FICHE COMPLETEE A JOINDRE OBLIGATOIREMENT AU BON DE DEMANDE D'EXAMEN POUR ANALYSE DE GENETIQUE MOLECULAIRE (TLF069) DES "LAMINOPATHIES ET VIEILLISSEMENT PREMATURE" PAR NGS POUR L'INDICATION "SYNDROME D'EHLERS-DANLOS (EDS)".

Le diagnostic clinique de l'un des sous-types d'EDS décrits ci-dessous est nécessaire et doit être argumenté (cases à cocher) afin que la demande soit considérée par le laboratoire. Base classification : *Malfait et al., American Journal of Medical Genetics Part C (Seminars in Medical Genetics) 175C:8–26 (2017)*

PATIENT	**PRESCRIPTEUR**	**DATE :**
nom :	nom :	**commentaire éventuel:**
prénom :	prénom :	
date de naissance :	service :	

Classical EDS (cEDS) (major *COL5A1,* rare *COL1A1*)

Autosomal dominant

- **Major criteria**

1. Skin hyperextensibility 1 and atrophic scarring ☐
2. Generalized joint hypermobility (GJH*) ☐

- **Minor criteria**

1. Easy bruising ☐
2. Soft, doughy skin ☐
3. Skin fragility (or traumatic splitting) ☐
4. Molluscoid pseudotumors ☐
5. Subcutaneous spheroids ☐
6. Hernia (or history thereof) ☐
7. Epicanthal folds ☐
8. Complications of joint hypermobility (e.g., sprains, luxation/ subluxation, pain, flexible flatfoot) ☐
9. Family history of a first degree relative who meets clinical criteria ☐

- **Minimal criteria suggestive for cEDS:**

– Major criterion (1): skin hyperextensibility and atrophic scarring
Plus
– Either major criterion (2): GJH
– And/or: at least three minor criteria

GJH = Generalized joint hypermobility

Classical-Like EDS (clEDS) (*TNXB*)

Autosomal Recessive

- **Major criteria**

1. Skin hyperextensibility, 9 with velvety skin texture and absence of atrophic scarring ☐
2. GJH with or without recurrent dislocations (most commonly shoulder and ankle) ☐
3. Easy bruisable skin/spontaneous ecchymoses ☐

- **Minor criteria**

1. Foot deformities: broad/plump forefoot, brachydactyly with excessive skin; pes planus; hallux valgus; piezogenic papules ☐
2. Edema in the legs in absence of cardiac failure ☐
3. Mild proximal and distal muscle weakness ☐
4. Axonal polyneuropathy ☐
5. Atrophy of muscles in hands and feet ☐
6. Acrogeric hands, mallet finger(s), clinodactyly, brachydactyly ☐
7. Vaginal/uterus/rectal prolapse ☐

- **Minimal criteria suggestive for clEDS:**

– All three major criteria AND a family history compatible with autosomal recessive transmission.

Cardiac-Valvular EDS (cvEDS) (*COL1A2* biallelic null)

Autosomal recessive

- **Major criteria**

1. Severe progressive cardiac-valvular problems (aortic valve, mitral valve) ☐
2. Skin involvement: skin hyperextensibility, 11 atrophic scars, thin skin, easy bruising ☐
3. Joint hypermobility (generalized or restricted to small joints) ☐

- **Minor criteria**

1. Inguinal hernia ☐
2. Pectus deformity (especially excavatum) ☐
3. Joint dislocations ☐
4. Foot deformities: pes planus, pes planovalgus, hallux valgus ☐

- **Minimal criteria suggestive for cvEDS:**

– Major Criterion (1): severe progressive cardiac-valvular problems
– AND a family history compatible with autosomal recessive inheritance
Plus
– Either: one other major criterion
– And/or: at least two minor criteria

Vascular EDS (vEDS) (major *COL3A1,* rare *COL1A1*)

Autosomal dominant

- **Major criteria**

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

- **Minor criteria**

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

- **Minimal criteria suggestive for vEDS:**

A family history of the disorder, arterial rupture or dissection in individuals

less than 40 years of age, unexplained sigmoid colon rupture, or 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.

Arthrochalasia EDS (aEDS) (*COL1A1, COL1A2*)

Autosomal dominant

- **Major criteria**

1. Congenital bilateral hip dislocation 21 ☐
2. Severe GJH, with multiple dislocations/subluxations 22 ☐
3. Skin hyperextensibility 22 ☐

- **Minor criteria**

1. Muscle hypotonia ☐
2. Kyphoscoliosis ☐
3. Radiologically mild osteopenia ☐
4. Tissue fragility, including atrophic scars ☐
5. Easy bruisable skin

- **Minimal criteria suggestive for aEDS:**

– Major criterion (1): Congenital bilateral hip dislocation
Plus
– Either major criterion (3): skin hyperextensibility
– Or major criterion (2): severe GJH withmultipledislocations/subluxations and at least two other minor criteria

Dermatosparaxis EDS (dEDS) (*ADAMTS2*)

Autosomal recessive

- **Major criteria:**

1. Extreme skin fragility with congenital or postnatal skin tears ☐
2. Characteristic craniofacial features, which are evident at birth or early infancy, or evolve later in childhood ☐
3. Redundant, almost lax skin, with excessive skin folds at the wrists and ankles ☐
4. Increased palmar wrinkling ☐
5. Severe bruisability with a risk of subcutaneous hematomas and haemorrhage ☐
6. Umbilical hernia ☐
7. Postnatal growth retardation ☐
8. Short limbs, hand and feet ☐
9. Perinatal complications due to connective tissue fragility ☐

- **Minor criteria**

1. Soft and doughy skin texture ☐
2. Skin hyperextensibility ☐
3. Atrophic scars ☐
4. GJH ☐
5. Complications of visceral fragility (e.g., bladder rupture, diaphragmatic rupture, rectal prolapse) ☐
6. Delayed motor development ☐
7. Osteopenia ☐
8. Hirsutism ☐
9. Tooth abnormalities ☐
10. Refractive errors (myopia, astigmatism) ☐
11. Strabismus ☐

- **Minimal criteria suggestive for dEDS:**

– Majorcriterion(1):extremeskinfragility
– AND major criterion (2): characteristic craniofacial features
Plus
– Either: one other major criterion
– And/or: three minor criteria

Kyphoscoliotic (kEDS) (*PLOD1, FKBP14*)

Autosomal recessive

- **Major criteria**

1. Congenital muscle hypotonia
2. Congenital or early onset kyphoscoliosis (progressive or non-progressive)
3. GJH with dislocations/subluxations (shoulders, hips, and knees in particular)

- **Minor criteria:**

1. Skin hyperextensibility
2. Easy bruisable skin
3. Rupture/aneurysm of a medium-sized artery
4. Osteopenia/osteoporosis
5. Blue sclerae
6. Hernia (umbilical or inguinal)
7. Pectus deformity
8. Marfanoid habitus
9. Talipes equinovarus
10. Refractive errors (myopia, hypermetropia)

- **Gene-specific minor criteria**

1. PLOD1

1. Skin fragility (easy bruising, friable skin, poor wound healing, widened atrophic scarring)
2 Scleral and ocular fragility/rupture
3. Microcornea
4. Facial dysmorphology

2. FKBP14

1. Congenital hearing impairment (sensorineural, conductive, or mixed)
2. Follicular hyperkeratosis
3. Muscle atrophy
4. Bladder diverticula

- **Minimal criteria suggestive for kEDS:**

– Major criterion (1): congenital muscle hypotonia
– AND major criterion (2): congenital or early-onset kyphoscoliosis
Plus
– Either major criterion (3): GJH
– And/or three minor criteria (either general or gene-specific criteria)

Brittle Cornea Syndrome (BCS) (*ZNF469, PRDM5*)

Autosomal recessive

- **Major criteria**

1. Thin cornea, with or without rupture (central corneal thickness often <400 mm)
2. Early onset progressive keratoconus
3. Early onset progressive keratoglobus
4. Blue sclerae

- **Minor criteria**

1. Enucleation or corneal scarring as a result of previous rupture
2. Progressive loss of corneal stromal depth, especially in central cornea
3. High myopia, with normal or moderately increased axial length
4. Retinal detachment
5. Deafness, often with mixed conductive and sensorineural components, progressive, higher frequencies often more severely affected ("sloping" pure tone audiogram),
6. Hypercompliant tympanic membranes
7. Developmental dysplasia of the hip
8. Hypotonia in infancy, usually mild if present
9. Scoliosis
10. Arachnodactyly
11. Hypermobility of distal joints
12. Pes planus, hallux valgus
13. Mild contractures of fingers (especially 5th)
14. Soft, velvety skin, translucent skin

- **Minimal criteria suggestive for kEDS:**

– Major criterion (1): thin cornea, with or without rupture (central corneal thinckness often < 100 micrometer)
Plus
– Either: at least one other major criterion
– And/or three other minor criteria

Musculocontractural EDS (*CHST14, DSE*)

(mcEDS)

- **Major criteria**

1. Congenital multiple contractures, characteristically adduction-flexion contractures and/or talipes equinovarus (clubfoot)
2. Characteristic craniofacial features, evident at birth or in early infancy
3. Characteristic cutaneous features including cluding skin hyperextensibility easy bruisability, skin fragility with atrophic scars, increased palmar wrinkling

- **Minor criteria**

1. Recurrent/chronic dislocations
2. Pectus deformities (flat, excavated)
3. Spinal deformities (scoliosis, kyphoscoliosis)
4. Peculiar fingers (tapering, slender, cylindrical)
5. Progressive talipes deformities (valgus, planus, cavum)
6. Large subcutaneous hematomas
7. Chronic constipation
8. Colonic diverticula
9. Pneumothorax/pneumohemothorax
10. Nephrolithiasis/cystolithiasis
11. Hydronephrosis
12. Cryptorchidism in males
13. Strabismus
14. Refractive errors (myopia, astigmatism)
15. Glaucoma/elevated intraocular pressure

- **Minimal criteria suggestive for mcEDS:**

– At birth or in early childhood: Major criterion (1): Congenital multiple contractures AND (2) characteristic craniofacial features
– In adolescence and in adulthood: Major criterion (1): Congenital multiple contractures AND (3) characteristic cutaneous features

Periodontal EDS (pEDS) (*C1R, C1S*)

Autosomal dominant

- **Major criteria**

– Severe and intractable periodontitis of early onset (childhood or adolescence)
– Lack of attached gingiva
– Pretibial plaques
– Family history of a first-degree relative who meets clinical criteria

- **Minor criteria**

– Easy bruising
– Joint hypermobility, mostly distal joints
– Skin hyperextensibility 43 and fragility, abnormal scarring (wide or atrophic)
– Increased rate of infections
– Hernias
– Marfanoid facial features
– Acrogeria
– Prominent vasculature

- **Minimal criteria suggestive for pEDS:**

– Major criterion (1): severe and intractable periodontitis of early onset (childhood or adolescence)
– OR major criterion (2): lack of attached gingiva
Plus
– At least two other major criteria and one minor criterion

Spondylodysplastic EDS (spEDS) (*B4GALT7, B3GALT6, SLC39A13*)

Autosomal recessive

- **Major criteria**

1. Short stature (progressive in childhood)
2. Muscle hypotonia (ranging from severe congenital, to mild later-onset)
3. Bowing of limbs

- **Minor criteria**

1. Skin hyperextensibility, 32 soft, doughy skin, thin translucent skin
2. Pes planus
3. Delayed motor development
4. Osteopenia
5. Delayed cognitive development

- **Gene-specific minor criteria**

– B4GALT7

– Radioulnar synostosis
– Bilateral elbow contractures or limited elbow movement
– GJH
– Single transverse palmar crease
– Characteristic craniofacial features
– Characteristic radiographic findings
– Severe hypermetropia
– Clouded cornea

– B3GALT6

– Kyphoscoliosis (congenital or early onset, progressive)
– Joint hypermobility, generalized or restricted to distal joints, with joint dislocations
– Joint contractures (congenital or progressive) (especially hands)
– Peculiar fingers (slender, tapered, arachnodactyly, spatulate, with broad distal phalanges)
– Talipes equinovarus
– Characteristic craniofacial features
– Tooth discoloration, dysplastic teeth
– Characteristic radiographic findings
– Osteoporosis with multiple spontaneous fractures
– Ascending aortic aneurysm
– Lung hypoplasia, restrictive lung disease

– SLC39A13:

– Protuberant eyes with bluish sclerae
– Hands with finely wrinkled palms
– Atrophy of the thenar muscles, and tapering fingers
– Hypermobility of distal joints
– Characteristic radiologic findings

- **Minimal criteria suggestive for spEDS:**

– Major criterion (1): short stature
– AND major criterion (2): muscle hypotonia
Plus
– Characteristic radiographic abnormalities and at least three other minor criteria (general or type-specific)

Myopathic EDS (mEDS) (COL12A1)

Autosomal dominant or recessive

- **Major criteria**

1. Congenital muscle hypotonia, and/or muscle atrophy, that improves with age
2. Proximal joint contractures (knee, hip, and elbow)
3. Hypermobility of distal joints

- **Minor criteria**

1. Soft, doughy skin
2. Atrophic scarring
3. Motor developmental delay
4. Myopathy on muscle biopsy

- **Minimal clinical criteria suggestive for mEDS:**

– Major criterion (1): congenital muscle hypotonia that improves with age
Plus
– Either: one other major criterion
– And/or: three minor criteria
Confirmatory molecular testing is obligatory to reach a final diagnosis.