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

Clair A. Francomano, MD
Department of Medical and Molecular Genetics
Indiana University School of Medicine

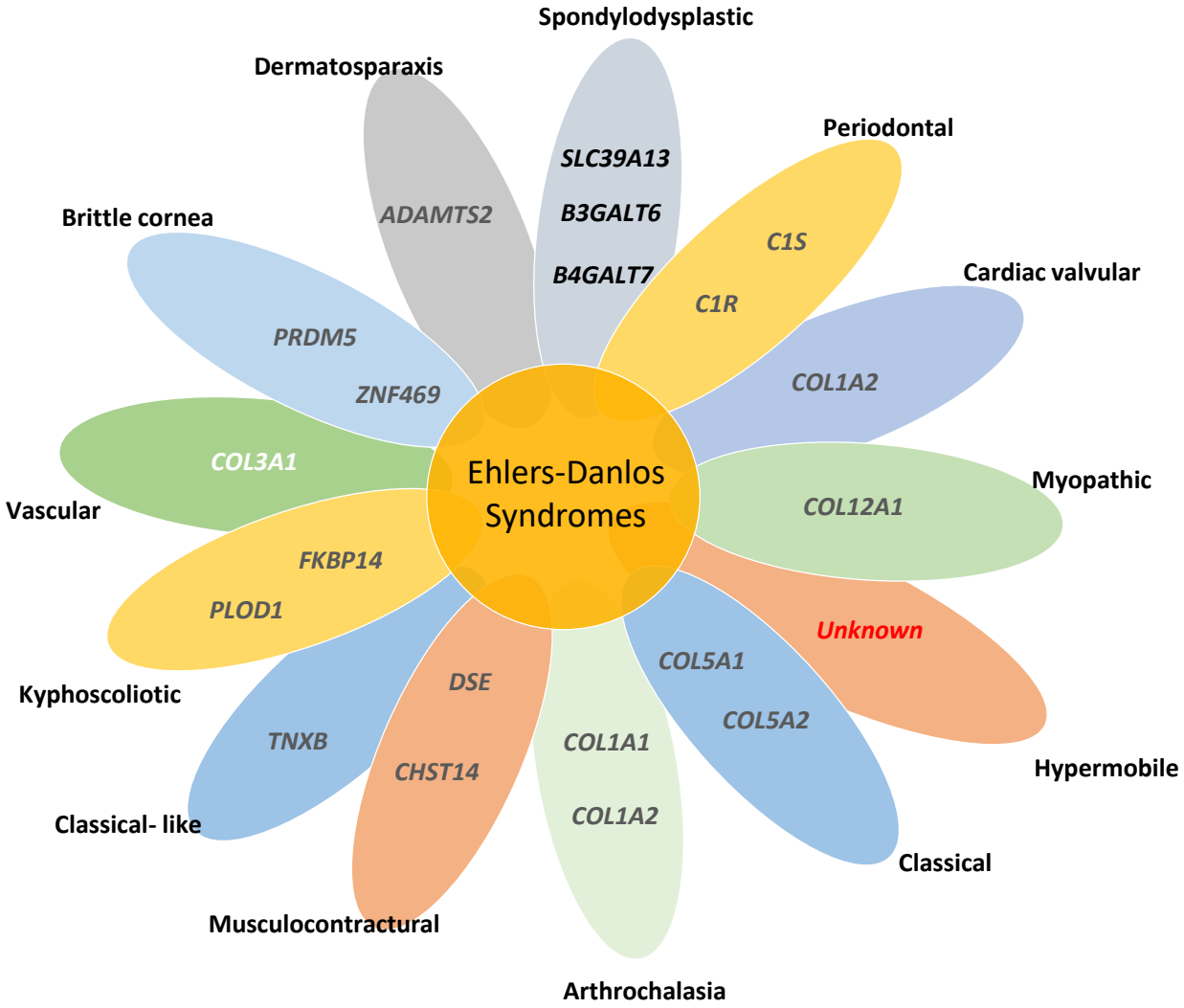
Spectrum of Joint Hypermobility

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	

Castori et al., 2017

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 α2 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	*B4GALT7*	β4GalT7 (Galactosyltransferase I)	AR
SpEDS_B3GALT6	*B3GALT6*	β3GalT6 (Galactosyltransferase II)	AR
MC-CHST14	*CHST14*	Dermatan 4-sulfotransferase 1	AR
MC-DSE	*DSE*	Dermatan sulfate epimerase 1	AR
Disorders linked to aberrant intracellular processes			
spEDS_SLC39A13	*SLC39A13*	ZIP13	AR
Brittle Cornea Syndrome	*ZN469/PRDM5*	ZNF469/PRDM5	AR
Disorders of complement pathway			
Periodontal EDS	*C1r/C1s*	C1R/C1S	AD

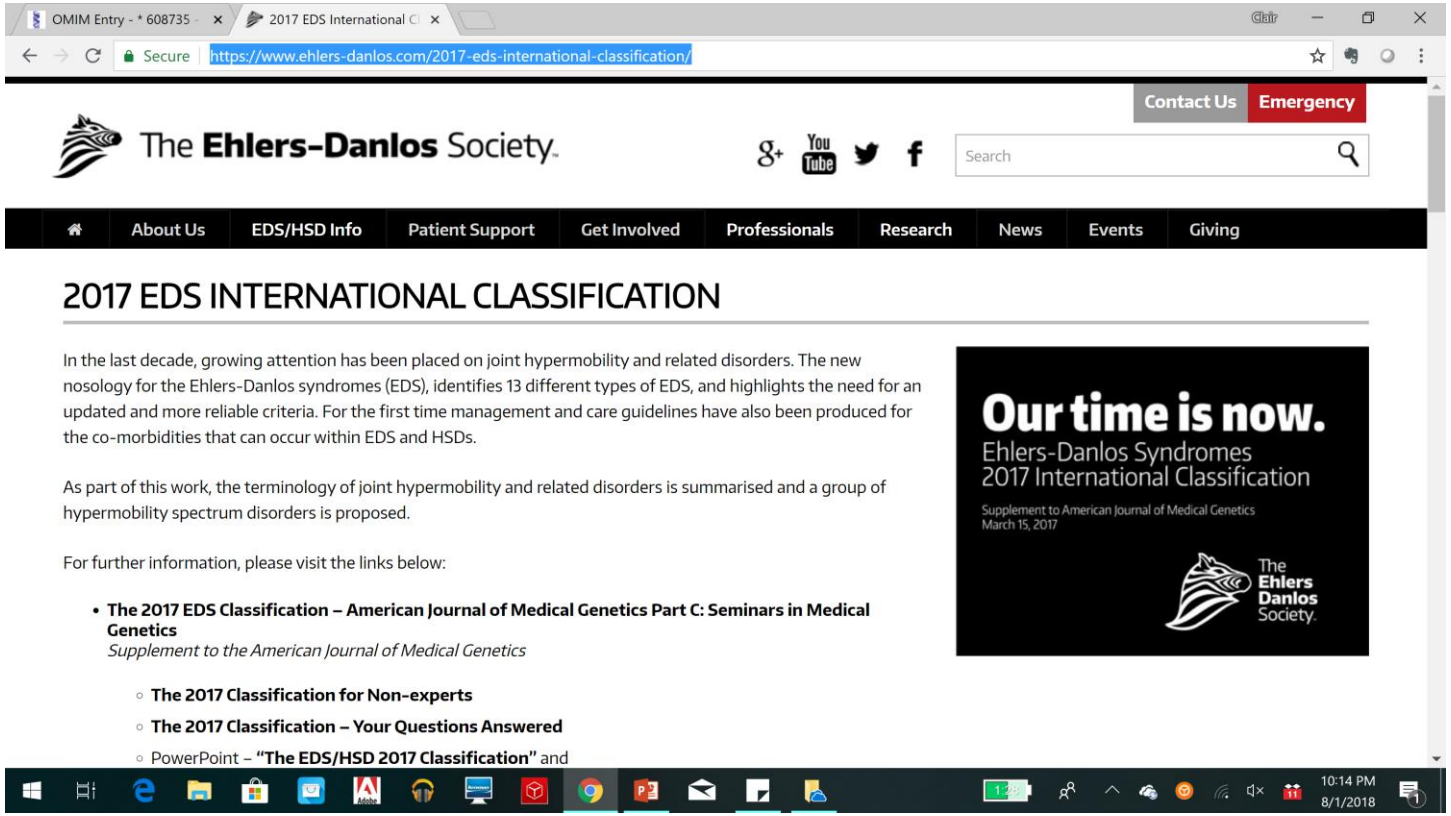
EDS types and their underlying genes



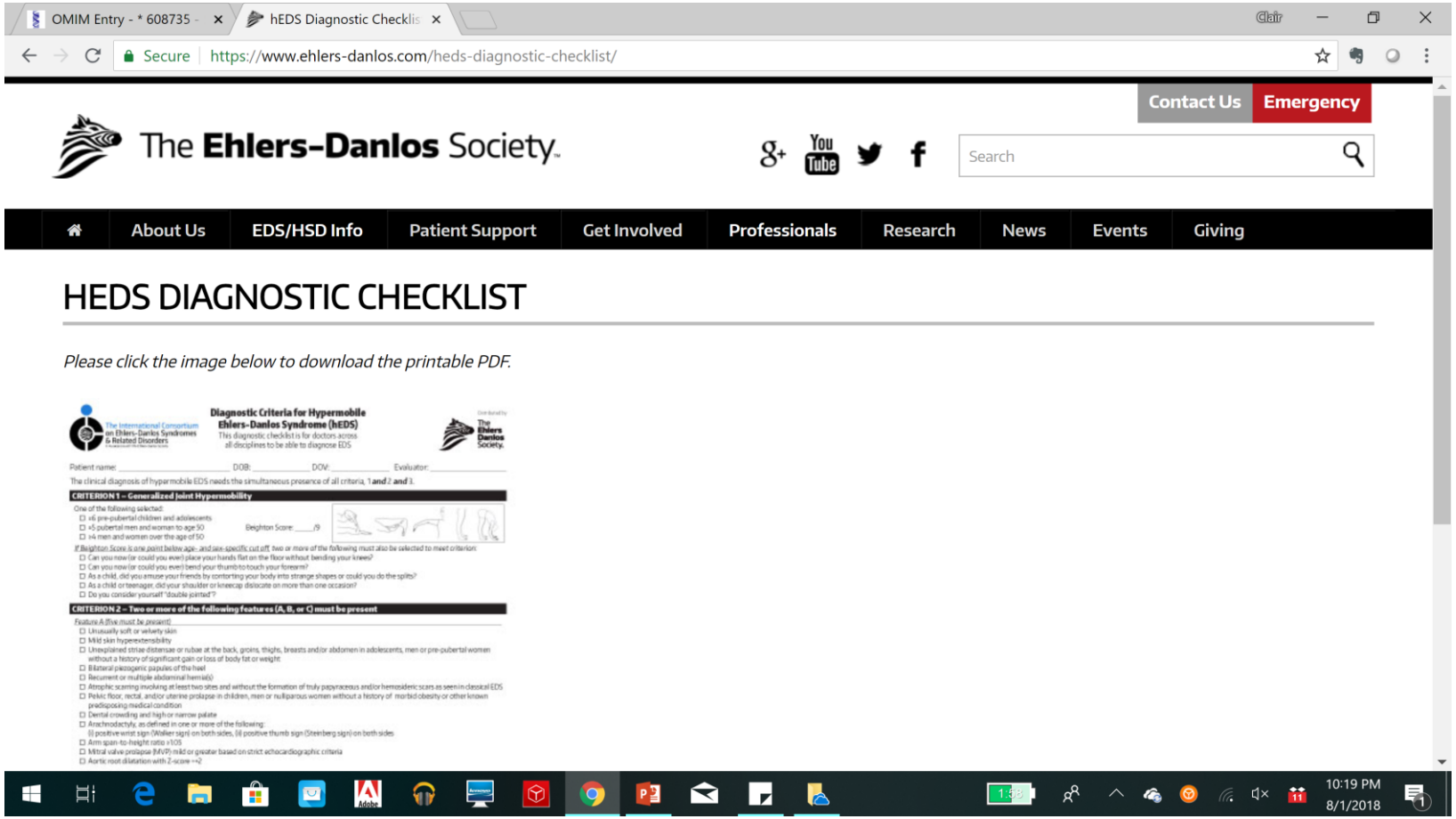
J Amberger, C Bochinni, A Hamosh, 2018

How is Ehlers-Danlos Syndrome Diagnosed?

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



What are the 2017 criteria for diagnosing hEDS?



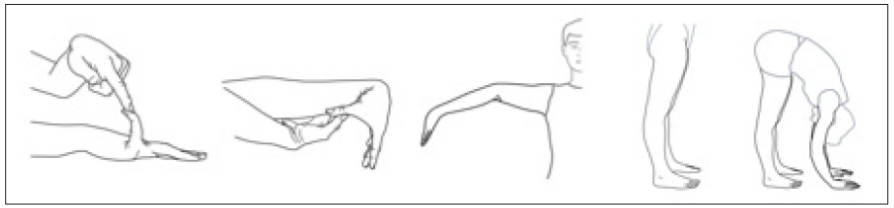
Criterion 1: Generalized Joint Hypermobility

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 ≥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

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

Feature C (must have at least one)

- ☐ Musculoskeletal pain in two or more limbs, recurring daily for at least 3 months
- ☐ Chronic, widespread pain for ≥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 Critera

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

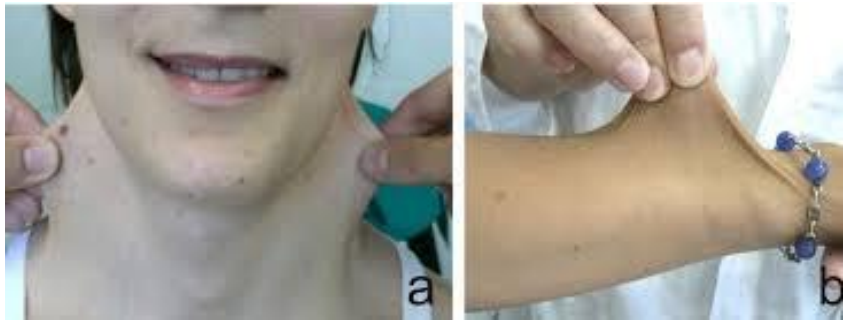
Clinical Diagnosis of Classical EDS:
2017 Criteria

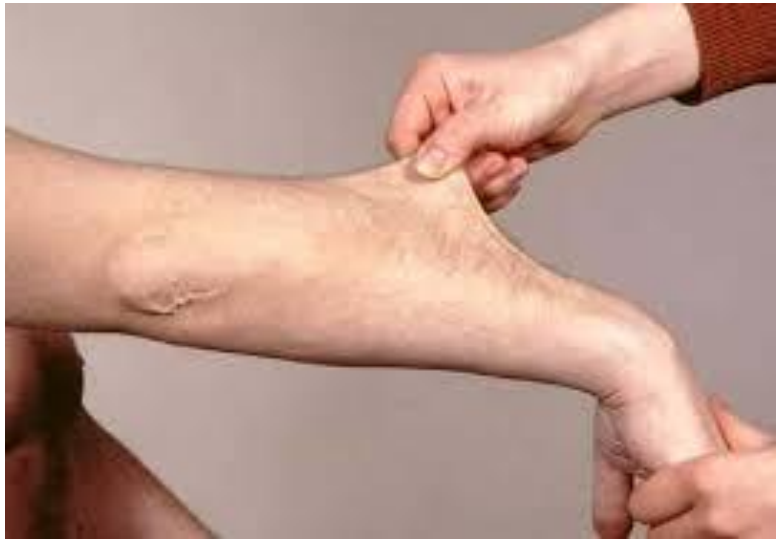
Major Criterion (1):
Skin hyperextensibility and atrophic scarring

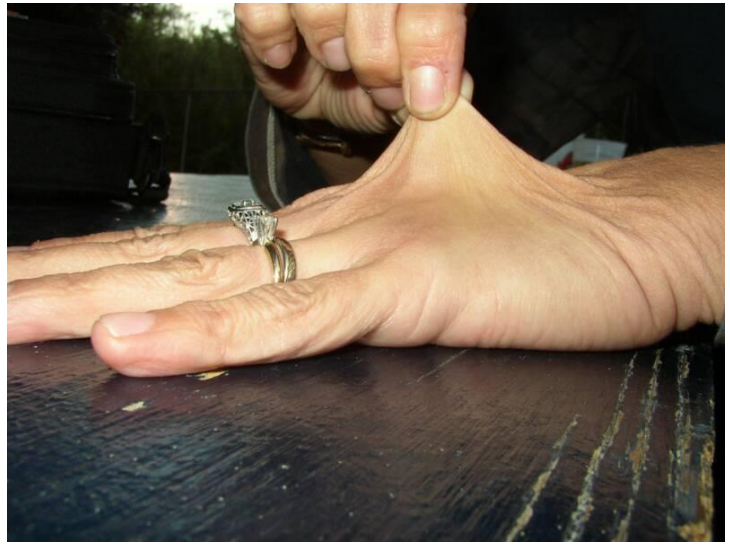
Plus

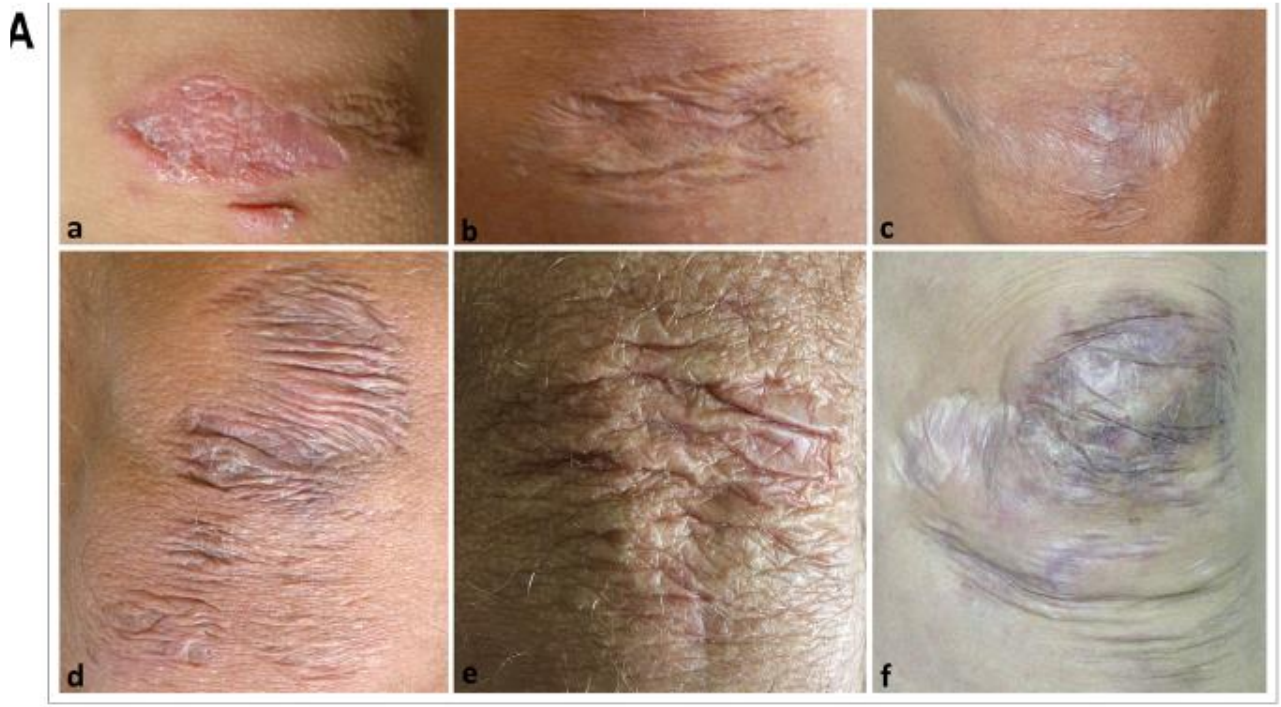
Either: Major criteria (2) – joint hypermobility
Or: three of the eight minor criteria

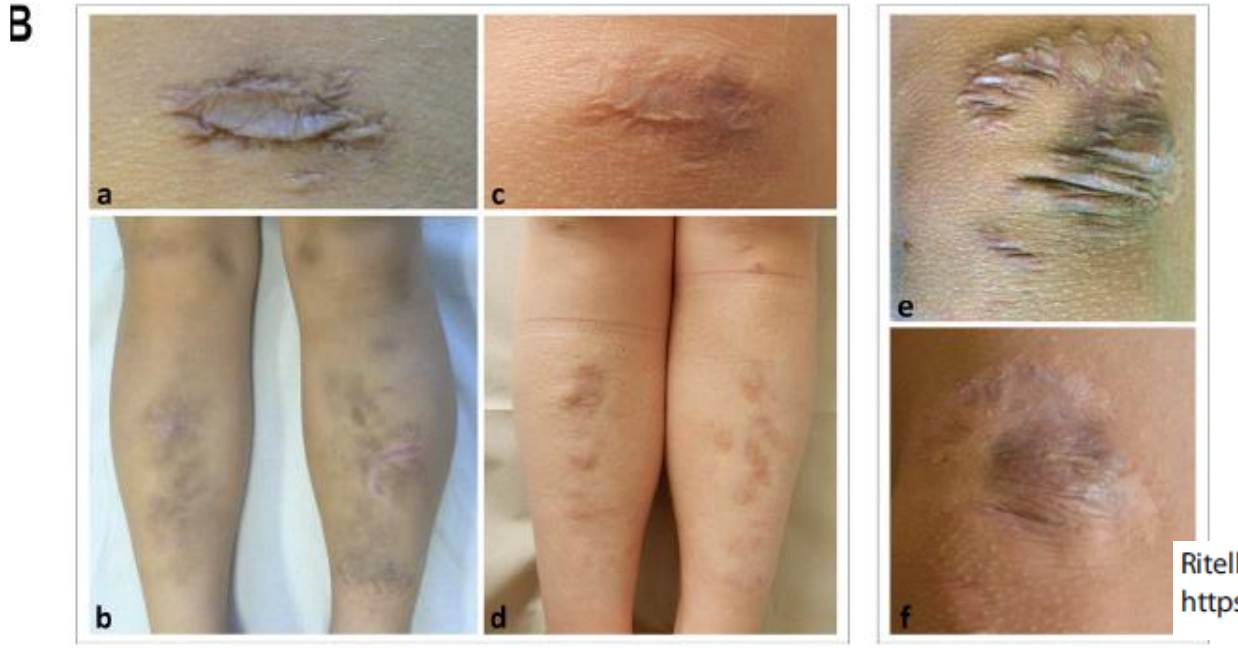
Skin Hyperextensibility











Ritelli *et al. Orphanet Journal of Rare Diseases* (2020) 15:197
https://doi.org/10.1186/s13023-020-01470-0


Beighton score
Give yourself 1 point
for each of the manoeuvres you can do,
up to a maximum of 9 points
Can you bend your thumb back
Can you bend your knee backwards?
Can you put your hands flat on the floor with your knees straight?
Can you bend your elbow backwards?
Can you bend your little finger up at 90° (right angle) to the back of your hand?
1 point
www.ehlers-danlos.org
T: 020 8736 5684

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

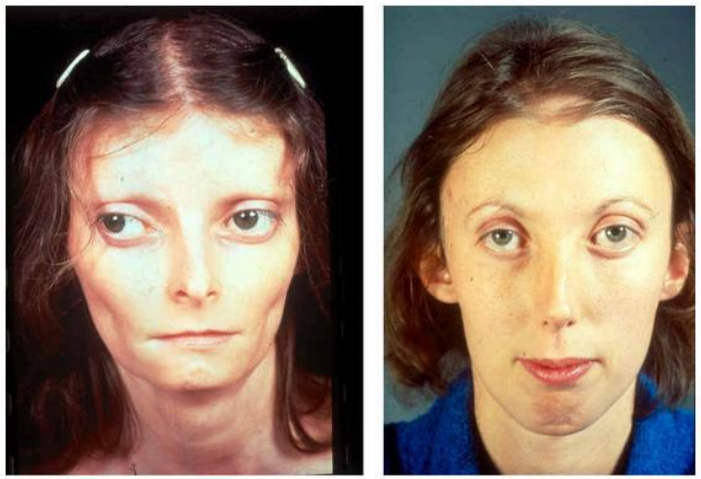
Identification of a pathogenic variant

in COL3A1

This is the gene that encodes

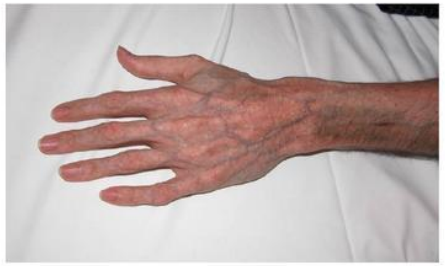
Type III Collagen

Vascular EDS



(a)

(b)



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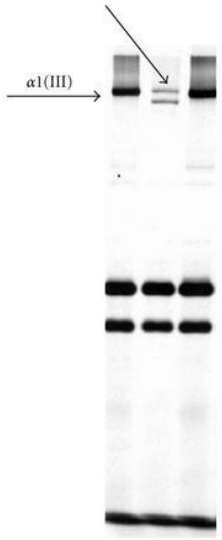

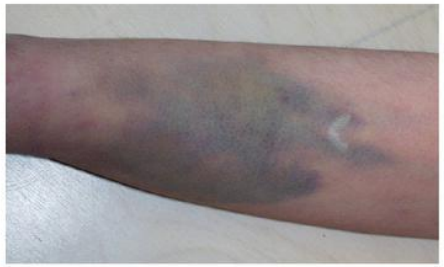

(d)

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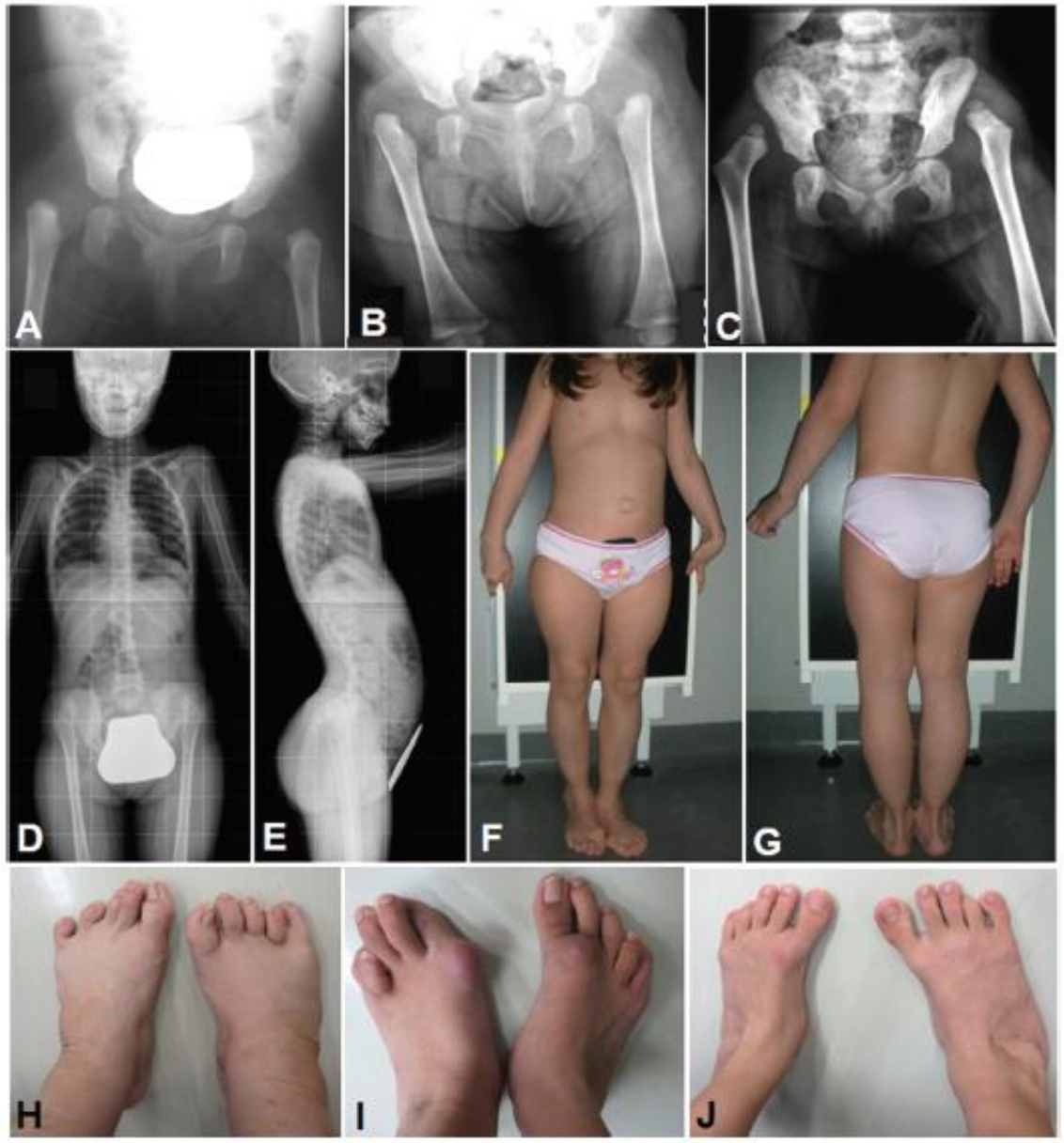
American Journal of Medical Genetics Part C (Seminars in Medical Genetics) 175C:70–115 (2017)

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 *

www.ehlers-danlos.com/pdf/2017-FINAL-AJMG-PDFs/Brady_et_al-2017-American_Journal_of_Medical_Genetics_Part_C-_Seminars_in_Medical_Genetics.pdf

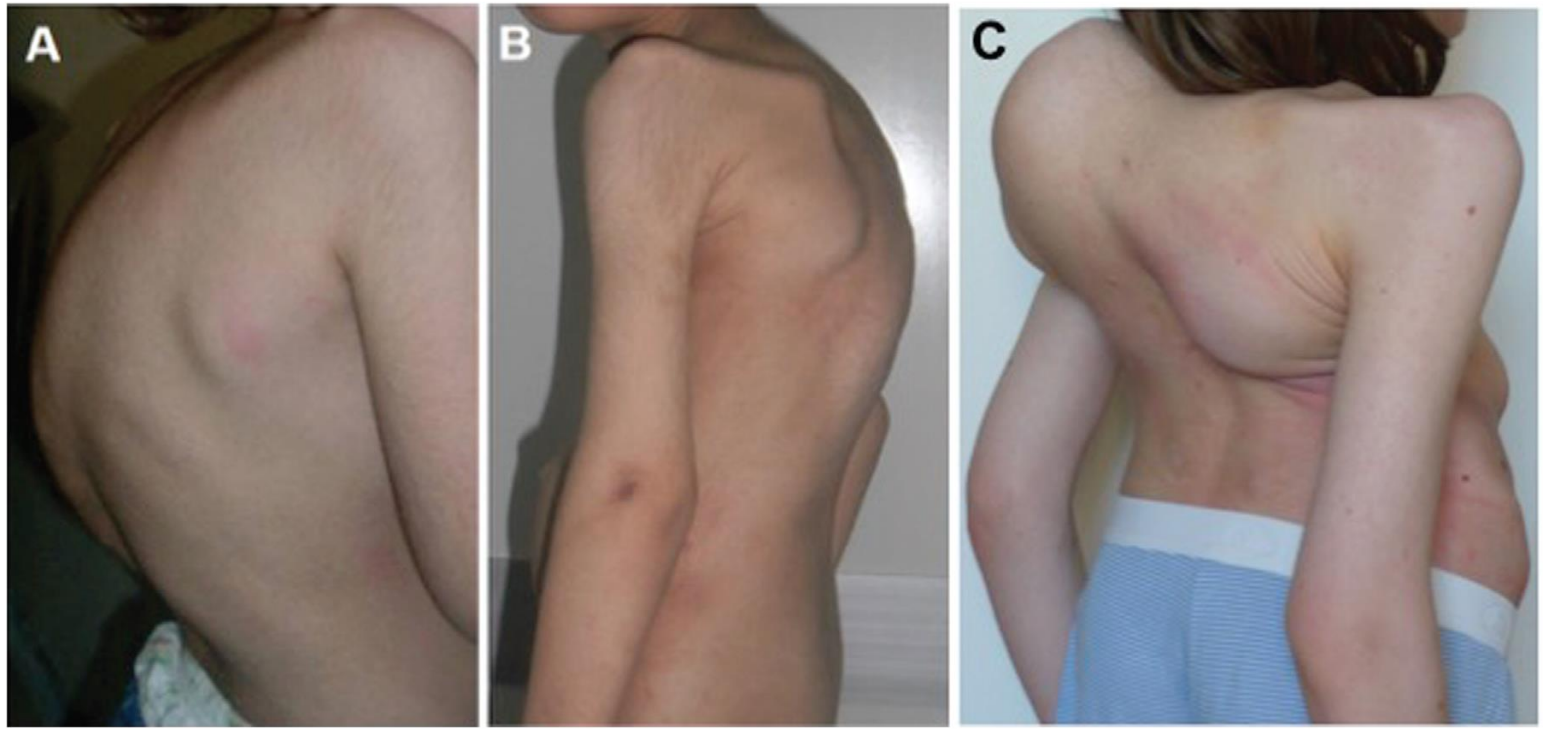


Arthrochalasia EDS

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

Brady et al. AJMG Part C Semin Med Genet 175C:70-115, 2017

Kyphoscoliotic EDS



- Kyphoscoliosis – severe, progressive
- Joint hypermobility
- Joint subluxations and dislocations

- Skin hyperextensibility
- Skin fragility
- Easy bruising
- Atrophic scarring

- Variants in PLOD1 – lysyl hydroxylase1

Brady et al. AJMG Part C Semin Med Genet 175C:70-115, 2017

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

Brady et al. AJMG Part C Semin Med Genet 175C:70-115, 2017

A Few Hallmarks….

If the patient has:	**Consider:**
• Severe congenital joint laxity	Arthrochalasia type
• Congenital hip dislocations	Arthrochalasia type
• Congenital hip dysplasia	Kyphoscoliotic type
• Severe aortic or mitral valve disease	Cardio-valvular type
• Classical picture with vascular fragility	Classical due to COL1A1
• Extreme skin fragility	Dermatosporaxis type Classical type
• Kyphoscoliosis and short stature	Kyphoscoliotic type Spondylodysplastic type Musculo-contractural 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

THANK YOU!

The ILC Foundation
The Ehlers-Danlos Society
The International EDS Consortium

My patients and their families