Classification, nosology and diagnostics of Ehlers-Danlos syndrome

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Abstract
Ehlers-Danlos syndrome (EDS) comprises a clinically and genetically heterogeneous group of heritable connective tissue disorders which has as cardinal features varying degrees of skin hyperextensibility, joint hypermobility, easy bruising and skin fragility. The 2017 New York nosology distinguishes 13 types of EDS, which all, except hypermobile EDS, have a known molecular basis. Hypermobile EDS is recognized as a common and often disabling disorder, incorporating benign joint hypermobility syndrome. EDS needs to be differentiated from other connective tissue disorders, in particular Marfan syndrome, Loeys-Dietz syndrome and cutis laxa. The frequent types of EDS can be diagnosed after careful history taking and clinical examination, but for definitive diagnosis, molecular confirmation is needed in all types. Management for EDS patients preferably is provided by multidisciplinary teams in expertise centres. After diagnosing EDS, genetic counselling is an essential part of the management of patients and their family.

Keywords: Ehlers-Danlos syndrome; classification; diagnosis

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INTRODUCTION
EDS comprises a clinically and genetically heterogeneous group of heritable connective tissue disorders (HCTD), mainly characterized by a variable degree of generalized joint hypermobility, skin hyperextensibility, easy bruising and skin fragility. In his classical monograph on EDS, published in 1970, Beighton described 5 EDS types: I = gravis (severe), II = mitis (mild), III = hypermobility, IV = ecchymotic, and V = X-linked.1 The Berlin classification listed 11 EDS types.2 Revision became necessary because of new biochemical, molecular and clinical data, leading to the Villefranche nosology of 1997, in which 6 EDS types were recognized.3 New clinical and molecular data required another revision, which was initiated during the Ehlers-Danlos Society International Symposium in New York, May 2016, the results of which have been published in the March 2017 issue of the American Journal of Medical Genetics Part C, Seminars in Medical Genetics.

The most striking changes were:
- incorporating EDS types which were published since the Villefranche nosology, leading to a total number of 13 types,4
- deciding - not unexpectedly though - that EDS hypermobility type and benign joint hypermobility syndrome (BJHS; also called joint hypermobility syndrome or hypermobility syndrome) are in fact part of one and the same clinical spectrum ranging from apparently symptomatic generalized joint hypermobility to the more disabled individuals fitting the new diagnostic criteria. These new criteria are more strict than the Villefranche criteria and the Brighton criteria for BJHS in order to define a homogeneous phenotype for management and scientific purposes. Its name is hypermobile EDS.

It always has been, and still is, a challenge to classify individual patients in one of the existing EDS types. Often this is not possible and therefore there is still room for new types. This is, among other things, due to:
- the clinical overlap between many of these EDS types

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- absence of a pathogenic variant in any of the known EDS associated genes in an important proportion of EDS patients.
- the presence of associated features which do not fit into one of the existing types.
- the absence of a laboratory test for hypermobile EDS.

EDS is not a rare disorder; the prevalence is estimated to be about 1:5000. The hypermobile type - by far the most common - and the classical type comprise more than 90% of all cases.\

**CLASSIFICATION AND NOSOLOGY**

The New York classification is based on clinical, biochemical and molecular data. The major clinical manifestations of EDS need some clarification, while in table 2, EDS types are grouped according to underlying genetic and pathogenic mechanisms; OMIM numbers are added.

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Type I (gravis) and type II (mitis)</td>
<td>Classical type</td>
<td>Classical EDS eEDS</td>
<td>AD</td>
<td>Major: COL5A1, COL5A1 Rare*: COL3A1 c.934C&gt;T, p.(Arg312)</td>
<td>Type V collagen Type I collagen</td>
</tr>
<tr>
<td>Vascular type</td>
<td>Vascular EDS eEDS</td>
<td>AD</td>
<td>Major: COL5A1 Rare: COL1A1 c.9534C&gt;T, p.(Arg312) Cys) c.1720C&gt;T, p.(Arg574Cys) c.3227C&gt;T, p.(Arg1093Cys)</td>
<td>Type III collagen Type I collagen</td>
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<td>Hypermobility type</td>
<td>Hypermobile EDS hEDS</td>
<td>AD</td>
<td>Unknown</td>
<td>Unknown</td>
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<td>Type VIIa and B</td>
<td>Arthrochalasia type</td>
<td>Arthrochalasia EDS dEDS</td>
<td>AD</td>
<td>COL1A1, COL1A2</td>
<td>Type I collagen</td>
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<tr>
<td>Type VIIc</td>
<td>Dermatosparaxis type</td>
<td>Dermatosparaxis EDS dEDS</td>
<td>AR</td>
<td>ADAMTS2</td>
<td>ADAMTS-2</td>
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<td>Type VIIa</td>
<td>Kyphoscoliotic type</td>
<td>Kyphoscoliotic EDS kEDS</td>
<td>AR</td>
<td>PLOD1 FKBP14</td>
<td>LH1 FKBP22</td>
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<tr>
<td>Type VIB</td>
<td>Brittle cornea syndrome BCs</td>
<td>AR</td>
<td>ZNF469 PRDM5</td>
<td>ZNF469 PRDM5</td>
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<td>Type VIB</td>
<td>Spondyloepiphyseal dysplasia EDS spEDS</td>
<td>AR</td>
<td>B4GAL37 B3GALT6 SLC39A13</td>
<td>b4GalT7 b3GalT6 ZIP13</td>
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<td>Type VIB</td>
<td>Musculocontractural EDS mcEDS</td>
<td>AR</td>
<td>CHST14 DSE</td>
<td>DISt1 DSE</td>
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<tr>
<td>Type VIB</td>
<td>Myopathic EDS mEDS</td>
<td>AD/ AR</td>
<td>COL12A1</td>
<td>Type XII collagen</td>
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<td>EDS VIII</td>
<td>Periodental EDS pEDS</td>
<td>AD</td>
<td>C1R C1S</td>
<td>C1r C1s</td>
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</tbody>
</table>

**Table 1** Classification of Ehlers-Danlos syndrome (adapted from)

In clinical practice, the clinical manifestations guide the choice for further investigations. The major clinical manifestations of EDS need some clarification, however.

Skin hyperextensibility should be tested at specific sites, e.g. the volar side of the non-dominant forearm or the dorsum of the hand by pulling up the skin until resistance is felt. In contrast to cutis laxa, a group of clinically and genetically heterogeneous disorders characterised by redundant, sagging and inelastic skin, with or without joint hypermobility, in EDS the skin snaps back after release. The upper limit of normal for the forearm and dorsum of the hand is about 1 1/2 cm. In young children, it is difficult to assess hyperextensibility due to the abundance of subcutaneous fat. Skin hyperextensibility can also be assessed at the dorsal aspect of the elbow in 90° flexion, where the upper limit of normal is 3 cm. Joint hypermobility is scored using the Beighton mobility scale (table 3). In the New York nosology, a score of 5/9 or more defines generalized hypermobility in both sexes, though it is known that joint mobility depends, apart from age, family and ethnic background, also on gender. Since laxity decreases with age, patients with a Beighton score >5/9 may be considered positive.

* EDS classical type with (propensity to) arterial rupture.

In clinical practice, the clinical manifestations guide the choice for further investigations. The major clinical manifestations of EDS need some clarification, however.

Based on their historical observations (five-point questionnaire = 5PQ; see footnote with table 4). For the diagnosis of hypermobile EDS different age and sex specific cut-off points were proposed (see table 4).
children under the age of about 5 years, the Beighton scale is less useful.

Generalised hypermobility is not rare: 5-10% of mainly female – secondary school age Caucasian children is hypermobile and this percentage is higher in Asian populations. Easy bruising is seen as spontaneous ecchymoses, frequently recurring in the same bodily regions, of which long-term signs are often visible as brownish discoloration (haemosiderin), in particular on knees and shins. If it is the predominant presenting sign, child abuse and bleeding disorders need to be considered first.

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**Table 2** EDS grouping according to underlying genetic and pathogenetic mechanisms (adapted from*"

<table>
<thead>
<tr>
<th>Berlin or earlier name</th>
<th>Villefranche name</th>
<th>New York name</th>
<th>OMIM</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>GROUP A: Disorders of collagen primary structure and collagen processing</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>EDS I</td>
<td>Classical type</td>
<td>Classical EDS (cEDS)</td>
<td>130000</td>
<td>COL5A1</td>
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<td>EDS II</td>
<td>Vascular type</td>
<td>Vascular EDS (vEDS)</td>
<td>130010</td>
<td>COL3A1</td>
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<td>EDS IV</td>
<td>Arthrochalasia type</td>
<td>Arthrochalasia EDS (aEDS)</td>
<td>130060</td>
<td>Type I collagen</td>
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<tr>
<td>EDS VIIC</td>
<td>Dermatosparaxis type</td>
<td>Dermatosparaxis EDS (dEDS)</td>
<td>225410</td>
<td>ADAMTS2</td>
</tr>
<tr>
<td>Cardiac-valvular EDS</td>
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<td>Cardiac-valvular EDS (cvEDS)</td>
<td>225320</td>
<td>Type I collagen</td>
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<tr>
<td>GROUP B: Disorders of collagen folding and collagen cross-linking</td>
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<td></td>
<td></td>
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<tr>
<td>Ocular-scoliotic EDS</td>
<td>Kyphoscoliotic type</td>
<td>Kyphoscoliotic EDS (kEDS-PLOD1)</td>
<td>225400</td>
<td>PLOD1</td>
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<tr>
<td>----</td>
<td>----</td>
<td>Kyphoscoliotic EDS (kEDS-FKBP14)</td>
<td>614557</td>
<td>FKBP14</td>
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<tr>
<td>GROUP C: Disorders of structure and function of myomatrix, the interface between muscle and Extracellular Matrix</td>
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<td>----</td>
<td>----</td>
<td>Classical-like EDS (cLEDSS)</td>
<td>606408</td>
<td>TNXB</td>
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<td>Myopathic EDS (mEDS)</td>
<td>616471</td>
<td>COL12A1</td>
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<tr>
<td>GROUP D: Disorders of glycosaminoglycan biosynthesis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDS progeroid type 1</td>
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<td>Spondylolophytic EDS (sEDS-B4GALT7)</td>
<td>130070</td>
<td>B4GALT7</td>
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<tr>
<td>EDS progeroid type 2</td>
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<td>Spondylolophytic EDS (sEDS-B3GALT6)</td>
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<td>B3GALT6</td>
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<td>Adducted thumb-clubfoot syndrome</td>
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<tr>
<td>Musculocontractual type EDS Kosho type</td>
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<tr>
<td>D4ST1 deficient EDS</td>
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<td>----</td>
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<td>Musculocontractual EDS (mEEdS-DCHST14)</td>
<td>601776</td>
<td>CHST14</td>
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<td>Musculocontractual EDS (mEEdS-DSE)</td>
<td>615539</td>
<td>DSE</td>
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<tr>
<td>GROUP E: Disorders of complement pathway</td>
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<tr>
<td>EDS VIIII</td>
<td>Periodontitis type</td>
<td>Periodontal EDS (pEDS)</td>
<td>130080</td>
<td>C1R, C1S</td>
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<tr>
<td>GROUP F: Disorders of intracellular processes (provisional)</td>
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<tr>
<td>Spondylochondrodysplastic EDS</td>
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<tr>
<td>Brittle cornea syndrome</td>
<td></td>
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<tr>
<td>Unresolved form of EDS</td>
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<tr>
<td>EDS III</td>
<td>Hypermobility type</td>
<td>Hypermobile EDS (hEDS)</td>
<td>130020</td>
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</table>

**Table 3** Beighton mobility scoring scale*

<table>
<thead>
<tr>
<th>Joint</th>
<th>Negative</th>
<th>Unilateral</th>
<th>Bilateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passive dorsiflexion of the 5th finger &gt; 90°</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Passive flexion of thumbs to the forearm</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hyperextension of the elbows &gt; 10°</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hyperextension of the knees &gt; 10°</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Forward flexion of the trunk with knees fully extended and palms resting on the floor</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Maximum total score</strong></td>
<td><strong>9</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* a score of 5/9 or more defines generalized joint hypermobility for both sexes (for hypermobile EDS age and sex related cut-off points are used; see table 4)
and papyraceous appearance. Internal organs like arteries, lungs, intestines, liver, spleen and uterus may also show fragility, predominantly in the vascular type.

Some features are regularly observed, but are not criteria of generalised hypermobility syndromes. One example is the presence of all 3 major criteria, i.e. skin hyperextensibility, generalized joint hypermobility and easy bruisability and a family history compatible with autosomal recessive inheritance. It is characterised by generalized hypermobility, with a remarkable laxity of finger joints. In contrast with the classical type, its inheritance is autosomal recessive, so most cases are sporadic and some occur in sibships. It is due to tenascin-X deficiency. In serum, tenascin-X is completely absent and mutation analysis of the TNX-B gene reveals bi-allelic mutations.

The cardiac valvular EDS is rare. Apart from typical EDS features, it is associated with severe aortic and/or mitral valve insufficiency, necessitating valve replacement at relatively young age. Minimal diagnostic criteria are the presence of severe progressive cardiac-valvular problems, family history compatible with AR inheritance plus either one other major criterion and/or at least 2 minor (for details see table 4). The inheritance is autosomal recessive. It is due to homozygous or compound heterozygous COL1A2 null mutations.

The vascular EDS is the most severe form of EDS. Minimal diagnostic criteria are the presence of a family history of vascular EDS, arterial rupture/dissection <40 years, unexplained sigmoid colon rupture or spontaneous pneumothorax in the presence of other features consistent with vascular EDS. These and a combination of minor criteria warrant verifying diagnostic tests, i.e. DNA analysis (for details see table 4). Diagnosis in children is difficult, particularly in the absence of a family history. The vascular type is inherited in an autosomal dominant fashion. Arterial rupture is the most common cause of sudden death and has its peak incidence in the 3rd or 4th decade. Acute abdominal and flank pain is a common presentation of an arterial or intestinal rupture and needs urgent investigation and treatment. Frank et al. showed that the type of COL3A1 mutation is associated with the phenotype and severity: patients with glycine substitutions, splice-site mutations and in-frame insertions–deletions have a more severe phenotype, including digestive events, compared to e.g. mutations leading to non-glycine missense variants or haplo-insufficiency, due to a null allele. The latter may delay onset of complications by almost 2 decades. A recent study showed that vEDS is characterized by a high frequency of de novo pathogenic variants, while parental mosaicism was rare.

For women with the vascular type, pregnancy and delivery pose specific risks, which warrant preconceptional counselling with an experienced obstetrician and clinical geneticist. There is considerable clinical overlap between the vascular type and Loeys-Dietz syndrome type 1 and 2 (OMIM 609192 and 610168 respectively), which are due to TGFBR1 (type 1) and TGFBR2 (type 2) mutations. Also other aortic aneurysm syndromes, such as Marfan syndrome, Thoracic Aortic Aneurysm and Dissection (TAAD), annulo-aortic ectasia should be included in the differential diagnosis.

The hypermobile EDS, incorporating BJHS, is dominated by generalized joint hypermobility and its possible sequelae, in particular chronic pain, which can be severe and invalidating, and possibly early osteoarthritis. As said before, the new diagnostic criteria are more strict than the Villefranche criteria and...
the Brighton criteria. The clinical diagnosis of hypermobile EDS needs the simultaneous presence of 3 criteria: criterion 1 = generalized joint hypermobility, criterion 2 = 2 or more of the features A, B and C (A = systemic manifestations of a more generalized connective tissue disorder; B = positive family history; C = musculoskeletal complications) and criterion 3 = absence of unusual skin fragility and exclusion of alternative diagnosis (for details see table 4). Recently, also cardiovascular dysautonomia (mainly postural tachycardia syndrome = POTS), functional gastrointestinal manifestations, sleep disturbance, fatigue, depression and anxiety disorders have been attributed to hypermobile EDS, but these are at the moment not sufficiently sensitive nor specific. Basically, there is no confirmative laboratory test for the hypermobility type, meaning that it is a purely clinical diagnosis. In 2015, Syx et al. reported linkage to chromosome 8p22-8p21.1 in a 3 generation Belgian family with EDS hypermobility type, whereby whole exome sequencing revealed a possibly involved gene. Up to now, BJHS was considered a separate entity with its own diagnostic criteria. It was already argued earlier that the hypermobility type and BJHS are in fact one and the same disorder with variable expression. Arguments put forward for this were among others the fact that haplo-insufficiency of TNX-B, assessed as about half of the normal activity of tenascin-X in blood, and/or heterozygosity for a pathogenic TNX-B mutation, is found both in cases with EDS hypermobility type and in cases in whom BJHS is the more likely diagnosis. Also, a changing phenotype from one diagnosis into the other in one individual and in some pedigrees the occurrence of both diagnoses argued for this statement.

Castori et al. proposed a framework for the classification of joint hypermobility and related syndromes.

The arthralgasia EDS is also rare, but diagnosable at birth. Minimal criteria suggestive for arthralgasia EDS are congenital bilateral hip dislocation plus either skin hyperextensibility or severe generalized joint hypermobility with multiple dislocations/subluxations and at least 2 other minor criteria (for details see table 4). It is inherited in an autosomal dominant fashion. It is due to specific mutations in COL1A1 or COL1A2. Larsen syndrome, which also features congenital luxations, should be in the differential diagnosis.

The dermatosparaxis EDS derives its name from a similar phenotype and biochemical defect in cattle, sheep, and other animals. It is the EDS type which has the closest resemblance to cutis laxa. However, in cutis laxa there is neither fragility nor bruising. Its mode of inheritance is autosomal recessive. It is one of the rarest of all types and since only very few cases have been described, possibly this type is characterised by other - as yet unrecognised - features. Recently, Van Damme et al. expanded the phenotype and suggested new diagnostic criteria. The New York nosology requires for its diagnosis extreme skin fragility with congenital or postnatal skin tears AND characteristic craniofacial features plus either 1 other major and/or 3 minor criteria (for details see table 4). It is due to bi-allelic mutations in ADAMTS2. The mode of inheritance is autosomal recessive.

The kyphoscoliotic EDS is a rare but severe form of EDS, manifesting itself often at or shortly after birth. The presence of congenital muscle hypotonia AND congenital or early onset kyphoscoliosis plus either generalized joint hypermobility and/or 3 minor criteria (either general or PLOD1 and FKBP14 gene-specific) warrants laboratory testing. Kyphoscoliotic EDS is genetically heterogeneous and can be caused by mutations in PLOD1 and FKBP14. Laboratory tests should start with measurement of the urinary lysyl and hydroxy-lysyl pyridinoline ratio. An increased ratio has a very high degree of sensitivity and specificity for PLOD1 mutations, but not for FKBP14 mutations (for details and molecular tests: see table 4). The mode of inheritance is autosomal recessive. Because of severe hypotonia, patients very often undergo a full scale neuromuscular work-up, including a muscle biopsy before the diagnosis is established. The differential diagnosis comprises all other causes of severe hypotonia, including neonatal Marfan syndrome.

The even rarer brittle cornea syndrome resembles the kyphoscoliotic type, but is generally milder. Minimal diagnostic criteria are thin cornea with or without rupture plus either at least one other major criterion and/or 3 minor criteria (for details see table 4). It shows a normal urinary lysyl and hydroxy-lysyl pyridinoline ratio, and is characterised by mutations in the genes ZNF469 or PRDM5.

Spondylo dysplastic EDS is genetically heterogeneous and is due to bi-allelic mutations in either B4GALT7 (former name progeroid type 1), B4GALT6 (former name progeroid type 2) or SLC39A13 (former name spondylochoreidysplastic type). There is considerable overlap with kyphoscoliotic EDS. Minimal diagnostic criteria are short stature AND muscle hypotonia plus characteristic radiographic abnormalities and at least 3 other minor criteria (general or gene-specific; see table 4).

The urinary lysyl and hydroxylysyl pyridinoline ratio is moderately increased (to approximately 1 compared to normal values of ~ 0.2) with HLPC for SLC39A13 mutations. Van Damme et al. described recently 12 patients with bi-allelic B3GALT6 mutations.

The musculocontractural EDS is due to bi-allelic mutations in either CHST14 gene (type 1) or more rarely DSE gene (type 2) and has also considerable clinical overlap with the kyphoscoliotic type. Uehara et al. described spinal involvement in 12 patients with CHST14 related mcEDS. Minimal diagnostic criteria are at birth or in early childhood congenital multiple contractures AND characteristic craniofacial features, while in adolescence and adulthood these are congenital multiple contractures AND characteristic cutaneous features (for details see table 4).

Myopathic EDS is caused by heterozygous or bi-allelic mutations in COL12A1. Minimal diagnostic criteria are congenital muscle hypotonia and/or muscle atrophy that improves with age plus either one other major criterion and/or three minor criteria (for details see table 4). The phenotype highly overlaps with collagen VI type related myopathies, i.e. Bethlem myopathy and Ullrich Congenital Muscular Dystrophy.

The periodontal EDS has some overlap with the classical type, but has progressive and aggressive
periodontitis as a distinguishing feature.\textsuperscript{13} Minimal diagnostic criteria are severe, intractable periodontitis of early onset (childhood or adolescence) OR lack of attached gingiva plus at least 2 other major criteria and one minor criterion (for details see table 4). In 2016, it was found that gain-of-function mutations in the \textit{CIR} gene or the \textit{CIS} gene, encoding serine proteinases, cause periodontal EDS.\textsuperscript{38} Recently, leukencephalopathy and peri-implant disease were described as additional features of PEDS.\textsuperscript{39,40}

In 2016, bi-allelic \textit{AE BP1} mutations were described in an autosomal recessive EDS variant, featuring joint hypermobility with joint dislocations, hyperextensible, translucent and redundant skin, poor wound healing with abnormal scarring, easy bruising and gastrointestinal, urogenital, cardiovascular and skeletal abnormalities. Its features overlap with several EDS types, particularly cEDS, mcEDS and spEDS. So far, 8 patients with bi-allelic \textit{AE BP1} mutations have been described. \textit{AE BP1} encodes ACLP, that associates with collagens in the extracellular matrix (ECM) and is highly expressed in collagen rich tissues like skin, vasculature and connective tissues.\textsuperscript{41,42,43,44} In OMIM it can be found under 618000, named EDS classic-like, 2. This new EDS variant is not added in any of the tables 1, 2, and 4.

The former EDS type V (X-linked) has been described in only 2 families and is not any longer accepted as belonging to the EDS spectrum; the same holds true for the former fibronec
tin deficient type X, familial articular hypermobility EDS XI and \textit{Filamin A} related EDS with heterotopia. The former type IX is an X-linked cutis laxa disorder and is renamed occipital horn syndrome; it is due to mutations in the gene \textit{ATP7A}, the same gene as is mutated in Menkes syndrome (disorder of copper metabolism).

For further reading, the excellent reviews by Malfait et al. and Byers and Murray are highly recommended.\textsuperscript{4,45} The whole March 2017 issue of the American Journal of Medical Genetics Part C, Seminars in Medical Genetics provided a very good update not only about EDS nosology and diagnostic criteria, but also about management aspects of the various types of EDS. Management for EDS patients preferably is provided by multidisciplinary teams in expertise centres. However, in a recent literature study concerning clinical practice guidelines specifically addressed to EDS the total absence of such guidelines was noted and many clinician and patient unmet needs were identified.\textsuperscript{46}

Joint hypermobility is a symptom of a large variety of syndromes. Among these, one finds - not surprisingly - other heritable connective tissue disorders like cutis laxa, osteogenesis imperfecta, Stickler syndrome, Loeys-Dietz syndrome and Marfan syndrome, but also skeletal dysplasias, inborn errors of metabolism, neuromuscular disorders, chromosomal abnormalities and syndromes like Larsen syndrome, Fragile X syndrome and Langer-Giedion syndrome.

\textbf{HOW TO REACH THE DIAGNOSIS EHLERS-DANLOS SYNDROME, INCLUDING CORRECT TYPING?}

Like always in clinical practice, the results of history taking, including a family history, and physical examination are the basis for planning additional investigations and finally reaching a diagnosis. Additional investigations are often biochemical as a first screen, followed by targeted DNA analysis. However, with the introduction of new DNA technologies, like next generation sequencing (NGS), rapid search for the disease causing mutation by molecular analysis of all known EDS genes (“the EDS panel”) at once has become possible. This is already standard routine diagnostic practice in many laboratories and will become routine in all in the near future. Copy number variation analysis for large deletions and duplications has also a place in the molecular analysis in cases where NGS did not reveal a mutation in AD types and only one mutation in AR types, while whole exome sequencing and whole genome sequencing will be indicated in the search for new types when all tests are negative.

As history taking and physical examination in relation to EDS are very important, these will be discussed below. Good history taking starts with identifying the exact symptoms and complaints, which compelled the patient to see a physician: when and how did they start and evolve, how were they treated (what were the results, - what was advised/prescribed by whom?). Specific questions should elucidate the presence or absence of:

- \textbf{Hypermobility and/or (sub)luxations.} If (sub)luxation occurred: which joint(s) were involved, how often did it occur, was it spontaneous (also the first time) and painful? Was it seen/treated by doctors? If necessary also the Five-Point Questionnaire (5PQ; see footnote in table 4).

- \textbf{Contractures? Congenital hip dislocation?} \textsuperscript{47,48}

- \textbf{Painful joints.}\textsuperscript{49} If so: which ones, when, under which circumstances, exercise related, warm and swollen, if so, for how long? Use of analgesics? Sprains? What are the major limitations in daily life?

- \textbf{Temporomandibular joint problems.}\textsuperscript{50}

- \textbf{Problems with bursae/tendons.}

- \textbf{(Spontaneous) fractures.}

- \textbf{Skin fragility and abnormal wound healing with wide atrophic scars.}

- \textbf{Eye problems, e.g. refractive errors, abnormal vision.}

- \textbf{Sprains? What are the major limitations in daily life?}

- \textbf{Cardiac problems? Cardiovascular autonomic dysfunction?}\textsuperscript{52}

- \textbf{Genito-urinary tract problems, e.g. uterine prolapse, voiding dysfunction.}

- \textbf{Abnormal exercise tolerance and/or fatigue.}\textsuperscript{51}

- \textbf{Sports performed? Type of work: blue or white collar?}

- \textbf{Pneumothorax?}

- \textbf{Psychiatric problems, like anxiety, depression, ADHD?}\textsuperscript{54}

- \textbf{Neurological problems?}\textsuperscript{55,56} \textbf{Headache? Migraine?}

- \textbf{Gastro-intestinal tract problems, e.g. constipation, diverticula, rectal prolapse.}\textsuperscript{53}

- \textbf{For female patients with children: pregnancy and delivery problems.}\textsuperscript{19}

- \textbf{Rupture of internal organs (arteries, lungs, intestines, spleen, uterus).}

- \textbf{Neurological problems?}\textsuperscript{55,56} \textbf{Headache? Migraine?}

- \textbf{Eye problems, e.g. refractive errors, abnormal vision.}

- \textbf{Hearing?}
- Growth?
- Motor and cognitive development?
- Dental problems?
- Miscellaneous: Gingivitis? Varicose veins? Abnormal effect of local anaesthesia?

The family history includes drawing a three generation pedigree with specific enquiry regarding hypermobility, easy bruising, abnormal scarring, arterial dissections and organ ruptures.

The physical examination is focused on signs relevant for connective tissue disorders:
- Build and biometry: height, weight, span and others when indicated. Marfanoid?
- Thorax: deformity?
- Back: (kypho)scoliosis?
- Neurological examination: muscle weakness? Reduction in vibration sense? Reduction of tendon reflexes?

After history taking, a differential diagnosis will be established, on which basis additional investigations, such as biochemical and/or DNA analysis in blood and/or cultured fibroblasts, derived from a skin biopsy, are planned, if clinically relevant and available for the suspected type(s). Morphological examination of a skin biopsy is of limited value, except in some types, particularly in dermatosparaxis EDS. On indication, the patient will be referred to an ophthalmologist, orthopaedic surgeon, neurologist and/or others.

DNA analyses are available as diagnostic services in most of the high and middle income countries. As already indicated, there is no DNA test available for hypermobile EDS. If there is any reason to believe the phenotype could be the classical-like, tenascin-X deficient type, then there is an indication to perform tenascin-X analysis in serum. If there is suspicion of vascular EDS, the threshold to do DNA analysis should be very low, because of the consequences of that diagnosis in terms of management and genetic counselling. For some of the other EDS types the same holds true, because of their severity, rareness, overlapping features with other EDS types and/or different modes of inheritance. In fact, for definite diagnosis molecular confirmation is needed for all types, except the hypermobile type.

**GENETIC COUNSELLING**

Since all the disorders which have been discussed have a genetic background, genetic counselling is an indispensable part of the management of patients and their families. During genetic counselling, information will be given about the mode of inheritance, recurrence risk, variability and penetrance of the disorder, the possibilities of prenatal diagnosis and diagnosis in relatives at risk and management. Prenatal diagnosis and diagnosis in relatives at risk is only possible if the causative DNA defect is known. A social worker should be available to assist whenever a need is perceived or requested. When there is a patient/parent support group, patients/parents should be informed. In case of a proband of non-EDS parents, it is essential to differentiate between an autosomal dominant (e.g. classical type) and an autosomal recessive type (e.g. classical-like, tenascin-deficient type); in the classical type the recurrence risk for a next child of these non-EDS parents is low (less than 1%) and for a child of the affected patient high (50%), while in the tenascin-deficient type the recurrence risk for a next child is high (25%) and for a child of the affected patient generally low (1% or less). It is important to be aware of the possibility of parental mosaicism in cases which are apparently de novo.

**CONCLUSION**

EDS is a fairly common, clinically and genetically heterogeneous disorder, belonging to the heritable disorders of connective tissue. The latest official classification of 2017 recognized 13 types. Since then another variant has been described and there is still room for the identification of other types. In individual patients it is a challenge to correctly type EDS, even after careful history taking and physical examination. Often a molecular diagnosis is needed for correct typing and NGS is thereby of great help. Management is preferably provided by a multidisciplinary team in expert centres. Genetic counselling is an integral part of its management.

**ACKNOWLEDGMENT**

Table 4 Diagnostic criteria, minimal criteria and verification of Ehlers-Danlos syndromes (data extracted from\(^4\))

<table>
<thead>
<tr>
<th>Types of EDS</th>
<th>Major diagnostic criteria</th>
<th>Minor diagnostic criteria</th>
<th>Suggestive minimal criteria for diagnosis</th>
<th>Verification of clinical diagnosis</th>
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<tbody>
<tr>
<td>Classical EDS</td>
<td>Skin hyperextensibility and atrophic scars. Generalized joint hypermobility</td>
<td>Easy bruising                                                                          Smooth, velvety skin                                                        Skin fragility (or traumatic splitting)                     Subcutaneous tumors Subcutaneous spheroids Hernia (or history thereof)</td>
<td>Skin hyperextensibility and atrophic scars, plus either generalized joint hypermobility and/or 3 minor criteria</td>
<td>Molecular screening of a targeted EDS gene panel, including at least COL5A1, COL5A2, COL1A1 and COL1A2. When not available transmission electron microscopy (TEM) of skin biopsy (collagen flowers) might be supportive</td>
</tr>
<tr>
<td>Cardiac-valvular EDS</td>
<td>Severe progressive cardiac-valvular problems. Skin hyperextensibility, atrophic scars, thin skin, easy bruising. Generalized or small joints hypermobility</td>
<td>Inguinal hernia. Pectus deformity (mostly excavatum). Joint dislocations. Foot deformities: pes (plano)valgus, hallux valgus.</td>
<td>Severe progressive cardiac-valvular problems AND family history compatible with AR inheritance plus either one other major criterion and/or at least 2 minor</td>
<td>Severe progressive cardiac-valvular problems AND family history compatible with AR inheritance plus either one other major criterion and/or at least 2 minor</td>
</tr>
<tr>
<td>Hypermobile EDS</td>
<td>Generalized joint hypermobility (GHJ) assessed by Beighton score (\geq 6) for prepubertal children and adolescents (\geq 5) for pubertal men and women up to the age of 50 (\geq 4) for those (\geq 50) years of age. If the Beighton score is 1 point below the age- and sex-specific</td>
<td>A systemic manifestations of a more generalized connective tissue disorder: 1. unusually soft or velvety skin. 2. mild skin hyperextensibility. 3. unexplained striae distensae. 4. bilateral piezogenic papules (heel). 5. recurrent or multiple abdominal hernias. 6. atrophic scarring at 2 or more sites without truly papyraceous and/or hemosideric scars. 7. pelvic floor, rectal and/or uterine prolapse in children.</td>
<td>1. Generalized joint hypermobility AND 2. Two or more among features A-C (A+B, A+C, B+C, A+B+C) must be present A: total of 5 must be present B: must be present C: 1 or more must be present AND 3. absence of unusual skin fragility AND</td>
<td>Not possible; hEDS is a clinical diagnosis. Sleep disturbance, fatigue, postural orthostatic tachycardia, functional gastro-intestinal disorders, dysautonomia, anxiety and depression are not part of the diagnostic criteria, but its presence may prompt consideration of hEDS in the differential diagnosis.</td>
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<tr>
<td>Arthrochalasia EDS</td>
<td>Congenital bilateral hip dislocation</td>
<td>Cut-off AND the 5-point questionnaire (5PQ)* is positive then a diagnosis of GJH can be made</td>
<td>Men or nulliparous women without obesity or other explanation 8. Dental crowding and high/narrow palate 9. Arachnodactyly (bilateral positive wrist or thumb sign) 10. Arm span-to-height ≥ 1.05 11. Mitral valve prolapse (strict echocardiographic criteria) 12. Aortic root dilatation with Z-score &gt; +2 B: one or more first degree relatives independently meeting the criteria for hEDS C: Musculoskeletal complications: 1. Pain in 2 or more limbs, recurring daily for at least 3 months 2. Chronic widespread pain for ≥ 3 months 3. Recurrent joint dislocations or frank joint instability in the absence of trauma (a or b) a. 3 or more dislocations in the same joint or 2 or more dislocations in 2 different joints occurring at different times b. Medical confirmation of joint instability at 2 or more sites</td>
<td>Exclusion of other heritable and acquired connective tissue disorders, including autoimmune rheumatologic disorders and exclusion of alternative diagnoses e.g. neuromuscular disorders, other heritable connective tissue disorders, and skeletal dysplasias</td>
</tr>
<tr>
<td>Dermatosparaxis EDS</td>
<td>Extreme skin fragility with congenital or postnatal skin tears</td>
<td>Characteristic craniofacial features Redundant, almost lax skin Increased palmar wrinkling Severe bruising Umbilical hernia Postnatal growth retardation Short limbs, hands and feet Perinatal complications due to connective tissue fragility</td>
<td>Soft and doughy skin texture Skin hyperextensibility Atrophic scars Generalized joint hypermobility Complications of visceral fragility (bladder/diaphragmatic rupture, rectal prolapse) Delayed motor development Osteopenia Hirsutism Tooth abnormalities Refractive errors (myopia, astigmatism) Strabismus</td>
<td>Extreme skin fragility with congenital or postnatal skin tears AND characteristic craniofacial features plus either 1 other major and/or 3 minor criteria</td>
</tr>
<tr>
<td>Kyphoscoliotic EDS</td>
<td>Congenital muscle hypotonia</td>
<td>Congenital or early onset kyphoscoliosis Generalized joint hypermobility with multiple dislocations/subluxations</td>
<td>Skin hyperextensibility Easy bruisable skin Rupture/aneurysm of a medium-sized artery Osteopenia/osteoporosis Blue sclerae Hernia (umbilical or inguinal) Pectus deformity Marfanoid habitus Talipes equinovarus</td>
<td>Congenital muscle hypotonia AND congenital or early onset kyphoscoliosis plus either generalized joint hypermobility and/or 3 minor criteria (general or gene-specific)</td>
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<td>Increased Dpyr/pyr (= LP/HP) ratio in urine by HPLC is highly sensitive for PLOD1-kEDS. Molecular analysis: MLPA of PLOD1 (duplication); if negative MLPA, targeted resequencing of a EDS gene panel, including PLOD1 and FKBP14, but also ZNF469.</td>
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<tr>
<td>Condition</td>
<td>Features</td>
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| Brittle Cornea syndrome | Refractive errors (myopia, hypermetropia)  
**PLOD1 specific minor criteria**  
Skin fragility (e.g. atrophic scarring, friable skin)  
Scleral/ocular fragility/rupture  
Microcornea  
Facial dysmorphology (e.g. low-set ears, epicanthal folds, down-slanting fissures, synophrys, high palate)  
**FKBP14 specific minor criteria**  
Congenital sensorineural, conductive or mixed hearing impairment  
Follicular hyperkeratosis  
Muscle atrophy  
Bladder diverticula |
| Spondylodysplastic EDS | Progressive short stature  
Muscle hypotonia (ranging severe congenital to mild later-onset)  
Bowing of limbs |

**PLOD1**  
**B3GALT6, SLC39A13, CHST14 and DSE**, because of overlapping phenotypes.  
If necessary CNV analysis for deletions and duplications.  
Supportive might be TEM of skin biopsies  
**PRDM5, B4GALT7, B3GALT6, SLC39A13, CHST14 and DSE**, because of overlapping phenotypes.  
If necessary CNV analysis for deletions and duplications.  
Molecular screening by targeted resequencing of a EDS gene panel, including **ZNF469 and PRDM5**, but also **PLOD1, FKBP14, B4GALT7, B3GALT6, SLC39A13, CHST14 and DSE**, because of overlapping phenotypes.  
If necessary CNV analysis for deletions and duplications.  
Molecular screening by targeted resequencing of a EDS gene panel, including **B4GALT7 and B3GALT6** but also **PLOD1, FKBP14, ZNF469, PRDM5, CHST14 and DSE**, because of overlapping phenotypes.  
GAG deficiency with **B4GALT7 and B3GALT6** mutations in cultured fibroblasts.  
Moderately increased LP/HP ratio (to approximately 1 compared to normal values of ~ 0.2) with HLPC for **SLC39A13** mutations.  
Molecular screening by targeted resequencing of a EDS gene panel, including **B4GALT7** and **B3GALT6** and **SLC39A13** but also **PLOD1, FKBP14, ZNF469, PRDM5, CHST14 and DSE**, because of overlapping phenotypes.  
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<table>
<thead>
<tr>
<th>EDS</th>
<th>Criteria</th>
<th>Features</th>
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<tr>
<td>Musculosontractura EDS</td>
<td>Recurrent/chronic dislocations Pectus deformities (flat, excavatum)</td>
<td>At birth or in early childhood Con genital multiple collateral and/or characteristic craniofacial features</td>
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<td>(Kyphoscoliosis Tapering, slender, cylindrical fingers)</td>
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<td>Large subcutaneous hematomas Chronic constipation</td>
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<td>Colonic diverticula Pneumon(hemo)thorax Nephro/cystolithiasis</td>
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<td>Hydronephrosis Cryptorchidism Strabismus Refractive errors (myopia,</td>
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<td>(valgus, planus, cavum) Appendix and/or clubfoot)</td>
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<td>Characteristic craniofacial features (hyperextensibility, bruising,</td>
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<td>fragility, atrophic scars, increased palmar wrinkling)</td>
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<td>Ascending aortic aneurysm Lung hypoplasia, restrictive lung disease</td>
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<td><strong>SLC39A13 specific minor criteria</strong></td>
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<td>Protuberant eyes with bluish sclerae</td>
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<td>Hands with finely wrinkled palms</td>
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<td>Atrophy of thenar muscles, tapering fingers Hypermobility of distal joints</td>
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<td>Characteristic radiographic findings</td>
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<td><strong>SLC39A13 specific minor criteria</strong></td>
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<td><strong>SLC39A13 specific minor criteria</strong></td>
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* The Five-Point Questionnaire (5PQ):
1. Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2. Can you now (or could you ever) bend your thumb to touch your forearm?
3. As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?
4. As a child or teenager, did your shoulder or kneecap dislocate on more than one occasion?
5. Do you consider yourself “double-jointed”?

A “yes” answer to two or more questions (= positive 5PQ) suggests joint hypermobility with 80–85% sensitivity and 80–90% specificity.


# In patients with an acquired connective tissue disorder (e.g. lupus, rheumatoid arthritis) additional diagnosis of hEDS requires meeting both features A and B of criterion 2. Feature C of criterion 2 (chronic pain and/or instability) cannot be counted towards a diagnosis of hEDS in this situation.
REFERENCES


