The Neuromuscular Differential Diagnosis of Joint Hypermobility

S. DONKEROORT, C.G. BONNEMANN, B. LOEYS, H. JUNGBLUTH, AND N.C. VOERMANS

Joint hypermobility is the defining feature of various inherited connective tissue disorders such as Marfan syndrome and various types of Ehlers–Danlos syndrome and these will generally be the first conditions to be considered by geneticists and pediatricians in the differential diagnosis of a patient presenting with such findings. However, several congenital and adult-onset inherited myopathies also present with joint hypermobility in the context of often only mild-to-moderate muscle weakness and should, therefore, be included in the differential diagnosis of joint hypermobility. In fact, on the molecular level disorders within both groups represent different ends of the same spectrum of inherited extracellular matrix (ECM) disorders. In this review we will summarize the measures of joint hypermobility, illustrate molecular mechanisms these groups of disorders have in common, and subsequently discuss the clinical features of: 1) the most common connective tissue disorders with myopathic or other neuromuscular features: Ehlers–Danlos syndrome, Marfan syndrome and Loeys-Dietz syndrome; 2) myopathy and connective tissue overlap disorders (muscle extracellular matrix (ECM) disorders), including collagen VI related dystrophies and FKBP14 related kyphoscoliotic type of Ehlers–Danlos syndrome; and 3) various (congenital) myopathies with prominent joint hypermobility including RYR1 and SEPN1-related myopathy. The aim of this review is to assist clinical geneticists and other clinicians with recognition of these disorders.

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KEY WORDS: myopathies; hypermobility; inherited connective tissue disorders; extracellular matrix


INTRODUCTION

Inherited connective tissue disorders such as Ehlers–Danlos syndrome (EDS) and Marfan syndrome are characterized by joint hypermobility and fragility of skin, blood vessels, and internal organs. There may also be associated mild-to-moderate muscle weakness, muscle hypoplasia, or hypotonia indicating clinical overlap with a group of inherited myopathies that may also feature joint hypermobility and skin changes and should, therefore, be considered in the differential diagnosis of these disorders.

Inherited myopathies represent a clinical spectrum with significant genetic and phenotypic heterogeneity ranging from severe and sometimes early fatal disorders to relatively mild conditions compatible with near normal life span. Recent advances in the genetic clarification of inherited myopathies have significantly improved our understanding of their pathogenesis and enabled classifications of these conditions based on both the clinical features and the primary genetic and biochemical defects. In addition to the pattern of muscle weakness, variable presence of other clinical findings such as central nervous system or cardiorespiratory...
involvement, cataracts, ophthalmoplegia, myotonia, muscle rippling, contractures, and spine rigidity may assist in defining specific phenotype–genotype correlations. Significant joint hypermobility can be a distinctive clinical feature in its own right and may confuse the differential diagnosis, in particular in patients where muscle weakness is not the most prominent finding at presentation [Voermans et al., 2008a]. Confirmatory genetic diagnosis is important for providing accurate prognosis, management, recurrence risk, genetic counseling, and for the development of therapeutic strategies.

In this review we will summarize the measures of joint hypermobility, illustrate molecular mechanisms shared between these groups of disorders, and subsequently discuss the clinical and genetic features of the: 1) most common connective tissue disorders with myopathic or other neuromuscular features (EDS, Marfan, and Loey–Dietz syndrome); 2) myopathy and connective tissue overlap disorders (“muscle extracellular matrix (ECM) disorders”); and 3) myopathies with prominent joint hypermobility. As such, this review does not cover all neuromuscular disorders with some degree of distal hypermobility (such as spinal muscular atrophy, nemaline myopathy, and certain forms of congenital muscular dystrophy), but rather concentrates on the connective tissue and muscle overlap disorders plus some selected myopathies in which hypermobility is a more consistent feature. The aim is to assist clinical geneticists and other clinicians with the recognition of these disorders.

ASSESSMENT OF JOINT HYPERMOBILITY

Joint hypermobility is defined as abnormally increased active and/or passive range of motion in a joint [Beighton et al., 1998]. Presence of multiple hypermobile joints can be referred to as generalized joint hypermobility and may be associated with recurrent (sub)luxations. When assessing joint mobility, the large physiological range related to sex, age, and race has to be taken into account. In fact, generalized joint hypermobility is the severe end of a spectrum of physiological joint mobility.

So far, the nomenclature and classification of joint hypermobility used in literature is variable: “hypermobility” is the term used in the diagnostic criteria of EDS and Marfan syndrome; in several case reports other terms are used: “hyperlaxity”, “joint laxity” and, even less specifically, “hyperlaxity” and “hyperextensibility.” Furthermore, description of how joint mobility is determined and which joints have been tested is often lacking. This may result in inaccuracy of the clinical description and consequently lead to under-recognition and underestimation of the presence of joint hypermobility in various myopathies [Voermans et al., 2009b] We have, therefore, advocated the use of the term “hypermobility” assessed by a standardized scale, the Beighton and Bulbena scores (Table I) [Bulbena et al., 1992; Beighton et al., 1998].

CLINICAL AND MOLECULAR OVERLAP

The pathophysiology of hypermobility is likely to be multifactorial, comprising factors affecting both dynamic joint function and connective tissue characteristics of the various ECM compartments in muscle, the myotendinous junction, tendon, and joint capsule [Voermans et al., 2008a] as well as the physical properties of the muscle cells themselves. The multifactorial etiology probably explains why joint hypermobility occurs in both myopathies and inherited connective tissue disorders.

Altered tendon and joint capsule structure and function may contribute to joint hypermobility in various myopathies. This point is illustrated by studies in zebrafish demonstrating that loss of selenoprotein-N function causes disruption of both muscle and myoseptum architecture [Deniziak et al., 2007], the latter being the connective tissue layer involved in force transmission through connecting tendons to muscle. Next, type VI collagen is present in bovine tendons, where it may be involved in organizing the ECM of fibrocartilage and provide a survival factor for fibrochondrocytes [Carvalho et al., 2007]; consequently, COL6 mutations may alter tendon structure and function. Furthermore, it has been suggested that RyR1-mediated calcium signaling plays a role in mechano-transduction pathways of fibroblasts in tendon [Wall and Banes, 2005] and hypothetically, RYR1 mutations may thus alter mechanic tendon function of tendon. However, this has not been investigated in detail and further research will be required.

This clinical overlap extends to the molecular level: ECM proteins involved in the pathophysiology of inherited connective tissue disorders (collagens I, III, V, IX, lysylhydroxylase, tenascin-X, fibrillin, fibrulin, elastin, and perlecans) are expressed not only in connective tissue of tendons and joint capsules, but also of muscle (endo-, peri-, and epimysium). Its structure and function may be altered as a consequence of mutations in any of these genes [Voermans et al., 2008a; Hubmacher and Apte, 2013]. Clinicians and researchers dealing with myopathies and inherited connective tissue disorders should be aware of this overlap. Only a multi-disciplinary approach will allow full recognition of the wide variety of symptoms present in the spectrum of ECM defects, which has important implications for scientific research, diagnosis, and for the treatment of these disorders.

Inherited Connective Tissue Disorders With Neuromuscular Features

Ehlers–Danlos syndrome

EDS is a clinically and genetically heterogeneous group of inherited connective tissue disorders characterized by various combinations of generalized joint hypermobility, skin hyperextensibility, and tissue fragility. In 1997, six main EDS types were defined, the hypermobility type, classical type, and vascular type, and the rare kyphoscoliotic type, arthrochalasis type, and dermatosparaxis type EDS (Table II)
TABLE I. Assessment of Joint Hypermobility

Bulbena score Degree of mobility by passive maneuvers in 9 joints.

Total score: 0–10. Hypermobility: score ≥5 (women) and ≥4 (men).

<table>
<thead>
<tr>
<th>Joint</th>
<th>Degree of Mobility</th>
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<tbody>
<tr>
<td>Hypermobility</td>
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<tr>
<td>Beighton score</td>
<td>Degree of mobility by passive maneuvers in 5 joints.</td>
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</table>

The Bulbena score includes one item on the presence of ecchymoses, which are uncommon in myopathies, and may therefore be a reasonable discriminator in differential diagnosis. Furthermore, in younger patients the Beighton score is less reliable and the Bulbena score is more useful.

Goniometer used for measurement of joint mobility.
<table>
<thead>
<tr>
<th>Disorder Mode of inheritance</th>
<th>Protein involved</th>
<th>Gene</th>
<th>Muscle involvement</th>
<th>Hypermobility/Dislocation/Contractures</th>
<th>Associated symptoms</th>
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<tbody>
<tr>
<td>Inherited connective tissue disorders with neuromuscular features</td>
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</tr>
<tr>
<td>Classic type (I/II) AD</td>
<td>Collagen V</td>
<td>COL5A1/A2</td>
<td>Muscle hypotonia, delayed gross motor development, fatigue</td>
<td>Generalized joint hypermobility with recurring joint dislocations (shoulder, patella, temporomandibular joints)</td>
<td>Skin hyperextensibility, easy bruising, velvety skin, widening of scars</td>
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<tr>
<td>Unknown</td>
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<td>Hypermobility type (III) AD</td>
<td>Tenascin-X</td>
<td>TNXB</td>
<td>Musculoskeletal pain</td>
<td>Generalized joint hypermobility with recurring joint dislocations (shoulder, patella, temporomandibular joints)</td>
<td>Easy bruising, velvety skin</td>
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<tr>
<td>Unknown</td>
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<tr>
<td>Vascular type (IV) AD</td>
<td>Collagen III</td>
<td>COL3A1</td>
<td>Tendon and muscle rupture</td>
<td>Distal joint hypermobility (hands/fingers), tendon and muscle rupture</td>
<td>Thin, translucent skin, extensive bruising, arterial/intestinal/uterine fragility or rupture, characteristic facial appearance, acrogeria, clubfoot, varicose veins, arteriovenous, carotid-cavernous fistula, pneumo(hemo) thorax, gingival recession</td>
</tr>
<tr>
<td>Kyphoscoliotic type (VIA) AR</td>
<td>Lysyl hydroxylase</td>
<td>PLOD</td>
<td>Severe muscle hypotonia at birth, delayed gross motor development</td>
<td>Distal joint hypermobility</td>
<td>Scoliosis, scleral fragility and rupture of the ocular globe, arterial rupture, osteopenia, marfanoid habitus, microcornea</td>
</tr>
<tr>
<td>Musculocontractural (VIB) AR</td>
<td>Dermatan-4-sulfotransferase</td>
<td>CHST14</td>
<td>Severe muscle hypotonia at birth, delayed gross motor development</td>
<td>Distal joint hypermobility</td>
<td>Scoliosis</td>
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<tr>
<td>Disorder Mode of inheritance</td>
<td>Protein involved</td>
<td>Gene</td>
<td>Muscle involvement</td>
<td>Hypermobility/Dislocation/Contractures</td>
<td>Associated symptoms</td>
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<tr>
<td>Aarthrochalasia type (VIIA) AD Collagen I</td>
<td></td>
<td>COL1A1</td>
<td>Polyhydramnios, bilateral clubfoot, congenital hypotonia, delayed gross motor development</td>
<td>Arthrogryposis, bilateral hip dislocation, and hypermobility of the shoulders, elbows, and knees</td>
<td>Facial dysmorphic features, skin hyperextensibility</td>
</tr>
<tr>
<td>EDS with progressive kyphoscoliosis, myopathy and hearing loss FK506-binding protein 14</td>
<td></td>
<td>FKB1P14</td>
<td>Severe muscle hypotonia at birth, delayed gross motor development</td>
<td>Distal joint hypermobility</td>
<td>Scoliosis, sensorineuronal hearing loss</td>
</tr>
<tr>
<td>Tenascin-X deficient type AR Tenascin-X</td>
<td></td>
<td>TNXB</td>
<td>Muscle weakness</td>
<td>Generalized joint hypermobility</td>
<td>Skin hyperextensibility, easy bruising, velvety skin</td>
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<tr>
<td>Marfan syndrome AD Fibrillin</td>
<td></td>
<td>FBN1</td>
<td>Muscle hypoplasia, muscle cramps, easy fatigability, generalized muscle weakness</td>
<td>Distal joint hypermobility (DIP/PIP/MCP joints, wrists), contractures (elbows)</td>
<td>Ascending aorta dilatation and rupture, arachnodactyly, scoliosis/spondylolisthesis, pectus excavatum, high palate, typical facial appearance</td>
</tr>
<tr>
<td>Loeys–Dietz syndrome AD</td>
<td></td>
<td>TGFB1/2 SMAD3, TGFBR1/2</td>
<td>Muscle hypotonia</td>
<td>Joint hypermobility, contractures (camptodactyly, club foot)</td>
<td>Hypertelorism, cleft palate/bifid uvula, widespread arterial and aortic aneurysm with arterial tortuosity</td>
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<td>Myopathy and connective tissue overlap syndromes</td>
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<tr>
<td>Ullrich Congenital myopathy (UCMD) AD/AR Collagen VI</td>
<td></td>
<td>COL6A1/A2/A3</td>
<td>Hypotonia, delayed motor milestones, profound muscle weakness. Onset in 1st decade; wheelchair bound.</td>
<td>Distal joint hypermobility, (MCP joints, PIP, and DIP joints), contractures (proximal joints)</td>
<td>Early respiratory failure, dermal features (hyperkeratosis, soft velvety skin, and a tendency to keloid or &quot;cigarette paper&quot; scar formation)</td>
</tr>
<tr>
<td>Bethlem myopathy (BM) AD Collagen VI</td>
<td></td>
<td>COL6A1/A2/A3</td>
<td>Hypotonia, delayed motor milestones, reduced fetal movements, mild muscle weakness (proximal &gt; distal, extensors &gt; flexors) Onset in 1st or 2nd decade</td>
<td>Distal joint hypermobility (DIP joints), flexion contractures (fingers, wrists, elbows, and ankles)</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>Disorder Mode of inheritance</td>
<td>Gene</td>
<td>Muscle involvement</td>
<td>Hypermobility/ Dislocation/ Contractures</td>
<td>Associated symptoms</td>
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<tr>
<td>Collagen VI look-alike syndromes AR</td>
<td>Candidate regions: ITGA9, ACVR2B, LAMR1, 3p23-p21</td>
<td>Congenital hypotonia, delayed motor milestones, reduced fetal movements, generalized muscle weakness (proximal &gt; distal)</td>
<td>Distal joint hypermobility, proximal contractures</td>
<td>Early respiratory failure, mild to moderate mental retardation, decreased pulmonary vital capacity, scoliosis</td>
<td></td>
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<tr>
<td>Unknown/AR</td>
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<td>Candidate proteins: Integrin alfa 9, Activin A, IIB receptor, Laminin receptor 1</td>
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<tr>
<td>Collagen XII related myopathy / EDS overlap syndrome AR</td>
<td>COL12A1</td>
<td>Generalized muscle weakness Mild facial weakness, and absent deep tendon reflexes Inability to stand or ambulate independently</td>
<td>Widespread joint hypermobility at birth combined with proximal contractures and progressive kyphoscoliosis</td>
<td>High arched palate</td>
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<td>Collagen 12</td>
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<tr>
<td>Myopathies with striking joint hypermobility</td>
<td>SEPN1</td>
<td>Hypotonia, reduced fetal movements, delayed motor milestones, muscle weakness (axial &gt; proximal &gt; distal)</td>
<td>Distal joint hypermobility (MCP); to a lesser degree in all other limb joints</td>
<td>Respiratory failure &gt;&gt; muscle weakness, spinal rigidity, scoliosis, secondary cardiac (right ventricular) involvement</td>
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<tr>
<td>Multi-minicore disease (MmD) AR</td>
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<td>Selenoprotein N “classic MmD”</td>
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<tr>
<td>AR Ryanodine receptor “MmD subgroups”</td>
<td>RYR1</td>
<td>Hypotonia, reduced fetal movements, delayed motor milestones, muscle weakness</td>
<td></td>
<td>(axial &gt; proximal &gt; distal) Subgroup with severe hip girdle weakness. Subgroup with marked distal weakness and wasting, predominantly the hands</td>
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<tr>
<td>Distal joint hypermobility (MCP), to a lesser degree in all other limb joints</td>
<td>Ophthalmoplegia, mild respiratory involvement, mild facial muscle weakness</td>
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</table>
A clinically distinct form results from tenascin-X (TNX) deficiency due to recessive mutations in the TNXB gene [Schalkwijk et al., 2001]. The list of other apparently more rare subtypes is gradually expanding (Table III) [Castori and Voermans, 2014; Sobey, 2014]. Hypermobility is present in all forms of EDS but mostly pronounced in the hypermobility, classical, and TNX-deficient type. In the vascular type, joint hypermobility is usually limited to the digits, whereas in the kyphoscoliotic type both fingers, wrists, toes, and ankles are severely affected. Proximal contractures may develop later in the course of the disease in this latter type (Fig. 1).

EDS is associated with a variety of neuromuscular features, initially documented in case reports and generally considered secondary to exercise avoidance prompted by joint hypermobility [Bertin et al., 1989; Beighton et al., 1998; Palmeri et al., 2003]. Muscle hypotonia, delayed motor milestones, fatigue, musculoskeletal pain, and muscle rupture are included in the diagnostic criteria [Beighton et al., 1998].

Over the last years these neuromuscular findings have been acknowledged as a primary aspect of the EDS phenotype. The first physiological study of muscle weakness in EDS was performed by Bilkey et al. in 1981 demonstrating that muscle weakness was primarily due to reduced joint proprioception and the tendency for minor subluxations, which in combination was thought to result in a different learned motor pattern [Bilkey et al., 1981]. In 2009, Voermans et al. performed a prospective study in 40 genetically or biochemically confirmed patients with EDS (vascular, classical, myopathic and joint hyperlaxity and contractures [LGMD2E+]) showing that mild-to-moderate neuromuscular involvement is common in these disorders (Voermans et al., 2009) and may include complaints of myalgia and limited exercise endurance, fatigue, and mild-to-moderate muscle weakness. Nerve conduction studies demonstrated reduced muscle fiber conduction velocity and decreased sensory responses.

<table>
<thead>
<tr>
<th>Disorder Mode of inheritance involved</th>
<th>Protein involved</th>
<th>Muscle involvement</th>
<th>Hypermobility/Dislocation/Contractures</th>
<th>Associated symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central core disease (CCD) AD/(AR)</td>
<td>RYR1</td>
<td>Muscle weakness with prominent involvement of hip girdle and axial muscles, mild facial weakness, rare bulbar involvement.</td>
<td>Generalized hypermobility, congenital hip dislocation common</td>
<td>(Mitral valve prolapse), malignant hyperthermia</td>
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<tr>
<td>Ryanodine receptor</td>
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<tr>
<td>Other core myopathies</td>
<td>MYH7 TTN</td>
<td>Progressive muscle weakness Mild facial weakness</td>
<td>Distal contractures (MYH7) Pronounced distal hypermobility (TTN)</td>
<td>Severe respiratory impairment (MYH7)</td>
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<tr>
<td>Myosin heavy chain 7 Titin</td>
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<tr>
<td>Limb girdle muscular dystrophy 2E with joint hyperlaxity and contractures (LGMD2E+) AR β-sarcoglycan Congenital myasthenic syndrome</td>
<td>SCGB:</td>
<td>Progressive limb girdle muscle weakness, onset 0–5 years, delayed motor milestones, mild facial weakness</td>
<td>Distal joint hypermobility (MCP and PIP joints), contractures (DIP joints)</td>
<td>Tachycardia, arrhythmia, chest pain, scoliosis, nocturnal dyspnea</td>
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</table>

AD: autosomal dominant inheritance; AR: autosomal recessive inheritance.

[Beighton et al., 1998] A clinically distinct form results from tenascin-X (TNX) deficiency as recently reviewed by Beighton et al. [2014]. The list of other apparently more rare subtypes is gradually expanding (Table III) [Castori and Voermans, 2014]. Hypermobility is present in all forms of EDS but mostly pronounced in the hypermobility, classical, and TNX-deficient type. In the vascular type, joint hypermobility may develop later in the course of the disease. In the kyphoscoliotic type, joint hypermobility is usually confined to the kyphoscoliotic type, whereas in the kyphoscoliotic type, joint hypermobility is usually confined to the kyphoscoliotic type. In the kyphoscoliotic type, joint hypermobility is usually confined to the kyphoscoliotic type.
an associated axonal sensory polyneuropathy in a minority of patients, and needle electromyography showed mild myopathic features with a mixed pattern of smaller and broader motor unit action potentials. Muscle biopsies showed mild myopathic changes (increased internal nuclei and fiber size variation) in 25% of EDS patients, with a lower density and shorter length of collagen fibrils in the ECM on electron microscopy (EM). Creatine kinase (CK) was only mildly elevated in 10% of patients (range 40–681 U/L). These clinical and histopathological findings confirmed that mild-to-moderate neuromuscular involvement is part of the EDS spectrum and that a muscle biopsy to investigate a co-existing myopathy or neuropathy is not necessarily indicated if otherwise diagnostic EDS features are present.

Recently, a patient with TNX-deficient EDS presenting with a predominantly myopathic phenotype was reported [Penisson-Besnier et al., 2013]. Clinical features included progressive axial and proximal limb muscle weakness, subclinical cardiac involvement, minimal skin hyperextensibility, no joint abnormalities, and a history of easy bruising. Muscle biopsy revealed mild myopathic changes, but no dystrophic features were observed, corresponding to previous reports [Voermans et al., 2007b]. The absence of Ullrich congenital muscular dystrophy (UCMD) or Bethlem myopathy (BM) myopathy features (no typical contractures, no skin features, only mild muscle MRI features of collagen VI myopathies, and no fibrosis on muscle biopsy) appeared to suggest that the different ECM protein defects have different impact on muscle structure: collagen VI deficiency gives rise to progressive increase of endomysial connective tissue, whereas TNX deficiency produces muscle “softness” but no endomysial fibrosis. This points to a different role of these and other ECM proteins implicated in EDS in muscle ECM development and functioning (Tables II and III).

Furthermore, EDS may present in the neonatal period with significant hypotonia and should, therefore, be considered in the initial differential diagnosis of the floppy infant syndrome [Yis et al., 2008; Voermans et al., 2008b]. Among the different subtypes of EDS, congenital muscle involvement is probably most pronounced in the kyphoscoliotic type (EDS VIA), due to autosomal-recessive (AR) PLOD1 mutations (missense and splice site mutations, deletions, and duplications). PLOD1 encodes lysyl hydroxylase, a catalyzing enzyme essential for the formation of hydroxylysine in collagens and collagen-like proteins, which are critical for the binding of carbohydrates, and therefore the stability of collagen cross links. Infants with this EDS type can be born with significant hypotonia, failure to thrive, delayed motor development, wrist, and hip dislocation, congenital, or early onset kyphoscoliosis. Other manifestations include ophthalmologic findings (scleral fragility, rupture of the ocular globe, microcornea) joint and skin hypermobility, marfanoid habitus, and contractures. Vascular complications including stroke and spontaneous arterial rupture have been reported [Brinckmann et al., 1998; Ha et al., 1994].

Additionally, recessive loss of function mutations in CHST14, encoding dermatin-4-sulfotransferase 1, result in muscularcontractural EDS (EDS kyphoscoliotic type VIB) with a clinical spectrum that includes significant congenital hypotonia, gross motor delay, muscle hypoplasia with progressive joint hypermobility, as well as progressive early onset kyphoscoliosis, joint contractures, club feet, characteristic facial
features, thin, and bruisable skin, atrophic scarring, and variable ocular involvement (Fig. 2) [Shimizu et al., 2011; Dundar et al., 2009]. Congenital bilateral thumb adduction may be a distinctive clinical finding [Kosho et al., 2010; Miyake et al., 2010; Malfait et al., 2010]. In one family autosomal recessive mutations in the dermatan sulphate epimerase (DSE) were found in a family with multisystemic musculocontractural, type 2 [Muller et al., 2013].

Mutations in FKBP14 cause a subtype of EDS that resembles CHST14 disorders. Patients present with severe congenital muscle hypotonia, progressive scoliosis, joint hypermobility, and hyperelastic skin, but unlike patients with CHST14, these patients also have sensorineural hearing impairment [Baumann et al., 2012; Murray et al., 2014]. CK levels ranged from normal to mildly elevated (range 60–300 IU/L), nerve conduction studies are normal, electromyography is normal in infancy but may show a myopathic pattern in adolescence and adulthood. Muscle biopsies may show a spectrum of histopathological features ranging from non-specific increased fiber size variability to more pronounced changes with fiber atrophy and proliferation of fatty tissue. Electron microscopy may show focal rearrangement of myofibrils with irregular Z-lines. Muscle MRI was normal in one patient but showed fatty replacement of muscle tissue, predominantly affected the rectus femoris, and vastus lateralis with relative sparing of the adductor compartment. FKBP14 is an ER protein that may have a catalytic function through accelerating cis-trains isomerization of peptidyl-propyl bonds. FKBP14 loss-of-function fibroblast
analysis showed disturbed distribution and impaired assembly of several ECM components specifically collagen type I and III and fibronectin.

Dominant de-novo mutations in \textit{COL1A1} are a rare cause of EDS and have been reported in a girl with severe EDS VIa of the arthrochalasia type [Nuytinck et al., 2000; Giunta et al., 2008]. Pregnancy in this case was complicated by polyhydramnios and bilateral clubfoot noted on prenatal ultrasound. At birth she was noted to have hypotonia, arthrogryposis, bilateral dislocation and hypermobility of the shoulders, elbows, and knees. At age 1 year she had facial dysmorphic features, delayed motor milestones, severe hypotonia, and skin and joint hypermobility. Genetic analysis of the \textit{COL1A1} gene showed a heterozygous missense affecting the splice acceptor site resulting in skipping of exon 6. The heterozygous Arg134Cys mutation in \textit{COL1A1} mutation has been identified in two unrelated patients with an EDS/osteogenesis imperfect (OI) overlap condition characterized by osteopenia, soft, and doughy skin with hyperextensibility, infrarenal aortic, and arterial aneurysms, joint hypermobility, pectus excavatum and easy bruising [Malfait et al., 2013]. Interestingly, mutations in the Gly-X-Y triplet repeat of \textit{COL1A1} gene result in osteogenesis imperfecta, indicating a wide phenotypical spectrum. These collagen I-related disorders all have a combination of joint hypermobility and muscle hypotonia and delay in motor development.

The study of Voermans et al. also demonstrated a correlation between residual TNX levels and the degree of neuromuscular involvement, pointing at a dose-effect relation between the ECM defect and muscle dysfunction. This phenomenon was subsequently supported by physiological studies in TNXB-deficient patients and \textit{tnxb} knock-out mice [Voermans et al., 2009c; Huijing et al., 2010; Gerrits et al., 2013]. These studies showed a reduction of force transmission between individual muscles and the surrounding fascia (“myofascial force transmission”) probably due to increased compliance (i.e., reduced elasticity) of the connective tissue surrounding the individual muscles. As a result, TNX-deficient muscles appear less capable of transmitting forces in other ways than via myotendinous force transmission and therefore function more independently. Such altered function probably requires adapted patterns of muscular coordination to allow effective physiological movements [Huijing et al., 2010]. The increased compliance of muscle ECM may also play a role in muscle weakness in other EDS types.

\textit{Marfan syndrome}

Marfan syndrome is characterized by ocular, skeletal, and cardiovascular manifestations and due to dominantly inherited mutations in the fibrillin-1 (\textit{FBN1}) gene. \textit{FBN1} encodes fibrillin-1, an ubiquitously expressed major component of ECM microfibrils with an important role for elastin deposition in elastic fibers. Variable expression in

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{finger_extensor.png}
\caption{Finger extensor weakness in hands of 25-year-old (A, B) and 18-year-old (F) female patients with Musculocontractural (VIB) type EDS. Proximal and distal muscle atrophy in arms and lower legs (C), dropping feet (E) and hyperkeratosis pillari (G) in the same patients. The first patient has been reported in [Voermans et al., 2012] at age of 23.}
\end{figure}
Marfan syndrome is the rule, but complete non-penetration has only rarely been documented. About 25% of mutations are dominantly acting de novo mutation. Joint hypermobility is usually most pronounced in distal joints and often accompanied by arachnodactyly (Fig. 3), but (congenital) joint contractures, particularly of the elbow, also occur frequently [Loeys et al., 2010].

Although Marfan himself considered muscle involvement integral to his syndrome, neuromuscular features have received little attention until recently. Gradually, muscle fatigue and, to a lesser extent, muscle weakness, muscle hypoplasia, myalgia, and cramps are being recognized as neuromuscular Marfan features [Grahame and Peyritz, 1995; Behan et al., 2003; Jones et al., 2007].

A systematic observational study on neuromuscular features in 10 patients with Marfan syndrome showed that various neuromuscular symptoms occur frequently and consist of a mild myopathy or polyneuropathy or both, which was more pronounced in the older patients [Voermans et al., 2009a]. The four oldest patients in this cohort (>50 years) reported muscle weakness and had functional impairments. Five patients had a mild-to-moderate reduction of vibration sense. Nerve conduction studies showed a mild axonal sensory polyneuropathy in four patients. The muscle biopsies obtained in two patients showed myopathic changes in a 56-year-old female patient, and was normal in a 32-year-old male. In addition, signs of a lumbosacral radiculopathy were found in four patients, which were associated with dural ectasia and spinal meningeal cysts. Although these findings were obtained in two patients showed myopathic changes in a 56-year-old female patient, and was normal in a 32-year-old male. In addition, signs of a lumbosacral radiculopathy were found in four patients, which were associated with dural ectasia and spinal meningeal cysts. Although these findings were found in a small cohort of patients, they indicate a need to increase the awareness of neuromuscular involvement and radicular symptoms that may become more pronounced over time in Marfan syndrome patients [Voermans et al., 2009a].

The abundant expression of fibrillin-1 in the skeletal muscle endomysium and perimysium suggests a causal link between muscle symptoms and the FBN1 mutation [Zhang et al., 1995]. In addition to its structural role in ECM, fibrillin-1 is also involved in regulating TGF-β signaling via LTBP binding and thus influences muscle function. Increased TGF-β signaling has been suggested to suppress the muscle regenerating capacity of the satellite cells [Hubmacher and Apte, 2013].

Loeys–Dietz syndrome (LDS)

LDS is a Marfan-related condition first described by Loeys et al. [2005]. The patients present with a typical triad of hypertelorism, cleft palate/bifid uvula with widespread arterial/aortic aneurysm and arterial tortuosity. Skeletal features shared with Marfan syndrome include pectus deformity, scoliosis, arachnodactyly but also joint hypermobility with camptodactyly, and club foot have described. Cervical spine instability has also been observed frequently [Erkula et al., 2010]. The condition is caused by mutations of genes encoding for components of the TGF-β signaling, such as TGF-β receptors 1 and 2 [Loeys et al., 2005], the actual cytokines TGFβ2 [Lindsay et al., 2012] and TGFβ3 [Bertoli-Avella et al., 2014] or the downstream effector SMAD3 [van de Laar et al., 2011], and these are now classified as LDS types 1–5 [MacCarrick et al., 2014], all with some degree of muscle involvement such as hypotonia, reduced muscle mass, and delayed motor development.

Myopathy and Connective Tissue Overlap Disorders

Collagen VI-related dystrophies and myopathies (COL 6-RD)

Collagen VI is an important ECM component and forms a microfibrillar network that is closely associated with the muscle cell and the surrounding basement membrane. It is also found in the interstitial space of many other tissues including tendon, skin, cartilage, and intervertebral discs. In muscle it is predominantly produced by the interstitial fibroblasts. The exact mechanism and the downstream effects of collagen VI deficiency on muscle cells are incompletely understood and may involve myofiber apoptosis as well as impaired autophagy [Grumati et al., 2010]. In tendon, collagen VI is presumably synthesized by the resident tendon fibroblast population, and assumes a distinctly pericellular orientation around these cells, and as such it may represent a survival factor for these cells.

Autosomal dominant (AD) and recessive (AR) mutations (including larger deletions) in each of the three collagen 6 genes COL6A1, COL6A2, and COL6A3 cause a spectrum of myopathies associated with a joint hypermobility, contractures, and characteristic skin findings. Dominant mutations in the COL6 genes affect collagen VI microfibril formation, resulting in disengagement of collagen VI from the basal lamina. Severe de novo dominant-negative COL6 mutations lead to UCMD, whereas the intermediate and BM phenotype can be caused by less severe dominant-negative mutations, or less commonly by COL6 recessive mutations [Bönennmann, 2011]. Recessive null mutations lead to a complete absence of collagen VI in the matrix and a severe UCMD phenotype. Approximately 5–10% of patients with a clinical diagnosis of COL6-RD do not have a mutation in COL6A1–3 and it is possible that their disease is caused by an unknown gene. Two related but less frequent phenotypes have been added to this spectrum: an AD limb-girdle muscular dystrophy phenotype and an AR myosclerosis phenotype reported in one family with mutations in COL6A2 [Merlini et al., 2008; Scacheri et al., 2002]; however, joint hypermobility is not a prominent feature in these latter two phenotypes.

The clinical hallmarks of UCMD are profound muscle weakness of early onset with respiratory insufficiency as disease progresses, with proximal joint contractures and striking hypermobility of mostly distal joints (toes, ankles, fingers, and wrists) [Lampe and Bushby, 2005]. Posteriorly protruding calcanei are commonly seen (Fig. 4). Affected children typically either
never achieve the ability to walk independently or do so only for a limited period of time. Congenital hip dislocations and kyphosis may be present at birth, and spinal rigidity, scoliosis, and variable proximal contractures develop early in the course of the disease. The distal hypermobility can gradually give way to marked long finger flexion contractures and tight Achilles tendons. Respiratory failure in the first or second decade is a common cause of death unless treated with nocturnal respiratory support. Cardiac involvement has not been documented to date [van der Kooi et al., 2006].

In BM, muscle weakness has a predominant proximal pattern and a milder course. Although often mildly symptomatic at birth or in infancy, symptoms typically manifest within the first or second decades, with frequently a history of neonatal hypotonia or torticollis, delayed motor milestones, or even decreased fetal movements [Jobis et al., 1996]. On the other hand some adult patients are only very mildly affected and remain unaware of weakness [Lampe and Bushby, 2005]. In childhood, the contractures may be preceded by hypermobility in the same joint, and be of a strikingly dynamic nature, appearing, and disappearing in various joints [Jobis et al., 1996]. However, nearly all patients eventually show flexion contractures of the fingers, wrists, elbows, and ankles, and those may contribute to the degree of overall disability as much as the associated weakness. Strikingly, hypermobility of distal interphalangeal joints can remain present (Fig. 5). Progression is slow and occasionally results in the patient being wheelchair-bound only after 25–40 years [Lampe and Bushby, 2005]. Respiratory failure can be part of the clinical spectrum and may even occur in ambulatory patients [Foley et al., 2013]. To date, there has been no evidence of cardiac involvement in BM [van der Kooi et al., 2006].

COL6-RD patients across the spectrum have distinct patterns of muscle involvement on MRI: the vastus muscles often show a rim of abnormal signal at the muscle periphery, with relative sparing of the central part (giving it a striped appearance), whereas the rectus femoris often shows a central area of abnormal signal known as the “central shadow” phenomenon [Merlini et al., 2008]. At calf level appearances are more variable but a significant proportion of patients with both BM and UCMD also show a rim of abnormal signal at the periphery of soleus and gastrocnemii [Mercuri et al., 2005; Bönnemann et al., 2014]. Muscle biopsy in UCMD patients demonstrates variable pathology, ranging from non-specific mild myopathic changes in particular early in the course to a more dystrophic appearance [Schessl et al., 2008]. Early findings emphasize atrophic rather than dystrophic changes. Additionally, variation in fiber size, type 1 fiber predominance, an increase in endomysial connective tissue, increased numbers of internal nuclei, and focal areas of necrosis, along with other evidence of muscle fiber

Figure 3. Hypermobility of distal interphalangeal joints and wrist in a 28-year-old male Marfan patient (A, B); arachnodactyly with positive thumb sign and wrist sign in a 27-year-old male Marfan patient (lower images (C, D) [Voermans et al., 2009].

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regeneration such as the presence of fibers containing fetal myosin can be found [Pepe et al., 2002]. Immunofluorescence analysis for collagen VI localization in UCMD biopsies may show dramatic reduction or absence of immunofluorescence in severe recessive patients, or a mislocalization in the dominant negative cases. The latter is best seen in staining protocols incorporating double labeling of the basement membrane (using for instance collagen IV or perlecan as a marker) along with collagen VI. In BM, muscle biopsy generally demonstrates a non-specific myopathy with fiber-size variation, few necrotic and regenerative fibers, and a mild increase in connective tissue. Standard collagen VI immunohistochemistry is often uninformative but may show mislocalization of collagen VI on double staining. In contrast, immunofluorescence labeling of collagen VI in skin fibroblast cultures allows detecting even very subtle alterations in collagen VI in COL6-RD patient fibroblasts and is highly predictive of COL6A mutations [Ishikawa et al., 2002; Lampe and Bushby, 2005].

**Collagen-6 look-like disorders**

Mercuri et al. [2004] reported five cases with congenital muscular dystrophy (CMD) associated with short stature, proximal contractures, rigidity of the spine, and distal joint hypermobility as well as early respiratory failure and mild to moderate cognitive disability (CMD with joint hyperlaxity). Hypermobility was present in distal fingers, toes, and ankles but the expression of collagen VI was confirmed to be normal on muscle biopsies in all five patients; in addition, in one informative family linkage to any of the three COL6 gene loci could be excluded [Mercuri et al., 2004]. In addition, Tetreault et al. [2006] reported 14 cases affected by autosomal recessive congenital muscular dystrophy (CMD) with distal joint hypermobility. All patients presented with muscle hypotonia at birth, generalized slowly progressive muscle weakness, and proximal contractures predominantly affecting ankle, knees, and shoulders co-existing with distal hypermobility, mainly observed in the fingers, wrists, toes, elbows, and cervical spine. No spinal rigidity was observed, but a mild to severe scoliosis was a frequent finding. Pulmonary vital capacity was usually diminished. CK was normal or only mildly increased, with muscle biopsy showing only non-specific myopathic features. Genetic studies excluded mutations in the three genes coding for collagen VI subunits and suggested linkage to a region on chromosome 3p23–21. This linkage was not found in cases with a similar phenotype in other centers, indicating genetic heterogeneity [Tetreault et al., 2006].

**Collagen XII related myopathy/EDS overlap syndrome**

Recent findings show that collagen XII mutations cause an EDS/myopathy overlap syndrome associated with muscle weakness and joint hypermobility in mice and humans [Hicks et al.,...
Collagen XII, the largest member of the fibril-associated collagens with interrupted triple helix (FACIT) family, assembles from three identical α-chains encoded by the COL12A1 gene. Collagen XII binds to collagen I-containing fibrils via its collagenous domain, whereas its large non-collagenous arms interact with other matrix proteins such as TNX. In dense connective tissues and bone, collagen XII is thought to regulate organization and mechanical properties of collagen fibril bundles [Chiquet et al., 2014].

The EDS/myopathy overlap phenotype was observed in two non-related families with a homozygous recessive loss-of-function mutation and a de novo dominant mutation in collagen XII (COL12A1), respectively [Zou et al., 2014]. The two siblings who were homozygous for the loss-of-function mutation showed widespread joint hypermobility at birth combined with generalized muscle weakness, proximal contractures, and progressive kyphoscoliosis. Both siblings had mild facial weakness, high palate, and absent deep tendon reflexes. Motor development was delayed, both siblings were able to get into sitting position, but unable to stand or ambulate independently. CK and nerve conduction velocities were normal, the muscle biopsy was myopathic with variability in fiber diameter, there was no evidence of degeneration or regeneration.

A de novo missense mutation in COL12A1 was identified in a boy with weakness and joint hyperlaxity and proximal joint contractures, noted in the first year of life. He had delayed motor development and started walking shortly before age 2 years. He had mild kyphosis; his contractures improved over time. Muscle ultrasound of the thigh showed increased echogenicity. Nerve conduction studies were normal. Muscle biopsy was consistent with a myopathy, there was mild variability in fiber diameter without evidence of degeneration or regeneration.

Around the same time, Hicks et al. [2014] identified dominantly acting COL12A1 missense mutations in five individuals from two families with a clinical phenotype resembling Bethlem myopathy. Symptoms started in childhood with generalized weakness with some improvement in adolescence followed by some progression of weakness later in life. Patients had predominant proximal weakness, contractures, hypertrophic scarring, and joint hyperlaxity. Pulmonary function testing was reduced in some. CK levels ranged from normal to moderately elevated (1800 U/L). MRI imaging showed severe atrophy of the rectus femoris and selective involvement of the femoral quadriceps, adductor and the medial gastrocnemium. A central shadow, typically seen in COL6-RD was not observed. One of the COL12A1 mutation identified was a substitution of a conserved glycine residue in the Gly-X-Y motif of the triple helix domain, a common hotspot.
for mutations in collagen disorders in general [Butterfield et al., 2013]. Dermal fibroblasts showed intracellular retention of Collagen XII and a subtle reduction in TNX [Hicks et al., 2014]. A mouse model with inactivation of the COL12A1 gene shows decreased grip strength, delay in fiber-type transition and deficiency in passive force generation. Corresponding to studies of TNX deficiency, these observations indicate a role for a matrix-based passive force-transducing elastic element in the evolution of weakness in these disorders. In general, the EDS/myopathy overlap phenotype emphasizes the emerging importance of the muscle ECM in the pathogenesis of muscle disease [Voermans et al., 2008a; Zou et al., 2014].

Myopathies With Striking Joint Hypermobility

**RYR1 and SEPN1 related myopathies**

The congenital myopathies with cores—Multi-minicore Disease (MmD) and Central Core Disease (CCD)—are among the most common congenital myopathies [Jungbluth et al., 2011; Maggi et al., 2013]. They are clinically and genetically heterogeneous and associated with variable characteristic abnormalities on oxidative stains that give rise to the cores. MmD and CCD due to the skeletal muscle ryanodine receptor (RyR1) gene (RYR1) mutations may be associated with marked generalized hypermobility not infrequently resulting in joint dislocations [Gamble et al., 1988], whereas MmD due to recessive mutations in the selenoprotein N (SEPN1) gene often features distal hypermobility in the upper limbs and may give rise to “marfanoid” features.

The skeletal muscle RyR1 plays a crucial role in excitation-contraction (E–C) coupling by releasing Ca²⁺ from sarcoplasmic reticulum (SR) stores. Two major hypotheses have been formulated concerning the pathogenesis of RyR1-related core myopathies, depletion of sarcoplasmic reticulum calcium stores with resulting increase in cytosolic calcium levels (“leaky channel” hypothesis), and disturbance of excitation-contraction coupling (E–C uncoupling hypothesis) [Trevos et al., 2008]. Whilst primary RyR1 malfunction seems to be the main molecular mechanism underlying dominantly inherited RyR1-related myopathies, recessive RyR1-related myopathies appear to be more variable with loss of calcium conductance, probably mediated by marked RyR1 protein reduction, a relatively common observation [Wilmshurst et al., 2010; Klein et al., 2012; Zhou et al., 2013].

Selenoprotein-N, is a glycoprotein localized in the endoplasmic reticulum and involved in various antioxidant defense systems and several metabolic pathways. SEPN1 is highly expressed during development [Castets et al., 2009] with a more specific role in myogenesis suggested by abundant expression in fetal muscle precursor cells and the observation of disturbed satellite cell function in the sepn1 −/− knockout mouse [Castets et al., 2011]. The close functional and spatial relationship between selenoprotein N and RyR1 reported in animal models [Denziak et al., 2007] and a structural motif similar to those found in calcium-binding proteins [Moghadaszadeh et al., 2001] suggest a role in calcium homeostasis, suggesting a molecular basis for the clinico-pathological overlap between SEPN1- and RyR1-related myopathies.

**Multiminicore disease (MmD)**

The “classic” (but probably not most common) phenotype of MmD is associated with autosomal-recessive mutations in SEPN1 and is characterized by predominantly axial muscle weakness, spinal rigidity, early scoliosis, and respiratory impairment. Some patients may exhibit a “marfanoid” habitus with arachnodactyly but ocular and cardiovascular features of Marfan syndrome are typically absent. In contrast, autosomal-recessive mutations in the skeletal muscle ryanodine receptor (RYR1) gene have been associated with a wider range of clinical features comprising external ophthalmoplegia, distal weakness and wasting or predominant hip girdle involvement resembling CCD [Ferreiro et al., 2012]. In the latter forms, there may also be a histopathologic continuum with CCD due to dominant RYR1 mutations, reflecting the common genetic background [Zhou et al., 2007]. Although multiminicore are a classic pathophysiological finding of RYR1 and SEPN1-related myopathy, biopsies can show a spectrum of findings consistent with congenital myopathies [Bharucha-Goebel et al., 2013].

All phenotypes may be associated with contractures (either arthrogryposis in early-onset forms or predominant Achilles tendon tightness of later onset in milder cases) and/or joint hypermobility, mostly pronounced in the hands (Fig. 6). If present, distal hypermobility tends to be more severe in patients with recessive RYR1 mutations than in those with SEPN1 mutations, but may be present in both and is often associated with atrophy of intrinsic hand muscles, hand hypotonia, and moderate weakness. Patellar and knee dislocations may be a feature [Gamble et al., 1988]. In the majority of patients, weakness is static or only slowly progressive, with the degree of respiratory impairment being the most important prognostic factor particularly in SEPN1-related forms.

The diagnosis of MmD is based on the presence of suggestive clinical features and the finding of multiple cores on histochemical muscle biopsy stains. Muscle MRI may aid genetic testing as patterns of selective muscle involvement are distinct depending on whether the mutations are in the SEPN1 [Mercuri et al., 2010] or the RYR1 gene [Jungbluth et al., 2004; Klein et al., 2011]. Mutational analysis of the RYR1 or the SEPN1 gene will be required to confirm the genetic diagnosis. Management is mainly supportive and in particular has to address the risk of marked respiratory impairment in SEPN1-related MmD and the possibility of malignant hyperthermia susceptibility in RYR1-related forms for the patient and carrier relatives.

**Central core disease (CCD)**

Central core disease (CCD) is caused mainly by dominant but also less
commonly by recessive *RYR1* mutations and typically presents in infancy with hypotonia or developmental delay and predominantly hip girdle and axial muscle weakness. Facial, bulbar, and respiratory involvement is minimal or absent. Progression is slow and almost all patients achieve the ability to walk independently, except the most severe neonatal cases, and those with very severe orthopedic complications; however, marked clinical variability, even within the same family, has been reported. Orthopedic complications are common in CCD and comprise congenital dislocation of hips, scoliosis, and foot deformities including talipes equinovarus and pes planus [Gamble et al., 1988]. Many patients have striking joint hypermobility, occasionally associated with patellar instability. Achilles tendon tightness occurs but other contractures are rare.

The term CCD refers to the characteristic, well-defined reduction of oxidative enzyme activity in the center of the muscle fiber reflecting the absence of mitochondria in this area. Serum CK is usually normal in CCD but may occasionally be mildly elevated, mainly in patients with additional exertional myalgia and muscle cramps. Muscle ultrasound shows a striking increase in echo intensity but relative sparing of the rectus femoris within the thigh, corresponding to a similarly consistent pattern of selective muscle involvement on muscle MRI, which may assist in differentiating *RYR1*-related CCD from other myopathies with overlapping histopathological features.

Genetic diagnosis is established by sequencing of the *RYR1* gene, bearing in mind that not infrequently two dominant *RYR1* mutations may be running in the same family and that *RYR1* variants of uncertain significance are not uncommon [Klein et al., 2012]. Accurate genetic diagnosis and familial segregation testing is of importance so appropriate precautions can be taken for malignant hyperthermia. The functional consequences of autosomal-recessive and dominant *RYR1* mutations have been outlined in the paragraph on MmD above.

**Other core myopathies**

Cores on muscle biopsy are a non-specific finding and apart from *SEPN1-* and *RYR1*-related myopathies have been recognized in a number of other genetic backgrounds. The most common forms among this group are *MYH7*-related MmD [Cullup et al., 2012] often associated with distal contractures as seen in other *MYH7*-related myopathies [Lamont et al., 2014] and *TTN*-related core myopathies [Chauveau et al., 2014] with highly variable clinic-pathological presentation, including pronounced distal hypermobility [Oates et al., 2014]. In contrast to the *SEPN1-* and *RYR1*-related forms,
primary cardiac involvement is very common in MYH7- and TTN-related core myopathies [Romero et al., 2014].

*Limb girdle muscular dystrophy 2 E with joint hyperlaxity and contractures (LGMD2E +)*

Kaindl et al. reported a family with a severe and progressive limb-girdle muscular dystrophy with joint hypermobility, contractures, and cardiopulmonary symptoms comprising chest pain, tachycardia, arrhythmias, and dyspnea [Kaindl et al., 2005]. Muscle weakness presented in the first decade, with delayed motor milestones and a progressive Duchenne-like muscular dystrophy including facial weakness, resulting in loss of ambulation around the age of 10 years. Hypermobility was most pronounced in proximal interphalangeal joints and, to a lesser extent, in knees and elbows. CK levels were elevated to 50 times of normal values. Genetic analysis revealed a homozygous -sarcoglycan gene, and hypotonia. However, since immunohistochemical studies showing complete absence of sarcoglycan A and B immunoreactivity. Some degree of joint hypermobility in these patients may be related to the muscle weakness and hypotonia. However, since β-sarcoglycan is not expressed in tendons or connective tissue, and hypermobility is not a common feature in other patients with β-sarcoglycan mutations, joint hypermobility, and contractures may also result from a contiguous gene syndrome.

**CONCLUDING REMARKS**

This review has focused on the overlap between connective tissue disorders and the congenital myopathies associated with joint hypermobility and skin features, emphasizing that some of the primary myopathies are an important consideration in the differential diagnosis of generalized joint hypermobility. Findings of joint hypermobility and muscle involvement should be evaluated in context of the patient’s overall phenotypic presentation to allow for accurate diagnosis.

The pattern of distribution of joint hypermobility, its dynamic nature as well as the co-existence of hypermobility with dislocations and contractures occur both in the myopathies and inherited connective tissue disorders discussed. Congenital myopathies are more often accompanied by distal rather than generalized hypermobility (distal and proximal interphalangeal and metacarpophalangeal joints of hands, distal interphalangeal joints of feet, wrists, and ankles), and one frequently finds congenital hip dislocation (in particular in COL6 and RYR1 related conditions. Another very distinctive feature in COL6 related dystrophies is a coexistence of pronounced distal joint hypermobility with prominent and progressive joint contractures, which typically occur in the shoulders, elbows, hips, knees, and Achilles tendons, but also in the finger flexors, so that there both evidence of joint hyper mobility as well as contractures in the hands and fingers.

We expect that this review will assist clinical geneticists and other specialists without primary neuromuscular expertise to better recognize these myopathies among patients presenting with joint hypermobility and muscle weakness, which is of importance for the clinical assessment but also (and increasingly) for the interpretation of whole exome sequencing results of uncertain significance.

**REFERENCES**


