain MRI may show structural abnormalities or white matter changes in some CMD subtypes such as merosin-deficient MDC1A, Walker-Warburg syndrome, muscle-eye-brain disease, and Fukuyama congenital muscular dystrophy (FCMD).
- Spinal muscular atrophy (SMA). SMA shows features of denervation rather than myopathic or dystrophic changes on muscle biopsy. It can usually be diagnosed by demonstrating mutations in the *SMN* gene.
- Forms of Ehlers-Danlos syndrome, classic type or Marfan syndrome. Neither of these disorders is typically associated with significant muscle weakness or an abnormal muscle biopsy, but they may be confused with Ullrich CMD because of joint laxity.
- Rigid spine syndromes (see Congenital Muscular Dystrophy Overview). A proportion of rigid spine syndromes are caused by mutations in the *SEPN1* gene (See also Multiminicore Disease), which may overlap with Ullrich CMD later as the phenotype develops.

Management

Evaluations Following Initial Diagnosis

Bethlem myopathy. To establish the extent of disease in an individual diagnosed with Bethlem myopathy:

- Evaluation of degree of muscle weakness and mobility
- Joint examination for contractures
- Physiotherapy assessment and advice regarding stretches/splints for contractures and mobility aids
- Possibly orthopedic evaluation if surgery is to be considered for tendon Achilles contractures
- Assessment of respiratory status by seeking history of clinical symptoms of nocturnal hypoventilation such as early morning nausea and headaches, daytime somnolence; inquire about frequency and severity of chest infections; if any concerns, perform spirometry and nocturnal pulse oximetry

Ullrich congenital muscular dystrophy (CMD). To establish the extent of disease in an individual diagnosed with Ullrich CMD:

- Evaluation of degree of muscle weakness and mobility
- Examination of back for scoliosis
- Joint examination for contractures and hyperlaxity
- Physiotherapy assessment and advice regarding stretches/splints for contractures and mobility aids such as swivel walkers and standing frames to achieve upright posture and protect against the development of scoliosis and other contractures
- Possibly x-rays of thoracolumbar spine and orthopedic evaluation if scoliosis is clinically suspected
- Possibly orthopedic evaluation if hip dislocation is suspected or surgery is to be considered for tendon Achilles contractures
- Assessment of respiratory status by seeking history of clinical symptoms of nocturnal hypoventilation such as early morning nausea and headaches, daytime somnolence; inquire about frequency and severity of chest infections; if any concerns, perform spirometry and nocturnal pulse oximetry
- Assessment of growth and feeding. Feeding difficulties may manifest as failure to thrive or excessive time taken to finish eating a meal.

Treatment of Manifestations

Bethlem myopathy. Physiotherapy and possibly orthopedic management of contractures are useful to maintain mobility. Contractures may be dynamic and may require stretching and splinting.

Symptoms of nocturnal hypoventilation respond well to noninvasive respiratory support such as mask ventilation [Wallgren-Pettersson et al 2004].

Approximately two-thirds of individuals over age 50 years need supportive aids for outdoor mobility [Jobsis et al 1999].

Ullrich **CMD.** Children require active physiotherapy management as soon as the diagnosis is established to promote mobility and independence. Early mobilization in standing frames is important to achieve upright posture and protect against the development of scoliosis and other contractures.

Contractures tend to be aggressive and may require surgery.

Feeding difficulties may manifest as failure to thrive or excessive time taken to finish eating a meal. Consultation with a nutrition specialist may be required to boost calorie intake; for serious problems, feeding by gastrostomy may be the best solution to promote a normal weight gain.

Respiratory support with nocturnal ventilation usually becomes necessary in the first or second decade and can be effective in reducing symptoms, promoting quality of life, and allowing normal schooling [Wallgren-Pettersson et al 2004].

Scoliosis frequently develops in the first or second decade and requires active management including surgery.

Prevention of Secondary Complications

Prophylaxis of chest infections with vaccination and physiotherapy as well as early and aggressive use of antibiotics may prevent further respiratory problems in both disorders.

Surveillance

Bethlem myopathy

- Clinical assessment of muscle weakness, joint contractures, and mobility to inform physiotherapeutic advice regarding stretches/splints and mobility aids
- Assessments of respiratory function to detect asymptomatic decline. (Assess clinically by seeking history of clinical symptoms of nocturnal hypoventilation such as early-morning nausea and headaches, daytime somnolence; inquire about frequency and severity of chest infections; if any concerns, perform spirometry and nocturnal pulse oximetry)

Assessments should be repeated regularly, possibly annually, depending on the clinical status of the individual.

Ullrich CMD

- Clinical assessment of muscle weakness, scoliosis, joint contractures, and mobility to inform physiotherapeutic advice regarding stretches/splints and mobility aids
- Once scoliosis is evident, regular orthopedic follow up
- Assessments of respiratory function to detect asymptomatic decline. (Assess clinically by seeking history of clinical symptoms of nocturnal hypoventilation such as early-morning nausea and headaches, daytime somnolence; inquire about frequency and severity of chest infections; if any concerns perform spirometry and nocturnal pulse oximetry);
- Clinical assessment of nutritional status

Assessments should be repeated regularly, possibly biannually, depending on the clinical status of the individual.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and

the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Bethlem myopathy is inherited in an autosomal dominant manner and Ullrich congenital muscular dystrophy (CMD) is classically inherited in an autosomal recessive manner, although four individuals with *de novo* dominant inheritance have been reported [Pan et al 2003, Baker et al 2005], and this mode of inheritance is also suspected in three other individuals [Lampe et al 2005].

- Individuals with Bethlem myopathy are heterozygous for a *COL6A1*, *COL6A2*, or *COL6A3* mutation and are symptomatic.
- Parents of individuals with autosomal recessive Ullrich CMD are usually heterozygous for a *COL6A1*, *COL6A2*, or *COL6A3* mutation but do not appear to manifest any related symptoms.

Risk to Family Members — Bethlem Myopathy

Parents of a proband

- Individuals diagnosed with Bethlem myopathy may have an affected parent.
- A proband with Bethlem myopathy may have the disorder as the result of a new gene mutation [Pan et al 2003]. The proportion of cases caused by *de novo* mutations is unknown.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include clinical assessment by a clinician specializing in muscle disorders and molecular genetic testing, if the mutation has been identified in the proband.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If a parent of the proband is affected, the chance that a sib will be affected is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- Although no instances of germline mosaicism have been reported, it remains a possibility.

Offspring of a proband. Each child of an individual with Bethlem myopathy has a 50% chance of inheriting the condition.

Other family members. The risk to other family members depends upon the genetic status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Risk to Family Members — Ullrich CMD

Parents of a proband

- The parents of a child with autosomal recessive Ullrich CMD are usually heterozygotes and therefore carry one mutant allele.

- Heterozygotes (carriers) are usually asymptomatic.
- Four individuals with *de novo* dominant Ullrich CMD have been reported [Pan et al 2003, Baker et al 2005]; this mode of inheritance has also been suspected in three other individuals [Lampe et al 2005]. Individuals with *de novo* dominant Ullrich CMD cannot be distinguished clinically from those with autosomal recessive Ullrich CMD.

Sibs of a proband. When both parents are carriers of autosomal recessive Ullrich CMD:

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being neither affected nor a carrier.
- Once an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 2/3.

The risk to the sibs of a proband with *de novo* dominant Ullrich CMD appears to be low. However, although no instances of germline mosaicism have as yet been reported, it remains a possibility.

Offspring of a proband

- The offspring of an individual with Ullrich CMD are obligate heterozygotes for a disease-causing mutation but are themselves unaffected unless they inherit a second mutation from their other parent.
- Each child of an individual with *de novo* dominant Ullrich CMD has, in theory, a 50% chance of inheriting the condition, however, to date no pregnancy and no affected parent-offspring pair has been reported.

Other family members. For autosomal recessive Ullrich CMD, each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier Detection

Carrier testing for family members at risk to be carriers of autosomal recessive Ullrich CMD is available on a clinical basis once the mutations have been identified in the proband.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

No laboratories offering direct molecular genetic testing for prenatal diagnosis for Bethlem myopathy or Ullrich CMD are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutation has been identified in an affected family member. For laboratories offering custom prenatal testing, see Testing.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation(s) has/have been identified in an affected family member. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Collagen Type VI-Related Disorders

Gene Symbol	Chromosomal Locus	Protein Name
COL6A1	21q22.3	Collagen alpha-1(VI) chain
COL6A2	21q22.3	Collagen alpha-2(VI) chain
COL6A3	2q37	Collagen alpha-3(VI) chain

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Collagen Type VI-Related Disorders

120220	COLLAGEN, TYPE VI, ALPHA-1; COL6A1
120240	COLLAGEN, TYPE VI, ALPHA-2; COL6A2
120250	COLLAGEN, TYPE VI, ALPHA-3; COL6A3
158810	BETHLEM MYOPATHY
254090	ULLRICH CONGENITAL MUSCULAR DYSTROPHY; UCMD

Table C. Genomic Databases for Collagen Type VI-Related Disorders

Gene Symbol	Locus Specific	Entrez Gene	HGMD
COL6A1	COL6A1	1291 (MIM No. 120220)	COL6A1
COL6A2	COL6A2	1292 (MIM No. 120240)	COL6A2
COL6A3	COL6A3	1293 (MIM No. 120250)	COL6A3

For a description of the genomic databases listed, click here.

Molecular Genetic Pathogenesis

Collagen VI is composed of three different peptide chains: α1(VI), α2(VI) (both 140 kd in size), and α3(VI) (260-300 kd in size) [Engvall et al 1986]. The α1(VI) and α2(VI) chains are encoded by two genes *(COL6A1* and *COL6A2* respectively) situated head-to-tail on chromosome 21q22.3 [Heiskanen et al 1995] and separated by 150 kb of genomic DNA, whereas *COL6A3*, the gene for the α3(VI) chain, maps to chromosome 2q37 [Weil et al 1988]. All three chains contain a central short triple helical domain of 335-336 amino acids with repeating Gly-Xaa-Yaa sequences flanked by large N- and C- terminal globular domains consisting of motifs of approximatley 200 amino acids each that are homologous to von Willebrand factor (vWF) type A domains [Chu et al 1990].

Normal allelic variants:

- ***COL6A1*** consists of 37 exons (35 of which are coding) and produces a single transcript encoding a protein of 1021 amino acids with two C-terminal and one N-terminal vWF type A-like domains.

- ***COL6A2***spans 30 exons (29 of which are coding) and has been shown to produce multiple alternatively spliced mRNAs that differ in the 5'-untranslated region as well as in the 3'-coding and noncoding sequences. It produces at least three α2(VI) protein variants (828-1019 amino acids) with distinct carboxyl termini, which similarly contain two C-terminal and one N-terminal vWF type A-like domain [Saitta et al 1990].
- ***COL6A3***comprises 44 exons (43 of which are coding) and encodes the α3(VI) chain, which can vary in size between 2970 and 3176 amino acids. The α3(VI) chain contains two C-terminal vWF type A-like domains, subdomains similar to type III fibronectin repeats and Kunitz protease inhibitors as well as six to ten N-terminal vWF type A-like domains, thus contributing most of the amino-terminal globular domain of the collagen VI heterotrimer. Various N-terminal exons of *COL6A3* are subject to alternative splicing and four variant transcripts encoding proteins with variably sized N-terminal globular domains have been characterized [Stokes et al 1991, Dziadek et al 2002].

Pathologic allelic variants: Single amino acid substitutions disrupting the Gly-Xaa-Yaa motif of the highly conserved triple helical domain of any of the three *COL6A* genes [Jobsis et al 1996; Pepe, Bertini et al 1999; Scacheri et al 2002, Lampe et al 2005; Lucioli et al 2005] constitute a frequent pathogenic mechanism. Splice-site mutations in *COL6A1* that cause skipping of exon 14 form the second most frequent group of mutations [Lamande et al 1999; Pepe, Giusti et al 1999; Pan et al 2003; Lampe et al 2005; Lucioli et al 2005]. Other splice-site mutations causing small in-frame deletions or insertions within domains flanking the triple helical domain have also been reported [Vanegas et al 2002; Lampe et al 2005; Lucioli et al 2005], and a frameshifting splice-site mutation causing nonsense-mediated mRNA decay as well as a missense mutation in an N-terminal *COL6A3* domain are thought to cause Bethlem myopathy via functional haploinsufficiency [Lamande, Bateman et al 1998; Sasaki et al 2000]. Given the high number of nonsynonymous polymorphic amino acid changes described for the collagen VI genes, it is difficult to be sure about the pathogenicity of missense mutations other than glycine substitutions within the triple helical domain.

In recessive Ullrich congenital muscular dystrophy (CMD), a large number of mutations appear to result in premature termination codons with consequent nonsense-mediated mRNA decay. Premature termination codons occur either by direct introduction of a termination codon at the genomic level [Demir et al 2002, Giusti et al 2005, Lampe et al 2005] or through frameshift-inducing genomic deletions [Higuchi et al 2001, Giusti et al 2005, Lampe et al 2005], insertions [Camacho Vanegas et al 2001], duplications [Lampe et al 2005] and splice changes [Camacho Vanegas et al 2001, Ishikawa et al 2002]. Splice mutations leading to in-frame exonic deletions as well as in-frame genomic deletions form another common mutation type in Ullrich CMD [Demir et al 2002, Ishikawa et al 2004, Baker et al 2005, Lampe et al 2005].

Bethlem myopathy and Ullrich CMD represent a clinical continuum in which individuals presenting with intermediate phenotypes could be considered to have either "mild Ullrich CMD" or "severe Bethlem myopathy." In this context, heterozygous single amino acid substitutions disrupting the Gly-Xaa-Yaa motif of the highly conserved triple helical domain have been described in individuals with a milder form of Ullrich CMD [Giusti et al 2005, Lampe et al 2005]. As for Bethlem myopathy, given the high number of nonsynonymous polymorphic amino acid changes described for the collagen VI genes, it is difficult to be sure about the pathogenicity of missense mutations other than glycine substitutions within the triple helical domain.

In dominant Ullrich CMD, heterozygously occurring splice mutations leading to in-frame exonic deletions as well as in-frame genomic deletions share a common motif: they preserve

a unique cysteine important for dimer formation, allowing secretion of abnormal tetramers with a consequent dominant-negative effect on microfibrillar assembly [Pan et al 2003, Baker et al 2005].

Normal gene product: Extracellular matrix molecules are critical for skeletal muscle stability, regeneration, and muscle cell matrix adhesion [Helbling-Leclerc et al 1995, Sewry & Muntoni 1999, Emery 2002]. Collagen VI is a ubiquitous extracellular matrix protein [von der Mark et al 1984] that forms a microfibrillar network in close association with the basement membrane around muscle cells and interacts with several other matrix constituents [Burg et al 1996, Kuo et al 1997, Wiberg et al 2003]. The assembly of collagen VI is a complex multistep process. Association of the three genetically distinct subunits, α1(VI), α2(VI), and α3(VI), to form a triple helical monomer is followed by staggered assembly into disulfide-bonded antiparallel dimers, which then align to form tetramers, also stabilized by disulfide bonds. Outside of the cell, tetramers, the secreted form of collagen VI, associate end to end to form the characteristic beaded microfibrils [Furthmayr et al 1983; Engvall et al 1986; Lamande, Sigalas et al 1998].

Abnormal gene product:

- **Bethlem myopathy.** Heterozygous single amino acid substitutions disrupting the Gly-Xaa-Yaa motif of the highly conserved triple helical domain of any of the three *COL6A* genes [Jobsis et al 1996; Pepe, Bertini et al 1999; Scacheri et al 2002; Lampe et al 2005; Lucioli et al 2005], depending on their location, appear to either interfere with intracellular chain assembly, thus leading to functional haploinsufficiency, or, following successful secretion, to cause kinking of the tetramers, thus affecting extracellular microfibril formation [Lamande et al 2002]. Functional haploinsufficiency via a dominant-negative effect has also been reported as the pathogenic mechanism for some missense and splice-site mutations [Lamande et al 1999].
- **Ullrich CMD.** Most recessive mutations reported to date are protein-truncating nonsense mutations. Some of them have been shown to result in absence of collagen VI because of nonsense-mediated mRNA decay [Zhang et al 2002]. Dominant heterozygously occurring splice mutations leading to in-frame exonic deletions as well as in-frame genomic deletions preserve a unique cysteine important for dimer formation, allowing secretion of abnormal tetramers with a consequent dominant-negative effect on microfibrillar assembly [Pan et al 2003, Baker et al 2005].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Muscular Dystrophy Association (MDA)
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www.muscular-dystrophy.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Author Notes

Newcastle Upon Tyne Hospitals: Patient Information

Revision History

- 6 April 2007 (me) Comprehensive update posted to live Web site
- 25 June 2004 (me) Review posted to live Web site
- 18 February 2004 (kf) Original submission