Collagen Type VI-Related Disorders

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Summary

**Clinical characteristics.** Collagen type VI-related disorders represent a continuum of overlapping phenotypes with Bethlem myopathy at the mild end, Ullrich congenital muscular dystrophy (CMD) at the severe end, and two rare, less well-defined disorders – autosomal dominant limb-girdle muscular dystrophy and autosomal recessive myosclerosis myopathy – in between. Although Bethlem myopathy and Ullrich CMD were defined long before their molecular basis was known, they remain useful for clarification of prognosis and management.

Bethlem myopathy, characterized by the combination of proximal muscle weakness and variable contractures, affects most frequently the long finger flexors, elbows, and ankles. Onset 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 progression, more than two thirds of affected individuals over age 50 years rely on supportive means for outdoor mobility. Respiratory involvement is rare and appears 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 ventilatory support in the first or second decade of life.

**Diagnosis/testing.** Diagnosis depends on typical clinical features; normal or only mildly elevated serum creatine kinase concentration; suggestive pattern on muscle magnetic resonance imaging (MRI); muscle biopsy with collagen VI immunolabeling (for suspected Ullrich CMD) or skin biopsy and dermal fibroblast culture with collagen VI immunolabeling (for suspected Bethlem myopathy); and molecular genetic testing of COL6A1, COL6A2, and COL6A3, the three genes encoding the three collagen VI peptide chains.

**Management.** Treatment of manifestations: As needed based on clinical findings: physiotherapy regarding stretching exercises, splinting, and mobility aids; orthopedic assessment if surgery for Achilles tendon contractures is being considered; therapy for scoliosis. Respiratory: evaluation for nocturnal hypoventilation; prophylaxis of chest infections with vaccination and

**Surveillance:** Routine assessment of: muscle weakness, scoliosis, joint contractures, and mobility; respiratory function; and nutritional status.

**Genetic counseling.** The Bethlem myopathy phenotype is usually inherited in an autosomal dominant manner and the UMD phenotype is usually inherited in an autosomal recessive manner; however, exceptions occur. In the few cases reported to date, it appears that autosomal dominant limb-girdle muscular dystrophy is inherited in an autosomal dominant manner and the myosclerosis myopathy phenotype is inherited in an autosomal recessive manner. Carrier testing for autosomal recessive collagen VI-related disorders and prenatal testing are possible if the pathogenic variants have been identified in an affected family member.

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**GeneReview Scope**

### Collagen Type VI-Related Disorders: Included Disorders

- Bethlem myopathy
- Ullrich congenital muscular dystrophy
- Collagen type VI-related autosomal dominant limb-girdle muscular dystrophy
- Autosomal recessive myosclerosis myopathy

For synonyms and outdated names see Nomenclature.

1. Disorders included in the *GeneReview* are those caused by mutation of *COL6A1, COL6A2*, or *COL6A3*. Forms of the disorder associated with other genes are not addressed in this *GeneReview*.

**Diagnosis**

The collagen type VI-related disorders, caused by mutation of *COL6A1, COL6A2*, or *COL6A3*, represent a clinical spectrum including Bethlem myopathy at the mild end, Ullrich congenital muscular dystrophy (CMD) at the severe end, and two less well-defined disorders – autosomal dominant limb-girdle muscular dystrophy and autosomal recessive myosclerosis myopathy – in between.

Note: Although these phenotypes are now recognized to comprise a continuum of overlapping phenotypes, the clinical designations are useful for clarification of prognosis and management.

**Clinical findings**

Bethlem myopathy is recognized clinically by the combination of the following [Jöbsis 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: 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].
- Serum creatine kinase concentration is normal or mildly elevated.

Muscle MRI. Bethlem myopathy and Ullrich CMD have distinct patterns of muscle involvement, although some overlap exists [Mercuri et al 2005].

- In thigh muscles:
  - In Bethlem myopathy the vasti muscles appear to be the most frequently and strikingly affected, with a rim of abnormal signal at the periphery of each muscle and relative sparing of the central part. A peculiar involvement of the rectus femoris with a central area of abnormal signal within the muscle is also a frequent finding. See Figure 1.
  - In Ullrich CMD more diffuse involvement is observed with relative sparing of the sartorius, gracilis, and adductor longus. See Figure 2.

- In calf muscles: Bethlem myopathy and Ullrich CMD often show a rim of abnormal signal at the periphery of soleus and gastrocnemii.

Figure 1.

Transverse T₁ weighted images through thigh muscles in four individuals with Bethlem myopathy (a-d). Note the relative sparing of the central part of the vastus lateralis with a rim of increased signal at the periphery of the muscle and the prominent (more...)
Figure 2.
Transverse T₁-weighted images through thigh muscles in four individuals with Ullrich CMD. Note the diffuse involvement of the thigh with relative sparing of sartorius, gracilis, and rectus femoris (arrows) in three young affected individuals (a-c). A (more...)

Tissue studies

Bethlem myopathy

- Muscle biopsy reveals myopathic or dystrophic changes. Collagen VI immunolabeling is often normal or shows only subtle alterations.
- Immunofluorescent analysis of collagen VI in dermal fibroblast cultures is predictive of Bethlem myopathy [Hicks et al 2008]. See Figure 3.

Figure 3.
Dermal fibroblasts in Bethlem myopathy A. Normal control with collagen VI labeling with antibody B. Negative control (in which no antibody was used and, thus, collagen is not labeled) Both panel A and B show an abundance of well-organized collagen VI (more...)

Ullrich CMD

- 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].
- Loss of collagen VI in dermal fibroblast cultures may be a useful adjunct to the diagnosis [Jimenez-Mallebrera et al 2006]. See Figure 3.

Molecular Genetic Testing

Genes. COL6A1, COL6A2, and COL6A3 are the three genes in which pathogenic variants are known to cause collagen type VI-related disorders.

Clinical testing

Table 1.
Summary of Molecular Genetic Testing used in Collagen VI-Related Disorders
<table>
<thead>
<tr>
<th>Gene</th>
<th>Proportion of Collagen VI-Related Disorders Attributed to Pathogenic Variants in This Gene</th>
<th>Test Method</th>
<th>Variants Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>COL6A1</td>
<td>38%</td>
<td>Sequence analysis</td>
<td>Sequence variants</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duplication/deletion analysis</td>
<td>Exon or whole-gene deletions</td>
</tr>
<tr>
<td>COL6A2</td>
<td>44%</td>
<td>Sequence analysis</td>
<td>Sequence variants</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duplication/deletion analysis</td>
<td>Exon or whole-gene deletions</td>
</tr>
<tr>
<td>COL6A3</td>
<td>18%</td>
<td>Sequence analysis</td>
<td>Sequence variants</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duplication/deletion analysis</td>
<td>Unknown; none reported</td>
</tr>
</tbody>
</table>

1. See Table A. Genes and Databases for chromosome locus and protein.
2. Author, personal observation
3. See Molecular Genetics for information on allelic variants.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Testing that identifies deletions/duplications not readily detectable by sequence analysis of the coding and flanking intron regions of genomic DNA; included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
6. Highly similar heterozygous genomic deletions were identified in a deletion-prone region of COL6A1 in two individuals, one with a BM and one with an Ullrich CMD phenotype [Pepe et al 2006].
7. A novel type of pathogenic variant underlying recessively inherited UCMD was reported in two families with Ullrich CMD with large genomic deletions of COL6A1 and COL6A2 on chromosome 21 [Foley et al 2011].
8. Large or whole-gene deletions appear to be rare in collagen VI-related disorders.
9. In addition to the finding described in footnote 5, a deep intron deletion in COL6A2 (identified by array CGH) was one of two biallelic pathogenic variants in an individual with a BM phenotype [Bovolenta et al 2010].
10. No deletions or duplications involving COL6A3 have been reported to cause collagen type VI-related disorders.
Testing Strategy

To confirm/establish the diagnosis in a proband

- Clinical evaluation
- Measurement of serum creatine kinase concentration
- Muscle MRI for Bethlem myopathy
  
  Note: Muscle MRI is not always done in Ullrich CMD because of the difficulty associated with sedating babies and small children.

- Tissue evaluation
  - For suspected Ullrich CMD: muscle biopsy with collagen VI immunolabeling
  - For suspected Bethlem myopathy: skin biopsy and dermal fibroblast culture with collagen VI immunolabeling

- Molecular genetic testing of \textit{COL6A1, COL6A2, COL6A3}

  Using genomic DNA derived from peripheral blood samples, sequence analysis of the three genes encoding collagen VI detected putative pathogenic variants in [Lampe et al 2005] (see Note):
  
  - 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

Note: (1) The low variant detection rate is largely attributable to the high degree of genetic heterogeneity in Bethlem myopathy and Ullrich CMD, rather than failure to detect \textit{COL6A} pathogenic variants; however, deep intronic and cryptic variants are not detectable by sequence analysis. Deletion/duplication analysis does not increase the variant detection frequency greatly, if at all. (2) The recent finding of compound heterozygous pathogenic variants for autosomal recessive forms of collagen type VI-related disorders emphasizes the importance of sequencing the entire coding region of the three genes (\textit{COL6A1, COL6A2, COL6A3}) to ensure detection of two mutant alleles, when present [Gualandi et al 2009].

Carrier testing for relatives at risk for autosomal recessive forms of collagen VI-related disorders requires prior identification of the pathogenic variants in the family.

Note: Carriers (heterozygotes) for autosomal recessive forms of collagen type VI-related disorders are not at risk of developing the disorder.

Predictive testing for at-risk asymptomatic adult family members requires prior identification of the pathogenic variants in the family.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies
require prior identification of the pathogenic variants in the family.

**Clinical Characteristics**

**Clinical Description**

The phenotypes associated with collagen type VI-related disorders, once thought to be distinct entities, were clinically defined long before their molecular basis was discovered. The collagen type VI-related disorders are now recognized to comprise a continuum of overlapping phenotypes with Bethlem myopathy at the mild end, Ullrich congenital muscular dystrophy (CMD) at the severe end, and two less well-defined disorders – autosomal dominant limb-girdle muscular dystrophy and autosomal recessive myosclerosis myopathy – in between. Although these phenotypes are now recognized to overlap and fall on a continuum, these clinical designations are useful for clarification of prognosis and management.

**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 [Jöbsis et al 1999, Pepe et al 1999b].

Respiratory muscle and especially diaphragmatic involvement necessitating artificial nocturnal respiratory support is part of the clinical spectrum but is rare and appears to be related to severe weakness occurring in later life [Haq et al 1999]. Respiratory failure may supervene prior to loss of ambulation and may be associated with diaphragmatic weakness [Haq et al 1999].

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.

**Other Phenotypes**

The two additional conditions included in the spectrum of collagen VI myopathies are:

- **Autosomal dominant limb-girdle muscular dystrophy** caused by pathogenic variants in *COL6A1/COL6A2* in three families and *COL6A3* in one family [Scacheri et al 2002]. Although some affected individuals had mild weakness with only limited functional impairment, others had a more severe, dystrophic-like weakness with findings including Gower’s maneuver, toe walking, and loss of ambulation. Joint contractures were either absent or much milder than those of typical Bethlem myopathy. Whereas findings of Bethlem myopathy are typically present in infancy, the age at onset in these three families ranged from infancy, to early childhood, to adulthood.

- **Autosomal recessive myosclerosis myopathy** caused by mutation of *COL6A2* in two individuals from one family [Merlini et al 2008]. Myosclerosis myopathy is characterized by difficulty in walking in early childhood, toe walking, and progressive contractures of calf muscles. In the early 30s the muscles are slender with a firm “woody” consistency and associated with contractures that restrict range of motion of many joints.

**Genotype-Phenotype Correlations**

In 42 individuals with collagen VI-related myopathy with onset before age two years, biallelic pathogenic variants that caused premature termination codons (associated with autosomal recessive inheritance) were associated with the most severe phenotypes (ambulation never achieved), whereas heterozygous *de novo* in-frame exon skipping and glycine missense variants (associated with autosomal dominant inheritance) were associated with the moderate-progressive phenotypes (loss of ambulation) [Briñas et al 2010].

In autosomal recessive Ullrich congenital muscular dystrophy (CMD), a large number of pathogenic variants appear to result in premature termination codons with consequent nonsense-

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 a milder form of Ullrich CMD [Giusti et al 2005, Lampe et al 2005]. As for Bethlem myopathy, given the high number of variants resulting in benign amino acid changes described for the genes encoding collagen VI subunits, it is difficult to be certain about the pathogenicity of missense variants other than glycine substitutions within the triple helical domain.

In autosomal dominant Ullrich CMD, heterozygous splice site variants leading to in-frame exon deletions and heterozygous in-frame deletions in the coding region 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].

Penetrance

Parents of individuals with recessively inherited collagen VI-related disorders are usually heterozygous for a COL6A1, COL6A2, or COL6A3 pathogenic variant, but do not appear to manifest any related symptoms.

Individuals with dominantly inherited collagen VI-related disorders are heterozygous for a COL6A1, COL6A2, or COL6A3 pathogenic variant and are symptomatic. However, careful clinical examination may be necessary to identify findings diagnostic of a collagen type VI-related disorder in their minimally symptomatic parents [Peat et al 2007].

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:

- Benign congenital myopathy
- Benign congenital muscular dystrophy
- Benign congenital myopathy with contractures
**Ullrich CMD** was first described as "congenital atonic sclerotic muscular dystrophy" [Ullrich 1930]. Other terms used in the past:

- Congenital hypotonic sclerotic muscular dystrophy
- Congenital muscular dystrophy with distal laxity

**Prevalence**

Prevalence is estimated at 0.77:100,000 in Bethlem myopathy and 0.13:100,000 in Ullrich CMD [Norwood et al 2009]; the disorders are probably currently underdiagnosed.

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

**Genetically Related (Allelic) Disorders**

No phenotypes other than those discussed in this GeneReview have been associated with mutation of COL6A1, COL6A2, or COL6A3.

**Differential Diagnosis**

The differential diagnosis of the two major phenotypes observed in the collagen VI-related disorders is discussed below. Of note, a normal to mildly elevated CK, suggestive findings on muscle MRI, and the lack of a cardiac phenotype generally distinguish the collagen type VI-related disorders from these other disorders.

**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 LAMA2-related muscular dystrophies (MDC1A) or MDC1C
(caused by pathogenic variants in \textit{FKRP}). In addition, brain MRI may show white matter changes in some CMD subtypes (e.g., \textit{LAMA2}-related muscular dystrophies) and structural abnormalities in others (e.g., 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 pathogenic variants in \textit{SMN1} or \textit{SMN2}.

- 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 pathogenic variants in \textit{SELENON} (\textit{SEPN1}) (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 and needs of an individual diagnosed with Bethlem myopathy, the following evaluations are recommended:

- 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
  - Seek 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 and needs of an individual diagnosed with Ullrich CMD, the following evaluations are recommended:

- 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
  ○ Seek 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 [Jöbsis 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.

**Evaluation of Relatives at Risk**

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.
Pregnancy Management

For a pregnant woman with a collagen VI-related disorder, no specific pregnancy management issues exist; however, prenatal physiotherapy may be indicated.

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.

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. —ED.

Mode of Inheritance

The collagen type VI-related disorders are inherited in an autosomal dominant or autosomal recessive manner.

- The Bethlem myopathy phenotype is usually inherited in an autosomal dominant manner, although autosomal recessive inheritance has been reported [Foley et al 2009, Gualandi et al 2009].

- The Ullrich congenital muscular dystrophy (CMD) phenotype is usually inherited in an autosomal recessive manner, although autosomal dominant inheritance has been reported in four individuals with de novo pathogenic variants [Pan et al 2003, Baker et al 2005], and suspected in three others [Lampe et al 2005].

- The autosomal dominant limb-girdle muscular dystrophy and myosclerosis myopathy phenotypes are inherited in an autosomal dominant and autosomal recessive manner, respectively.

- Most individuals with an autosomal dominant collagen type VI disorder (i.e., who are heterozygous for a COL6A1, COL6A2, or COL6A3 pathogenic variant) are symptomatic.

- Parents of individuals with an autosomal recessive collagen type VI disorder (i.e., who are usually heterozygous for a COL6A1, COL6A2, or COL6A3 pathogenic variant) do not appear to manifest any related symptoms.

- Individuals with an autosomal dominant collagen type VI disorder caused by a de novo pathogenic variant cannot be distinguished clinically from those with an autosomal recessive collagen type VI disorder.
Risk to Family Members — Autosomal Dominant Inheritance

Parents of a proband

- Individuals diagnosed with an autosomal dominant collagen type VI-related disorder may have an affected parent.

- A proband with an autosomal dominant collagen type VI-related disorder may have the disorder as the result of a new pathogenic variant [Pan et al 2003]. The proportion of cases caused by a de novo pathogenic variant is thought to be greater than 50% [Allamand et al 2011].

- Recommendations for the evaluation of parents of a proband with an apparent de novo pathogenic variant include clinical assessment by a clinician specializing in muscle disorders and molecular genetic testing, if the variant has been identified in the proband.

Sibs of a proband

- The risk to the sibs of a proband depends on the genetic status of the proband's parents.

- If a parent of the proband has the pathogenic variant identified in the proband and/or is affected, the chance that a sib will inherit the variant is 50%.

- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low, but greater than that of the general population because of possible reduced penetrance in the parent and/or germline mosaicism. Although no instances of germline mosaicism have been reported, it remains a possibility.

Offspring of a proband. Each child of an individual with an autosomal dominant collagen VI-related disorder has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents. If a parent has the pathogenic variant identified in the proband and/or is affected, his or her family members may be at risk.

Risk to Family Members — Autosomal Recessive Inheritance

Parents of a proband

- The parents of a child with an autosomal recessive collagen type VI-related disorder are usually heterozygotes and, therefore, carry one mutant allele.

- Heterozygotes (carriers) are usually asymptomatic.

Sibs of a proband

- 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.

**Offspring of a proband.** The offspring of an individual with an autosomal recessive collagen type VI-related disorder are obligate heterozygotes for a pathogenic variant but are themselves unaffected unless they inherit a second pathogenic variant from their other parent.

**Other family members.** 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 of being carriers of an autosomal recessive collagen type VI-related disorder is possible if the pathogenic variants have been identified in an affected family member.

**Related Genetic Counseling Issues**

**Family planning**

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

**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, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

**Prenatal Testing and Preimplantation Genetic Diagnosis**

If the pathogenic variants have been identified in an affected family member, prenatal diagnosis for a pregnancy at increased risk and preimplantation genetic diagnosis are possible.

**Resources**

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.*

- **Cure CMD**
  19401 South Vermont Avenue
  Suite J100
  Torrance CA 90502
  **Phone:** 323-250-2399
  **Fax:** 310-684-2023
Email: info@curecmd.org
www.curecmd.org

- **Muscular Dystrophy Association - USA (MDA)**
  222 South Riverside Plaza
  Suite 1500
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  Email: mda@mdausa.org
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- **Congenital Muscle Disease International Registry (CMDIR)**
  The CMDIR is a patient self-report registry with the goal to register the global congenital muscle disease population including persons with congenital myopathy, congenital muscular dystrophy, and congenital myasthenic syndrome. The CMDIR registers affected individuals of all ages with symptoms from birth through late onset (limb-girdle).
  Registrants will receive educational information and connections to others in the CMD community, and will be contacted about potential participation in clinical trials for their CMD subtype.
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  www.cmdir.org

**Molecular Genetics**

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.*

**Table A.**

Collagen Type VI-Related Disorders: Genes and Databases

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Protein</th>
<th>Locus-Specific Databases</th>
<th>HGMD</th>
<th>ClinVar</th>
</tr>
</thead>
</table>

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

**Table B.**

OMIM Entries for Collagen Type VI-Related Disorders (View All in OMIM)

<table>
<thead>
<tr>
<th>OMIM</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>120220</td>
<td>COLLAGEN, TYPE VI, ALPHA-1; COL6A1</td>
</tr>
<tr>
<td>120240</td>
<td>COLLAGEN, TYPE VI, ALPHA-2; COL6A2</td>
</tr>
<tr>
<td>120250</td>
<td>COLLAGEN, TYPE VI, ALPHA-3; COL6A3</td>
</tr>
<tr>
<td>158810</td>
<td>BETHLEM MYOPATHY 1; BTHLM1</td>
</tr>
<tr>
<td>254090</td>
<td>ULLRICH CONGENITAL MUSCULAR DYSTROPHY 1; UCMD1</td>
</tr>
</tbody>
</table>

**Molecular Genetic Pathogenesis**

Collagen VI comprises the three peptide chains \( \alpha_1(VI) \), \( \alpha_2(VI) \) (both 140 kd in size), and \( \alpha_3(VI) \) (260-300 kd in size) [Engvall et al 1986]. The \( \alpha_1(VI) \) and \( \alpha_2(VI) \) chains are encoded by the genes **COL6A1** and **COL6A2**, respectively, which are situated head-to-tail on chromosome 21q22.3 [Heiskanen et al 1995] and separated by 150 kb of genomic DNA. **COL6A3**, the gene encoding the \( \alpha_3(VI) \) chain, is on 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 approximately 200 amino acids each homologous to von Willebrand factor (vWF) type A domains [Chu et al 1990].

**Gene structure**

- **COL6A1** comprises 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** comprises 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 \( \alpha_2(VI) \) 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].

For a detailed summary of gene and protein information, see Table A, Gene.

**Pathogenic allelic variants**


- Pathogenic variants that introduce premature termination codons (splice sites and out of frame deletions/insertions) form the second most frequent group at 28%.


- Other splice site variants causing small in-frame deletions or insertions in regions that encode domains flanking the triple helical domain make up 8% of the total of pathogenic variants in COL6A1, COL6A2 and COL6A, with large genomic deletions appearing to be rare and occurring at a frequency of around 2% [Vanegas et al 2002, Lampe et al 2005, Lucioli et al 2005].

Given the high number of variants that result in benign amino acid changes described for the three genes encoding the three collagen VI peptide chains, it is difficult to be sure about the pathogenicity of missense variants other than glycine substitutions within the triple helical domain.

The assembly of collagen VI is a complex multi-step 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, Lamandé et al 1998].

Abnormal gene product

- **Autosomal dominant collagen type VI-related disorders.** 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 [Jöbsis et al 1996, Pepe et al 1999a, Scacheri et al 2002, Lampe et al 2005, Lucioli et al 2005], depending on their location, appear to either interfere with intracellular chain assembly or, following successful secretion, cause kinking of the tetramers, thus affecting extracellular microfibril formation [Lamandé et al 2002]. Functional haploinsufficiency via a dominant-negative effect has also been reported as the pathogenic mechanism for some missense and splice-site variants [Lamandé et al 1999]. Heterozygous splice site variants (associated with autosomal dominant disease) leading to in-frame exon 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].

- **Autosomal recessive collagen type VI-related disorders.** Most variants associated with autosomal recessive disease reported to date are protein-truncating nonsense variants. Some have been shown to result in absence of collagen VI because of nonsense-mediated mRNA decay [Zhang et al 2002].

References

**Literature Cited**


explore allelic and genetic heterogeneity in collagen VI-related myopathies. BMC Med Genet. 2010;11:44. [PMC free article: PMC2850895] [PubMed: 20302629]


Wallgren-Pettersson C, Bushby K, Mellies U, Simonds A. 117th ENMC workshop: ventilatory support in congenital neuromuscular disorders -- congenital myopathies, congenital muscular dystrophies, congenital myotonic dystrophy and SMA (II) 4-6 April


**Suggested Reading**


[PubMed: 16092630]


Chapter Notes

Author Notes

Newcastle upon Tyne Hospitals: Patient Information

Revision History

- 9 August 2012 (me) Comprehensive update posted live
- 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

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