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Collagen VI-Related Dystrophies

Synonyms: COL6-Related Dystrophies (COL6-RDs)

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Summary

Clinical characteristics

Collagen VI-related dystrophies (COL6-RDs) represent a continuum of overlapping clinical phenotypes with Bethlem muscular dystrophy at the milder end, Ullrich congenital muscular dystrophy (UCMD) at the more severe end, and a phenotype in between UCMD and Bethlem muscular dystrophy, referred to as intermediate COL6-RD.

- Bethlem muscular dystrophy is characterized by a combination of proximal muscle weakness and joint contractures. Hypotonia and delayed motor milestones occur in early childhood; mild hypotonia and weakness may be present congenitally. By adulthood, there is evidence of proximal weakness and contractures of the elbows, Achilles tendons, and long finger flexors. The progression of weakness is slow, and more than two thirds of affected individuals older than age 50 years remain independently ambulatory indoors, while relying on supportive means for mobility outdoors. Respiratory involvement is not a consistent feature.
- UCMD is characterized by congenital weakness, hypotonia, proximal joint contractures, and striking hyperlaxity of distal joints. Decreased fetal movements are frequently reported. Some affected children acquire the ability to walk independently; however, progression of the disease results in a loss of ambulation by age ten to eleven years. Early and severe respiratory insufficiency occurs in all individuals, resulting in the need for nocturnal noninvasive ventilation (NIV) in the form of bilevel positive airway pressure (BiPAP) by age 11 years.
- Intermediate COL6-RD is characterized by independent ambulation past age 11 years and respiratory insufficiency that is later in onset than in UCMD and results in the need for NIV in the form of BiPAP by the late teens to early 20s. In contrast to individuals with Bethlem muscular dystrophy, those with intermediate COL6-RD typically do not achieve the ability to run, jump, or climb stairs without use of a railing.

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Diagnosis/testing

The diagnosis of a COL6-RD can be suspected in a proband with characteristic clinical features, muscle imaging features, and muscle immunohistochemical features. The diagnosis can be confirmed by identification of a heterozygous or biallelic pathogenic variant(s) in *COL6A1*, *COL6A2*, or *COL6A3*.

Management

Treatment of manifestations

- **Bethlem muscular dystrophy.** BiPAP as needed to support nocturnal ventilation and prevent right heart strain; scoliosis treatment per orthopedics; if surgical treatment for scoliosis is needed, coordinate with orthopedics, anesthesia, intensive care, and pulmonary specialists; physical therapy and occupational therapy to provide recommendations for joint stretching, swimming, and aquatherapy; treatment of Achilles tendon contractures per orthopedist.
- **UCMD / intermediate COL6-RD.** BiPAP to support ventilation and prevent right heart strain. Use of insufflator/exsufflator to promote airway clearance; treatment of scoliosis per orthopedist; if surgical treatment for scoliosis is needed, coordinate with orthopedics, anesthesia, intensive care, and pulmonary specialists; physical therapy and occupational therapy to provide recommendations for joint stretching, swimming, and aquatherapy; treatment of Achilles tendon contractures per orthopedist; feeding and nutrition support as needed for failure to thrive.

Surveillance

- **Bethlem muscular dystrophy.** Respiratory surveillance including annual pulmonary function tests (PFTs) in the upright and supine positions and polysomnogram for assessing for nocturnal hypoventilation with BiPAP initiation and follow-up polysomnograms as needed; annual clinical and radiographic assessment of scoliosis; annual cardiac evaluation with echocardiogram and EKG; annual physical therapy and occupational therapy assessment of muscle weakness, joint contractures, and need for mobility devices.
- **UCMD / intermediate COL6-RD.** Respiratory surveillance including PFTs in the upright and supine positions every six months and polysomnogram to assess for nocturnal hypoventilation for timely initiation of NIV in the form of BiPAP with follow-up polysomnograms every one to two years; annual clinical and radiographic assessment of scoliosis; annual cardiac evaluation with echocardiogram and EKG; physical therapy and occupational therapy assessments of muscle weakness, joint contractures, and need for mobility devices every six months; nutritional assessments every six months. Because respiratory insufficiency is a leading cause of failure to thrive, assessments of ventilation (with PFTs and polysomnogram) are essential as surveillance both for respiratory insufficiency and for failure to thrive.

Genetic counseling

The COL6-RDs can be inherited in an autosomal dominant or an autosomal recessive manner. Bethlem muscular dystrophy is usually inherited in an autosomal dominant manner, although autosomal recessive inheritance has also been reported. UCMD and intermediate COL6-RD are typically caused by a *de novo* autosomal dominant *COL6A1*, *COL6A2*, or *COL6A3* pathogenic variant. Less commonly, UCMD and intermediate COL6-RD are inherited in an autosomal recessive manner. Parental somatic mosaicism (and concomitant germline mosaicism) is not uncommon in the autosomal dominant COL6-RDs.

- **Autosomal dominant.** If a parent of the proband has the pathogenic variant identified in the proband and/or is affected, the risk to the sibs of inheriting the variant is 50%. The severity of COL6-RD manifestations may vary among family members who are heterozygous for the same pathogenic variant.
- **Autosomal recessive.** If both parents are known to be heterozygous for a pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an

asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives requires prior identification of the *COL6A1, COL6A2,* or *COL6A3* pathogenic variants in the family.

Once the *COL6A1*, *COL6A2*, or *COL6A3* pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

GeneReview Scope

Collagen VI-Related Dystrophies (COL6-RDs): Included Phenotypes [1]
• Bethlem muscular dystrophy • Ullrich congenital muscular dystrophy (UCMD) • Intermediate COL6-RD

For synonyms and outdated names see Nomenclature.
1. Disorders included in the *GeneReview* are those caused by pathogenic variants in *COL6A1*, *COL6A2*, or *COL6A3*. Forms of the disorder associated with other genes are not addressed in this *GeneReview*.

Diagnosis

Formal diagnostic criteria for collagen VI-related dystrophies (COL6-RDs) have not been established.

The COL6-RDs are caused by a pathogenic variant(s) in *COL6A1*, *COL6A2*, or *COL6A3* and represent a clinical spectrum including Bethlem muscular dystrophy at the milder end, Ullrich congenital muscular dystrophy (UCMD) at the more severe end, and intermediate COL6-RD, between Bethlem muscular dystrophy and UCMD.

Note: Although these phenotypes are now recognized to comprise a continuum of overlapping phenotypes, the clinical designations are useful for providing a prognosis of future motor and pulmonary function and thus help to improve anticipatory clinical care.

Suggestive Findings

A COL6-RD **should be suspected** in individuals with the following clinical, imaging, and tissue findings.

Clinical Findings

Bethlem muscular dystrophy

- Proximal muscle weakness
- Joint contractures, typically affecting the long finger flexors, elbows, ankles, and shoulders

UCMD

- Congenital weakness and hypotonia
- Congenital torticollis
- Congenital hip dislocation
- Abnormal positioning of the hands and feet at birth (with the hands in a position of wrist flexion and the feet in a position of ankle dorsiflexion)
- Early kyphoscoliosis
- Proximal joint contractures (hips, knees, shoulders, and elbows)
- Striking hyperlaxity of distal joints
- Round face with mild facial erythema (over the cheeks)

- Weakness either preventing independent ambulation or resulting in loss of ambulation / full-time dependence on wheelchair-assisted mobility by approximately age ten to 11 years [Nadeau et al 2009, Briñas et al 2010, Foley et al 2013]
- Progressive respiratory insufficiency uniformly necessitating the initiation of noninvasive ventilation (NIV) in the form of bilevel positive airway pressure (BiPAP) while sleeping by approximately age 11 years [Foley et al 2013, Yonekawa et al 2013] with some individuals needing the addition of daytime noninvasive ventilatory support beginning in their 20s

Intermediate COL6-RD

- Congenital weakness and hypotonia
- Congenital torticollis
- Congenital hip dislocation
- Proximal muscle weakness
- Joint contractures, typically affecting the long finger flexors, elbows, ankles, and shoulders
- At the same time, striking hyperlaxity of distal joints
- Weakness resulting in full-time dependence on wheelchair-assisted mobility by approximately age 19 years [Foley et al 2013]
- Progressive respiratory insufficiency resulting in nocturnal hypoventilation and need for NIV in the form of BiPAP while sleeping by approximately late teens / early 20s [Foley et al 2013]

Clinical and laboratory findings – all COL6-RDs

- Intelligence is normal to high.
- Characteristic skin features include keratosis pilaris or follicular keratosis, keloid scars, and/or atrophic or "cigarette-paper" scars [Pepe et al 2002, Nadeau & Muntoni 2008].
- Serum creatine kinase concentration is normal or mildly elevated.

Imaging Findings

Muscle MRI is an excellent diagnostic tool to identify suggestive findings of a COL6-RD and guide which individuals should undergo molecular analysis of *COL6A1*, *COL6A2,* and *COL6A3*. Some muscle MRI findings are more common and/or more striking in Bethlem muscular dystrophy, although some overlap exists among COL6-RD subtypes [Mercuri et al 2005, Mercuri et al 2010]. COL6-RD muscle imaging findings may be more difficult to recognize in older individuals with UCMD or intermediate COL6-RD as the muscles become more affected with age. Of note, similar muscle imaging patterns may be seen in other conditions, including calpainopathy [Barp et al 2020].

Upper leg

- In Bethlem muscular dystrophy the vastus lateralis muscle is typically strikingly affected, with a rim of abnormal signal along the periphery of the vastus lateralis and relative sparing of the central part, often referred to as an "outside-in" pattern. The rectus femoris muscle typically has evidence of abnormal signal within a central area of the muscle, surrounded by normal-appearing muscle, often referred to as a "central cloud" pattern [Bönnemann 2011] (see Figure 1). Of note, these same patterns can be appreciated in muscle ultrasound performed in individuals with Bethlem muscular dystrophy [Bönnemann et al 2003].
- In UCMD more diffuse involvement is typically observed with relative sparing of the sartorius, gracilis, and adductor longus. The "outside-in" pattern in the vastus lateralis and the "central cloud" pattern in the rectus femoris muscle may also been seen; however, as the disease progresses, these findings may be less obvious (see Figure 2).
- In intermediate COL6-RD the same muscle MRI findings described in Bethlem muscular dystrophy and UCMD can be seen.

Lower leg. In Bethlem muscular dystrophy, intermediate COL6-RD, and UCMD a rim of abnormal signal at the periphery of soleus and gastrocnemii muscles can be seen.

Tissue Studies

Bethlem muscular dystrophy / intermediate COL6-RD

- Muscle biopsy early in the disease may show nonspecific myopathic changes but subsequently will show more typical dystrophic changes (degeneration, regeneration, and replacement of muscle with fat and fibrous connective tissue).
- Collagen VI immunolabeling of muscle tissue may show decreased collagen VI expression or mislocalized collagen VI (not colocalizing when double stained with other basement membrane markers such as perlecan, laminin or collagen IV) (Figure 3.)
- Immunocytochemical analysis of collagen VI in dermal fibroblast cultures can demonstrate decreased and/or abnormal-appearing collagen VI extracellular matrix deposition with increased intracellular retention seen with cell permeabilization for dominant-acting pathogenic variants [Hicks et al 2008] (Figure 4).

UCMD / intermediate COL6-RD

- Muscle biopsy commonly shows dystrophic features (degeneration, regeneration, and replacement of muscle with fat and fibrous connective tissue). Note: Muscle biopsies in children younger than age 30 months can have minimal findings (e.g., fiber atrophy, fiber type disproportion) with no evidence of dystrophic features [Schessl et al 2008].
- Collagen VI immunolabeling of muscle ranges from absent collagen VI to mislocalized collagen VI (not colocalizing when double stained with other basement membrane markers such as perlecan, laminin, or collagen IV) [Pan et al 2003, Ishikawa et al 2004].
- Immunocytochemical analysis of collagen VI in dermal fibroblast cultures may demonstrate loss of collagen VI matrix deposition or deposition of a dysmorphic matrix with strong intracellular immunoreactivity seen with permeabilization in those with dominant-acting pathogenic variants. It thus can be a useful adjunct to the diagnosis [Jimenez-Mallebrera et al 2006].

Establishing the Diagnosis

The diagnosis of a COL6-RD **is established** in a proband with the characteristic clinical, muscle imaging, and muscle immunohistochemical features described in Suggestive Findings and a heterozygous or biallelic pathogenic (or likely pathogenic) variant(s) in *COL6A1*, *COL6A2*, or *COL6A3* identified by molecular genetic testing (see Table 1).

(1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) The identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (concurrent gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas comprehensive genomic testing does not. Because the phenotypes of COL6-RDs are broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see

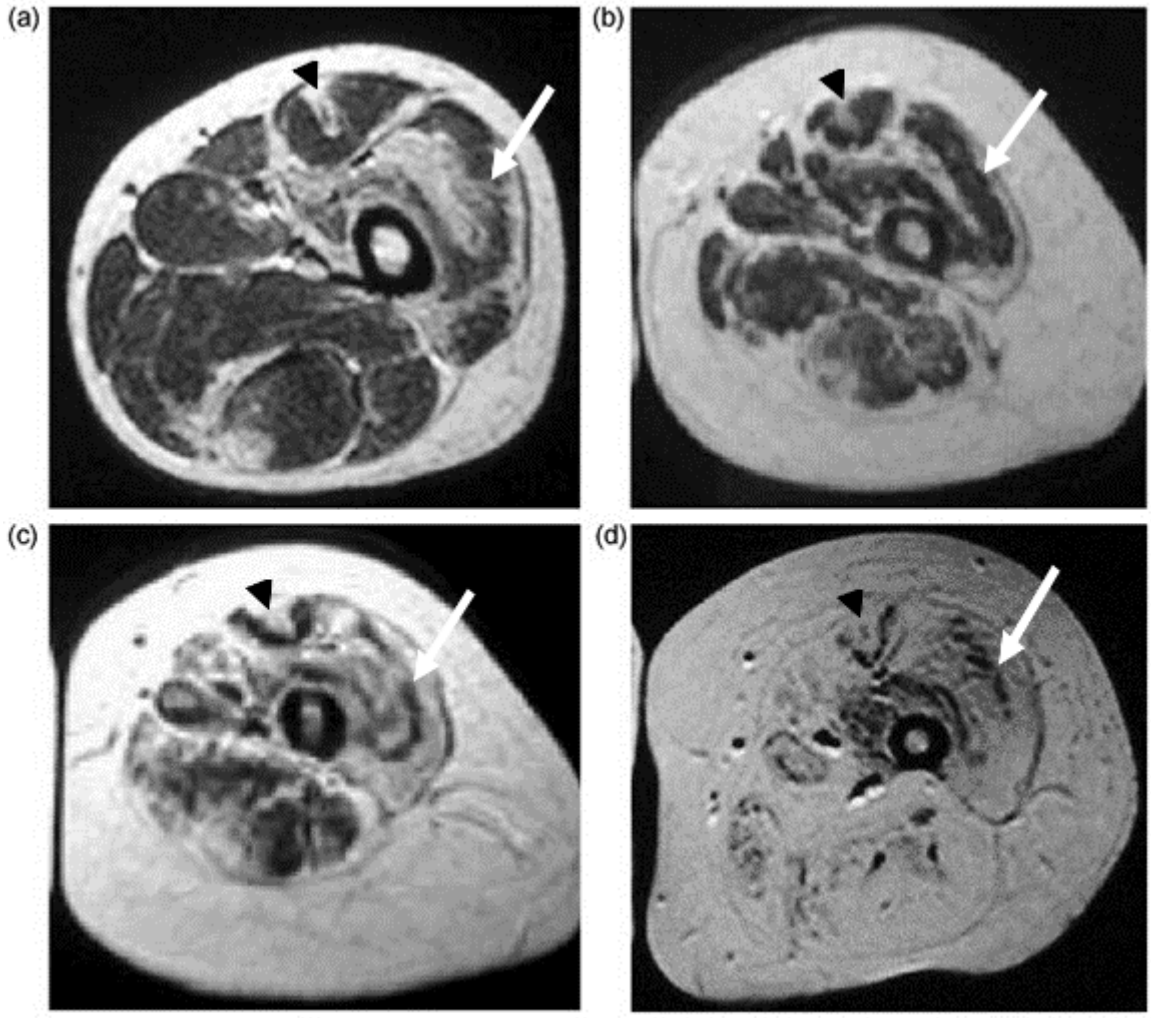

Figure 1. Muscle MRI findings in Bethlem muscular dystrophy

Axial T_1-weighted images of the upper leg muscles of four individuals with Bethlem muscular dystrophy (a-d). Note the relative sparing of the central part of the vastus lateralis (white arrows) with a rim of increased signal at the periphery of the muscle consistent with an "outside-in" pattern and the prominent increase in signal intensity in the central part of the rectus femoris (black arrowheads) consistent with a "central cloud" pattern (a-d). Both imaging patterns can still be appreciated in the two older individuals of the group, who have evidence of more diffuse involvement (c and d).

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Option 1), whereas those with a phenotype less distinguishable from many other inherited disorders with myopathy / muscular dystrophy are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic findings suggest the diagnosis of a COL6-RD, molecular genetic testing approaches can include **concurrent gene testing** or use of a larger **multigene panel**:

- **Concurrent gene testing.** Sequence analysis of *COL6A1*, *COL6A2*, and *COL6A3* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

  Note: Sequence analysis should include the common *COL6A1* deep intronic pathogenic variant c.930+189C>T (see Molecular Pathogenesis).

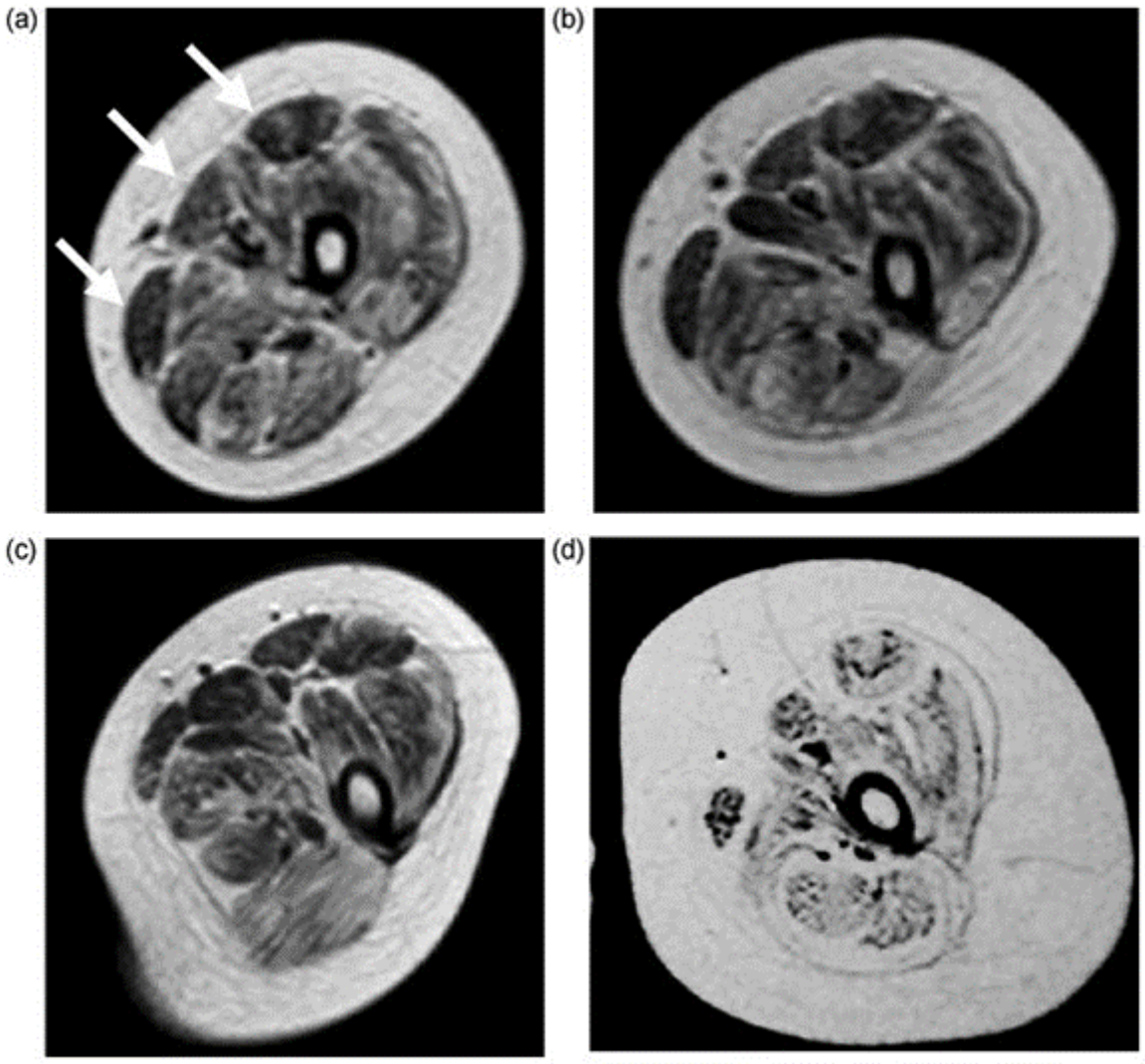

Figure 2. Muscle MRI findings in Ullrich congenital muscular dystrophy (UCMD)

Axial T_1-weighted images of the upper leg muscles of four individuals with UCMD. There is diffuse involvement of the thigh with relative sparing of sartorius, gracilis, and rectus femoris muscles (arrows) in the younger affected individuals (a-c). A similar pattern can be seen in the oldest affected individual of the group (d). All four individuals (a-d) have relative sparing of the central part of the vastus lateralis.

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- **A myopathy / muscular dystrophy multigene panel** that includes *COL6A1*, *COL6A2*, *COL6A3*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in these panels and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. (5) Sequence analysis should include the common *COL6A1* deep intronic pathogenic variant c.930+189C>T (see Molecular Pathogenesis).

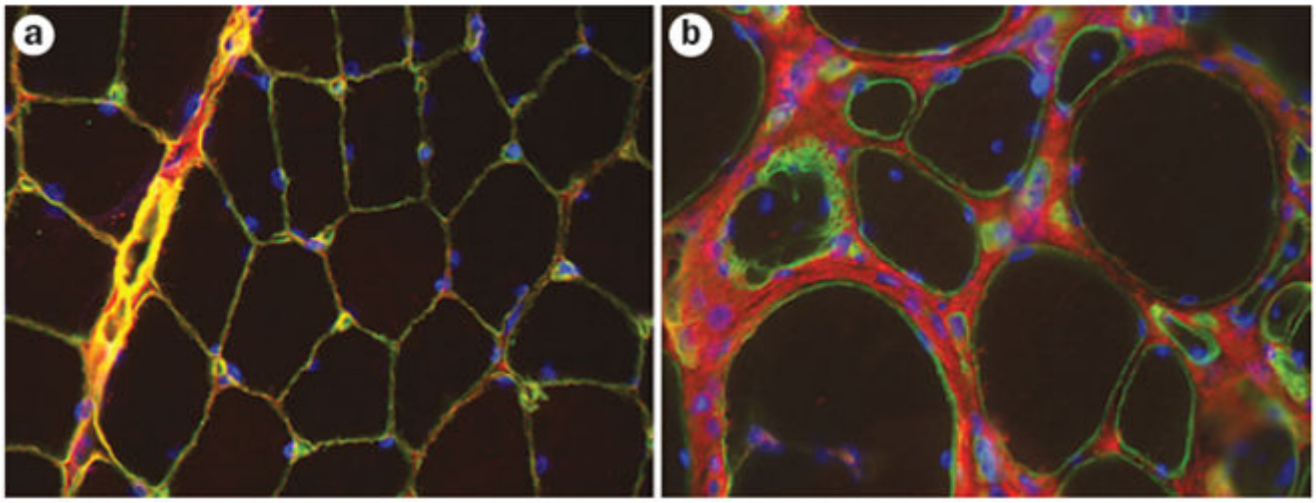

Figure 3. Collagen VI immunohistochemical labeling in muscle in COL6-RD

a. Collagen VI (red) and laminin γ-1 (green) colocalize in the basement membrane (resulting in a yellow color) in muscle from an individual without neuromuscular disease.

b. Collagen VI staining (red) does not colocalize with laminin subunit γ-1 (green) in the basement membrane in muscle from an individual with COL6-RD due to a dominant pathogenic variant in a COL6 gene, which affects the function of the collagen VI protein via a dominant-negative mutational mechanism.

Reproduced from Bönnemann [2011]

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by a myopathy / muscular dystrophy, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

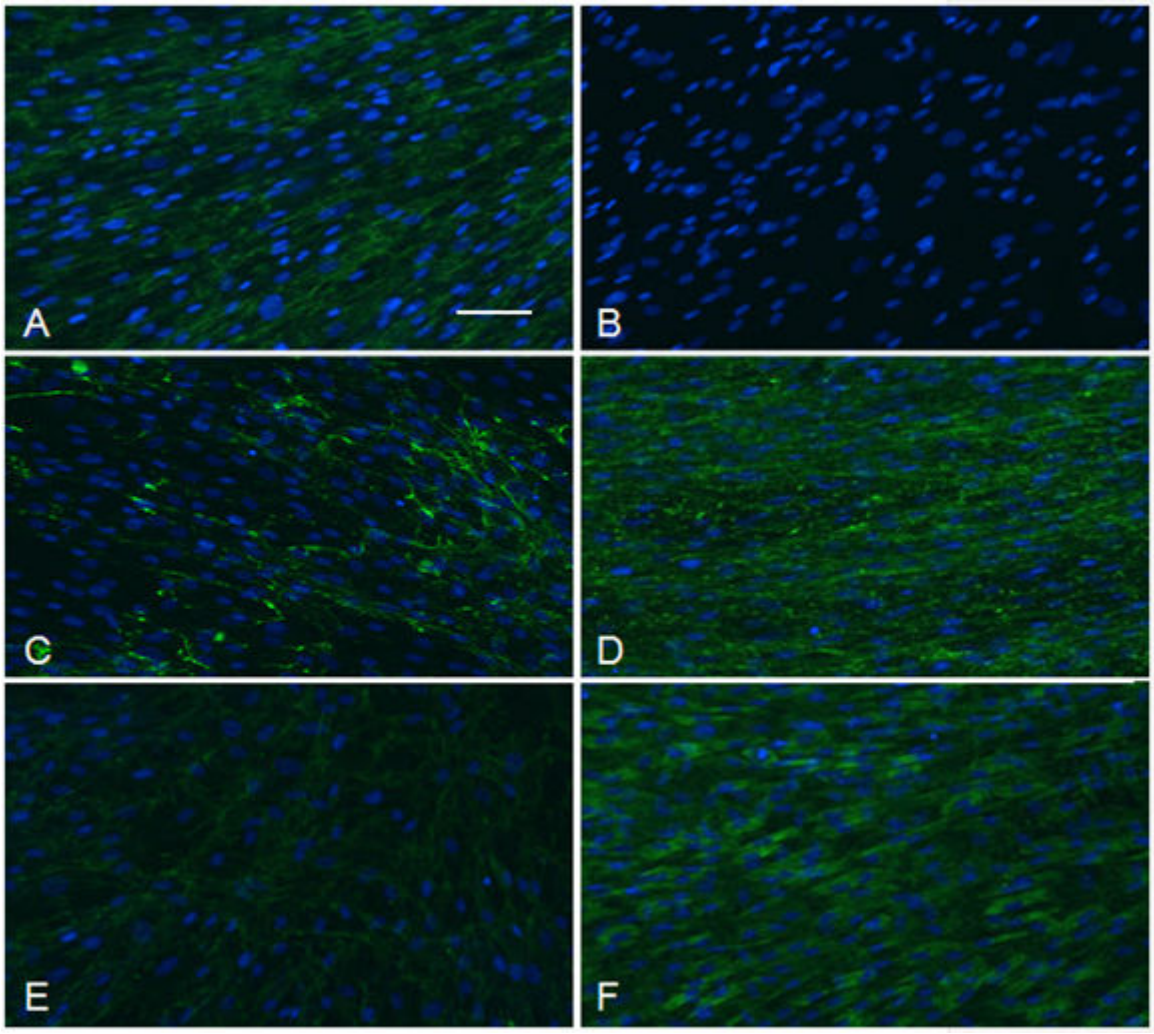

Figure 4. Collagen VI immunocytochemical studies in dermal fibroblasts in COL6-RD

A. The normal control with collagen VI labeling with antibody demonstrates an abundance of well-organized collagen VI microfibrils in a linear, unidirectional trend.

B. The negative control (with no antibody) does not label collagen VI.

C-F. The four major abnormal patterns of collagen VI expression observed in individuals with Bethlem muscular dystrophy are shown: (C) "disorganized" (disruption of the linear arrangement of mostly unidirectional microfibrils); (D) "stippling" (small "dots" of collagen VI labeling); (E) "rarefication" (less collagen VI compared to normal control); and (F) intracellular "retention" (collagen VI is only detected when detergent enhances cell permeability).

Scale bar (A) = 100 µm

Reproduced from Hicks et al [2008]

Table 1. Molecular Genetic Testing Used in Collagen VI-Related Dystrophies

Gene [1, 2]	Proportion of Pathogenic Variants Identified in Each Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
COL6A1	35%-38% [6]	>99%	<1% [7, 8]
COL6A2	44%-46% [6]	>99%	<1% [8]

Table 1. continued from previous page.

Gene [1, 2]	Proportion of Pathogenic Variants Identified in Each Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
COL6A3	18%-19% [6]	~99%	<1% [9]

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on variants detected in this gene.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or 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. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Percentages reported from two different COL6-RD cohorts: one with 258 pathogenic variants identified [Allamand et al 2011] and one with 72 pathogenic variants identified [Fan et al 2018]
7. Highly similar heterozygous genomic deletions were identified in a deletion-prone region of *COL6A1* in two individuals, one with Bethlem muscular dystrophy and one with UCMD [Pepe et al 2006].
8. A large genomic deletion of *COL6A1* and *COL6A2* was reported in two families with UCMD [Foley et al 2011].
9. A deletion in *COL6A3* was reported in one individual with UCMD [Lampe et al 2005].

Clinical Characteristics

Clinical Description

The phenotypes associated with collagen VI-related dystrophies (COL6-RDs), once thought to be distinct entities, were clinically defined long before their molecular basis was discovered. The COL6-RDs are now recognized to comprise a continuum of overlapping phenotypes with Bethlem muscular dystrophy at the mild end, Ullrich congenital muscular dystrophy (UCMD) at the severe end, and phenotypes in between that are now collectively categorized within a subgroup called intermediate COL6-RD. These clinical phenotypic designations play an important role in providing a prognosis for future motor and pulmonary function and thus help in improving anticipatory clinical care.

Bethlem Muscular Dystrophy

The onset of symptoms of Bethlem muscular dystrophy can range from congenital to mid-adulthood. Obvious congenital manifestations are more rare but can include hypotonia and torticollis. Most individuals report a history of hypotonia, delayed motor milestones, and a tendency toward W-sitting, related to laxity of the hip joints [Jöbsis et al 1999]. Most individuals attain the ability to climb stairs without holding onto a railing [Natera-de Benito et al 2021], jump, and run during childhood. Proximal muscle weakness and joint contractures are slowly progressive over time. By adulthood, most individuals have difficulty rising from a seated position due to proximal weakness and have prominent contractures of the long finger flexors, elbows, and Achilles tendons. The inability to extend the fingers due to contractures of the long finger flexors when palms are placed together, wrists are dorsiflexed, and elbows are flexed and elevated is a typical finding in Bethlem muscular dystrophy and thus has been called the "Bethlem sign" [Pepe et al 2002, Bönnemann 2011].

As a result of slowly progressive proximal muscle weakness and progressive joint contractures, more than two thirds of affected individuals older than age 50 years rely on supportive means (e.g., canes, crutches, wheelchair) for outdoor mobility [Jöbsis et al 1996].

Respiratory muscle weakness, in particular of the diaphragm, can result in respiratory insufficiency resulting in nocturnal hypoventilation and necessitating nocturnal noninvasive ventilation (NIV) in the form of bilevel

positive airway pressure (BiPAP). In retrospective studies of Bethlem muscular dystrophy, the use of nocturnal NIV is less common and was required later in life [Mohire et al 1988, Haq et al 1999, van der Kooi et al 2006, Foley et al 2013]. In one cohort of individuals, 7/43 (16%) had a forced vital capacity (FVC) of less than 70% predicted [van der Kooi et al 2006]. An analysis of FVC measurements in 43 individuals did not demonstrate a statistically significant relationship between age and FVC, and only 1/43 (2%) had initiated nocturnal NIV [Foley et al 2013]. However, uniform screening for nocturnal hypoventilation with an overnight polysomnogram was not possible in the aforementioned studies, and thus nocturnal hypoventilation may be more prevalent particularly among older individuals than previously recognized.

Cardiac function is normal in individuals with Bethlem muscular dystrophy; any cardiac findings have been interpreted as unrelated to Bethlem muscular dystrophy [van der Kooi et al 2006].

Skin findings in Bethlem muscular dystrophy include keratosis pilaris or follicular keratosis, which is typically prominent along the extensor surfaces of the arms and legs and keloid scars [Lampe et al 2005], which can occur seemingly spontaneously (in regions of the skin not affected by surgical incision or known trauma) [Collins et al 2012].

Ullrich Congenital Muscular Dystrophy

The first signs of UCMD can be noted in utero, with decreased fetal movement frequently reported [Ullrich 1930a, Ullrich 1930b, Furukawa & Toyokura 1977, Nonaka et al 1981, Bertini & Pepe 2002]. Characteristic features at birth include hypotonia, torticollis, contractures of the proximal joints, hyperlaxity of the distal joints, kyphoscoliosis, abnormal positioning of the hands and feet at birth (with the hands in a position of wrist flexion and the feet in a position of ankle dorsiflexion), congenital hip dislocation, and prominent calcanei.

Independent walking is typically the most advanced motor milestone achieved in children with UCMD [Natera-de Benito et al 2021]. Not all children with UCMD acquire the ability to walk independently; some children acquire the ability to walk on their knees only. In individuals with UCMD who achieve independent ambulation, progression of muscle weakness and joint contractures result in a loss of ambulation and full-time dependence on wheelchair-assisted mobility by age ten to 11 years [Nadeau et al 2009, Briñas et al 2010, Foley et al 2013]. After becoming dependent on wheelchair-assisted mobility, most individuals with UCMD have relatively stable muscle weakness, while contractures of the large joints continue to progress and significantly contribute to the overall level of disability [Bönnemann 2011].

Progressive, severe respiratory insufficiency occurs in all individuals with UCMD, resulting in the need for nocturnal NIV on average by age 11 years [Foley et al 2013, Yonekawa et al 2013]. Without adequate respiratory support, individuals with UCMD can succumb to respiratory failure during the teenage years [Nonaka et al 1981, Nadeau et al 2009, Bönnemann 2011, Foley et al 2013].

Congenital kyphoscoliosis may occur. Typically, there is spinal rigidity with concomitant scoliosis, which in one cohort manifested by a mean age of seven years, with scoliosis surgical repair performed at a mean age of 11 years [Nadeau et al 2009]. In individuals who attain independent ambulation, the onset of scoliosis precedes the loss of ambulation [Nadeau et al 2009, Yonekawa et al 2013].

Transient feeding difficulties can occur, requiring nasogastric tube feeding during the newborn period [Nadeau et al 2009] or later gastrostomy tube feeding for failure to thrive [Lampe et al 2005]. The possibility of unrecognized nocturnal hypoventilation and a lack of or insufficient NIV support while sleeping should always be considered in individuals with UCMD with failure to thrive, as sleep hypoventilation from respiratory insufficiency is a leading cause of failure to thrive in individuals with UCMD from childhood through teenage years.

There has been no evidence of primary cardiac involvement in UCMD. In those individuals with respiratory insufficiency in whom NIV in the form of BiPAP has not been initiated or the BiPAP pressures are insufficient,

right-sided heart strain can be observed on echocardiography, and cor pulmonale can develop when left untreated. With the optimization of NIV support / BiPAP pressures, right-sided heart function typically normalizes.

Skin findings in UCMD include keratosis pilaris or follicular keratosis (typically prominent along the extensor surfaces of the arms and legs), keloid scars, and atrophic or "cigarette-paper" scars [Nadeau & Muntoni 2008].

Intermediate COL6-RD

The onset of intermediate COL6-RD is typically congenital with signs and symptoms including hypotonia, torticollis, hip dislocation, proximal joint contractures, and distal joint hyperlaxity. Infants typically demonstrate evidence of proximal muscle weakness; however, they usually attain the ability to rise from the floor without assistance (without holding onto furniture or another person) [Natera-de Benito et al 2021].

Progressive joint contractures affecting shoulders, elbows, long finger flexors, hips, knees, and ankles occur. The combination of progressive muscle weakness and joint contractures leads to loss of ambulation and need for full-time wheelchair-assisted mobility by an average age of 19 years [Foley et al 2013].

Progressive respiratory insufficiency occurs in all individuals with intermediate COL6-RD. The onset of decline in pulmonary function occurs later than in individuals with UCMD. Nocturnal hypoventilation and the need for NIV in the form of BiPAP occurs by the late teens to early 20s [Foley et al 2013]. The decline in pulmonary function and the need for initiation of NIV may occur while individuals remain ambulatory; therefore, careful surveillance of pulmonary function is essential.

There has been no evidence of primary cardiac involvement in intermediate COL6-RD. In those individuals with respiratory insufficiency in whom NIV in the form of BiPAP has not been initiated or the BiPAP pressures are insufficient, right-sided heart strain can be observed on echocardiography, and cor pulmonale can develop when left untreated. With the optimization of NIV support / BiPAP pressures, right-sided heart function typically normalizes.

Skin findings in intermediate COL6-RD include keratosis pilaris or follicular keratosis (typically prominent along the extensor surfaces of the arms and legs), keloid scars, and atrophic or "cigarette-paper" scars [Lampe et al 2005].

Genotype-Phenotype Correlations

COL6-RDs can be caused by either autosomal dominant or autosomal recessive pathogenic variants in *COL6A1*, *COL6A2*, and *COL6A3* (see Molecular Genetics).

Pathogenic variants associated with autosomal dominant inheritance in *COL6A1*, *COL6A2*, and *COL6A3* typically occur near the N terminal of the triple helical (TH) domain, which contains a critical region of 10 to 15 Gly-X-Y triplets; in-frame exon-skipping variants and glycine substitutions in this region tend to result in more severe phenotypes [Pace et al 2008, Butterfield et al 2013].

Pathogenic variants associated with autosomal recessive inheritance are typically nonsense or frameshift variants [Camacho Vanegas et al 2001]. However, biallelic missense variants may be pathogenic when located near the C-terminal end of the TH domain, where they will be excluded from assembly [Baker et al 2005, Petrini et al 2005, Zhang et al 2010].

COL6A1

- In-frame skipping of exon 14, encoding the dimer-stabilizing cysteine residue of the α1(VI) chain, tends to result in a milder phenotype (Bethlem muscular dystrophy to intermediate COL6-RD) [Foley et al 2013, Fan et al 2018].

- A deep intronic pathogenic variant in intron 11 (c.930+189C>T), resulting in a splice-gain event causing insertion of a pseudoexon and disruption of the N-terminal region of the TH domain, is associated with a consistent phenotype including delayed onset (with a paucity of neonatal symptoms and normal motor development during the first 1-2 years of life) followed by a rapid acceleration to severe UCMD with loss of ambulation and full-time dependence on wheelchair-assisted mobility by an average age of nine years, and initiation of nocturnal NIV by an average age of 13 years [Cummings et al 2017, Bolduc et al 2019].

COL6A2

- Nonsense variant p.Arg468Ter is located within the TH domain. When homozygous, this variant results in a complete loss of function of collagen VI and manifests as a UCMD phenotype [Valencia et al 2013].
- Nonsense variant Gln819Ter, which is 3' downstream of the C1 domain, results in a truncated α2(VI) chain lacking the C2 domain but not a complete loss of function of collagen VI. When homozygous, this variant results in a milder phenotype of Bethlem muscular dystrophy in which the severity of the joint contractures outweighs the muscle weakness. This phenotype has been referred to as "myosclerosis," and the muscles are reported to have a "woody" feel [Bradley et al 1973, Merlini et al 2008].

COL6A3. In-frame skipping of exon 16 results in the deletion of amino acids at the N-terminal region of the TH domain of the α3(VI) chain but conserves the cysteine residues needed for higher-order assembly and thus has a strong dominant negative effect, resulting in a more severe phenotype (UCMD) [Briñas et al 2010, Foley et al 2013, Bolduc et al 2014, Fan et al 2018].

Penetrance

Parents of individuals with recessively inherited COL6-RDs are usually heterozygous for a *COL6A1*, *COL6A2*, or *COL6A3* pathogenic variant, but they do not manifest clinical symptoms of COL6-RD, even when predicted to be haploinsufficient for the respective gene.

Individuals with dominantly inherited COL6-RDs are heterozygous for a *COL6A1*, *COL6A2*, or *COL6A3* pathogenic variant and are typically symptomatic.

Nomenclature

Bethlem muscular dystrophy. "Bethlem myopathy" was first used in 1976 to describe a "benign myopathy with autosomal dominant inheritance" [Bethlem & Wijngaarden 1976]. Since that time, "Bethlem myopathy" has been used to refer to the milder form of COL6-RD; however, over time it has been recognized that this is indeed a muscular dystrophy (and not a myopathy), as the histology of the muscle progresses to reveal more typical dystrophic changes (degeneration and regeneration and replacement of muscle with fat and fibrous connective tissue) and thus is consistent with that of a muscular dystrophy. Other terms in use:

- Mild form of COL6-related myopathy
- Mild form of COL6-related dystrophy
- Mild collagen VI myopathy

Ullrich congenital muscular dystrophy was first described in 1930 as a "congenital atonic sclerotic muscular dystrophy" [Ullrich 1930a, Ullrich 1930b]. Other terms in use:

- Severe form of COL6-related myopathy
- Severe form of COL6-related dystrophy
- Early-severe collagen VI myopathy
- Moderate-progressive collagen VI myopathy

Intermediate COL6-RD was first described in 2011 as "intermediate" phenotypes of COL6-RDs [Bönnemann 2011]. Historically, individuals with "intermediate" phenotypes of COL6-RD were classified as having "mild UCMD" or "severe Bethlem myopathy." A classification system for distinguishing an "intermediate" COL6-RD phenotype has been proposed based on both motor function and pulmonary function criteria [Foley et al 2013]. Other terms in use:

- Mild UCMD
- Severe Bethlem myopathy
- Moderate-progressive collagen VI myopathy
- Mild early-onset collagen VI myopathy

Prevalence

The exact prevalence of the COL6-RDs remains unknown. In northern England the prevalence of Bethlem muscular dystrophy is estimated at 0.77:100,000, and the prevalence of UCMD is estimated at 0.13:100,000 [Norwood et al 2009]. The COL6-RDs are the second most common form of congenital muscular dystrophy (CMD) in Japan (after Fukuyama CMD) [Okada et al 2007]. In an Australian study based on muscle immunohistochemistry, the COL6-RDs were the second most common form of CMD (after α-dystroglycanopathies) [Peat et al 2008].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* have been associated with *COL6A1*, *COL6A2*, or *COL6A3* pathogenic variants.

Differential Diagnosis

The differential diagnosis of the phenotypes observed in the collagen VI-related dystrophies (COL6-RDs) is discussed in this section. Of note, a normal-to-mildly elevated CK, suggestive findings on muscle MRI, lack of a cardiac phenotype, and normal-to-high intelligence are hallmarks of the COL6-RDs and help in distinguishing them from other disorders.

Bethlem Muscular Dystrophy

When joint contractures are subtle or missed, the major differential diagnoses are the limb-girdle muscular dystrophies (LGMDs) (see Limb-Girdle Muscular Dystrophy Overview).

When joint contractures are a prominent feature, the major differential diagnoses are those summarized in Table 2a.

Table 2a. Disorders with Joint Contractures to Consider in the Differential Diagnosis of Bethlem Muscular Dystrophy

Gene(s)	DiffDx Disorder	MOI	Clinical Characteristics
CAPN3	Calpainopathy (LGMD2A, LGMDR1)	AR (AD)	Typically assoc w/prominent atrophy of periscapular & biceps muscles but may present w/more "contractural" phenotype
EMD *FHL1* *LMNA*	Emery-Dreifuss muscular dystrophy	XL AD [1]	Joint contractures (beginning in early childhood), slowly progressive muscle weakness & wasting, & cardiac involvement
FHL1	*FHL1*-related myopathy (OMIM 300696)	XL	Early & rapidly progressive severe weakness, early respiratory failure, & presence of reducing bodies on muscle histology
LAMA2	*LAMA2* muscular dystrophy (partial laminin-211 deficiency)	AR	Abnormal appearance of white matter on brain MRI, high CK levels, & evidence of mild sensorimotor demyelinating neuropathy on NCVs

Table 2a. continued from previous page.

Gene(s)	DiffDx Disorder	MOI	Clinical Characteristics
TTN	*TTN*-related myopathy (specifically the "contractural" phenotype) [2]	AR	Webbed neck, arthrogryposis, & findings on muscle MRI & US of sparing (normal appearance) of semitendinosus muscle in contrast to abnormal appearance of other hamstring muscles (semimembranosus & biceps femoris muscles)

AD = autosomal dominant; AR = autosomal recessive; CK = creatine kinase; DiffDx = differential diagnosis; MOI = mode of inheritance; NCVs = nerve conduction studies; US = ultrasound; XL = X-linked
1. More rarely, Emery-Dreifuss muscular dystrophy is caused by biallelic pathogenic variants in *LMNA*.
2. Oates et al [2018]

Ullrich Congenital Muscular Dystrophy and Intermediate COL6-RD

Note: Unlike Ullrich congenital muscular dystrophy (UCMD) and intermediate COL6-RD, the disorders in Table 2b are typically *not* associated with:

- The presence at birth of torticollis, kyphoscoliosis, and abnormal positioning of the hands & feet;
- The combination of proximal joint contractures with distal joint hyperlaxity;
- Muscle imaging findings in the rectus femoris muscle (of a "central cloud" pattern) and vastus lateralis muscle (of an "outside-in" pattern).

Table 2b. Disorders with Congenital Onset to Consider in the Differential Diagnosis of UCMD / Intermediate COL6-RD

Gene(s) [1]	Diff Dx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/UCMD / Intermediate COL6-RD	Distinguishing from UCMD / Intermediate COL6-RD
COL12A1	Ehlers-Danlos / myopathy overlap syndrome (OMIM 616471)	AR AD	Kyphoscoliosis, hypotonia, joint laxity, delayed motor milestones, prominent calcanei, soft skin	• Generally have pronounced & widespread joint laxity • May have joint dislocations • Typically have elongated face • Palate is often significantly high-arched. • Respiratory insufficiency may present earlier (severe form). Weakness may be mostly distal (milder form). • Muscle biopsy is typically myopathic.
PLOD1 *FKBP14*	Kyphoscoliotic Ehlers-Danlos syndrome (see *FKBP14* kyphoscoliotic EDS & *PLOD1* kyphoscoliotic EDS)	AR	Kyphoscoliosis, hypotonia, joint hyperlaxity, delayed motor milestones, soft skin	May have skin fragility, recurrent joint dislocations, ocular abnormalities, &/or hearing loss (in *FKBP14*-EDS)
COL1A1 *COL5A1* *COL5A2*	Classic Ehlers-Danlos syndrome	AD	Joint hyperlaxity, delayed motor milestones, soft skin	Not typically assoc w/significant muscle weakness or abnormal muscle biopsy findings
FBN1	Marfan syndrome	AD	Joint hyperlaxity, delayed motor milestones, soft skin	Not typically assoc w/significant muscle weakness or abnormal muscle biopsy findings

Table 2b. continued from previous page.

Gene(s) [1]	Diff Dx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/UCMD / Intermediate COL6-RD	Distinguishing from UCMD / Intermediate COL6-RD
FBN2	Congenital contractural arachnodactyly (Beals syndrome)	AD	Kyphoscoliosis, joint contractures, joint hyperlaxity, delayed motor milestones	• Hallmark findings of arachnodactyly & abnormal pinnae (crumpled superior helix) • May have high-arched palate
TTN	Titinopathy or *TTN*-related myopathy (OMIM 188840)	AD AR	• Neonatal hypotonia, weakness (esp axial & proximal), abnormal positioning of hands & feet • Muscle biopsy may have histologic appearance of CFTD.	• At birth hands are typically in position of bilateral wrist extension w/ulnar deviation; feet are typically in position of foot eversion. • May have cardiac involvement • Muscle histology often has prominent central nuclei. • Muscle imaging shows particular involvement of semitendinosus muscle.
RYR1	Central core disease (OMIM 117000); *RYR1*-related myopathy (OMIM 255320)	AD AR	• Neonatal hypotonia, weakness (esp axial & proximal), poor weight gain, respiratory insufficiency • Muscle biopsy may have histologic findings of cores on oxidative stains & CFTD. • Muscle biopsy may have prominent adipose tissue.	• In AR forms, extraocular movements are ↓ & muscle histology has central nuclei. • Muscle imaging shows sparing of rectus femoris muscle.
SELENON	*SELENON*-related myopathy (multiminicore disease; rigid spine muscular dystrophy) OMIM 602771)	AR	• Neonatal hypotonia, weakness (esp axial & proximal), poor weight gain, respiratory insufficiency • Muscle biopsy may have histologic findings of cores on oxidative stains & CFTD.	Usually assoc w/striking weakness of neck extension (head drop) & may drag head on ground while crawling.
B3GALNT2 *B4GAT1* (*B3GNT1*) *CHKB* *DOLK* *DPM1* *DPM2* *DPM3* *FKRP* *FKTN* *GMPPB* *CRPPA* (*ISPD*) *LAMA2* *LARGE1* *LMNA* *POMGNT1* *POMGNT2*	Other forms of CMD [2]	AR	Neonatal hypotonia, weakness (predominantly axial & proximal), poor weight gain, respiratory insufficiency	• May have eye abnormalities, abnormal findings on brain MRI, cognitive involvement, &/or cardiac involvement. • Usually assoc w/serum CK concentrations higher than those observed in UCMD / intermediate COL6-RD

Table 2b. continued from previous page.

Gene(s) [1]	Diff Dx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/UCMD / Intermediate COL6-RD	Distinguishing from UCMD / Intermediate COL6-RD
POMK *POMT1* *POMT2* *RXYLT1* (*TMEM5*)				
SMN1	Spinal muscular atrophy	AR	Hypotonia, weakness, poor weight gain, respiratory insufficiency	• Evidence of fasciculations on muscle ultrasound • Features of denervation on muscle biopsy

AD = autosomal dominant; AR = autosomal recessive; CFTD = congenital fiber type disproportion; CK = creatine kinase; CMD = congenital muscular dystrophy; DiffDx = differential diagnosis; MOI = mode of inheritance; XL = X-linked
1. Disorders are ordered by relevance, with diagnoses most similar to UCMD and intermediate COL6-RD listed first.
2. Selected genes associated with the main CMD subtypes; see Bönnemann et al [2014].

Management

Evaluations Following Initial Diagnosis

Bethlem muscular dystrophy. To establish the extent of disease and needs in an individual diagnosed with Bethlem muscular dystrophy, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Bethlem Muscular Dystrophy

System/Concern	Evaluation	Comment
Musculoskeletal	• Neuromuscular exam to evaluate degree & distribution of muscle weakness & its effects on mobility • Exam of joint contractures, esp assessing for asymmetry of Achilles tendon contractures • PT & OT assessment	
Pulmonary	Baseline polysomnogram w/continuous CO_2 monitoring	During childhood to assess ventilation during deep sleep
	Pulmonary function tests in both upright (seated) & supine (lying down) positions w/forced vital capacity monitored closely	Starting at age 5 yrs
Cardiology	Eval w/cardiologist incl echocardiogram & EKG	To evaluate for right-sided heart strain in those w/respiratory insufficiency who are not using NIV or have inadequate BiPAP pressures
Other	Consultation w/clinical geneticist &/or genetic counselor	

BiPAP = bilevel positive airway pressure; NIV = noninvasive ventilation; OT = occupational therapy; PT = physical therapy

Ullrich congenital muscular dystrophy (UCMD) / intermediate collagen VI-related dystrophy (COL6-RD). To establish the extent of disease and needs in an individual diagnosed with UCMD, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with UCMD / Intermediate COL6-RD

System/Concern	Evaluation	Comment
Constitutional	Assessment of growth & feeding	• Feeding difficulties may manifest as FTT during 1st 1-2 yrs of life. • FTT at age 10-12 yrs may reflect inadequately supported ventilation.
Musculoskeletal	• Neuromuscular exam to evaluate degree & distribution of muscle weakness & its effects on mobility • Exam of joint contractures & joint hyperlaxity • Exam of back for evidence of stiffness &/or scoliosis • PT & OT assessment	
Pulmonary	Baseline polysomnogram w/CO_2 monitoring	During childhood to assess ventilation during deep sleep
	Pulmonary function tests should be performed in both upright (seated) & supine (lying down) positions w/forced vital capacity monitored closely	Starting at age 5 yrs
Cardiology	Eval w/cardiologist incl echocardiogram & EKG	To evaluate for right-sided heart strain in those w/ respiratory insufficiency who are not using NIV or have inadequate BiPAP pressures
Other	Consultation w/clinical geneticist &/or genetic counselor	

BiPAP = bilevel positive airway pressure; FTT = failure to thrive; NIV = noninvasive ventilation; OT = occupational therapy; PT = physical therapy

Treatment of Manifestations

Bethlem muscular dystrophy

- Disproportionate weakness of the diaphragm can cause nocturnal hypoventilation, even in individuals who remain independently ambulant. For forced vital capacity (FVC) measurements of 60% predicted or lower, noninvasive ventilation (NIV) in the form of bilevel positive airway pressure (BiPAP) should be initiated during a polysomnogram – with pressures adjusted to ensure adequate ventilation – and then consistently used while sleeping. If nocturnal BiPAP is started, BiPAP pressures should be carefully monitored and adjusted during repeat polysomnogram monitoring in order to provide adequate pressures as the body grows / pressure requirements increase related to progressive respiratory insufficiency.
- If BiPAP is not initiated when needed or inadequate BiPAP pressures are used, right-sided heart strain can be seen on echocardiogram monitoring. Optimization of BiPAP pressures can help to prevent the development of cor pulmonale.
- Surgical repair of scoliosis is rarely needed in individuals with Bethlem muscular dystrophy. If scoliosis surgery is considered, carefully planning for supporting respiratory needs preoperatively, intraoperatively, and postoperatively should be coordinated with orthopedic surgery, anesthesia, intensive care, and pulmonary teams.
- Physical therapy and occupational therapy assessments can provide recommendations for joint stretching and swimming/aquatherapy exercises, which promote stretching of the joints and conditioning of the muscles. Strategies to avoid excessive joint strain should be discussed with a physical therapist and occupational therapist, given that joint pain has been reported by some individuals with Bethlem muscular dystrophy.
- If Achilles tendon contractures are severe or asymmetric, thus adversely affecting gait, Achilles tendon release surgery can provide increased range of motion, especially if the Achilles tendon release is followed

by casting. A noninvasive approach that can help promote improved range of motion of the Achilles tendons is serial casting.
- Surgical intervention on any joint contractures (beyond Achilles tendon release surgery) is not recommended, given the high postoperative risk of fixed contractures with complete loss of range of motion in individuals with Bethlem muscular dystrophy who have undergone joint surgery. New surgical approaches with the potential of avoiding the postoperative risk of fixed contractures should be carefully considered in consultation with neuromuscular specialists, physical therapists, and occupational therapists.

UCMD / intermediate COL6-RD

- NIV in the form of BiPAP is needed in all individuals with UCMD by approximately age 11 years and all individuals with intermediate COL6-RD by the teenage years.
- Use of an insufflator/exsufflator such as with a cough assist machine is essential for promoting coughing and expectoration of phlegm and airway clearance during respiratory infections and should be used as frequently as possible in order to help prevent the progression of upper respiratory infections to lower respiratory tract infections (pneumonias).
- Right-sided heart strain can be evident on echocardiogram in individuals with respiratory insufficiency who are not using NIV in the form of BiPAP when needed or who are using BiPAP at pressures that are inadequate for supporting ventilation. If left unadjusted, cor pulmonale can develop. Right-sided heart function typically normalizes once BiPAP pressures are adequate for supporting nocturnal ventilation.
- Bracing for scoliosis should be carefully approached, given how important movement of the chest wall is for respiration/ventilation in individuals with COL6-RDs. If spinal bracing is considered, a brace that does not cover the lower thorax and is less restrictive of chest wall movement should be considered (e.g., Garchois plexidur brace). Surgical repair of scoliosis using various forms of fixed instrumentation and dynamic instrumentation (in young and still growing children) is commonly indicated for individuals with UCMD and intermediate COL6-RD, the timing of which is based on the degree of spine curvature and the rate of progression. In preparation for scoliosis surgery, careful coordination between orthopedic, anesthesia, intensive care, and pulmonary teams is essential for planning the preoperative, intraoperative, and postoperative respiratory needs. In particular, NIV in the form of BiPAP should be initiated prior to scoliosis surgery. Most individuals with UCMD or intermediate COL6-RD will need to be extubated directly to BiPAP following scoliosis surgery, and thus BiPAP initiation prior to surgery is essential both for optimizing lung function preoperatively and for assuring familiarity and comfort with BiPAP postoperatively.
- Physical therapists and occupational therapists can provide recommendations for stretching of the joints as well as for swimming and aquatherapy exercises, which promote stretching of the joints and conditioning of the muscles.
- If Achilles tendon contractures are severe or are asymmetric, thus adversely affecting gait, Achilles tendon release surgery by an orthopedic surgeon can provide increased range of motion, especially if Achilles tendon release is followed by casting. Surgical intervention on any joint contractures (beyond Achilles tendon release surgery) is not recommended, given the high postoperative risk of fixed contractures with complete loss of range of motion / no movement at the joint in individuals with UCMD or intermediate COL6-RD who have undergone surgeries that disrupt the joint capsule. New surgical approaches with the potential of avoiding the postoperative risk of fixed contractures should be carefully considered in consultation with neuromuscular specialists, physical therapists, and occupational therapists.
- Feeding via a gastrostomy tube may be indicated for maintaining adequate nutrition and weight. The recurrence of failure to thrive at age ten to 12 years should prompt an evaluation for nocturnal hypoventilation via polysomnogram with continuous CO_2 monitoring.

Surveillance

Bethlem muscular dystrophy

- Respiratory function surveillance is of utmost importance, since unrecognized respiratory insufficiency is a leading cause of morbidity and mortality. Pulmonary function tests (PFTs) should be performed in both the upright (seated) and supine (lying down) positions at least annually to monitor the FVC. For FVC measurements of 60% predicted or lower, NIV in the form of BiPAP should be planned for and initiated during a polysomnogram – with pressures adjusted while CO_2 is monitored – in order to ensure that BiPAP pressures provide adequate ventilation.
- Annual clinical and radiographic assessment of scoliosis
- Annual cardiac evaluation with echocardiogram and EKG to evaluate for evidence of right-sided heart strain
- Annual neuromuscular assessment by physical therapy and occupational therapy including an evaluation of the distribution of muscle weakness and joint contractures to inform recommendations for stretching regimens and mobility devices. Potential asymmetries of joint contractures are important to assess, given their effect on gait, sitting posture, and overall function.

UCMD / intermediate COL6-RD

- Respiratory function surveillance is of utmost importance in UCMD and intermediate COL6-RD, since unrecognized or underrecognized respiratory insufficiency is the leading cause of morbidity and mortality. PFTs should be performed in both the upright (seated) and supine (lying down) positions every six months to monitor the FVC. For FVC measurements of 60% predicted or lower, NIV in the form of BiPAP should be planned for and initiated during a polysomnogram – with pressures adjusted while CO_2 is monitored – in order to ensure BiPAP pressures provide adequate ventilation.
- Annual clinical and radiographic spine assessment for scoliosis and kyphoscoliosis
- Annual cardiac evaluation with echocardiogram and EKG to screen for evidence of right-sided heart strain
- Annual neuromuscular evaluation by physical therapy and occupational therapy including an evaluation of the distribution of muscle weakness and joint contractures to inform recommendations for stretching regimens and mobility devices. Potential asymmetries of joint contractures are important to assess, given their effect on gait, sitting posture, and overall function.
- Annual nutrition assessment

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 COL6-RD, careful pulmonary surveillance during pregnancy for potential increased needs for ventilatory support is recommended, particularly given the disproportionate weakness of the diaphragm in the COL6-RDs. A prenatal physiotherapy assessment for hip dislocation and/or hip contractures may be recommended, given that the presence and degree of decreased range of motion at the hips could affect considerations for delivery. An assessment of the overall level of muscle weakness is also recommended, which may help in predicting the degree of weakness of abdominal muscles and thus the potential for a difficult birthing process, which could also affect considerations for delivery.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for 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, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

The collagen VI-related dystrophies (a continuum of overlapping phenotypes encompassing Bethlem muscular dystrophy, Ullrich congenital muscular dystrophy [UCMD], and intermediate collagen VI-related dystrophy [COL6-RD]) are associated with both autosomal dominant and autosomal recessive inheritance.

Bethlem muscular dystrophy is usually inherited in an autosomal dominant manner, although autosomal recessive inheritance has also been reported [Foley et al 2009, Gualandi et al 2009].

UCMD and intermediate COL6-RD are typically caused by a *de novo* autosomal dominant pathogenic variant of *COL6A1*, *COL6A2*, or *COL6A3* [Allamand et al 2011, Bönnemann 2011, Butterfield et al 2013, Bolduc et al 2019, Aguti et al 2020]. Less commonly, UCMD and intermediate COL6-RD are inherited in an autosomal recessive manner.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Some individuals diagnosed with autosomal dominant COL6-RD have an affected parent.
- Approximately 50%-75% of individuals diagnosed with COL6-RD have the disorder as the result of a *de novo* *COL6A1*, *COL6A2*, or *COL6A3* pathogenic variant [Allamand et al 2010, Allamand et al 2011].
- Molecular genetic testing is recommended for the apparently asymptomatic parents of a proband with a presumed *de novo* pathogenic variant and for the parents of a proband with a positive family history (if the genetic status of the parents of a proband has not already been established).
- If the pathogenic variant found in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline – or somatic and germline – mosaicism [Armaroli et al 2015]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in germ cells only.
- It should be noted that parental somatic mosaicism (and concomitant germline mosaicism) is not uncommon in the COL6-RDs [Armaroli et al 2015, Donkervoort et al 2015, D'Amico et al 2017, Fan et al 2018], and it is important to consider this possibility given the implications for recurrence risk assessment. Clinical findings in a mosaic parent may range from obvious manifestations to very subtle/mild findings apparent only on detailed neuromuscular clinical examination and/or muscle imaging.

- The family history of some individuals diagnosed with autosomal dominant COL6-RD may appear to be negative due to failure to recognize the disorder in a mildly symptomatic family member, early death of the parent before the onset of symptoms, or late onset in an affected parent. Therefore, an apparently negative family history cannot be confirmed unless detailed neuromuscular clinical examination of the parents has been performed and molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant 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 risk to the sibs of inheriting the variant is 50%.
- The severity of COL6-RD manifestations may vary among family members who are heterozygous for the same pathogenic variant. The most significant intrafamilial clinical variability is observed in families segregating *COL6A1*, *COL6A2*, or *COL6A3* pathogenic variants associated with intermediate COL6-RD.
- If the proband has a known pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is presumed to be greater than that of the general population because of the significant possibility of parental mosaicism. Parental somatic mosaicism (and concomitant germline mosaicism) with full penetrance of the pathogenic variant in heterozygous offspring is not uncommon in the COL6-RDs [Donkervoort et al 2015].
- If the parents have not been tested for the pathogenic variant but are clinically unaffected, the recurrence risk to the sibs of a proband is presumed to be greater than that of the general population because of possibility of reduced penetrance in a heterozygous parent or parental somatic and germline mosaicism.

Offspring of a proband. Each child of an individual with an autosomal dominant COL6-RD has a 50% chance of inheriting the *COL6A1*, *COL6A2*, or *COL6A3* 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, the parent's family members may be at risk.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *COL6A1*, *COL6A2*, or *COL6A3* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *COL6A1*, *COL6A2*, or *COL6A3* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Individuals who are heterozygotes (carriers) for a pathogenic variant associated with autosomal recessive COL6-RD do not appear to develop manifestations of the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *COL6A1*, *COL6A2*, or *COL6A3* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.

- Individuals who are heterozygotes (carriers) for a pathogenic variant associated with autosomal recessive COL6-RD do not appear to develop manifestations of the disorder.

Offspring of a proband. Unless an affected individual's reproductive partner also has an autosomal recessive COL6-RD or is a carrier, offspring will be obligate heterozygotes for a pathogenic variant in *COL6A1*, *COL6A2*, or *COL6A3*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *COL6A1*, *COL6A2*, or *COL6A3* pathogenic variant.

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the *COL6A1*, *COL6A2*, or *COL6A3* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic 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. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022]. Note: DNA can also be extracted from a dermal fibroblast culture, which may be available when a skin biopsy has been performed for COL6-RD diagnostic purposes (immunocytochemistry to assess collagen VI expression).

Prenatal Testing and Preimplantation Genetic Testing

Once the *COL6A1*, *COL6A2*, or *COL6A3* pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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**

  Phone: 562-444-5656

  www.curecmd.org

- **Muscular Dystrophy Association (MDA) - USA**

  Phone: 833-275-6321

  www.mda.org

- **Muscular Dystrophy UK**

  United Kingdom

  Phone: 0800 652 6352

  www.musculardystrophyuk.org

- **Congenital Muscle Disease International Registry (CMDIR)**

  The CMDIR is a global partnership of patient advocacy organizations, researchers, and clinicians, all working toward the same goal: to find treatments for congenital muscle disease.

  CMDIR/Cure CMD

  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 VI-Related Dystrophies: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
COL6A1	21q22.3	Collagen alpha-1(VI) chain	COL6A1 homepage - Leiden Muscular Dystrophy pages	COL6A1	COL6A1
COL6A2	21q22.3	Collagen alpha-2(VI) chain	COL6A2 homepage - Leiden Muscular Dystrophy pages	COL6A2	COL6A2
COL6A3	2q37.3	Collagen alpha-3(VI) chain	COL6A3 homepage - Leiden Muscular Dystrophy pages	COL6A3	COL6A3

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 VI-Related Dystrophies (View All in OMIM)

120220	COLLAGEN, TYPE VI, ALPHA-1; COL6A1
120240	COLLAGEN, TYPE VI, ALPHA-2; COL6A2
120250	COLLAGEN, TYPE VI, ALPHA-3; COL6A3
158810	BETHLEM MYOPATHY 1A; BTHLM1A
254090	ULLRICH CONGENITAL MUSCULAR DYSTROPHY 1A; UCMD1A
255600	MYOSCLEROSIS, AUTOSOMAL RECESSIVE
620725	BETHLEM MYOPATHY 1B; BTHLM1B
620726	BETHLEM MYOPATHY 1C; BTHLM1C
620727	ULLRICH CONGENITAL MUSCULAR DYSTROPHY 1B; UCMD1B
620728	ULLRICH CONGENITAL MUSCULAR DYSTROPHY 1C; UCMD1C

Molecular Pathogenesis

Collagen VI is expressed in the extracellular matrices of several tissues and tissue components including muscle, blood vessels, nerves, skin, tendons, cartilage, intervertebral discs, lenses, and internal organs [Hessle & Engvall 1984, Keene et al 1988, Kuo et al 1997]. The extracellular matrix of skeletal muscle has been termed the "myomatrix" [Bönnemann 2011], with the collagen VI-related dystrophies (COL6-RDs) thus being considered primary disorders of the myomatrix.

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 [Furthmayr et al 1983, Chu et al 1988, Colombatti et al 1995], which then align to form tetramers, also stabilized by disulfide bonds [Furthmayr et al 1983, Chu et al 1988, Bonaldo et al 1990, Chu et al 1990]. The tetramers are then secreted extracellularly and align in an end-to-end fashion, forming beaded microfilaments as the final product of collagen VI assembly [Furthmayr et al 1983, Engvall et al 1986, Lamandé et al 1998, Baldock et al 2003].

Mechanism of disease causation

- **Pathogenic variants associated with autosomal dominant inheritance.** Heterozygous variants causing in-frame exon skipping (e.g., splice site variants, in-frame deletions) in any of the three COL6 genes are a common cause of all severities of COL6-RD. Dominantly acting exon skips occur at exons located in the N-terminal region of the triple helical (TH) domains of the collagen VI α chains. A strong dominant-negative effect can result from an in-frame exon skip variant if it does not disrupt the essential cysteine residues for dimer and tetramer formation. As a result, mutated and normal monomers assemble into dimers and tetramers, so that only 1/4 of the dimers and 1/16 of the tetramers are composed entirely of normal chains. Since 15/16 tetramers contain mutated chains, and mutated tetramers cannot properly align with normal tetramers, the final assembly of collagen VI microfibrils cannot proceed. A milder dominant-negative effect can result from dominant variants that disrupt the essential cysteine residues, preventing the formation of monomers and dimers with abnormal collagen VI chains. As a result, all tetramers secreted are composed of normal collagen VI chains, albeit at less than half the quantity of controls [Pan et al 2003, Baker et al 2005, Lampe et al 2005, Pepe et al 2006, Lampe et al 2008].

  Other dominant-negative variants that commonly occur in the COL6-RDs are heterozygous single-amino-acid substitutions disrupting the Gly-Xaa-Yaa motifs of the highly conserved N-terminal triple helical domains of any of the three COL6 genes, so-called glycine variants [Lampe et al 2005, Lucioli et al 2005]. Similar to the exon skip pathogenic variants, such pathogenic glycine variants will act as dominant when located in the "assembly competent" N-terminal end of the triple helical domain.

  An additional recurrent dominant-negative pathogenic variant consists of a deep-intronic change in intron 11 of *COL6A1* (c.930+189C>T), which creates a donor splice site that prompts the insertion of a 72-nucleotide in-frame pseudoexon into approximately half of the mRNA transcripts originating from the pathogenic variant allele [Cummings et al 2017, Bolduc et al 2019]. This mRNA translates into an α1(VI) chain in which the N-terminus of the triple helical domain is interrupted by a 24-amino acid sequence insertion, but in which the cysteine residue critical for dimerization is not affected, thus allowing incorporation of the variant chain into collagen VI assembly and secretion, resulting in a strong dominant-negative effect and impaired microfibrillar assembly [Bolduc et al 2019]. Due to its deep intronic location, this pathogenic variant may be missed on exon-only-based platforms.

- **Autosomal recessively acting loss-of-function pathogenic variants.** Most pathogenic variants associated with autosomal recessive disease in the COL6-RDs to date are nonsense or frameshift variants [Camacho Vanegas et al 2001]. Some pathogenic variants have been shown to result in the absence of collagen VI

because of nonsense-mediated mRNA decay [Zhang et al 2002]. Biallelic nonsense variants in the COL6 genes usually result in a severe phenotype [Camacho Vanegas et al 2001, Higuchi et al 2001, Ishikawa et al 2002, Peat et al 2007, Briñas et al 2010].

Intragenic deletions and splice site variants can also result in a transcript which is out of frame [Ishikawa et al 2002, Lucarini et al 2005] or a chain which is assembly incompetent (pathogenic variants at the C terminal region of the triple helical domain) [Lampe et al 2008]. The observation that heterozygous deletions of *COL6A1* and/or *COL6A2* do not result in COL6-RD indicates that haploinsufficiency of the COL6 genes is not a mechanism of disease causation [Foley et al 2011].

Of note, missense variants in compound heterozygosity with other missense variants may be pathogenic – the pathogenicity of which depends on the location and effects of the particular variants. Homozygous missense variants are a less common cause of COL6-RD but can result in a phenotype of UCMD if affecting crucial functions or interactions of the collagen VI protein [Baker et al 2005, Petrini et al 2005, Zhang et al 2010].

Gene-specific laboratory considerations

- Given the highly polymorphic nature of *COL6A1*, *COL6A2*, and *COL6A3*, clarification of variants of uncertain significance requires careful study. This is particularly true for missense variants outside the highly conserved N-terminal triple helical domains. For variants of uncertain significance, segregation testing, muscle imaging (MRI and/or ultrasound), and studies of collagen VI immunoreactivity in muscle and dermal fibroblasts (immunohistochemical studies and immunocytochemistry studies) are essential [Bönnemann 2011]. To identify variants affecting splicing, studies performed on RNA (extracted from skin fibroblasts or muscle) can be helpful [Camacho Vanegas et al 2001, Ishikawa et al 2002, Lucarini et al 2005].
- A recurrent deep-intronic *COL6A1* variant in intron 11 (c.930+189C>T) can be missed with exome sequencing or targeted sequencing (exon-only based platforms).

Table 5. Collagen VI-Related Dystrophies: Notable Pathogenic Variants by Gene

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
COL6A1	NM_001848.3 NP_001839.2	c.1056+1G>A	p.Gly320_Asp352del	Common variants that result in exon 14 skipping (Note: Other genomic variants may lead to exon 14 skipping) [Foley et al 2013, Fan et al 2018].
		c.1056+5G>A	p.Gly335_Asp352del	
		c.930+189C>T	p.Lys310_Gly311ins24	Common variant in intron 11 that induces an in-frame pseudoexon insertion [Cummings et al 2017, Bolduc et al 2019].
COL6A2	NM_001849.4 NP_001840.3	c.1402C>T	p.Arg468Ter	Common variant that in homozygosity results in loss of function [Valencia et al 2013].
		c.2455C>T	p.Gln819Ter	Common variant that in homozygosity results in a truncated α2(VI) chain lacking C2 domain [Bradley et al 1973, Merlini et al 2008].
COL6A3	NM_004369.4 NP_004360.2	c.6210+1G>A	p.Gly2053_Pro2070del	Common variants that result in exon 16 skipping [Briñas et al 2010, Foley et al 2013, Bolduc et al 2014, Fan et al 2018].
		c.6210+5G>A		

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Genes from Table 1 in alphabetic order.

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References

Literature Cited

Aguti S, Bolduc V, Ala P, Turmaine M, Bönnemann CG, Muntoni F, Zhou H. Exon-skipping oligonucleotides restore functional collagen vi by correcting a common COL6A1 mutation in Ullrich CMD. Mol Ther Nucleic Acids. 2020;21:205–16. PubMed PMID: 32585628.

Allamand V, Merlini L, Bushby K. Consortium for Collagen VI-Related Myopathies. 166th ENMC International Workshop on collagen type VI-related myopathies, 22-24 May 2009, Naarden, the Netherlands. Neuromuscul Disord. 2010;20:346–54. PubMed PMID: 20211562.

Allamand V, Briñas L, Richard P, Stojkovic T, Quijano-Roy S, Bonne G. ColVI myopathies: where do we stand, where do we go? Skelet Muscle. 2011;1:30. PubMed PMID: 21943391.

Armaroli A, Trabanelli C, Scotton C, Venturoli A, Selvatici R, Brisca G, Merlini L, Bruno C, Ferlini A, Gualandi F. Paternal germline mosaicism in collagen VI related myopathies. Eur J Paediatr Neurol. 2015;19:533–6. PubMed PMID: 25978941.

Baker NL, Morgelin M, Peat R, Goemans N, North KN, Bateman JF, Lamande SR. Dominant collagen VI mutations are a common cause of Ullrich congenital muscular dystrophy. Hum Mol Genet. 2005;14:279–93. PubMed PMID: 15563506.

Baldock C, Sherratt MJ, Shuttleworth CA, Kielty CM. The supramolecular organization of collagen VI microfibrils. J Mol Biol. 2003;330:297–307. PubMed PMID: 12823969.

Barp A, Laforet P, Bello L, Tasca G, Vissing J, Monforte M, Ricci E, Choumert A, Stojkovic T, Malfatti E, Pegoraro E, Semplicini C, Stramare R, Scheidegger O, Haberlova J, Straub V, Marini-Bettolo C, Løkken N, Diaz-Manera J, Urtizberea JA, Mercuri E, Kynčl M, Walter MC, Carlier RY. European muscle MRI study in limb girdle muscular dystrophy type R1/2A (LGMDR1/LGMD2A). J Neurol. 2020;267:45–56.

Bertini E, Pepe G. Collagen type VI and related disorders: Bethlem myopathy and Ullrich scleroatonic muscular dystrophy. Eur J Paediatr Neurol. 2002;6:193–8. PubMed PMID: 12374585.

Bethlem J, Wijngaarden GK. Benign myopathy, with autosomal dominant inheritance. A report on three pedigrees. Brain. 1976;99:91–100. PubMed PMID: 963533.

Bolduc V, Zou Y, Ko D, Bönnemann CG. siRNA-mediated Allele-specific Silencing of a COL6A3 Mutation in a Cellular Model of Dominant Ullrich Muscular Dystrophy. Mol Ther Nucleic Acids. 2014;3:e147. PubMed PMID: 24518369.

Bolduc V, Foley AR, Solomon-Degefa H, Sarathy A, Donkervoort S, Hu Y, Chen GS, Sizov K, Nalls M, Zhou H, Aguti S, Cummings BB, Lek M, Tukiainen T, Marshall JL, Regev O, Marek-Yagel D, Sarkozy A, Butterfield RJ, Jou C, Jimenez-Mallebrera C, Li Y, Gartioux C, Mamchaoui K, Allamand V, Gualandi F, Ferlini A, Hanssen E, Wilton SD, Lamandé SR, MacArthur DG, Wagener R, Muntoni F, Bönnemann CG, et al. A recurrent COL6A1 pseudoexon insertion causes muscular dystrophy and is effectively targeted by splice-correction therapies. JCI Insight. 2019;4:e124403. PubMed PMID: 30895940.

Bönnemann CG, Brockmann K, Hanefeld F. Muscle ultrasound in bethlem myopathy. Neuropediatrics. 2003;34:335–6. PubMed PMID: 14681763.

Bönnemann CG, Wang CH, Quijano-Roy S, Deconinck N, Bertini E, Ferreiro A, Muntoni F, Sewry C, Béroud C, Mathews KD, Moore SA, Bellini J, Rutkowski A, North KN. Members of International Standard of Care Committee for Congenital Muscular Dystrophies. Diagnostic approach to the congenital muscular dystrophies. Neuromuscul Disord. 2014;24:289–311. PubMed PMID: 24581957.

Bönnemann CG. The collagen VI-related myopathies: muscle meets its matrix. Nat Rev Neurol. 2011;7:379–90. PubMed PMID: 21691338.

Bonaldo P, Russo V, Bucciotti F, Doliana R, Colombatti A. Structural and functional features of the alpha 3 chain indicate a bridging role for chicken collagen VI in connective tissues. Biochemistry. 1990;29:1245–54. PubMed PMID: 2322559.

Bradley WG, Hudgson P, Gardner-Medwin D, Walton JN. The syndrome of myosclerosis. J Neurol Neurosurg Psychiatry. 1973;36:651–60. PubMed PMID: 4793163.

Briñas L, Richard P, Quijano-Roy S, Gartioux C, Ledeuil C, Lacène E, Makri S, Ferreiro A, Maugenre S, Topaloglu H, Haliloglu G, Pénisson-Besnier I, Jeannet PY, Merlini L, Navarro C, Toutain A, Chaigne D, Desguerre I, de Die-Smulders C, Dunand M, Echenne B, Eymard B, Kuntzer T, Maincent K, Mayer M, Plessis G, Rivier F, Roelens F, Stojkovic T, Taratuto AL, Lubieniecki F, Monges S, Tranchant C, Viollet L, Romero NB, Estournet B, Guicheney P, Allamand V. Early onset collagen VI myopathies: genetic and clinical correlations. Ann Neurol. 2010;68:511–20. PubMed PMID: 20976770.

Butterfield RJ, Foley AR, Dastgir J, Asman S, Dunn DM, Zou Y, Hu Y, Donkervoort S, Flanigan KM, Swoboda KJ, Winder TL, Weiss RB, Bönnemann CG. Position of glycine substitutions in the triple helix of COL6A1, COL6A2, and COL6A3 is correlated with severity and mode of inheritance in collagen VI myopathies. Hum Mutat. 2013;34:1558–67. PubMed PMID: 24038877.

Camacho Vanegas O, Bertini E, Zhang RZ, Petrini S, Minosse C, Sabatelli P, Giusti B, Chu ML, Pepe G. Ullrich scleroatonic muscular dystrophy is caused by recessive mutations in collagen type VI. Proc Natl Acad Sci USA. 2001;98:7516–21. PubMed PMID: 11381124.

Chu ML, Conway D, Pan TC, Baldwin C, Mann K, Deutzmann R, Timpl R. Amino acid sequence of the triple-helical domain of human collagen type VI. J Biol Chem. 1988;263:18601–6. PubMed PMID: 3198591.

Chu ML, Pan TC, Conway D, Saitta B, Stokes D, Kuo HJ, Glanville RW, Timpl R, Mann K, Deutzmann R. The structure of type VI collagen. Ann N Y Acad Sci. 1990;580:55–63. PubMed PMID: 2337306.

Collins J, Foley AR, Straub V, Bönnemann CG. Spontaneous keloid formation in patients with Bethlem myopathy. Neurology. 2012;79:2158. PubMed PMID: 23170014.

Colombatti A, Mucignat MT, Bonaldo P. Secretion and matrix assembly of recombinant type VI collagen. J Biol Chem. 1995;270:13105–11. PubMed PMID: 7768905.

Cummings BB, Marshall JL, Tukiainen T, Lek M, Donkervoort S, Foley AR, Bolduc V, Waddell LB, Sandaradura SA, O'Grady GL, Estrella E, Reddy HM, Zhao F, Weisburd B, Karczewski KJ, O'Donnell-Luria AH, Birnbaum D, Sarkozy A, Hu Y, Gonorazky H, Claeys K, Joshi H, Bournazos A, Oates EC, Ghaoui R, Davis MR, Laing NG, Topf A, Kang PB, Beggs AH, North KN, Straub V, Dowling JJ, Muntoni F, Clarke NF, Cooper ST, Bönnemann CG, MacArthur DG, et al. Improving genetic diagnosis in Mendelian disease with transcriptome sequencing. Sci Transl Med. 2017;9:eaal5209. PubMed PMID: 28424332.

D'Amico A, Fattori F, Tasca G, Petrini S, Gualandi F, Bruselles A, D'Oria V, Verardo M, Carrozzo R, Niceta M, Udd B, Ferlini A, Tartaglia M, Bertini E. Somatic mosaicism represents an underestimated event underlying collagen 6-related disorders. Eur J Paediatr Neurol. 2017;21:873–83. PubMed PMID: 28760337.

Donkervoort S, Hu Y, Stojkovic T, Voermans NC, Foley AR, Leach ME, Dastgir J, Bolduc V, Cullup T, de Becdelièvre A, Yang L, Su H, Meilleur K, Schindler AB, Kamsteeg EJ, Richard P, Butterfield RJ, Winder TL, Crawford TO, Weiss RB, Muntoni F, Allamand V, Bönnemann CG. Mosaicism for dominant collagen 6 mutations as a cause for intrafamilial phenotypic variability. Hum Mutat. 2015;36:48–56. PubMed PMID: 25204870.

Engvall E, Hessle H, Klier G. Molecular assembly, secretion, and matrix deposition of type VI collagen. J Cell Biol. 1986;102:703–10. PubMed PMID: 3456350.

Fan Y, Liu A, Wei C, Yang H, Chang X, Wang S, Yuan Y, Bönnemann C, Wu Q, Wu X, Xiong H. Genetic and clinical findings in a Chinese cohort of patients with collagen VI-related myopathies. Clin Genet. 2018;93:1159–71. PubMed PMID: 29419890.

Foley AR, Hu Y, Zou Y, Columbus A, Shoffner J, Dunn DM, Weiss RB, Bönnemann CG. Autosomal recessive inheritance of classic Bethlem myopathy. Neuromuscul Disord. 2009;19:813–7. PubMed PMID: 19884007.

Foley AR, Hu Y, Zou Y, Yang M, Medne L, Leach M, Conlin LK, Spinner N, Shaikh TH, Falk M, Neumeyer AM, Bliss L, Tseng BS, Winder TL, Bönnemann CG. Large genomic deletions: a novel cause of Ullrich congenital muscular dystrophy. Ann Neurol. 2011;69:206–11. PubMed PMID: 21280092.

Foley AR, Quijano-Roy S, Collins J, Straub V, McCallum M, Deconinck N, Mercuri E, Pane M, D'Amico A, Bertini E, North K, Ryan MM, Richard P, Allamand V, Hicks D, Lamandé S, Hu Y, Gualandi F, Auh S, Muntoni F, Bönnemann CG. Natural history of pulmonary function in collagen VI-related myopathies. Brain. 2013;136:3625–33. PubMed PMID: 24271325.

Furthmayr H, Wiedemann H, Timpl R, Odermatt E, Engel J. Electron-microscopical approach to a structural model of intima collagen. Biochem J. 1983;211:303–11. PubMed PMID: 6307276.

Furukawa T, Toyokura Y. Congenital, hypotonic-sclerotic muscular dystrophy. J Med Genet. 1977;14:426–9. PubMed PMID: 604494.

Gualandi F, Urciuolo A, Martoni E, Sabatelli P, Squarzoni S, Bovolenta M, Messina S, Mercuri E, Franchella A, Ferlini A, Bonaldo P, Merlini L. Autosomal recessive Bethlem myopathy. Neurology. 2009;73:1883–91. PubMed PMID: 19949035.

Haq RU, Speer MC, Chu ML, Tandan R. Respiratory muscle involvement in Bethlem myopathy. Neurology. 1999;52:174–6. PubMed PMID: 9921869.

Hessle H, Engvall E. Type VI collagen. Studies on its localization, structure, and biosynthetic form with monoclonal antibodies. J Biol Chem. 1984;259:3955–61. PubMed PMID: 6368554.

Hicks D, Lampe AK, Barresi R, Charlton R, Fiorillo C, Bönnemann CG, Hudson J, Sutton R, Lochmüller H, Straub V, Bushby K. A refined diagnostic algorithm for Bethlem myopathy. Neurology. 2008;70:1192–9. PubMed PMID: 18378883.

Higuchi I, Shiraishi T, Hashiguchi T, Suehara M, Niiyama T, Nakagawa M, Arimura K, Maruyama I, Osame M. Frameshift mutation in the collagen VI gene causes Ullrich's disease. Ann Neurol. 2001;50:261–5. PubMed PMID: 11506412.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389–97. PubMed PMID: 35834113.

Ishikawa H, Sugie K, Murayama K, Ito M, Minami N, Nishino I, Nonaka I. Ullrich disease: collagen VI deficiency: EM suggests a new basis for muscular weakness. Neurology. 2002;59:920–3. PubMed PMID: 12297580.

Ishikawa H, Sugie K, Murayama K, Awaya A, Suzuki Y, Noguchi S, Hayashi YK, Nonaka I, Nishino I. Ullrich disease due to deficiency of collagen VI in the sarcolemma. Neurology. 2004;62:620–3. PubMed PMID: 14981181.

Jimenez-Mallebrera C, Maioli MA, Kim J, Brown SC, Feng L, Lampe AK, Bushby K, Hicks D, Flanigan KM, Bönnemann C, Sewry CA, Muntoni F. A comparative analysis of collagen VI production in muscle, skin and fibroblasts from 14 Ullrich congenital muscular dystrophy patients with dominant and recessive COL6A mutations. Neuromuscul Disord. 2006;16:571–82. PubMed PMID: 16935502.

Jöbsis GJ, Keizers H, Vreijling JP, de Visser M, Speer MC, Wolterman RA, Baas F, Bolhuis PA. Type VI collagen mutations in Bethlem myopathy, an autosomal dominant myopathy with contractures. Nat Genet. 1996;14:113–5. PubMed PMID: 8782832.

Jöbsis GJ, Boers JM, Barth PG, de Visser M. Bethlem myopathy: a slowly progressive congenital muscular dystrophy with contractures. Brain. 1999;122:649–55. PubMed PMID: 10219778.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519–22. PubMed PMID: 28959963.

Keene DR, Engvall E, Glanville RW. Ultrastructure of type VI collagen in human skin and cartilage suggests an anchoring function for this filamentous network. J Cell Biol. 1988;107:1995–2006. PubMed PMID: 3182942.

Kuo HJ, Maslen CL, Keene DR, Glanville RW. Type VI collagen anchors endothelial basement membranes by interacting with type IV collagen. J Biol Chem. 1997;272:26522–9. PubMed PMID: 9334230.

Lamandé SR, Sigalas E, Pan TC, Chu ML, Dziadek M, Timpl R, Bateman JF. The role of the alpha3(VI) chain in collagen VI assembly. Expression of an alpha3(VI) chain lacking N-terminal modules N10-N7 restores collagen VI assembly, secretion, and matrix deposition in an alpha3(VI)-deficient cell line. J Biol Chem. 1998;273:7423–30. PubMed PMID: 9516440.

Lampe AK, Dunn DM, von Niederhausern AC, Hamil C, Aoyagi A, Laval SH, Marie SK, Chu ML, Swoboda K, Muntoni F, Bönnemann CG, Flanigan KM, Bushby KM, Weiss RB. Automated genomic sequence analysis of the three collagen VI genes: applications to Ullrich congenital muscular dystrophy and Bethlem myopathy. J Med Genet. 2005;42:108–20. PubMed PMID: 15689448.

Lampe AK, Zou Y, Sudano D, O'Brien KK, Hicks D, Laval SH, Charlton R, Jimenez-Mallebrera C, Zhang RZ, Finkel RS, Tennekoon G, Schreiber G, van der Knaap MS, Marks H, Straub V, Flanigan KM, Chu ML, Muntoni F, Bushby KM, Bönnemann CG. Exon skipping mutations in collagen VI are common and are predictive for severity and inheritance. Hum Mutat. 2008;29:809–22. PubMed PMID: 18366090.

Lucarini L, Giusti B, Zhang RZ, Pan TC, Jimenez-Mallebrera C, Mercuri E, Muntoni F, Pepe G, Chu ML. A homozygous COL6A2 intron mutation causes in-frame triple-helical deletion and nonsense-mediated mRNA decay in a patient with Ullrich congenital muscular dystrophy. Hum Genet. 2005;117:460–6. PubMed PMID: 16075202.

Lucioli S, Giusti B, Mercuri E, Vanegas OC, Lucarini L, Pietroni V, Urtizberea A, Ben Yaou R, de Visser M, van der Kooi AJ, Bönnemann C, Iannaccone ST, Merlini L, Bushby K, Muntoni F, Bertini E, Chu ML, Pepe G. Detection of common and private mutations in the COL6A1 gene of patients with Bethlem myopathy. Neurology. 2005;64:1931–7. PubMed PMID: 15955946.

Mercuri E, Lampe A, Allsop J, Knight R, Pane M, Kinali M, Bönnemann C, Flanigan K, Lapini I, Bushby K, Pepe G, Muntoni F. Muscle MRI in Ullrich congenital muscular dystrophy and Bethlem myopathy. Neuromuscul Disord. 2005;15:303–10. PubMed PMID: 15792870.

Mercuri E, Clement E, Offiah A, Pichiecchio A, Vasco G, Bianco F, Berardinelli A, Manzur A, Pane M, Messina S, Gualandi F, Ricci E, Rutherford M, Muntoni F. Muscle magnetic resonanceimaging involvement in muscular dystrophies with rigidity of thespine. Ann Neurol. 2010;67:201–8. PubMed PMID: 20225280.

Merlini L, Martoni E, Grumati P, Sabatelli P, Squarzoni S, Urciuolo A, Ferlini A, Gualandi F, Bonaldo P. Autosomal recessive myosclerosis myopathy is a collagen VI disorder. Neurology. 2008;71:1245–53. PubMed PMID: 18852439.

Mohire MD, Tandan R, Fries TJ, Little BW, Pendlebury WW, Bradley WG. Early-onset benign autosomal dominant limb-girdle myopathy with contractures (Bethlem myopathy). Neurology. 1988;38:573–80. PubMed PMID: 3352914.

Nadeau A, Muntoni F. Skin changes in Ullrich congenital muscular dystrophy. Neuromuscul Disord. 2008;18:982. PubMed PMID: 18948005.

Nadeau A, Kinali M, Main M, Jimenez-Mallebrera C, Aloysius A, Clement E, North B, Manzur AY, Robb SA, Mercuri E, Muntoni F. Natural history of Ullrich congenital muscular dystrophy. Neurology. 2009;73:25–31. PubMed PMID: 19564581.

Natera-de Benito D, Foley AR, Domínguez-González C, Ortez C, Jain M, Mebrahtu A, Donkervoort S, Hu Y, Fink M, Yun P, Ogata T, Medina J, Vigo M, Meilleur KG, Leach ME, Dastgir J, Díaz-Manera J, Carrera-García L, Expósito-Escudero J, Alarcon M, Cuadras D, Montiel-Morillo E, Milisenda JC, Dominguez-Rubio R, Olivé M, Colomer J, Jou C, Jimenez-Mallebrera C, Bönnemann CG, Nascimento A. Association of initial maximal motor ability with long-term functional outcome in patients with COL6-related dystrophies. Neurology. 2021;96:e1413–e1424. PubMed PMID: 33441455.

Nonaka I, Une Y, Ishihara T, Miyoshino S, Nakashima T, Sugita H. A clinical and histological study of Ullrich's disease (congenital atonic-sclerotic muscular dystrophy). Neuropediatrics. 1981;12:197–208. PubMed PMID: 7290342.

Norwood FL, Harling C, Chinnery PF, Eagle M, Bushby K, Straub V. Prevalence of genetic muscle disease in Northern England: in-depth analysis of a muscle clinic population. Brain. 2009;132:3175–86. PubMed PMID: 19767415.

Oates EC, Jones KJ, Donkervoort S, Charlton A, Brammah S, Smith JE 3rd, Ware JS, Yau KS, Swanson LC, Whiffin N, Peduto AJ, Bournazos A, Waddell LB, Farrar MA, Sampaio HA, Teoh HL, Lamont PJ, Mowat D, Fitzsimons RB, Corbett AJ, Ryan MM, O'Grady GL, Sandaradura SA, Ghaoui R, Joshi H, Marshall JL, Nolan MA, Kaur S, Punetha J, Töpf A, Harris E, Bakshi M, Genetti CA, Marttila M, Werlauff U, Streichenberger N, Pestronk A, Mazanti I, Pinner JR, Vuillerot C, Grosmann C, Camacho A, Mohassel P, Leach ME, Foley AR, Bharucha-Goebel D, Collins J, Connolly AM, Gilbreath HR, Iannaccone ST, Castro D, Cummings BB, Webster RI, Lazaro L, Vissing J, Coppens S, Deconinck N, Luk HM, Thomas NH, Foulds NC, Illingworth MA, Ellard S, McLean CA, Phadke R, Ravenscroft G, Witting N, Hackman P, Richard I, Cooper ST, Kamsteeg EJ, Hoffman EP, Bushby K, Straub V, Udd B, Ferreiro A, North KN, Clarke NF, Lek M, Beggs AH, Bönnemann CG, MacArthur DG, Granzier H, Davis MR, Laing NG. Congenital titinopathy: comprehensive characterization and pathogenic insights. Ann Neurol. 2018;83:1105–24. PubMed PMID: 29691892.

Okada M, Kawahara G, Noguchi S, Sugie K, Murayama K, Nonaka I, Hayashi YK, Nishino I. Primary collagen VI deficiency is the second most common congenital muscular dystrophy in Japan. Neurology. 2007;69:1035–42. PubMed PMID: 17785673.

Pace RA, Peat RA, Baker NL, Zamurs L, Mörgelin M, Irving M, Adams NE, Bateman JF, Mowat D, Smith NJ, Lamont PJ, Moore SA, Mathews KD, North KN, Lamandé SR. Collagen VI glycine mutations: perturbed assembly and a spectrum of clinical severity. Ann Neurol. 2008;64:294–303. PubMed PMID: 18825676.

Pan TC, Zhang RZ, Sudano DG, Marie SK, Bönnemann CG, Chu ML. New molecular mechanism for Ullrich congenital muscular dystrophy: a heterozygous in-frame deletion in the COL6A1 gene causes a severe phenotype. Am J Hum Genet. 2003;73:355–69. PubMed PMID: 12840783.

Peat RA, Baker NL, Jones KJ, North KN, Lamandé SR. Variable penetrance of COL6A1 null mutations: implications for prenatal diagnosis and genetic counselling in Ullrich congenital muscular dystrophy families. Neuromuscul Disord. 2007;17:547–57. PubMed PMID: 17537636.

Peat RA, Smith JM, Compton AG, Baker NL, Pace RA, Burkin DJ, Kaufman SJ, Lamandé SR, North KN. Diagnosis and etiology of congenital muscular dystrophy. Neurology. 2008;71:312–21. PubMed PMID: 18160674.

Pepe G, Bertini E, Bonaldo P, Bushby K, Giusti B, de Visser M, Guicheney P, Lattanzi G, Merlini L, Muntoni F, Nishino I, Nonaka I, Yaou RB, Sabatelli P, Sewry C, Topaloglu H, van der Kooi A. Bethlem myopathy (BETHLEM) and Ullrich scleroatonic muscular dystrophy: 100th ENMC international workshop, 23-24 November 2001, Naarden, the Netherlands. Neuromuscul Disord. 2002;12:984–93. PubMed PMID: 12467756.

Pepe G, Lucarini L, Zhang RZ, Pan TC, Giusti B, Quijano-Roy S, Gartioux C, Bushby KM, Guicheney P, Chu ML. COL6A1 genomic deletions in Bethlem myopathy and Ullrich muscular dystrophy. Ann Neurol. 2006;59:190–5. PubMed PMID: 16278855.

Petrini S, Tessa A, Stallcup WB, Sabatelli P, Pescatori M, Giusti B, Carrozzo R, Verardo M, Bergamin N, Columbaro M, Bernardini C, Merlini L, Pepe G, Bonaldo P, Bertini E. Altered expression of the MCSP/NG2 chondroitin sulfate proteoglycan in collagen VI deficiency. Mol Cell Neurosci. 2005;30:408–17. PubMed PMID: 16169245.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Schessl J, Goemans NM, Magold AI, Zou Y, Hu Y, Kirschner J, Scot R, Bönnemann CG. Predominant fiber atrophy and fiber type disproportion in early ullrich disease. Muscle Nerve. 2008;38:1184–91. PubMed PMID: 18720506.

Ullrich O. Kongenitale, atonisch-sklerotische Muskeldystrophie, ein weiterer Typus der heredodegenerativen Erkrankungen des neuromuskulaeren Systems. Z Ges Neurol Psychiatr. 1930a;126:171–201.

Ullrich O. Kongenitale atonisch-sklerotische Muskeldystrophie. Monatsschr Kinderheilkd. 1930b;47:502–10.

Valencia CA, Ankala A, Rhodenizer D, Bhide S, Littlejohn MR, Keong LM, Rutkowski A, Sparks S, Bönnemann C, Hegde M. Comprehensive mutation analysis for congenital muscular dystrophy: a clinical PCR-based enrichment and next-generation sequencing panel. PLoS One. 2013;8:e53083. PubMed PMID: 23326386.

van der Kooi AJ, de Voogt WG, Bertini E, Merlini L, Talim FB, Ben Yaou R, Urtziberea A, de Visser M. Cardiac and pulmonary investigations in Bethlem myopathy. Arch Neurol. 2006;63:1617–21. PubMed PMID: 17101832.

Yonekawa T, Komaki H, Okada M, Hayashi YK, Nonaka I, Sugai K, Sasaki M, Nishino I. Rapidly progressive scoliosis and respiratory deterioration in Ullrich congenital muscular dystrophy. J Neurol Neurosurg Psychiatry. 2013;84:982–8. PubMed PMID: 23572247.

Zhang RZ, Sabatelli P, Pan TC, Squarzoni S, Mattioli E, Bertini E, Pepe G, Chu ML. Effects on collagen VI mRNA stability and microfibrillar assembly of three COL6A2 mutations in two families with Ullrich congenital muscular dystrophy. J Biol Chem. 2002;277:43557–64. PubMed PMID: 12218063.

Zhang RZ, Zou Y, Pan TC, Markova D, Fertala A, Hu Y, Squarzoni S, Reed UC, Marie SK, Bönnemann CG, Chu ML. Recessive COL6A2 C-globular missense mutations in Ullrich congenital muscular dystrophy: role of the C2a splice variant. J Biol Chem. 2010;285:10005–15. PubMed PMID: 20106987.

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