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# Stretching Boundaries: A Comprehensive Review of Ehlers-danlos Syndrome and its Subtypes

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***Abstract***

*The Ehlers-Danlos syndromes (EDS) encompass 13 inheritable disorders affecting connective tissue. These conditions arise from genetic alterations impacting the structure of connective tissue. Every variant of Ehlers-Danlos syndrome (EDS) exhibits distinct features and has specific diagnostic criteria. While certain traits such as joint hypermobility, skin hyperextensibility, and tissue fragility are common across all types of EDS. The range of clinical presentations spans from minor skin and joint looseness to severe physical impairment and potentially life-threatening vascular issues. The current Villefranche classification identifies six subtypes, many of which are associated with mutations in genes responsible for fibrillar collagens or enzymes engaged in the post-translational modification of these proteins. Classic or vascular EDS results from mutations in type V and type III collagen respectively, while mutations affecting the processing of type I collagen contribute to kyphoscoliosis, arthrochalasis, and dermatosparaxis types of EDS. The list of conditions included in the process of differential diagnosis for Ehlers-Danlos syndrome (EDS) encompasses fibromyalgia, autosomal dominant polycystic kidney disease, Marfan syndrome, hypermobility spectrum disorders, chronic fatigue syndrome, osteogenesis Imperfecta Type 1, Cutis laxa syndromes, Loey-Dietz syndrome, and depression. This review investigates Ehlers-Danlos syndrome (EDS), encompassing its diverse subtypes, genetic origins, pathophysiology, clinical manifestations, and diagnostic protocols. It sheds light on the intricate challenges faced by individuals with EDS due to the unpredictable symptomatology. The review underscores the necessity for holistic care paradigms to address the multifaceted needs of EDS patients, aiming to advance both clinical understanding and management strategies for this complex disorder.*

**Keywords:** Ehlers-danlos, genetic disorder, hypermobile, COL3A1, COL5A1, COL5A2

## INTRODUCTION

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Ehlers-Danlos syndrome (EDS) refers to a group of relatively uncommon genetic disorders affecting connective tissue, characterized by various features such as skin hyperextensibility, joint hypermobility, and tissue fragility.4 The estimated prevalence of Ehlers-Danlos syndrome ranges from 1 in 5000 to 1 in 100,000, depending on the specific subtype, although this may be underestimated. The precise prevalence of each EDS subtype remains uncertain 5, with the hypermobile type (hEDS) being the most prevalent, while some types are considerably rare. These disorders can be differentiated from each other and are often identifiable through a combination of family history and clinical evaluation. This evaluation involves examining the

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degree and type of involvement of the skin, joints, skeleton, and vasculature. While the genetic basis for most types of EDS has been elucidated, the hypermobile type remains genetically diverse. Genetic testing may offer diagnostic utility for several of these disorders [1-4].

Complications associated with these syndromes can include chronic pain, dysautonomia, gastrointestinal dysmotility, mast cell activation, as well as anxiety and phobic states. With advancements, numerous new variants have been identified, often presenting as more complex and clinically overlapping conditions [5].

While symptoms typically manifest in childhood, they tend to exacerbate and become more pronounced during adulthood. Figure 1 given below shows some common features of skin and joint hypermobility upon exercise experienced by person having EDS. Table 1 represents types of EDS with genetic basis and protein involved.

## PATHOPHYSIOLOGY OF EHLERS-DANLOS SYNDROME

The underlying pathophysiology of most Ehlers-Danlos syndrome (EDS) subtypes stems from heritable mutations affecting the synthesis and processing of collagen, a crucial structural protein in the body. These mutations can occur in various genes associated with collagen production, disrupting collagen structure and function.

The inheritance patterns of these mutations can vary, with some subtypes exhibiting autosomal dominant inheritance, where a single copy of the mutated gene from one parent is sufficient to cause the disorder, while others may follow autosomal recessive inheritance, requiring both alleles of the gene to be mutated for the condition to manifest. It is noteworthy that spontaneous mutations can also occur, leading to identical genotypes and phenotypes in affected individuals.

Collagen is integral to the integrity of numerous body systems, including the skin, joints, blood vessels, and organs. As a result, the symptoms of EDS can be diverse and widespread. For example, abnormalities in collagen synthesis can lead to hyperextensible skin, joint hypermobility, and fragile blood vessels, predisposing individuals to frequent dislocations, easy bruising, and potentially life-threatening vascular complications. Additionally, collagen defects can affect organ function, contributing to gastrointestinal issues, uterine fragility, and cardiac abnormalities observed in some EDS subtypes.

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**Figure 1.** Skin that exhibits increased extensibility and generalized joint hypermobility upon physical examination [42].

**Table 1.** Types of EDS with genetic basis and protein involved.

| Clinical EDS Subtype | Inheritance Pattern | Genetic Basis | Protein | Diagnostic Criteria |
|---|---|---|---|---|
| Classical EDS | Autosomal Dominant | Major: COL5A1, COL5A1 Rare: COL1A1 | Type V collagen | Skin hyperextensibility (Beighton score of ≥ 5 if ≤ 49 years old, ≥ 4 if ≥ 50 years old **[6]** |
| Classical-like EDS | Autosomal Recessive | TNXB | Tenascin XB | Skin hyperextensibility, with velvety skin texture and absence of atrophic scarring<br>GJH with or without recurrent dislocations **[7]** |
| Cardiac-valvular EDS | Autosomal Recessive | COL1A2 (biallelic mutations leading to COL1A2 NMD and absence of pro α2(I) collagen chains) | Type I collagen | Joint hypermobility limited or more marked at hands/ feet, skin hyperextensibility, mitral valve insufficiency, genua recurvata [**8]** |
| Vascular EDS | Autosomal Dominant | Major: COL3A1 Rare: COL1A1 | Type III collagen | Arterial rupture at a young age, bowel perforation, uterine rupture during pregnancy [**9]** |
| Hypermobile EDS | Autosomal Dominant | Unknown | Unknown | Beighton score ≥ 5 (in adults), joint hypermobility complications, chronic joint pain (arthralgia for ≥ 3 months), systemic manifestations **[10]** |
| Arthrochalasia EDS | Autosomal Dominant | COL1A1, COL1A2 | Type I collagen | Congenital bilateral hip dislocation, severe joint hypermobility, characteristic facial features, skin hyperelasticity, easy bruising [**11]** |
| Dermatosparaxis EDS | Autosomal Recessive | ADAMTS2 | ADAMTS-2 | Severe skin fragility, sagging redundant skin, easy bruising, characteristic facial appearance, hernias, rupture of internal organs [**12]** |
| Kyphoscoliotic EDS | Autosomal Recessive | PLOD1, FKBP14, FKBP22 | LH1 | Congenital muscle hypotonia, progressive scoliosis, joint hypermobility, characteristic facial appearance [**13]** |
| Brittle Cornea syndrome | Autosomal Recessive | ZNF469, PRDM5 | ZNF469, PRDM5 | Thin, fragile cornea leading to corneal rupture or rupture of other ocular tissues, keratoconus, blue sclerae, hyperelasticity of the skin, [**14]** |
| Spondylodysplastic EDS | Autosomal Recessive | B4GALT7, B3GALT6, SLC39A13 | β4GalT7, β3GalT6, ZIP13 | Short stature, skeletal dysplasia, joint laxity, characteristic facial features, progressive kyphoscoliosis, hypotonia, easy bruising [**7]** |
| Musculocontractural EDS | Autosomal Recessive | CHST14, DSE | D4ST1, DSE | Distinctive craniofacial features, multiple congenital contractures, club feet, characteristic skin features, variable severity of developmental delay [**15]** |
| Myopathic EDS | Autosomal Dominant or Autosomal Recessive | COL12A1 | Type XII collagen | Congenital muscle hypotonia, proximal joint contractures, distal joint hypermobility, muscle atrophy, characteristic facial features, skin hyperelasticity **[16]** |
| Periodontal EDS | Autosomal Dominant | C1R, C1S | C1r, C1s | Premature loss of primary and secondary teeth, hypermobile temporomandibular joints, gingival |

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| | | | | |
|---|---|---|---|---|
| | | | | recession, hyperelasticity of the skin **[17]** |

Overall, the complex interplay of genetic mutations affecting collagen synthesis and the widespread distribution of collagen throughout the body underlie the variable and multisystemic nature of EDS [18-20]. The defect in collagen is present in at a minimum at least six variants of EDS. The vascular type, also designated as type IV, is caused by a reduction in type III collagen levels due to COL3A1 gene mutations. These mutations result in increased fragility of connective tissue, leading to ruptures in arteries, uterus, and intestines, often resulting in premature death. Variants V and VI occur due to lysyl oxidase enzyme and hydroxylase deficits, crucial enzymes involved in collagen synthesis. Type VII is characterized by a deficiency in amino-terminal procollagen peptidase. Abnormal copper metabolism is responsible for Type IX, while Type X is associated with nonfunctional plasma fibronectin [18, 21, 22].

As the classical variety, types I and II of Ehlers-Danlos syndrome (EDS), are thoroughly understood clinically, yet elucidating the underlying molecular mechanisms of the disorder in most affected individuals has proven to be a challenge. Several explanations have been proposed for the difficulty in identifying mutations, genetic heterogeneity, technical constraints, and difficulties in allele expression are all factors contributing to this challenge. It has been established that genetic heterogeneity plays a significant role as a contributing factor, with causative mutations pinpointed in genes such as Tenascin X, COL5A1, and COL5A2, and presumed to be associated with the COL1A2 gene. Nevertheless, in numerous families inheriting EDS through an autosomal dominant inheritance pattern, linkage to loci was observed to contain the COL5A1 or COL5A2 genes. To investigate whether instability of allele products could explain the failure to detect certain mutations, polymorphic variants identified within the COL5A1 gene were examined in a cohort of 16 individuals, and mRNA was analyzed to evaluate the expression of both gene copies and splicing alterations.

The analysis revealed a mutation at the splice site in one individual and demonstrated that in six individuals, mRNA derived from one allele of the COL5A1 gene was either not expressed or highly unstable. Minor deletions or insertions were identified in five of these instances, but the mutation remained undetected in the sixth instance. Hence, while up to fifty per cent of the mutations responsible for it is probable that EDS types I and II are located in the COL5A1 gene, a significant proportion of these mutations lead to substantially reduced mRNA levels from the altered allele due to nonsense-mediated mRNA decay [23].

## CLINICAL FEATURES OF SOME OF THE MOST COMMON TYPES OF EDS-

### Hypermobile EDS

Hypermobility-type Ehlers-Danlos syndrome (hEDS) is acknowledged as a relatively milder subtype of Ehlers-Danlos syndrome, yet it presents notable clinical complexities. Here's a thorough analysis of its fundamental traits:

#### *Skin Characteristics*

Individuals with hEDS often display soft and mildly hyperextensible skin. This quality, characterized by its velvety texture, serves as a significant clinical indicator of the syndrome.

#### *Hypermobility and Instability of Joints are Prominent Aspects*

A defining trait of hEDS is joint instability, with subluxations and dislocations occurring frequently, sometimes even without significant trauma. The hypermobility of joints is prominent, elevating the risk of instability and dislocation.

#### *Joint Degeneration Disorder*

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Chronic joint instability and hypermobility in hEDS contribute to premature degenerative changes within the joints. This degenerative joint disease results in chronic pain and compromised joint function over time, significantly impacting daily life.

***Chronic Pain***

Chronic pain is a prevalent and debilitating aspect of hEDS. Distinguished from acute pain experienced during joint incidents, chronic pain can be widespread and persistent, affecting both physical and mental well-being.

***Easy Bruising***

Fragile skin and blood vessels in hEDS predispose individuals to easy bruising, even with minor trauma. This susceptibility to bruising is a characteristic clinical feature.

***Functional Bowel Disorders and Cardiovascular Autonomic Dysfunction***

Functional bowel disorders, such as irritable bowel syndrome, and cardiovascular autonomic dysfunction are common in hEDS. These issues can manifest as gastrointestinal symptoms and dysautonomia, leading to dizziness, fainting, and irregular heart rate.

***The Dilation of the Aorta's Root***

While aortic root dilatation can occur in hEDS, it typically presents as a mild condition. However, without significant dilatation, the likelihood of aortic dissection is usually not heightened.

***Psychological Dysfunction and Emotional Challenges***

Psychological dysfunction, psychosocial impairment, and emotional struggles are frequently observed in individuals with hEDS. These may stem from chronic pain and physical limitations, underscoring the importance of comprehensive management strategies.

In summary, hEDS encompasses a range of clinical manifestations that extend beyond joint hypermobility, affecting various body systems. A comprehensive comprehension of these characteristics is essential for accurate diagnosis and holistic management of the syndrome [24-27]. Figure 2 depicts patient having skin hyperextensibility, indicated by their thumbs' passive resistance to the flexor facets of their forearms. The mandible also exhibits a notable deviation to the left.

**Vascular Ehlers-Danlos Syndrome (vEDS)**

***Fragility of Arteries, Intestines, and/or Uterus***

Individuals with vEDS exhibit fragility in their arteries, intestines, and/or uterus, which is a defining feature of the syndrome.

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**Figure 2.** The patient presents with skin hyperextensibility, thumbs passively able to appose to the flexor aspects of the forearms, and left mandibular deviation [43].

***Easy Bruising***

Easy bruising is a common manifestation in individuals with vEDS, with even minor trauma resulting in bruising.

***Characteristic Facial Attributes***

The facial features of individuals with vEDS often include a thin vermilion of the lips, micrognathia (small jaw), narrow nose, and prominent eyes, contributing to a characteristic appearance.

***Translucent and Thin Skin***

A notable physical trait in vEDS is the presence of thin and translucent skin, which may be more apparent in certain areas of the body.

***The Extremities May Display a Prematurely Aged Appearance***

The extremities may exhibit an aged appearance, which can be discernible even in younger individuals with vEDS.

***Presentation Signs***

Common presenting signs in adults with vEDS include arterial rupture, organ rupture, or gastrointestinal perforation, which may occur spontaneously or after dissection, aneurysm, or arteriovenous fistulae.

***Diagnosis in Childhood***

A significant proportion (60%) of individuals identified with vEDS before reaching 18 years of age have a history within the family indicative, which often prompts early evaluation and diagnosis.

***Neonatal Presentation***

Neonates with vEDS may present with various musculoskeletal anomalies such as dislocation of the hip, limb inadequacy, clubfoot, and/or amniotic bands, underscoring the multisystemic nature of the disorder.

***Complications in Children***

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Interestingly, about fifty per cent of children subjected to vEDS testing without a family history were positive and presented with major complications by the age of 11, indicating the potential severity of the condition even without familial predisposition.

***Minor Diagnostic Features***

In children without major complications, the presence of thin skin, easy bruising, distal joint hypermobility, and club feet are often observed, serving as additional diagnostic clues for clinicians [28-30]. Figure 3 depicts upon CT angiography of the abdomen, a ruptured splenic vein aneurysm (indicated by the thin arrow) and thrombus formation (indicated by the thick arrow) in the portal vein were observed in a 51-year-old woman with vascular Ehlers-Danlos syndrome.

**Classical EDS**

***Introduction to Villefranche Criteria:***

The Villefranche criteria, introduced by Beighton et al. in 1998, serve as a standardized framework for identifying classical Ehlers-Danlos Syndrome (EDS), a hereditary connective tissue disorder [31].

***Major Features***

*Skin Hyperextensibility:* Individuals with classical EDS often demonstrate remarkable skin hyperextensibility, allowing their skin to be stretched beyond normal limits without tearing. This hyperextensibility is particularly evident on areas such as the neck, elbows, and knees.

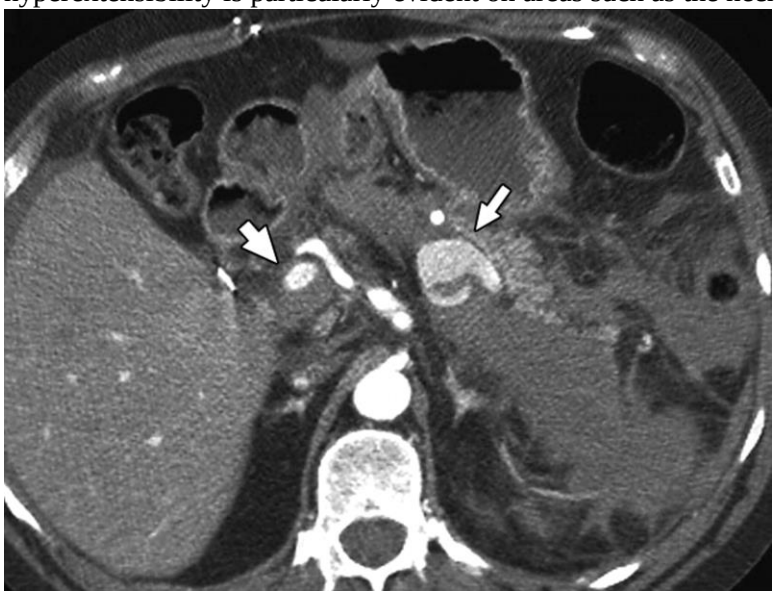

**Figure 3.** Abdominal CT angiography reveals a ruptured splenic vein aneurysm (thin arrow) and portal vein thrombus formation (thick arrow) in a 51-year-old woman with vascular Ehlers-Danlos syndrome [44].

*Widened Atrophic Scars:* Characteristic of classical EDS, widened atrophic scars result from the impaired wound healing process and fragile nature of connective tissue. These scars are often wider than typical scars and appear atrophic due to the lack of collagen deposition.

*Joint Hypermobility:* Joint hypermobility is a hallmark feature, with affected individuals exhibiting increased range of motion in multiple joints. This hypermobility can lead to joint instability, frequent dislocations, and chronic joint pain.

***Minor Signs***

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*Smooth and Soft Skin Texture:* The skin of individuals with classical EDS may have a distinct smooth and soft texture, often described as velvety to the touch.

*Molluscoid Pseudotumors:* These are benign growths resembling molluscs that may develop beneath the skin, particularly in areas prone to trauma or pressure.

*Small Rounded Formations Beneath the Skin:* Subcutaneous spheroids or spherules are small, round nodules palpable beneath the skin's surface, representing localized areas of abnormal connective tissue.

*Complications from Joint Hypermobility:* Joint hypermobility can predispose individuals to various complications, including recurrent joint sprains, dislocations/subluxations, and the development of flat feet (pes planus).

*Muscle Hypotonia and Delayed Development of Large Muscle Movements:* Muscle hypotonia, or decreased muscle tone, is commonly observed in individuals with classical EDS, leading to delays in achieving gross motor milestones and large muscle movement coordination.

*Susceptibility to Bruising:* Fragile blood vessels in classical EDS increase susceptibility to bruising, resulting in the formation of ecchymoses (bruises) even from minor trauma.

*Indications of Tissue Flexibility:* Classical EDS may manifest with various signs of tissue extensibility and fragility, such as hernias (including umbilical and inguinal hernias), anal prolapse in childhood, and cervical insufficiency.

*Surgical Complications:* Individuals with classical EDS are at increased risk of surgical complications, particularly postoperative hernias, due to underlying tissue fragility and impaired wound healing.

*Positive Family History:* A positive family history of classical EDS or related symptoms strengthens the diagnostic suspicion and aids in confirming the diagnosis through genetic testing [32].

***Relevance of Villefranche Criteria***

Despite advancements in diagnostic techniques, the Villefranche criteria remain essential for identifying classical EDS cases due to their comprehensive nature and clinical significance. They provide clinicians with a standardized approach to diagnosing classical EDS based on a combination of major and minor indicators, ensuring accurate identification and appropriate management of affected individuals [33]. The Figure 4 demonstrates the distinction between hypermobile Ehlers-Danlos Syndrome (hEDS) and classical Ehlers-Danlos Syndrome (cEDS), which is associated with mutations in the COL5A1, COL5A2, or COL1A1 genes, in terms of aberrant scarring and satellite cutaneous symptoms.

**Kyphoscoliotic EDS**

Infants diagnosed with kyphoscoliotic EDS often demonstrate significant muscle weakness, resulting in notable floppiness. Consequently, achieving developmental milestones like sitting and walking may be delayed, prompting investigations for potential neuromuscular conditions due to the severity of their symptoms. As they progress into childhood, difficulties with walking may become increasingly apparent. Skin manifestations in kyphoscoliotic EDS may include stretchiness, softness, and a tendency to bruise easily. Skin fragility may also lead to the formation of widened, atrophic scars.

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**Figure 4.** Distinguishing between abnormal scarring and satellite cutaneous signs in hypermobile Ehlers-Danlos Syndrome (hEDS) and classical Ehlers-Danlos Syndrome (cEDS) attributed to mutations in COL5A1, COL5A2, or COL1A1 genes [45].

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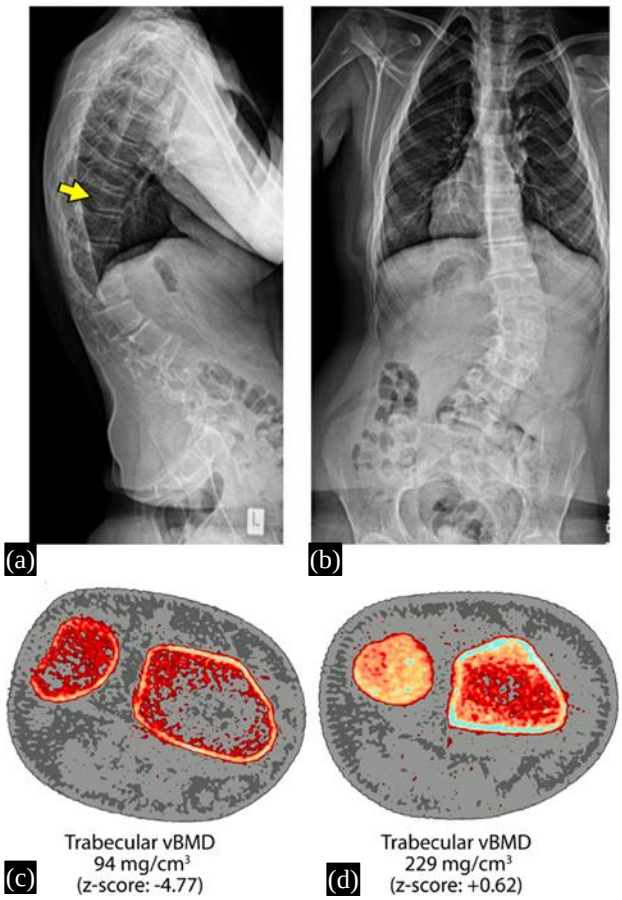


**Figure 5.** Radiological images of a 14-year-old with PLOD1-related kyphoscoliotic Ehlers–Danlos syndrome show vertebral compression fracture at T9, kyphosis of 70° at T11, and lordosis of 35° at L2 on lateral spine X-ray. Anteroposterior spine X-ray reveals dextroscoliosis of 35° at L1. Forearm pQCT scan demonstrates lower trabecular vBMD at distal radius metaphysis compared to age-matched control [46].

An uncommon feature observed in kyphoscoliotic EDS is the potential for a smaller-than-average cornea, occasionally resulting in eyeball rupture due to the weakened eye wall. Figure 5 (a-d) depicts asignificant abnormalities in a series of radiological scans of a 14-year-old with kyphoscoliotic Ehlers-Danlos syndrome connected to PLOD1. A spinal compression fracture can be seen at T9 on a lateral spine X-ray, along with a noticeable 70° kyphosis at T11 and a 35° lordosis at L2. Furthermore, an X-ray of the anteroposterior spine shows 35° dextroscoliosis at L1. When compared to age-matched controls, a forearm pQCT scan indicates a lower trabecular volumetric bone mineral density (vBMD) near the distal radius metaphysis.

Additional reported characteristics may encompass:

- Reduced bone density (osteopenia) without a heightened fracture risk.
- A tall and slender physique with elongated digits.
- Fragility of artery walls, increasing susceptibility to ruptures in medium-sized arteries.

Kyphoscoliosis, a spinal curvature abnormality, often develops during childhood and progresses gradually. In severe cases, orthopaedic interventions such as surgery may be necessary to address spinal deformities. These detailed clinical features collectively define the presentation of kyphoscoliotic EDS, guiding diagnostic and therapeutic approaches [34].

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## DIAGNOSIS

The usual diagnostic criteria for Ehlers-Danlos disorders include clinical symptoms and family history. To test for EDSs, a physical examination should concentrate on the joints and skin. Testing for skin hyperextensibility should involve pulling the skin on the neck, dorsum of the hand, and/or volar surface of the forearm.

The skin is stretched until it meets resistance, at which point it is seen that the swollen skin contracts. These individuals typically have white, delicate, thin skin that seems velvety to the touch.

Early detection of EDS is crucial to start providing these individuals with the right care, which includes musculoskeletal therapy, genetic counselling for patients and their families, cardiovascular screening for vascular and valve issues, and maximising perioperative care [35].

### Testing Strategy

#### *Blood Work*

In over 98% of instances of vascular EDS, the thorough sequencing of COL3A1 within a certified clinical laboratory is considered highly effective in detecting the causative genetic alteration. For classical EDS diagnosis confirmation, identifying pathogenic mutations in COL5A1 or COL5A2 can serve as supporting evidence. As the number of identifiable mutations has expanded, molecular testing has become the primary diagnostic approach for classical EDS. Typically, the initial phase of testing involves sequencing COL5A1 [36, 37].

#### *Beighton Criteria*

The Beighton score, ranging from 0 to 9, assesses hypermobility, which impacts approximately 10 to 20% of individuals. This scoring system evaluates five specific joints: little finger extension, thumb extension, elbow extension, knee extension, and hamstrings. Each joint receives one point for hypermobility. A diagnosis of joint hypermobility syndrome is confirmed by meeting either of the following criteria: scoring four points or more on flexibility tests or scoring two points or more on historical inquiries [38].

#### *CT/MRI*

When Ehlers-Danlos syndrome (EDS) is suspected, medical assessments may include CT scans, MRI scans, and echocardiography to investigate potential cardiovascular concerns. These tests can detect issues such as abnormalities in the mitral valve or aortic dilation. Additionally, MRI imaging might reveal specific brain lesions indicative of EDS [39].

#### *Tissue Biopsy*

Performing a tissue biopsy with electron microscopic analysis is an option for evaluating classic abnormalities in collagen appearance. However, this technique is rarely employed in clinical practice [40].

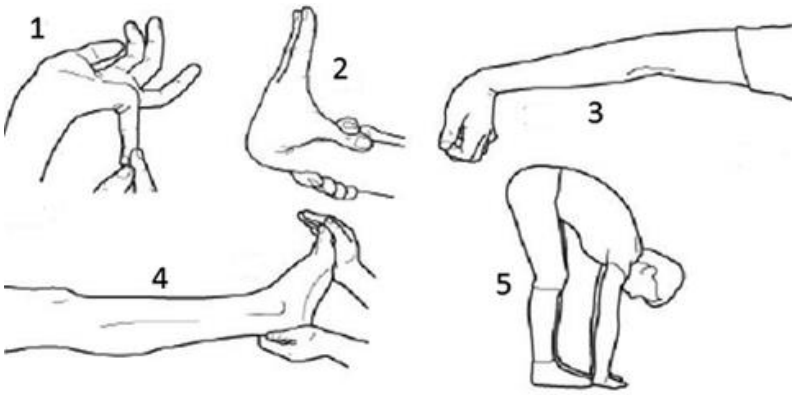


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**Figure 6.** Beighton scoring systerm for hypermobility [47].

***Tilt Table Test for Postural Hypotension***

If a patient is suspected of having Ehlers-Danlos syndrome (EDS) and experiences pre-syncope symptoms despite negative cardiovascular findings, a tilt table test might be suggested. This test aims to assess the presence of associated conditions, such as postural orthostatic tachycardia syndrome, or other forms of dysautonomia [41]. Beighton has defined some scoring paprameters for hypermobility which are depicted in Figure 6.

## CONCLUSION

In summary, this review has provided an overview of the clinical aspects of Ehlers-Danlos Syndrome (EDS), highlighting its various symptoms and diagnostic challenges. From joint hypermobility to skin fragility, EDS presents a range of clinical features that can impact patients' daily lives. While diagnosis can be complex, it is essential for healthcare providers to remain vigilant and considerate of the diverse manifestations of EDS. By understanding and addressing these clinical aspects, we can strive to improve the quality of care and support for individuals living with this condition. Continued research and collaboration among healthcare professionals will be crucial in furthering our understanding and management of EDS in the future.

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