2017 International EDS Classification

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on behalf of
The International Consortium on EDS and Related Disorders

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

Type of EDS (Older nomenclature)	Mode of Inheritance	Molecular Defect
Classical (EDS I and II)	AD	Type V collagen
Hypermobility (EDS III)	AD	unknown
Vascular (EDS IV)	AD	Type III collagen
Kyphoscoliosis (EDS VI)	AR	Deficiency of Lysyl hydroxylase
Arthrochalasia (EDS VII)	AD	Type I collagen
Dermatosporaxis (EDS VII)	AR	Type I collagen processing

Beighton et al., 1998

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X-linked EDS (type V)	XL
Periodontitis type (type VIII)	AD
Fibronectin-deficient EDS (type X)	?
Familial hypermobility syndrome	AD
Progeroid EDS	?
Unspecified forms	-

Classification of EDS Types: 2017

Classical EDS (cED)	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 syndrome (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: 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
- In case of unavailability of genetic testing, electron microscopy findings of collagen flowers on skin biopsy can support the clinical diagnosis
- Absence of these confirmatory findings does not exclude the diagnosis, however alternative diagnoses should be considered in the absence of a type V collagen gene mutation or electron microscopy findings

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 for 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 should all 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

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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

1997 Criteria for Hypermobility Type EDS

Major Criteria:

- Skin involvement (hyperextensibility and/or smooth velvety skin)
- Generalized joint hypermobility

Minor Criteria:

- Recurring joint dislocations
- Chronic joint/limb pain
- Positive family history

The presence of one or both of the major criteria is necessary for clinical diagnosis; the presence of one or more minor criteria contributes to the diagnosis but in the absence of a major criterion, they are not sufficient to establish a diagnosis.

Beighton et al., 1998

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 $\geq$ 6
- Men and women, post-puberty up to age 50 $\geq$ 5
- Men and women older than 50 $\geq$ 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

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 and B, B and C, or A and C)

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

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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

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 prerequisites 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.
- In patients with an acquired/autoimmune connective tissue disorder 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
- Exclusion of alternative diagnoses that may also include joint hypermobility by means of hypotonia and/or connective tissue laxity.

Syndrome: Definition

A pattern of anomalies, at least one of which is morphologic, known or thought to be causally related (Hannekam et al, 2013)

The presence of joint hypermobility in combination with secondary musculoskeletal anomalies does not suffice for delineation of a genetic syndrome

Joint hypermobility may occur independently or in the context of multiple genetic disorders

Classifying joint hypermobility

Persons with asymptomatic joint hypermobility

- Localized
- Generalized
- Peripheral

Persons with a well-defined syndrome with joint hypermobility

Individuals with symptomatic joint hypermobility, not meeting diagnostic criteria for a syndrome

Hypermobility Spectrum Disorders

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	

Why were co-morbidities not included in the hEDS Diagnostic criteria?

Not enough is yet known about the relationship between various co-morbidities and hEDS (or any of the other types)

I don't know if I meet all those diagnostic criteria. Will my diagnosis be changed?

Unless you have a reason to seek a change in diagnosis, there is no need to do so at this time.

If you are interested in seeing whether you meet the more stringent criteria for hEDS, you may certainly speak with the physician who made your diagnosis to see whether you meet the new criteria.

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