Hereditary Disorders of Connective Tissue: Overview

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Disclosures

- I have no conflicts to disclose

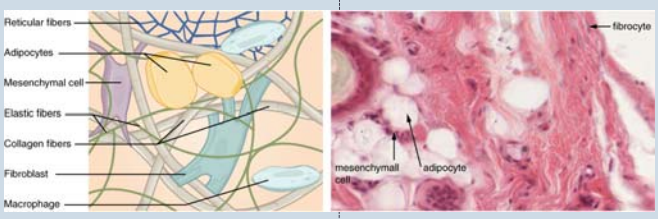
Joint Hypermobility

- Seen in over 140 clinical syndromes listed in Online Mendelian Inheritance in Man (OMIM)
- Congenital anomaly syndromes
- Short stature syndromes
- Hereditary disorders of connective tissue

Connective Tissue Supports and Protects

- Bones
- Cartilage
- Tendons
- Ligaments

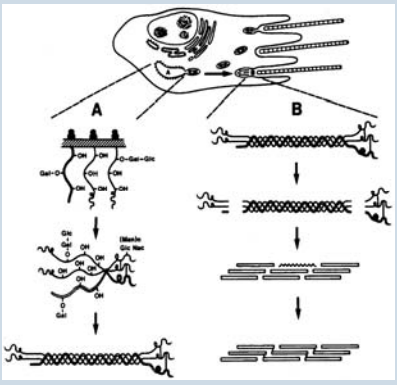
- Collagen Fibers
- Elastic Fibers
- Mucopolysaccharides



Fibrillar Collagens

- Major structural components of the extracellular matrix
- Include collagen types I, II, III, V, IX, and XI
- Trimeric molecules (three chains)
- May be made up of three identical or genetically distinct chains, called alpha chains

Fibrillar Collagens



Biochemical Society Transactions (1999) , - -
www.biochemsoctrans.org

Hereditary Disorders of Connective Tissue

- Marfan syndrome
- Loeys-Dietz syndrome
- Stickler syndrome
- Osteogenesis Imperfecta
- Ehlers-Danlos syndromes

Marfan Syndrome

- Aneurysmal dilation of the ascending aorta
- Dislocation of the ocular lenses
- Tall stature
- Scoliosis
- Pectus deformity
- Arachnodactyly (long, narrow fingers and toes)
- Dolicostenomelia (tall, thin body habitus)

- Caused by mutations in Fibrillin-1

Marfan Syndrome

Loeys-Dietz Syndrome

- Aortic dilation with dissection
- Tortuous blood vessels
- Craniofacial features
  - Hypertelorism
  - Malar hypoplasia
  - Cleft palate or bifid uvula

- Caused by mutations in TGFBR1 and TGFBR2

as well as 3 other genes in the TGF pathway

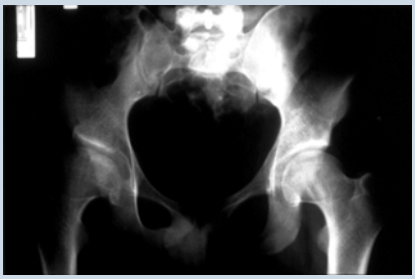
Loeys-Dietz Syndrome

Stickler Syndrome

- Vitreo-retinal degeneration
- Sensori-neural hearing loss
- Premature osteoarthritis
- Cleft palate or bifid uvula
- Pierre-Robin anomaly
- Spondylo-epiphyseal dysplasia

- Caused by mutations in COL2A1, COL11A1 and COL11A2

Stickler syndrome

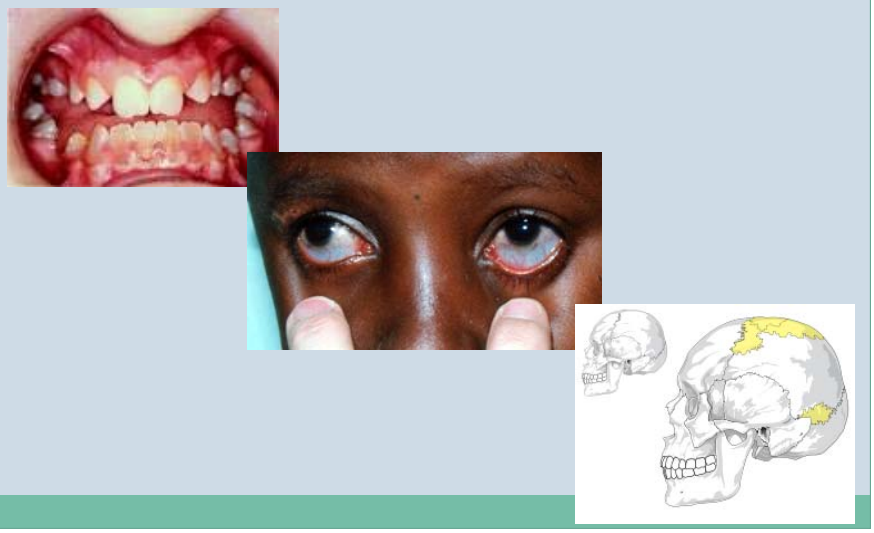


Osteogenesis Imperfecta (Brittle Bone Disease)

- Four major types
- Two types present with average stature
- Frequent fractures
- Blue Sclerae
- Dentinogenesis imperfecta
- Hearing loss
- Wormian bones

- Caused by mutations in Type I collagen and 17 others
- OI gene variant database: https://oi.gene.le.ac.uk/home.php

Osteogenesis Imperfecta



Ehlers-Danlos Syndrome

- Spectrum of monogenic disorders
- Wide range of phenotypic severity
- Predominantly affecting joints, skin, blood vessels and internal organs to varying degrees

EDS: Molecular Causes

- Most forms are caused by defects in one of the fibrillar collagens or of enzymes involved in fibrillar collagen processing
- Recent research has identified defects in biosynthesis of other molecules in the extraceullar matrix and molecules involved in intracellular trafficking, secretion and assembly of ECM molecules

Classification of the Ehlers-Danlos syndrome based on the Villefranche nosology

New	Gene	Protein	Transmission
Classical	*COL5A1* *COL5A2*	Type V procollagen	AD
Hypermobility	*?*	?	AD
Vascular	*COL3A1*	Type III procollagen	AD
Kyphoscoliosis	*PLOD1*	Lysyl hydroxylase	AR
Arthrochalasis	*COL1A1* *COL1A2*	Type I collagen (N-propeptide-processing)	AD
Dermatosparaxis	*ADAMTS2*	Procollagen N proteinase	AR

Beighton et al, AJMG, 1998

Classification of EDS Types: 2017

Classical type	AD
Classical-like EDS (clEDS)	AR
Cardiac-valvular EDS (cvEDS)	AR
Vascular EDS (vEDS)	AD
Hypermobile EDS (hEDS)	AD
Arthrochalasia EDS (aEDS)	AD
Dermatosparaxis EDS (dEDS)	AR

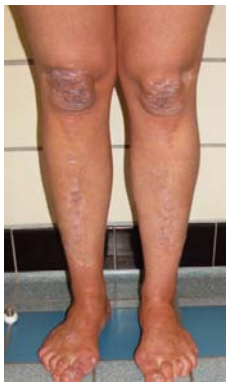
Kyphoscoliotic EDS (kEDS)	AR
Brittle cornea synsrome (BCS)	AR
Spondylodysplastic EDS (spEDS)	AR
Musculocontractural EDS (mcEDS)	AR
Myopathic EDS (mEDS)	AD or AR
Periodontal EDS (pEDS)	AD

Classical EDS (cEDS): 2017 Criteria

Major criteria

1. Skin hyperextensibility and atrophic scarring
2. Joint hypermobility

Classical EDS: Skin Findings



DePaepe and Malfait, 2012

http://www.epharmapedia.com/diseases/profile/167/Ehlers-Danlos-syndrome.html?lang=en

Classical EDS: Minor Diagnostic 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

cEDS: Verification of Clinical Diagnosis

- Confirmatory analysis is recommended for any patient meeting the recommended clinical criteria
- Molecular analysis of *COL5A1* and *COL5A2* genes identifies a causal mutation in more than 90% of the patients and should be used as the standard confirmatory test

Vascular EDS (vEDS): 2017 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: 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 of vEDS

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

In the presence of other features consistent with vEDS, any of these ffindings should lead to diagnostic studies to determine if the individual has vEDS.

Testing for vEDS should also be considered in the presence of a combination of the other 'minor' clinical features listed above

vEDS: Diagnostic Confirmation

The diagnosis of vEDS rests on the identification of a causative variant in one allele of *COL3A1*

Hypermobile EDS (hEDS)

- New criteria designed to emphasize syndromic nature of the condition, reduce clinical heterogeneity and facilitate research into underlying cause(s)
- It is expected that further clinical experience and research will lead to revision of these criteria with time

Hypermobile EDS: 2017 Diagnostic Criteria

Clinical diagnosis of hEDS requires the presence of

Criteria 1, 2, AND 3

Hypermobile EDS: Criterion 1

Generalized Joint Hypermobility (GJH)

Beighton Score

Prepubertal children and adolescents	≥ 6
Men and women, post-puberty up to age 50	≥ 5
Men and women older than 50	≥ 4

If the Beighton score is 1 point below the cutoff and the 5PQ is "positive" (at least 2 positive items), a diagnosis of GJH may be made.

Generalized Joint Hypermobility

33

- 5-Point Questionnaire

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?

Hypermobile EDS: Criterion 2

2 or more of the following features:

A: Systemic manifestations of a more generalized connective tissue disorder

B: Positive family history

C: Musculoskeletal complications

Feature A: Systemic manifestations of a more generalized connective tissue disorder

At least 5 of the following must be present:

- Unusually soft or velvety skin
- Mild skin hyperextensibility
- Unexplained striae without a history of significant weight change
- Bilateral piezogenic papules of the heel
- Recurrent or multiple abdominal hernia(s) (e.g. umbilical, inguinal, crural)
- Atrophic scarring involving at least two sites and without the formation of truly papyraceous and/or hemosideric scars as seen in classical EDS

(continued on next slide)

Feature A: Systemic manifestations of a more generalized connective tissue disorder (cont.)

- 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 (Steinberg sign) on both sides; (ii) positive thumb sign (Walker 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 B: Positive Family History

- One or more first degrees relatives independently meeting the diagnostic criteria for hEDS

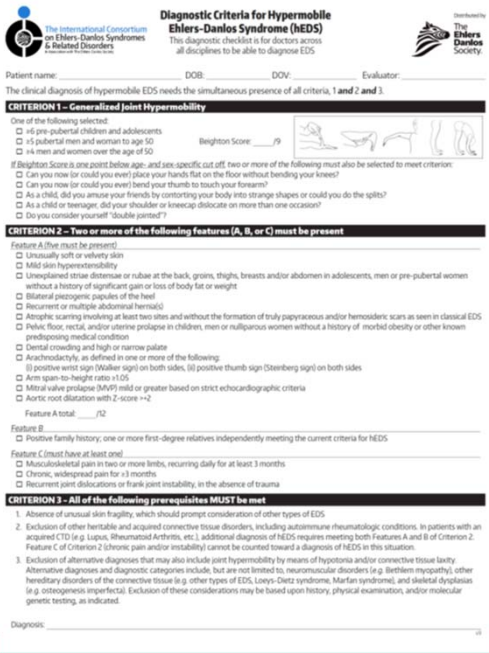
Feature C: Musculoskeletal Complications

At least one of the following:

- 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
  a. Three or more atraumatic dislocations in the same joint or two or more atraumatic dislocations in two different joints occurring at different times
  b. Medical confirmation of joint instability at 2 or more sites, unrelated to trauma

Criterion 3: All required

- Absence of unusual skin fragility, which should prompt consideration of other types of EDS
- Exclusion of other heritable and acquired connective tissue disorders, including autoimmune rheumatologic conditions.
- Exclusion of alternative diagnoses that may also include joint hypermobility by means of hypotonia and/or connective tissue laxity.



The International Consortium on Ehlers-Danlos Syndromes & Related Disorders

Diagnostic Criteria for Hypermobile Ehlers-Danlos Syndrome (hEDS)

This diagnostic checklist is for doctors across all disciplines to be able to diagnose EDS

Distributed by The Ehlers Danlos Society

Patient name: _____ DOB: _____ DOV: _____ 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
- ☐ ≥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 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.

Diagnosis: _____

The 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	

EDS and Hypermobility Spectrum Disorders Often Present with Complex Phenotypes

- Chronic pain – musculoskeletal and/or neuropathic
- Chronic fatigue/sleep disturbance
- Headaches
- TMJ
- Autonomic dysfunction
- Gastrointestinal dysmotility, abdominal pain, IBS
- Urinary symptoms – urgency, frequency, incontinence
- Mast cell activation syndrome

If you can't connect the issues, think connective tissues!

Estimated Prevalence of HDCT

• Ehlers-Danlos syndrome	1/5,000
• Marfan Syndrome	1/5000
• Stickler syndrome	1/7500-1/9000
• Osteogenesis Imperfecta	6-7/100,000
• Loeys-Dietz syndrome	Unknown

Helpful Websites

- Marfan Foundation: www.marfan.org
- Loeys Dietz Syndrome Foundation: www.loeysdietz.org
- Stickler Involved People: www.stickler.org
- Osteogenesis Imperfecta Foundation: www.oif.org
- Ehlers-Danlos Society: www.ehler-danlos.com
- EDS Classification Issue – American J Med Genet

https://www.ehlers-danlos.com/2017-eds-international-classification/


THANK YOU!