Collagen VI related muscle disorders

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Mutations in the genes encoding collagen VI (COL6A1, COL6A2, and COL6A3) cause Bethlem myopathy (BM) and Ullrich congenital muscular dystrophy (UCMD), two conditions which were previously believed to be completely separate entities. BM is a relatively mild dominantly inherited disorder characterised by proximal weakness and distal joint contractures. UCMD was originally described as an autosomal recessive condition causing severe muscle weakness with proximal joint contractures and distal hyperlaxity. Here we review the clinical phenotypes of BM and UCMD and their diagnosis and management, and provide an overview of the current knowledge of the pathogenesis of collagen VI related disorders.

The discovery of the underlying molecular basis of many muscular dystrophies and myopathies over recent years has highlighted the importance of the link between the cytoskeleton and the extracellular matrix in skeletal muscle. Extracellular matrix and basal lamina molecules are now known to be critical for skeletal muscle stability, regeneration, and muscle cell matrix adhesion. Collagen VI is a ubiquitous extracellular matrix protein which forms a microfibrillar network in close association with the basement membrane around muscle cells and which interacts with several other matrix constituents. Mutations in the genes encoding any of the three collagen VI chains have been demonstrated in Bethlem myopathy (MIM 158810) and Ullrich congenital muscular dystrophy (MIM 254090).

In this review we discuss the clinical phenotypes of Bethlem myopathy (BM) and Ullrich congenital muscular dystrophy (UCMD), the muscle pathology in these disorders, the role of collagen VI in their causation and provide a reappraisal of this important and under-recognised group of disorders.

BETHLEM MYOPATHY

Bethlem myopathy was first described in 1976 by Bethlem and van Wijngaarden as an autosomal dominantly inherited mild proximal myopathy with long flexion contractures occurring in 28 individuals of three Dutch pedigrees. It has subsequently been reported worldwide (for extensive review see De Visser et al). Although BM is classically described as a mild disorder with its major impact in adult life it is often possible in retrospect to elicit a history of neonatal hypotonia or torticollis, delayed motor milestones, or even decreased fetal movements. Usually patients will become symptomatic within the first or second decade, however, as some adult patients remain unaware of weakness, an age of onset cannot always be reliably established. The development of contractures is a hallmark of this condition. The contractures may be of a strikingly dynamic nature during childhood, appearing and disappearing in various joints, but nearly all patients eventually show flexion contractures of the fingers, wrists, elbows, and ankles (fig 1, panels A–D) and these, in addition to weakness, contribute to disability. Strikingly, hypermobility of distal interphalangeal joints can be present together with long finger flexion contractures. Where contractures are prominent, BM may resemble Emery–Dreifuss muscular dystrophy, particularly when a rigid spine is present. However, in other patients the contractures may be relatively subtle, leading to potential confusion in diagnosis with cases of limb girdle muscular dystrophy. Immunohistochemical testing (that is, western blotting and immunohistochemistry) carried out on the muscle biopsy or molecular genetic testing, or both, can help to exclude alternative diagnoses such as sarcoglycanopathy, calpainopathy, and dysferlinopathy as well as X linked or autosomal dominant Emery–Dreifuss muscular dystrophy.

BM patients typically have moderate predominantly proximal weakness and atrophy with the extensors more involved than the flexors. Muscle magnetic resonance imaging (MRI) shows variable severity of muscle involvement paralleling the severity of motor function impairment, with a characteristic pattern of involvement of the peripheral region of the vastus lateralis and hamstring muscles but relative sparing of their central parts. This peripheral predominance of pathology in BM has also been observed using muscle ultrasound and described as “central shadow sign.”

The condition is in most cases slowly progressive and more than two thirds of patients over 50 years of age will require aids for ambulation, especially outdoors. Whereas cardiac involvement is usually absent, respiratory muscle and especially diaphragmatic involvement necessitating nocturnal respiratory support is rarely reported in association with severe weakness in later life. In addition, unusual skin features may be present in some BM patients, including follicular hyperkeratosis and keloid formation or “cigarette paper” scarring (see fig 1E).

Abbreviations: BM, Bethlem myopathy; CMD, congenital muscular dystrophy; UCMD, Ullrich congenital muscular dystrophy; vWF, von Willebrand factor
Figure 1. Typical clinical features of Bethlem myopathy (panels A to E) and Ullrich congenital muscular dystrophy (panels F to I) (see text).
Electromyography typically shows a myopathic pattern of low amplitude, short duration motor unit action potentials\(^{17}\) and the serum creatine kinase is normal or only mildly raised (usually less than five times the upper limit of normal).\(^{19}\) The histopathological features of a BM muscle biopsy are non-specifically myopathic, usually consisting of a marked variation in muscle fibre diameter with possible increase of fatty tissue and occasional necrotic or dystrophic fibres.\(^{20,21}\)

**ULLRICH CONGENITAL MUSCULAR DYSTROPHY**

UCMD, on the other hand, is classically described as an autosomal recessive condition. It is a clinically and genetically distinct entity within the congenital muscular dystrophies.\(^{30}\)

UCMD was first described by Ullrich in 1930,\(^{31,32}\) and subsequent publications confirmed a likely autosomal recessive inheritance and a recognisable pattern of disease.\(^{33-42}\) The hallmarks of UCMD are muscle weakness of early onset with proximal joint contractures (fig 1, panel H) and striking hyperelasticity of the distal joints (fig 1, panels I to K). Posteriorly protruding calcanei are commonly seen (fig 1G). Weakness is profound and children typically either never achieve the ability to walk independently, or walk independently for short periods only.\(^{43,44}\) Intelligence is normal. With progression of the disease, there is typically development of spinal rigidity and scoliosis and variable proximal contractures, while with time the distal hyperlaxity can give way to marked long finger flexion contractures and tight Achilles tendons.\(^{45}\) Respiratory failure in the first or second decade is a common cause of death unless treated with nocturnal respiratory support, but cardiac involvement is not documented to date.\(^{41,42}\) There is frequent failure to thrive. Other distinctive features observed in UCMD patients are congenital hip dislocations\(^{46,47}\) and a transient kyphotic deformity at birth as well as follicular hyperkeratosis over the extensor surfaces of upper and lower limbs, soft velvety skin on the palms and soles, and the tendency to keloid or “cigarette paper” scar formation\(^{45,47}\) (fig 1F).

Muscle MRI shows a characteristic pattern with diffuse involvement of the thigh muscles with relative sparing of sartorius, gracilis, adductor longus, and rectus.\(^{47}\)

As for BM, the serum creatine kinase activity in UCMD patients is usually normal or mildly increased (rarely more than five times the upper limit of normal)\(^{48,49}\) and electromyography reveals action potentials of low amplitude and short duration.\(^{49}\) Variable pathology, ranging from non-specific mild myopathic changes to more dystrophic-like changes, can be observed in muscle biopsies from UCMD patients, the spectrum including variation in fibre size, type I fibre predominance, increased endomysial connective tissue, increased numbers of internal nuclei, and focal areas of necrosis, along with more indirect evidence of muscle fibre regeneration such as the presence of fibres containing fetal myosin.\(^{50-52}\) In the neonatal period, the differential diagnosis includes other forms of congenital muscular dystrophy (CMD), congenital myopathies, spinal muscular atrophy, and forms of Ehlers–Danlos syndrome or Marfan syndrome. Other types of CMD do not generally present with the distal hyperlaxity characteristic of UCMD and are usually associated with serum creatine kinase levels higher than those observed in UCMD.\(^{53,54}\) Biochemical testing (that is, western blotting and immunohistochemistry) carried out on the muscle biopsy, along with molecular genetic testing, can help to establish the diagnosis of some CMD subtypes such as MDC1A or MDC1C (FKRP mutations).\(^{56,57}\) In addition, brain MRI may show structural abnormalities or white matter changes in some CMD subtypes such as MDC1A, Walker–Warburg syndrome, muscle-eye-brain disease, and Fukuyama CMD.\(^{58,59}\) Spinal muscular atrophy can usually be diagnosed by demonstrating mutations in the SMN gene\(^{60}\) and the muscle biopsy shows features of denervation rather than myopathic or dystrophic changes.\(^{59}\) Forms of Ehlers–Danlos syndrome or Marfan syndrome are usually not associated with significant muscle weakness or an abnormal muscle biopsy, but may be confused with UCMD because of joint laxity.\(^{61,62}\) Rigid spine syndromes, a proportion of which are caused by mutations in the SEPNI gene, may overlap with UCMD later as the phenotype develops.\(^{63,64}\)

**COLLAGEN VI**

In 1996 linkage studies in BM demonstrated locus heterogeneity, with loci on chromosome 21q22.3\(^4\) and 2q37,\(^5\) respectively, and identified COL6A1-3 as candidate genes. Mutations in all three genes have now been identified in both BM and UCMD. Collagen VI is a ubiquitous extracellular matrix protein that is present in the stroma but also forms a microfibrillar network in close association with the basement membrane of most tissues.\(^{65-67}\) It is composed of three different peptide chains (α1(VI) and α2(VI)—both 140 kDa in size—and α3(VI), which is much larger (260–300 kDa).

**Genomic organisation**

The α1(VI) and α2(VI) chains are encoded by two genes (COL6A1 and COL6A2 respectively) situated in a head to tail organisation on chromosome 21q22.3\(^6\) (NT 011515), separated by 150 kb of genomic DNA. COL6A3, the gene for the α3(VI) chain, maps to chromosome 2q37\(^7\) (NT 005120). All three chains contain a central short triple helical domain of 335 to 336 amino acids with repeating Gly-Xaa-Yaa sequences, flanked by two large N- and C-terminal globular domains made up of motifs of 200 amino acids each, which are homologous to von Willebrand factor (vWF) type A domains\(^68-72\) (fig 2). COL6A1, which consists of 37 exons (35 coding), contains one promoter\(^73\) and produces a single transcript (NM_001848) encoding a protein of 1021 amino acids (NP_001839) with two C-terminal and one N-terminal vWF type A-like domains. Two different promoters have been described for the 30 exons (29 coding) spanning COL6A2.\(^66\) It has also been shown to produce multiple alternatively spliced mRNAs which differ in the 5’-untranslated region as well as the 3’-coding and non-coding sequences, producing at least three α2(VI) protein variants with distinct carboxyl termini\(^74-77\) which similarly contain two C-terminal and one N-terminal vWF type A-like domains.

The COL6A3 gene comprises 44 exons (43 coding) and encodes the α3(VI) chain, which can vary in size between 2970 and 3176 amino acids. The α3(VI) chain contains two C-terminal vWF type A-like domains, subdomains similar to type III fibronectin repeats, and Kunitz protease inhibitors as well as 6-10 N-terminal vWF type A-like domains, thus contributing most of the amino-terminal globular domain of the collagen VI heterotrimer. Various N-terminal exons of COL6A3 are subject to alternative splicing and four variant transcripts encode proteins with variably sized N-terminal globular domains.\(^69-72\)

**Macromolecular structure**

The assembly of collagen VI is a complex multistep process. Equimolar 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 disulphide bonded antiparallel dimers, which then align to form tetramers, also stabilised by disulphide bonds (fig 3).

Engineered mutation experiments indicate that, as with fibrillar collagens, the collagen VI triple helix folds from the C to the N terminus with folding being nucleated by C-terminal Gly-Xaa-Yaa triplets, with a high proportion of prolines in the Y-position, which have the potential of being hydroxylated by prolyl-4-hydroxylase.\(^73\) Hydroxyproline was found to be the Y
Mutations with predicted changes

UCMD

- Splice site change / in-frame exonic deletion
- Missense change Affecting glycine
- Insertion / genomic deletion / duplication / splice site change causing frameshift and PTC

BM

- Splice site change / in-frame exonic deletion
- Missense change Affecting glycine
- Insertion / duplication / splice site change causing frameshift and PTC

The figure shows the genomic organisation of collagen VI and localisation of genomic changes reported for BM and UCMD to date. The figure is stratified by clinical phenotype.

![Genomic organisation of collagen VI and localisation of genomic changes reported for BM and UCMD to date](image)

Figure 2 Genomic organisation of collagen VI and localisation of genomic changes reported for BM and UCMD to date; modification from Chu et al.61 The triple helical domains contain a single cysteine residue (depicted as "C") which is important for dimer assembly. The localisation of the genomic changes reported for BM and UCMD to date is shown stratified by clinical phenotype.

Figure 3 Schematic model of collagen VI assembly; modification from Furthmayr et al.76 and Zhang et al.84

![Schematic model of collagen VI assembly](image)

Further stabilisation of the dimers may be achieved by supercoiling of the overlapping triple helices. This has been observed by negative staining electron microscopy76 and is further supported by the position of hydrophobic patches along and around the triple helix of the monomers, which—according to Fourier transform calculations—would be buried along the central line of contact of the molecules only in a supercoiled dimer with a pitch of 37.5 nm.85 Transfection experiments have shown that COL6A3 subdomains N10–N6 are not required for the molecular assembly of collagen VI.83,86 However, the role of the C-terminal globular domain of COL6A2 in the proper alignment of tetramers and for heterotopic interactions with other matrix molecules remains unproven.

Outside the cell, tetramers—the secreted form of collagen VI—associate end to end through overlapping N-terminal globular domains to form beaded microfibrils with a distinctive 100 nm periodicity, comprising beaded globular domains separated by short triple helical regions.26–31
<table>
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<tr>
<th>Location and domain</th>
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<th>Predicted consequence</th>
<th>Comments</th>
<th>Phenotype</th>
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<td>p.Gly335_Asp352del</td>
<td>Exon14 skipping; heterozygous change in one three generation family</td>
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<td>Heterozygous change in 1/77 individuals</td>
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All published data adjusted by authors to reference sequences NM_001848 for COL6A1, NM_001849 for COL6A2, and NM_004369 for COL6A3.

*Plus unpublished data.

AD LGMD, autosomal dominant limb girdle muscular dystrophy; BM, Bethlem myopathy.
Collagens undergo various steps of post-translational modification, such as hydroxylation of certain proline and lysine residues and glycosylation of certain hydroxylysine and asparagine residues.70 96 The N-terminal end of α3(VI) has several potential glycosylation sites which could generate additional molecular heterogeneity by attachment of branched oligosaccharides.70 Immuno-electron microscopy studies show that collagen VI forms a highly branched filamentous network in the extracellular matrix94 which encircles interstitial collagen fibres and is particularly abundant close to the cells and in intimate contact with basement membranes surrounding muscle fibres.70,93 In the murine myotendinous junction it has been found to associate with the perimysial lamina of the muscle cells as well as with the inserting tendon collagen fibrils.91 The amino-terminal domain of α1(VI) interacts with the carboxy-terminal globular domain of collagen IV in vitro92 and immunofluorescent labelling of skeletal muscle shows colocalisation of type IV with type VI collagen, thus suggesting that one of the major functions of collagen VI is to anchor the basement membrane to the underlying connective tissue.7 Collagen VI also interacts with several other extracellular matrix constituents in vitro, including the fibrillar collagens I94 and II,95 fibril-associated collagen XIV,96 perlecan,97 and microfibril associated glycoprotein MAGP1, which is found in association with elastin in elastic fibres.98 A further possible role for collagen VI microfibril supramolecular assemblies is as scaffolds for the formation of the structurally critical fibrillar collagen networks through connection with the small proteoglycans decorin and biglycan,99–101 and as fibrillogenesis modulators in proximity to growing fibrils. Apart from these mechanical functions, in vitro experiments also suggest that collagen VI is involved in cell cycle signalling102–104 and contributes to the maintenance of tissue homeostasis. It mediates interactions of cells with the extracellular matrix,105–107 and, through interconnection with the fibronectin microfibrillar system, is implicated in the development of the matrix supramolecular structure.108 In this way the collagen VI network could have an important role in repair processes such as wound healing, as well as in tissue development and architecture.

**COLLAGEN VI MUTATIONS AND MUSCLE DISEASE**

**Mutation detection techniques**

Various mutation detection techniques have been applied to BM and UCMD patients, and the number of reported genetic changes is now in excess of 60 (summary shown in fig 2 and tables 1 and 2). As experience of mutation detection in these genes accumulates, it is clear that polymorphisms, even involving non-synonymous amino acid changes, are common.79 114 Some particular “hot spots” for mutations are beginning to emerge, as is a high frequency of splice site changes, and an enrichment of mutations caused by small in-frame deletions or insertions. It is difficult to be sure about their pathogenicity. As yet, two of these missense mutations (marked with an asterisk in fig 2) have been shown to cosegregate with the phenotype in large multigeneration families and to be absent in 190 healthy control chromosomes.21 120 In addition, one of the latter (marked with a double asterisk) has been shown to interfere with protein folding both by homology modelling and radioimmunoassay data,121 but additional confirmatory data are not available for the remainder of the missense changes; these therefore need to be interpreted with caution.

**Mutations in UCMD**

A large number of the mutations reported for patients with UCMD (10 mutations in 11 kindreds) appear to result in premature termination codons with consequent nonsense mediated mRNA decay and loss of the mutated chain. The premature termination codons occur either by direct introduction of a stop codon at the genomic level,114 127 or through frameshift inducing genomic deletions,114 123 insertions,124 duplications,114 and splice changes.124 125 In addition to five different missense mutations substituting glycine in the triple helical Gly-Xaa-Yaa motif which have been found in seven kindreds,114 eight other missense changes have been reported within the triple helical and C-terminal domains of COL6A2 and the N-terminal domains of COL6A3.118 126 As noted above, where additional confirmatory data are lacking for missense changes they need to be interpreted with caution.

Splice site mutations which cause skipping of COL6A1 exon 14 during pre-mRNA splicing and the consequent in-frame deletion of 18 amino acids from the triple helical domain of the α1(VI) chain form the second most frequent group of mutations in BM. Three different genomic mutations resulting in this missplicing have been identified in six kindreds.79 114 127 The shortened α1(VI) chains allow intracellular monomer formation but lack a unique cysteine and prevent further assembly of the mutated chains into dimers and tetramers, resulting in production of half the normal amount of collagen VI.79 117 The ensuing reduction of collagen VI in the extracellular matrix can be confirmed by immunohistochemical techniques in cultured fibroblasts. Other splice site mutations causing small in-frame deletions or insertions within domains flanking the triple helical domain, such as the N1 domain of COL6A1 or the C1 domain of COL6A2, have also been reported.114 118 Ancillary data are only available for one of these118 and it remains unclear whether their pathogenicity reflects a similar partial dominant negative effect or haploinsufficiency. The latter has been proposed as the pathogenic mechanism for a frameshifting splice site mutation which causes nonsense mediated mRNA decay.119 Missense mutations other than glycine substitutions within the triple helical domain have been reported for 19 kindreds.53 114 126 However, given the highly polymorphic nature of the collagen VI genes (more than 25 non-synonymous polymorphic amino acid changes have been described to date114 131), it is difficult to be sure about their pathogenicity. As yet, two of these missense mutations (marked with an asterisk in fig 2) have been shown to cosegregate with the phenotype in large multigeneration families and to be absent in 190 healthy control chromosomes.21 120 In addition, one of the latter (marked with a double asterisk) has been shown to interfere with protein folding both by homology modelling and radioimmunoassay data,121 but additional confirmatory data are not available for the remainder of the missense changes; these therefore need to be interpreted with caution.

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Splice site mutations which cause skipping of COL6A1 exon 14 during pre-mRNA splicing and the consequent in-frame deletion of 18 amino acids from the triple helical domain of the α1(VI) chain form the second most frequent group of mutations in BM. Three different genomic mutations resulting in this missplicing have been identified in six kindreds.79 114 127 The shortened α1(VI) chains allow intracellular monomer formation but lack a unique cysteine and prevent further assembly of the mutated chains into dimers and tetramers, resulting in production of half the normal amount of collagen VI.79 117 The ensuing reduction of collagen VI in the extracellular matrix can be confirmed by immunohistochemical techniques in cultured fibroblasts. Other splice site mutations causing small in-frame deletions or insertions within domains flanking the triple helical domain, such as the N1 domain of COL6A1 or the C1 domain of COL6A2, have also been reported.114 118 Ancillary data are only available for one of these118 and it remains unclear whether their pathogenicity reflects a similar partial dominant negative effect or haploinsufficiency. The latter has been proposed as the pathogenic mechanism for a frameshifting splice site mutation which causes nonsense mediated mRNA decay.119 Missense mutations other than glycine substitutions within the triple helical domain have been reported for 19 kindreds.53 114 126 However, given the highly polymorphic nature of the collagen VI genes (more than 25 non-synonymous polymorphic amino acid changes have been described to date114 131), it is difficult to be sure about their pathogenicity. As yet, two of these missense mutations (marked with an asterisk in fig 2) have been shown to cosegregate with the phenotype in large multigeneration families and to be absent in 190 healthy control chromosomes.21 120 In addition, one of the latter (marked with a double asterisk) has been shown to interfere with protein folding both by homology modelling and radioimmunoassay data,121 but additional confirmatory data are not available for the remainder of the missense changes; these therefore need to be interpreted with caution.

**Mutations in UCMD**

A large number of the mutations reported for patients with UCMD (10 mutations in 11 kindreds) appear to result in premature termination codons with consequent nonsense mediated mRNA decay and loss of the mutated chain. The premature termination codons occur either by direct introduction of a stop codon at the genomic level,114 127 or through frameshift inducing genomic deletions,114 123 insertions,124 duplications,114 and splice changes.124 125 In addition to five different missense mutations substituting glycine in the triple helical Gly-Xaa-Yaa motif which have been found in seven kindreds,114 eight other missense changes have been reported within the triple helical and C-terminal domains of COL6A2 and the N-terminal domains of COL6A3.118 126 As noted above, where additional confirmatory data are lacking for missense changes they need to be interpreted with caution.

Splice site mutations leading to in-frame exonic deletions as well as in-frame genomic deletions form another very common mutation type in UCMD. To date 12 different mutations, located in the triple helical domains of COL6A1-3 as well as the C-terminal domains of COL6A2, have been reported in 16 kindreds.79 114 122 126 127 A heterozygously occurring de novo large genomic deletion in COL6A1, which causes an in-frame deletion of 33 amino acids near the N-terminus of the triple helical domain, has been reported to result in a classical UCMD phenotype.79 Its mutant α1(VI) chain preserves a unique cysteine important for dimer formation, allowing secretion of abnormal tetramers with a consequent dominant negative effect on microfibrillar assembly. A
<table>
<thead>
<tr>
<th>Location and domain</th>
<th>Nucleotide change</th>
<th>Predicted consequence</th>
<th>Comment</th>
<th>Reference</th>
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<tbody>
<tr>
<td>COL6A1 intron8</td>
<td>TH c.804-857_893+6del99</td>
<td>p.Gly269_Lys301del</td>
<td>Deletion exon9-10; heterozygous change in one individual (de novo)</td>
<td>UCMD 79</td>
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<tr>
<td>COL6A1 exon9</td>
<td>TH c.841 G＞A</td>
<td>p.Gly281Arg</td>
<td>Heterozygous change in 1/77 individuals who is also compound heterozygous for Arg498His in COL6A2</td>
<td>UCMD 114</td>
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<td>COL6A1 exon10</td>
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<td>UCMD 114</td>
</tr>
<tr>
<td>COL6A1 intron12</td>
<td>TH c.957-1+G＞R</td>
<td>p.Gly311_Lys319del</td>
<td>Exon12 skipping; heterozygous change in one individual (de novo)</td>
<td>UCMD 126</td>
</tr>
<tr>
<td>COL6A1 intron27</td>
<td>TH c.1776-1+G＞R</td>
<td>p.Gly581_Asp592del</td>
<td>Exon27 skipping; homozygous change in 1/76 individuals (parents heterozygous)</td>
<td>UCMD 114</td>
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<tr>
<td>COL6A2 exon3</td>
<td>N1 c.688_689 dupAC</td>
<td>p.Ile231ProfsX8</td>
<td>Heterozygous change in 1/77 individuals who is also compound heterozygous for complex insertion/deletion causing exon 27 skipping in COL6A2</td>
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<tr>
<td>COL6A2 intron5</td>
<td>TH c.801+631_882del</td>
<td>p.Gly268_Ile294del</td>
<td>Deletion exon6 and partial deletion of exon7; heterozygous change in one individual (mother mosaic carrier)</td>
<td>UCMD 126</td>
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<tr>
<td>COL6A2 exon6</td>
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<td>p.Gly283Arg</td>
<td>Heterozygous change in 1/78 individuals</td>
<td>UCMD 114</td>
</tr>
<tr>
<td>COL6A2 intron9</td>
<td>TH c.955-2 A＞G</td>
<td>p.Gly319_Lys333del</td>
<td>Exon10 skipping; heterozygous change in 1/78 individuals</td>
<td>UCMD 114</td>
</tr>
<tr>
<td>COL6A2 exon13</td>
<td>TH c.1147_1151 insC</td>
<td>p.Glu386ArgfsX64</td>
<td>Homozygous change in one individual (parents heterozygous)</td>
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<tr>
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<td>TH c.1270-1+G＞C</td>
<td>p.Gly424AlafsX138 and</td>
<td>Heterozygous change in one individual who is also compound heterozygous for splice change causing deletion of exon24 in COL6A2 with consequent frameshift and premature termination codon</td>
<td>UCMD 127</td>
</tr>
<tr>
<td>COL6A2 intron17</td>
<td>TH c.1459-2 A＞G</td>
<td>p.Gly487_Ala495delX8</td>
<td>Missplicing with partial loss of exon18; heterozygous change in 3 individuals; 2/3 are siblings and compound heterozygous for splice change causing deletion of exon24 in COL6A2 with consequent frameshift and premature termination codon</td>
<td>UCMD 124</td>
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<tr>
<td>COL6A2 exon20</td>
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<td>p.Gly531Arg</td>
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<td>UCMD 114</td>
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<tr>
<td>COL6A2 intron23</td>
<td>TH/C1 c.2321-1+G＞C</td>
<td>p.Glu591_Glu605delX148</td>
<td>Deletion exon24 causing frameshift; heterozygous change in one individual who is also compound heterozygous for frameshifting duplication in exon3 of COL6A2 causing premature termination codon (father carrier)</td>
<td>UCMD 125</td>
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<tr>
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<td>p.Leu837ProfsX13</td>
<td>Heterozygous change in one individual who is also compound heterozygous for Leu837Pro (father carrier)</td>
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<tr>
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<td>C1 c.2151 T＞C</td>
<td>p.Glu717Val</td>
<td>Heterozygous change in 1/78 individuals; no confirmatory data</td>
<td>UCMD 114</td>
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<td>C2 c.2319 T＞A</td>
<td>p.Arg777Gln</td>
<td>Heterozygous change in 1/78 individuals; no confirmatory data</td>
<td>UCMD 114</td>
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<tr>
<td>COL6A2 exon27</td>
<td>C1/C2 c.2453-2+G＞G</td>
<td>p.Glu717ValfsX13</td>
<td>Heterozygous change in 1/78 individuals; no confirmatory data</td>
<td>UCMD 114</td>
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<tr>
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<td>C2 c.2689 G＞A</td>
<td>p.Glu897Val</td>
<td>Heterozygous change in 1/78 individuals; no confirmatory data</td>
<td>UCMD 114</td>
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Table 2

<table>
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<th>Predicted consequence</th>
<th>Phenotype</th>
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<td>c.1393 C&gt;T</td>
<td>p.Arg465X</td>
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<td>COL6A3 exon 8</td>
<td>c.3191 G&gt;A</td>
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<td>UCMD</td>
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<tr>
<td>COL6A3 exon 9</td>
<td>c.4184 G&gt;A</td>
<td></td>
<td>UCMD</td>
</tr>
<tr>
<td>COL6A3 exon 11</td>
<td>c.5020 G&gt;A</td>
<td></td>
<td>UCMD</td>
</tr>
<tr>
<td>COL6A3 exon 16</td>
<td>c.6157-9_6177del</td>
<td>Exon16 skipping</td>
<td>UCMD</td>
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<tr>
<td>COL6A3 intron 16</td>
<td>c.6210 G&gt;A</td>
<td>Exon16 skipping</td>
<td>UCMD</td>
</tr>
<tr>
<td>COL6A3 exon 27</td>
<td>c.6816 G&gt;A</td>
<td>Exon27 skipping</td>
<td>UCMD</td>
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</table>

Pathogenicity of mutations and the UCMD carrier conundrum

It is beginning to be possible to draw some conclusions on genotype–phenotype correlations. Specific mutations tend to be strictly associated with either a BM or a UCMD phenotype (Tables 1 and 2). The triple helical glycine substitution Gly290Arg in COL6A1 forms the only exception to this observation: it was found as a heterozygous change in two patients with severe BM as well as two patients with a comparatively mild UCMD phenotype, suggesting there might be a spectrum of collagen VI related disorders rather than two strictly separate entities.

Heterozygous triple helical glycine substitutions are encountered in other collagen disorders such as Ehlers–Danlos syndrome type IV (OMIM 120180) and osteogenesis imperfecta type I (OMIM 166200), where their dominant negative effect has been explained by altered post-translational processing, delayed triple helical monomer folding, or disturbed formation of multimeric assemblies. For collagen VI, glycine substitutions towards the N-terminus of the triple helix have been shown to cause kinking of the tetramers, which reduces their ability to form microfibrils. Only one triple helical glycine mutation has been found in the C-terminal part and is present homozygously in a UCMD patient. Artificially introduced mutations toward the triple helical C-terminus severely impair triple helical monomer association, presumably by interfering with the nucleation of triple helix folding. Mutated chains would not be effectively incorporated into monomers, which should lead to virtual absence of collagen VI in the extracellular matrix when homozygously present, or secretion of half the normal amount of collagen VI if present in a heterozygous state, similar to functional haploinsufficiency. In this context it is interesting to note that virtually no BM mutations (which would be assumed to be dominantly acting) have been documented in the C-terminal part of the triple helix.
Conversely, a large number of recessively acting in-frame deletions in UCMD patients appear to cluster in the C-terminal triple helix which might interfere with monomer formation in a similar way.

It remains intriguing that the heterozygous parents of UCMD patients, in particular parents who carry a single copy of a mutation known to cause nonsense mediated mRNA decay, are clinically unaffected. A study showed that mRNA levels in fibroblasts with a single *COL6A2* nonsense mutation can be reduced to 57–73% of normal controls, but long term collagen VI extracellular matrix deposition is virtually normal.\(^8^4\) If haploinsufficiency does not lead to myopathic symptoms in parents in UCMD patients, it is difficult to understand how it could cause a BM phenotype.\(^1^1^9\) It is tempting to speculate whether phenotypic variation may arise from alternative splicing, modifying polymorphisms, or the influence of other genes yet to be identified but up to now this conundrum has remained unresolved. Alternative splicing is used to explain the surprisingly mild phenotype in a patient with a homozygous nonsense mutation in the N8 domain of *COL6A3*.\(^1^2^2\) For a large number of the in-frame deletions and missense changes the exact pathogenic mechanism has not yet been fully elucidated, but site specific effects impairing particular steps in the complex intracellular and extracellular assembly process of collagen VI are likely to explain the degree of the negative effect of individual mutations.\(^8^6\)\(^1^2^1\)

**COLLAGEN VI PROTEIN EXPRESSION**

Collagen VI immunohistochemistry in BM and UCMD is variable and can show anything from a mild reduction of endomysial/basal lamina collagen VI staining to a complete absence of collagen VI in the extracellular matrix.\(^2^7\)\(^4^7\)\(^1^1^1\) (fig 4B). In BM patients, immunostaining with various collagen VI antibodies in muscle biopsies is usually normal and cannot therefore be used for diagnostic purposes. Deficiency of the basal lamina component laminin β1 in muscle biopsies of adult patients with BM has been reported but is not specific.\(^2^2\)\(^1^3^2\) This phenomenon has not been commonly reported in UCMD, which might in part be related to the patient’s age at muscle biopsy, as secondary laminin β1 deficiency may only become apparent in adulthood.\(^1^3^1\)\(^1^3^4\) If laminin β1 is secondarily deficient, staining is characteristically reduced in the muscle fibre basal lamina but not in the basal lamina of capillaries, suggesting that collagen VI mutations specifically affect the myofibre basal lamina.\(^2^3\)

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**Figure 4** Immunolabelling of collagen VI in skeletal muscle (panels A and B) and cultured dermal fibroblasts (panels C to E). Collagen VI is virtually absent in basement membrane surrounding muscle fibres of a UCMD patient with a homozygous splice mutation causing in-frame deletion in N-terminal triple helical domain of α3(VI) (B) when compared with a normal control (A). Fibroblasts from an unaffected control individual (C), the UCMD patient described above (D), and a BM patient with a heterozygous missense mutation in the N2 domain of α3(VI) (E) were grown in the presence of 50 μg/ml L-ascorbic acid phosphate for five days after confluence. When stained with a collagen VI specific antibody (MAB3303, Chemicon) collagen VI is not detectable in the extracellular matrix of the UCMD patient and appears reduced and less organised in the BM patient (E) when compared with the normal control (C).
Muscle biopsies from UCMD patients do often show complete or partial absence of collagen VI immunolabelling, so this can be very useful diagnostically (fig 4B). One report from Japan, however, found collagen VI to be present in the interstitium but absent from the sarcotekoma in a group of patients with a clinical diagnosis of UCMD by using double immunostaining for collagen VI and IV.135 Electron microscopic findings described a lack of connection between microfibrils in the interstitium and the basal lamina but intriguingly, these investigators were unable to identify mutations in seven of the eight patients they studied. An earlier electronmicroscopic study of collagen VI negative UCMD muscle biopsies described a space between muscle fibres and connective tissue, with folding of the plasma membrane and thickening of the basal lamina. The basal lamina appeared intact in itself, even in degenerating muscle fibres, with disorganised myofibrils, indicating a loose connection between the basal lamina and other extracellular matrix collagens.135 Capillaries in muscle biopsy specimens from UCMD patients have been described as being devoid of collagen VI, with associated capillary fenestration on electron microscopy136; however, in skin biopsies of UCMD patients the papillary dermis and the hair follicles show a reduced amount of collagen VI protein while vessels, peripheral nerves, smooth muscle, and sweat glands show labelling comparable with normal controls.137

**DIAGNOSIS OF COLLAGEN VI RELATED DISORDERS AND THERAPEUTIC CONSIDERATIONS**

Detection of mutations in the three collagen VI genes remains the gold standard for diagnosis. Mutation detection rates are high in genetic counselling settings, but in one high throughput genomic sequencing study of 79 patients reached 66% for BM and 79% for UCMD,138 but seemed much lower in a study of a Japanese cohort of patients.127 137 Owing to the large size of the genes involved, diagnostic mutation analysis is currently problematic. The diagnosis of BM and UCMD depends on the typical clinical features, with the serum creatine kinase concentration usually being normal or only mildly increased. Muscle biopsy shows myopathic or dystrophic changes, with collagen VI immunolabelling of the endomysium and basal lamina usually normal in BM (with the exception of a few cases showing patchy minor abnormalities) and ranging from absent to moderately or markedly reduced in UCMD (fig 4, panel B). Collagen VI immunolabelling studies on dermal fibroblasts appear to be more sensitive than muscle immunohistochemistry and can be a useful adjunct (fig 4, panels C to E). In the past, linkage analysis has also been used for UCMD families,138 but the recent description of de novo dominant mutations causing UCMD139 140 means this can no longer be regarded as a reliable method to exclude collagen VI related disease.

**Genetic counselling**

In fully characterised families genetic counselling is straightforward. BM is inherited in an autosomal dominant manner and UCMD is classically described as an autosomal recessive disorder. However, some caveats have emerged from our better understanding of these disorders: First, distinguishing between BM and UCMD in a neonate may not be easy, as BM can occur de novo113 and may present at birth. Further follow-up should allow the recognition of a milder phenotype; in fact, it is becoming clear that BM and UCMD represent opposite end points of a clinical continuum in which individuals presenting with intermediate phenotypes could be considered to have either “mild UCMD” or “severe BM.” In addition, autosomal dominant inheritance now needs to be considered when counselling families for UCMD. Delineation of a specific mutation which has previously been consistently recognised as being associated with either BM or UCMD may help to resolve some of these counselling issues.

**Prenatal diagnosis**

Prenatal diagnosis for UCMD has been undertaken in a consanguineous family where the disease was consistent with linkage to COL6A3, and collagen VI immunolabelling in the proband’s skeletal muscle was severely reduced.139 Haplotype analysis together with the immunohistochemical absence of collagen VI in chorionic villus samples were used to determine that the fetus was affected, and later on this was confirmed by examining fetal skeletal muscle. For families where the muscle biopsy of the proband shows absence of collagen VI immunolabelling, examination of a chorionic villus biopsy—preferably in conjunction with linkage analysis—thus does offer a potential route for prenatal diagnosis even if the causative mutation in the family is not known.

**Specific therapeutic issues**

Treatment for patients with BM and UCMD is supportive and follows identical principles, but depends in its intensity on the severity of symptoms and the age of onset.

Children with a severe UCMD phenotype require active management as soon as the diagnosis is established, to promote mobility and independence. Early mobilisation in a standing frame is important to achieve upright posture and protect against the development of scoliosis and other contractures. Regular stretching and splinting are used to keep contractures at bay and maintain mobility both for UCMD and BM patients, but there have been no formal studies on the efficacy of these measures. The contractures of UCMD patients in particular tend to be aggressive and may require surgical release on more than one occasion in order to maintain or achieve a certain level of mobility. In BM the contractures may be of a strikingly dynamic nature during early childhood, which makes it advisable to try to delay possible orthopaedic management until established contractures emerge. Scoliosis often develops in UCMD patients in the first or second decade of life and may require active management including spinal surgery to prevent progression.

Respiratory failure is a common complication of UCMD, whereas in BM it appears to be rare and related to more severe weakness in later life. Follow up with regular assessments of respiratory function, including spirometry and overnight pulse oximetry studies, is important for all patients with collagen VI related disorders to detect asymptomatic decline.140 Respiratory support with nocturnal ventilation usually becomes necessary in the first or second decade for UCMD patients and can be effective in reducing symptoms, promoting quality of life, and allowing normal schooling.140 141 In BM, respiratory failure with diaphragmatic involvement may supervene even before loss of ambulation, and symptoms of nocturnal hypoventilation respond well to non-invasive respiratory support such as mask ventilation.140 Prophylaxis of chest infections with influenza and pneumococcal vaccination and physiotherapy, as well as early and aggressive use of antibiotics, may prevent further respiratory problems in both BM and UCMD.140

In addition, feeding difficulties in UCMD patients can manifest as failure to thrive or excessive time taken to finish eating a meal. Consultation with a nutrition specialist may be needed to boost energy intake; for serious problems, feeding by gastrostomy may be the best solution to promote a normal weight gain.

**Potential future therapeutic options**

A collagen VI deficient (Col6a1−/−) mouse model with a muscle histology phenotype resembling BM has been generated.142 Recently, mitochondrial dysfunction was shown to be implicated in the pathogenesis of its myopathic phenotype, with the
muscle ultrastructural defects appearing to be at least partially reversible by treatment with cyclosporin A. These findings clearly have interesting implications with regard to pharmacological treatment options for collagen VI related disorders. However, before embarking on treatment trials based on this single study it will be important to demonstrate that a similar cyclosporin A responsive mitochondrial dysfunction can be demonstrated in humans patients affected by BM or UCMD, and to check whether the mitochondrial dysfunction found in collagen VI deficient mice is specific for this disorder or might be present in mice models of other muscular dystrophies and thus represent a common pathogenic end point.

CONCLUSIONS
The genetics of the collagen VI related muscular dystrophies are complex. Independent description of the two distinct clinical phenotypes, Bethlem myopathy and Ulrich congenital muscular dystrophy, was followed by the discovery that both of these disorders are caused by mutations in collagen VI. Subsequent reports of clinical phenotypes and associated mutations have led to a blurring of the boundaries between these disorders with classical BM and UCMD now forming opposite end points of a phenotypic spectrum. Collagen VI is composed of three different peptide chains which are encoded by three large genes, and its assembly involves several different stages. Different mutations have been shown to have variable effects on protein assembly, secretion, and its ability to form a functioning extracellular network. This multitude of possible mutational mechanisms and modes of inheritance has important consequences for the genetic counseling of patients and their families. Currently no curative therapeutic approaches have reached a clinical level, but supportive treatment can dramatically improve longevity and quality of life.

DATA ACCESS
Accession numbers and URLs for data presented herein are as follows:

- GenBank, http://www.ncbi.nlm.nih.gov/GenBank/ (for sequences of the COL6A1 transcript [accession number NM_001848], the COL6A2 isoforms 2c2a [accession number NM_001849], 2c2a [accession number NM_058174] and 2c2a* [NM_058175] as well as the full length isoform of COL6A3 [accession number NM_004369] and its 4 variant transcripts [NM_057164, NM_057165, NM_057166 and NM_057167])
- Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/(for BM [MIM 158810] and UCMD [MIM 254090])
- http://www-genome.utah.edu/BMD/collagensnp/ (for collagen VI sequence variations)

ACKNOWLEDGEMENTS
We thank Dr Margaret Johnson for providing figures 4A and 4B and Dr Carsten Bönßmann for his general support and help with figures 4C, 4D, and 4E. This work was supported by an MDC (Muscular Dystrophy Campaign) grant to the Newcastle Muscle Centre. AKL gratefully acknowledges funding by a Welcome entry level fellowship and subsequently by a Patrick Berthoud fellowship.

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