

# Hereditary Disorders of Connective Tissue with an emphasis on The Ehlers-Danlos Syndromes

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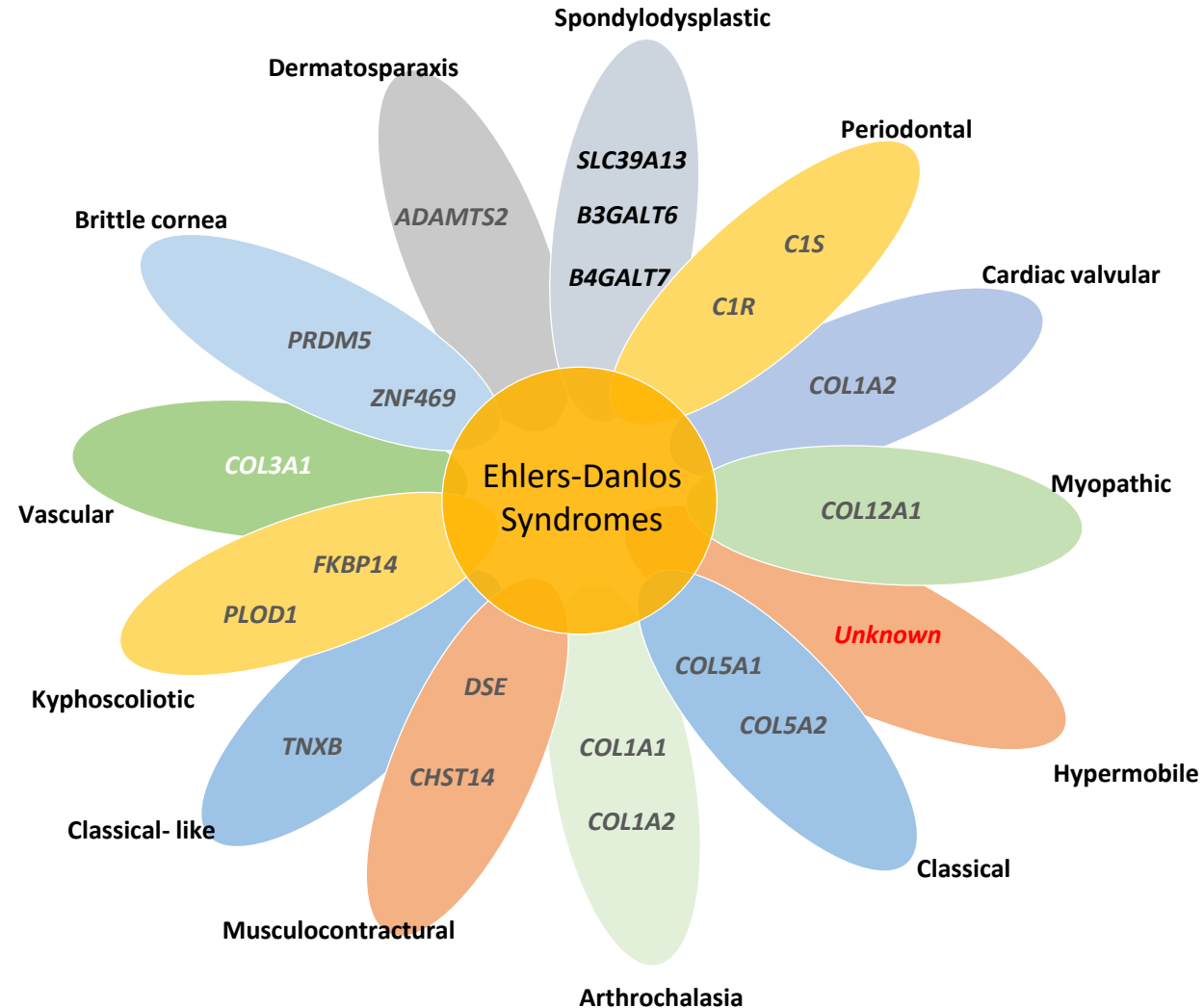
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# Spectrum of Joint Hypermobility

Type	Beighton score	Musculoskeletal involvement	Notes
Asymptomatic GJH	Positive	Absent	
Asymptomatic PJH	Usually negative	Absent	JH typically limited to hands and/or feet
Asymptomatic LJH	Negative	Absent	JH limited to single joints or body parts
G-HSD	Positive	Present	
P-HSD	Usually negative	Present	JH typically limited to hands and/or feet
L-HSD	Negative	Present	JH limited to single joints or body parts
H-HSD	Negative	Present	Historical presence of JH
hEDS	Positive	Possible	

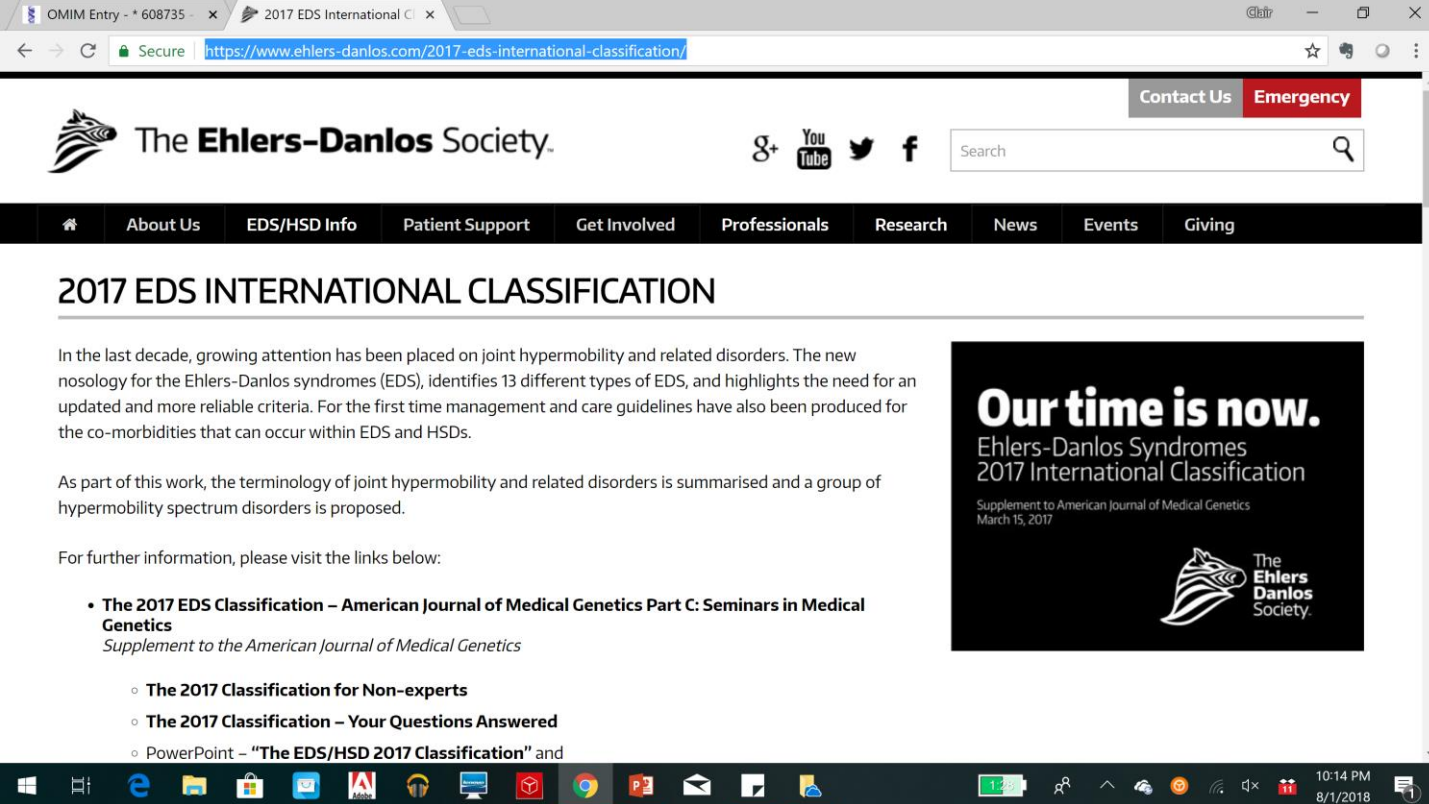
Disorders of fibrillar collagen primary structure and processing , folding and crosslinking			
Classical EDS	COL5A1/COL5A2	Type V collagen	AD
Vascular EDS	COL3A1	Type III collagen	AD
Cardiac-valvular EDS	COL1A2	Type I collagen (total absence of $\alpha$ 2 chain)	AR
Arthrochalasia EDS	COL1A1/COL1A2	Type I collagen (N-propeptide processing)	AD
Dermatosparaxis EDS	ADAMTS2	ADAMTS-2	AR
Kyphoscoliotic EDS-PLOD1	PLOD1	Lysylhydroxylase 1	AR
Kyphoscoliotic EDS-FKBP14	FKBP14	FKBP22	AR
Disorders of structure and function of the myomatrix, the interface between muscle and ECM			
Classical-like EDS	TNXB	Tenascin-X	AR
Myopathic EDS	COL12A1	Collagen XII	AR/AD
Disorders of glycosaminoglycan biosynthesis			
SpEDS_B4GALT7	<i>B4GALT7</i>	$\beta$ 4GalT7 (Galactosyltransferase I)	AR
SpEDS_B3GALT6	<i>B3GALT6</i>	$\beta$ 3GalT6 (Galactosyltransferase II)	AR
MC-CHST14	<i>CHST14</i>	Dermatan 4-sulfotransferase 1	AR
MC-DSE	<i>DSE</i>	Dermatan sulfate epimerase 1	AR
<i>Disorders linked to aberrant intracellular processes</i>			
spEDS_SLC39A13	<i>SLC39A13</i>	ZIP13	AR
Brittle Cornea Syndrome	<i>ZN469/PRDM5</i>	ZNF469/PRDM5	AR
<i>Disorders of complement pathway</i>			
Periodontal EDS	<i>C1r/C1s</i>	C1R/C1S	AD

# EDS types and their underlying genes



# How is Ehlers-Danlos Syndrome Diagnosed?

- According to the 2017 Diagnostic Criteria
- <https://www.ehlers-danlos.com/2017-eds-international-classification/>



The screenshot shows a web browser window displaying the website of The Ehlers-Danlos Society. The URL in the address bar is <https://www.ehlers-danlos.com/2017-eds-international-classification/>. The page features a navigation menu with links for Home, About Us, EDS/HSD Info, Patient Support, Get Involved, Professionals, Research, News, Events, and Giving. The main content area is titled "2017 EDS INTERNATIONAL CLASSIFICATION" and contains the following text:

In the last decade, growing attention has been placed on joint hypermobility and related disorders. The new nosology for the Ehlers-Danlos syndromes (EDS), identifies 13 different types of EDS, and highlights the need for an updated and more reliable criteria. For the first time management and care guidelines have also been produced for the co-morbidities that can occur within EDS and HSDs.

As part of this work, the terminology of joint hypermobility and related disorders is summarised and a group of hypermobility spectrum disorders is proposed.

For further information, please visit the links below:

- **The 2017 EDS Classification – American Journal of Medical Genetics Part C: Seminars in Medical Genetics**  
*Supplement to the American Journal of Medical Genetics*
  - **The 2017 Classification for Non-experts**
  - **The 2017 Classification – Your Questions Answered**
  - PowerPoint – “The EDS/HSD 2017 Classification” and

On the right side of the page, there is a promotional graphic for the "Our time is now. Ehlers-Danlos Syndromes 2017 International Classification" supplement to the American Journal of Medical Genetics, dated March 15, 2017. The graphic includes the Ehlers-Danlos Society logo.

# What are the 2017 criteria for diagnosing hEDS?

The screenshot shows a web browser window displaying the Ehlers-Danlos Society website. The browser's address bar shows the URL <https://www.ehlers-danlos.com/heds-diagnostic-checklist/>. The website header includes the logo for The Ehlers-Danlos Society, social media icons for Google+, YouTube, Twitter, and Facebook, and a search bar. A navigation menu below the header contains links for About Us, EDS/HSD Info, Patient Support, Get Involved, Professionals, Research, News, Events, and Giving. The main content area is titled "HEDS DIAGNOSTIC CHECKLIST" and includes a link to download a printable PDF. The PDF content is visible, showing the title "Diagnostic Criteria for Hypermobile Ehlers-Danlos Syndrome (hEDS)" and the text "The clinical diagnosis of hypermobile EDS needs the simultaneous presence of all criteria, 1 and 2 and 3." The checklist is divided into two main sections: "CRITERION 1 - Generalized Joint Hypermobility" and "CRITERION 2 - Two or more of the following features (A, B, or C) must be present".

OMIM Entry - \* 608735 - x hEDS Diagnostic Checklist x

Secure <https://www.ehlers-danlos.com/heds-diagnostic-checklist/>

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## HEDS DIAGNOSTIC CHECKLIST

Please click the image below to download the printable PDF.

**Diagnostic Criteria for Hypermobile Ehlers-Danlos Syndrome (hEDS)**  
This diagnostic checklist is for doctors across all disciplines to be able to diagnose EDS.

Patient name: \_\_\_\_\_ DOB: \_\_\_\_\_ DOW: \_\_\_\_\_ Evaluator: \_\_\_\_\_

The clinical diagnosis of hypermobile EDS needs the simultaneous presence of all criteria, 1 and 2 and 3.

### CRITERION 1 - Generalized Joint Hypermobility

One of the following selected:

- ≥6 pre-pubertal children and adolescents
- ≥3 pubertal men and women ≥ age 50
- ≥4 men and women over the age of 50

Beighton Score: \_\_\_\_\_/9

If Beighton Score is one point below age- and site-specific cut-off, two or more of the following must also be selected to meet criterion:

- Can you now (or could you ever) place your hands flat on the floor without bending your knees?
- Can you now (or could you ever) bend your thumb to touch your forearm?
- As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?
- As a child or teenager, did your shoulder or knee(s) dislocate on more than one occasion?
- Do you consider yourself "double jointed"?

### CRITERION 2 - Two or more of the following features (A, B, or C) must be present

Feature A (five must be present):

- Unusually soft or waxy skin
- Mild skin hyperextensibility
- Unexplained striae distensae or rubor at the back, groin, thighs, breasts and/or abdomen in adolescents, men or pre-pubertal women without a history of significant gain or loss of body fat or weight
- Bilateral periorbital papules of the eyelid
- Recurrent or multiple abdominal hernias
- Atrophic scarring involving at least two sites and without the formation of truly pyrocnous and/or hemorrhagic scars as seen in classical EDS
- Pelvic floor, rectal, and/or uterine prolapse in children, men or nulliparous women without a history of morbid obesity or other known predisposing medical condition
- Dental crowding and high or narrow palate
- Arachnodactyly, as defined in one or more of the following:
  - i) positive wrist sign (Walker sign) on both sides, ii) positive thumb sign (Steinberg sign) on both sides
- Arm span to height ratio < 1.05
- Mitral valve prolapse (MVP) mild or greater based on strict echocardiographic criteria
- Aortic root dilatation with Z-score < -2

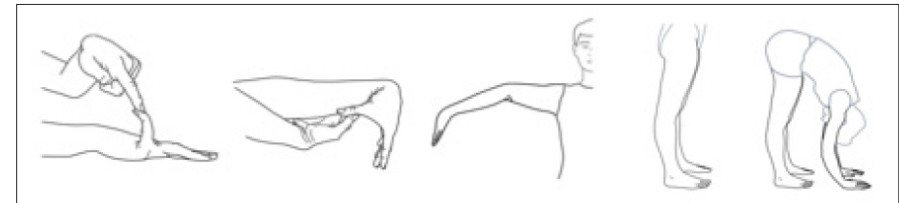
# Criterion 1: Generalized Joint Hypermobility

## CRITERION 1 – Generalized Joint Hypermobility

One of the following selected:

- ≥6 pre-pubertal children and adolescents
- ≥5 pubertal men and woman to age 50
- ≥4 men and women over the age of 50

Beighton Score: \_\_\_\_/9



*If Beighton Score is one point below age- and sex-specific cut off, two or more of the following must also be selected to meet criterion:*

- Can you now (or could you ever) place your hands flat on the floor without bending your knees?
- Can you now (or could you ever) bend your thumb to touch your forearm?
- As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?
- As a child or teenager, did your shoulder or kneecap dislocate on more than one occasion?
- Do you consider yourself “double jointed”?

# Criterion 2: Two out of Three Features

## **CRITERION 2 – Two or more of the following features (A, B, or C) must be present**

### *Feature A (five must be present)*

---

- Unusually soft or velvety skin
- Mild skin hyperextensibility
- Unexplained striae distensae or rubae at the back, groins, thighs, breasts and/or abdomen in adolescents, men or pre-pubertal women without a history of significant gain or loss of body fat or weight
- Bilateral piezogenic papules of the heel
- Recurrent or multiple abdominal hernia(s)
- Atrophic scarring involving at least two sites and without the formation of truly papyraceous and/or hemosideric scars as seen in classical EDS
- Pelvic floor, rectal, and/or uterine prolapse in children, men or nulliparous women without a history of morbid obesity or other known predisposing medical condition
- Dental crowding and high or narrow palate
- Arachnodactyly, as defined in one or more of the following:
  - (i) positive wrist sign (Walker sign) on both sides, (ii) positive thumb sign (Steinberg sign) on both sides
- Arm span-to-height ratio  $\geq 1.05$
- Mitral valve prolapse (MVP) mild or greater based on strict echocardiographic criteria
- Aortic root dilatation with Z-score  $> +2$

Feature A total: \_\_\_\_/12



### *Feature B*

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- Positive family history; one or more first-degree relatives independently meeting the current criteria for hEDS

### *Feature C (must have at least one)*

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- Musculoskeletal pain in two or more limbs, recurring daily for at least 3 months
- Chronic, widespread pain for  $\geq 3$  months
- Recurrent joint dislocations or frank joint instability, in the absence of trauma

### **CRITERION 3 - All of the following prerequisites MUST be met**

1. Absence of unusual skin fragility, which should prompt consideration of other types of EDS
2. Exclusion of other heritable and acquired connective tissue disorders, including autoimmune rheumatologic conditions. In patients with an acquired CTD (e.g. Lupus, Rheumatoid Arthritis, etc.), 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 toward a diagnosis of hEDS in this situation.
3. Exclusion of alternative diagnoses that may also include joint hypermobility by means of hypotonia and/or connective tissue laxity. Alternative diagnoses and diagnostic categories include, but are not limited to, neuromuscular disorders (e.g. Bethlem myopathy), other hereditary disorders of the connective tissue (e.g. other types of EDS, Loeys-Dietz syndrome, Marfan syndrome), and skeletal dysplasias (e.g. osteogenesis imperfecta). Exclusion of these considerations may be based upon history, physical examination, and/or molecular genetic testing, as indicated.

# Other Hereditary Disorders of Connective Tissue to Consider

- Marfan Syndrome
  - Aortic root aneurysms and rupture
  - Dislocation of the ocular lenses
  - Spontaneous pneumothorax
- Stickler Syndrome
  - Premature osteoarthritis
  - Premature hearing loss
  - Retinal detachments
- Fibromuscular dysplasia
  - “nutcracker” appearance to the arteries on vascular imaging
- Cutis laxa
  - Loose redundant skin that returns slowly to its original shape when stretched

# Classical EDS: Diagnostic Criteria

## Major Criteria

1. Skin hyperextensibility and atrophic scarring
2. Generalized joint hypermobility

## Minor Criteria

Easy bruising

Soft, doughy skin

Skin fragility (or traumatic splitting)

Molluscoid pseudotumours

Subcutaneous spheroids

Hernia (or history thereof)

Epicanthal folds

Complications of joint hypermobility (e.g. sprains, luxation/subluxation, pain, flexible flatfoot)

Family history of a first degree relative who meets clinical criteria

# Clinical Diagnosis of Classical EDS: 2017 Criteria

Major Criterion (1):

Skin hyperextensibility and atrophic scarring

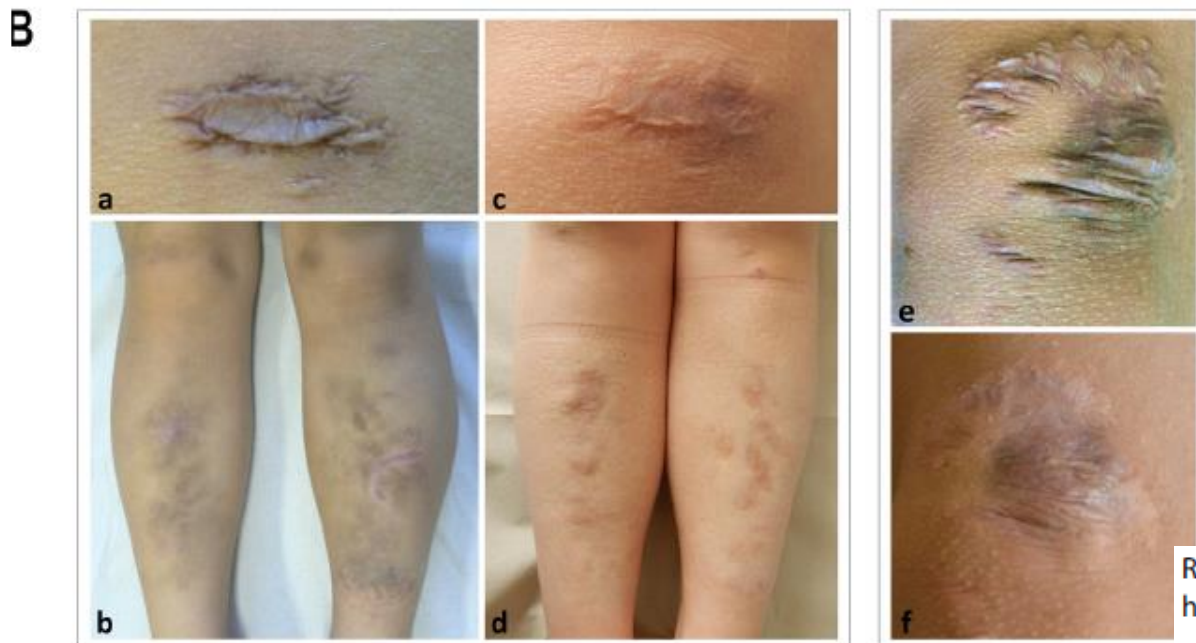
**Plus**

Either: Major criteria (2) – joint hypermobility

Or: three of the eight minor criteria

# Skin Hyperextensibility







# Beighton score



Elbow-Knee Support Unit

www.ebs.org.uk

Give yourself 1 point for each of the manoeuvres you can do, up to a maximum of 9 points



1 point

Can you bend your thumb back into the palm of your forearm?

1 point

1 point

Can you put your hands flat on the floor with your knees straight?

1 point

1 point

Can you bend your little finger up at 90° (right angle) to the back of your hand?

1 point

Can you bend your knee backwards?

1 point

1 point

Can you bend your elbow backwards?

1 point

1 point

MAKING OUR JOINTS VISIBLE

[www.ehlers-danlos.org](http://www.ehlers-danlos.org)  
T: 020 8736 5664



# Confirmation of Classical EDS

Identification of a pathogenic variant  
in COL5A1 or COL5A2

These are the genes that encode  
Type V Collagen

# Vascular EDS (vEDS) Diagnostic Criteria

- ***Major criteria***
- Family history of vEDS with documented causative variant in *COL3A1*
- Arterial rupture at a young age
- Spontaneous sigmoid colon perforation in the absence of known diverticular disease or other bowel pathology
- Uterine rupture during the third trimester in the absence of previous C-section and/or severe peripartum perineum tears
- Carotid-cavernous sinus fistula (CCSF) formation in the absence of trauma

# Vascular EDS (vEDS) Diagnostic Criteria

## *Minor criteria*

- Bruising unrelated to identified trauma and/or in unusual sites such as cheeks and back.
- Thin, translucent skin with increased venous visibility
- Characteristic facial appearance
- Spontaneous pneumothorax
- Acrogeria
- Talipes equinovarus
- Congenital hip dislocation
- Hypermobility of small joints
- Tendon and muscle rupture
- Keratoconus
- Gingival recession and gingival fragility
- Early-onset varicose veins (under age 30 and nulliparous if female)

# Minimal Criteria Suggestive for vEDS

- Family history of the disorder
- Arterial rupture or dissection in individuals <40 years of age
- Unexplained sigmoid colon rupture
- Spontaneous pneumothorax

# Confirmation of Vascular EDS

Identification of a pathogenic variant  
in COL3A1

This is the gene that encodes  
Type III Collagen

# Vascular EDS



(a)



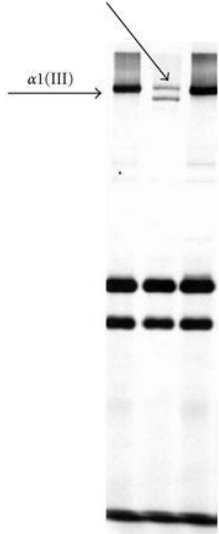
(b)



(c)




(d)



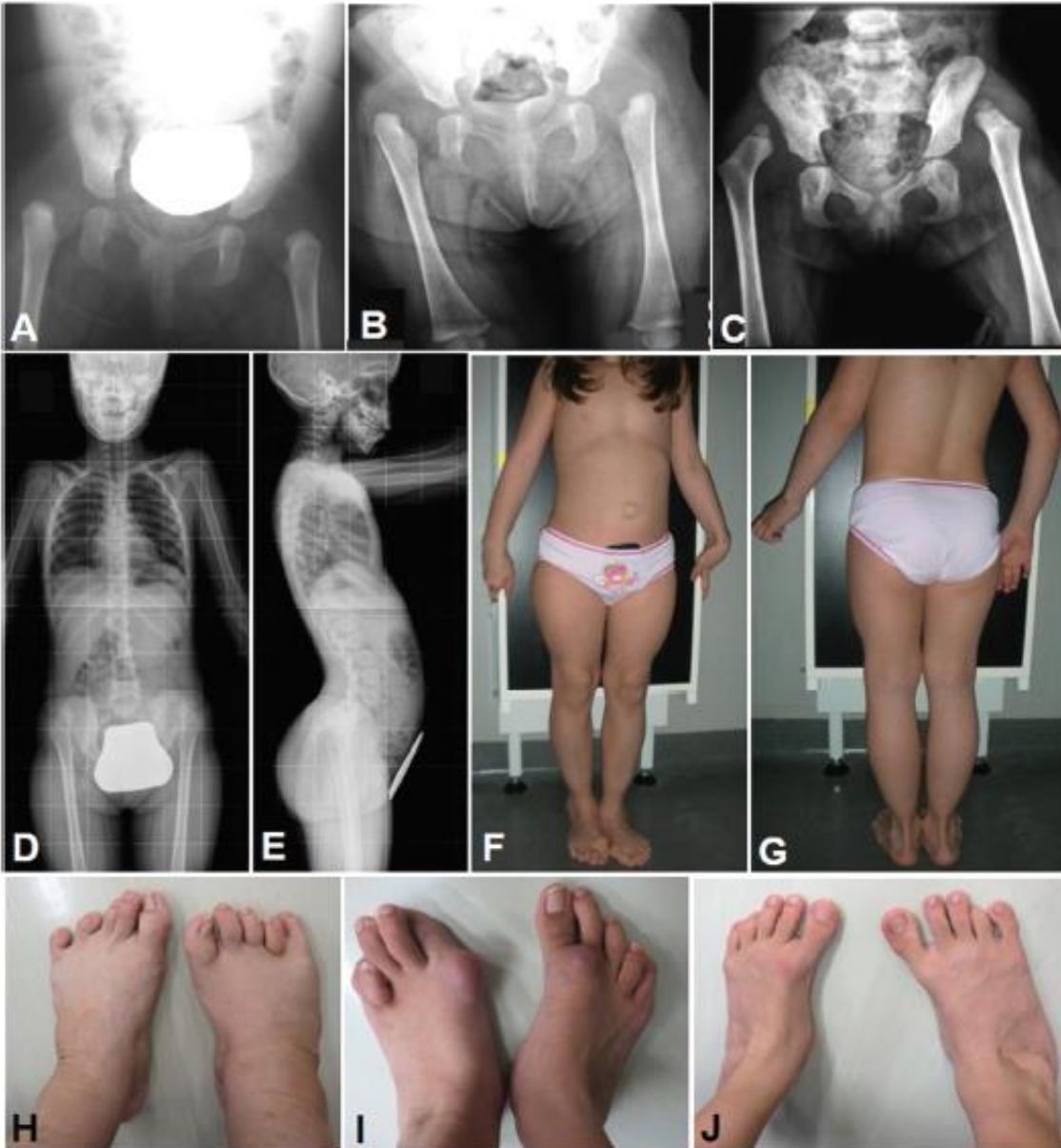
(e)

**R E S E A R C H R E V I E W**

# **The Ehlers–Danlos Syndromes, Rare Types**

**ANGELA F. BRADY, SERWET DEMIRDAS, SYLVIE FOURNEL-GIGLEUX, NEETI GHALI,  
CECILIA GIUNTA, INES KAPFERER-SEEBACHER, TOMOKI KOSHO,  
ROBERTO MENDOZA-LONDONO, MICHAEL F. POPE, MARIANNE ROHRBACH,  
TIM VAN DAMME, ANTHONY VANDERSTEEN, CAROLINE VAN MOURIK,  
NICOL VOERMANS, JOHANNES ZSCHOCKE, AND FRANSISKA MALFAIT \***

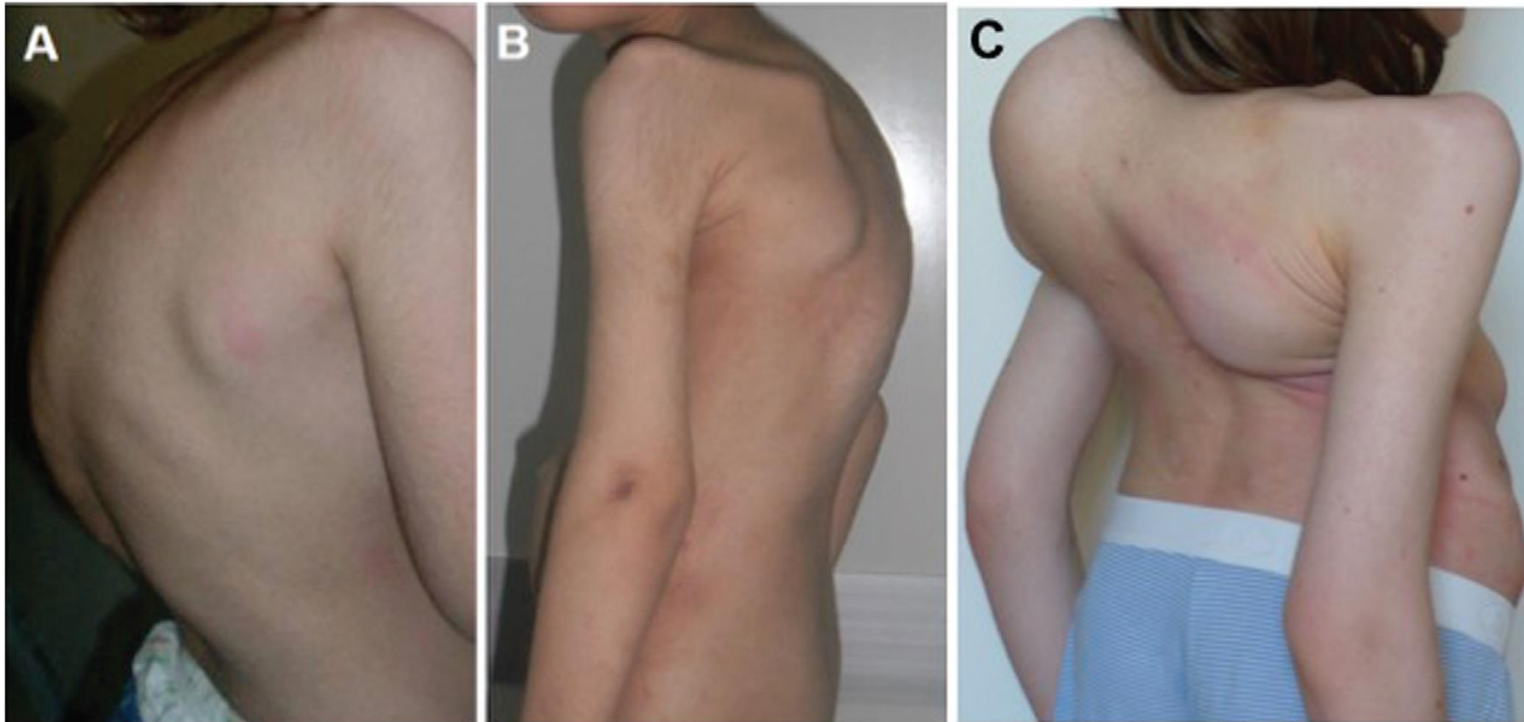
# Arthrochalasia EDS



- Severe generalized joint hypermobility
- Congenital bilateral hip dislocation
- Recurrent subluxations and dislocations of both small and large joints
- Variants in COL1A1 and COL1A2



# Kyphoscoliotic EDS



- Kyphoscoliosis – severe, progressive
- Joint hypermobility
- Joint subluxations and dislocations
- Skin hyperextensibility
- Skin fragility
- Easy bruising
- Atrophic scarring
- Variants in PLOD1 – lysyl hydroxylase1

# Brittle Cornea Syndrome

## *Variants in ZN469/PRDM5*



- Joint hypermobility - may be limited to small joints
- Joint subluxations and dislocations
- Hip dysplasia
- Kyphoscoliosis
- Foot deformities
  
- Soft, velvety skin
- Translucent skin
- No atrophic scarring
  
- High risk of corneal perforation and ocular rupture
- Keratoconus
- High myopia
- Blue sclerae
  
- Hearing loss

# A Few Hallmarks....

## **If the patient has:**

- Severe congenital joint laxity
- Congenital hip dislocations
- Congenital hip dysplasia
  
- Severe aortic or mitral valve disease
- Classical picture with vascular fragility
  
- Extreme skin fragility
  
- Kyphoscoliosis and short stature

## **Consider:**

- Arthrochalasia type
- Arthrochalasia type
- Kyphoscoliotic type
  
- Cardio-valvular type
- Classical due to COL1A1
  
- Dermatosporaxis type
- Classical type
  
- Kyphoscoliotic type
- Spondylodysplastic type
- Musculo-contractional type

# When to think about CSF Leaks

- If the nature of the headache changes
- If the person has had a lumbar puncture
- If the person has had any surgical procedure involving the dura such as spinal anesthesia
- If the person reports unusual drainage from their nose or ears



A photograph showing the rear view of a zebra's back and tail. The zebra's body is covered in characteristic black and white horizontal stripes. The tail is visible, with a tuft of dark hair at the end. The background is a blurred natural setting with dry grass and some green plants.

THANK YOU!

The ILC Foundation

The Ehlers-Danlos Society

The International EDS Consortium

My patients and their  
families