Ehlers-Danlos Syndrome, Classical Type

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SCIENTIFIC MEETING - RARER TYPES
TOKYO 2019

Classical EDS: History

- Beighton, 1968: EDS Gravis and Mitis
- Beighton, 1988: EDS Types I and II
- Villefranche nosology, 1997: Classical EDS
- International classification, 2017: Revised diagnostic criteria

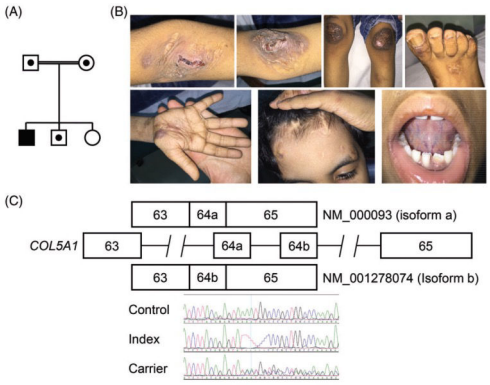
- 1996: Identification of mutations in COL5A1

(Nicholls et al., 1996; Wenstrup et al., 1996; De Paepe et al., 1997)

Molecular Mechanisms

- 75% of pathogenic variants are in COL5A1 and lead to haploinsufficiency
- Decreased levels of type V collagen most common pathogenic cause
- Remaining pathogenic variants – splice site variants and single site variants may alter secretory efficiency and/or incorporation into triple helix
- COL5A2 variants seem associated with a more severe phenotype
- No COL5A2 null alleles or variants in COL5A3 identified
- No variants in COL5A1 or COL5A2 in 5-10% of clinically diagnosed persons with cEDS
- <1% COL1A1 variants

Autosomal Recessive cEDS Splice Site Variant in COL5A1



Alzahrani et al, Clinical Genetics, 2017

Diagnostic Criteria

Major criteria

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

Minor Diagnostic Criteria

1. Easy bruising
2. Soft, doughy skin
3. Skin fragility (or traumatic splitting)
4. Molluscoid pseudotumours
5. Subcutaneous spheroids
6. Hernia (or history thereof)
7. Epicanthal folds
8. Family history of a first degree relative who meets clinical criteria

To Establish a Clinical Diagnosis

Major Criterion (1): Skin hyperextensibility **and** atrophic scarring

Plus

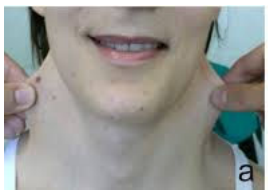
- Either: Major criteria (2) – joint hypermobility
- Or: three of the eight minor criteria

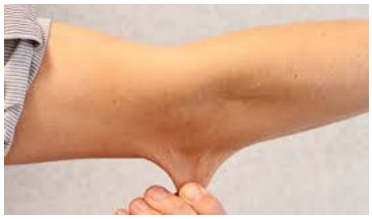
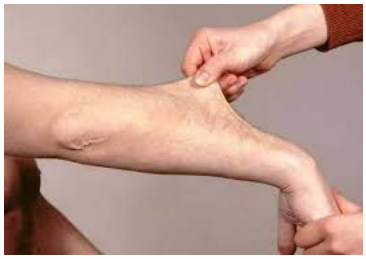
Clinical considerations

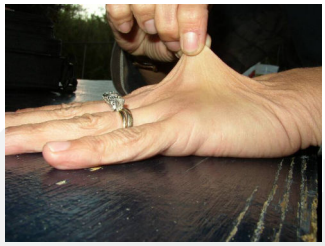
Skin is considered hyperextensible if it can be stretched over a standardized cut-off in three of the following areas

- 1.5 cm - distal part of the forearms and the dorsum of the hands
- 3 cm - neck, elbow and knees

Skin Hyperextensibility



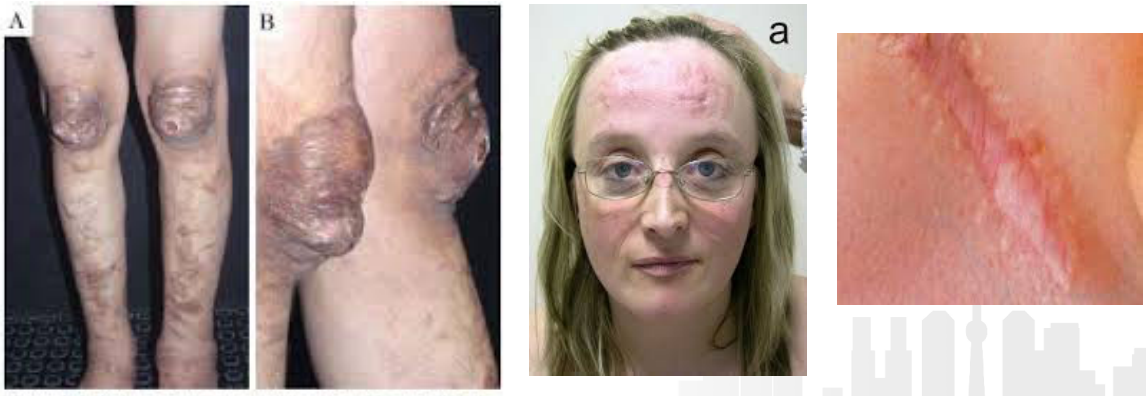





Scarring

- Abnormal scarring can range in severity.
- Most patients have extensive atrophic scars at a number of sites.
- These can sometimes be haemosiderotic.
- A minority of patients are more mildly affected.

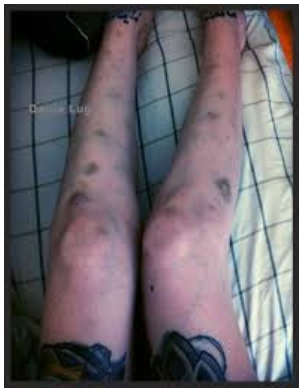
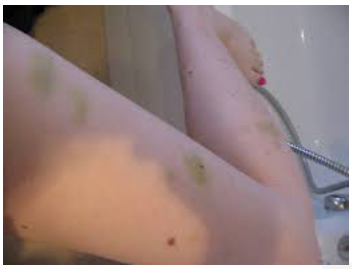
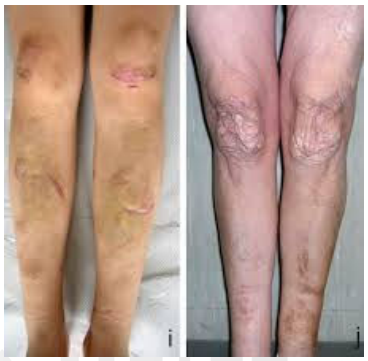
Scarring



Clinical Considerations (2)

- Easy bruising may occur anywhere on the body, without traumatic provocation
- The pretibial area often remains stained with hemosiderin from previous bruises
- Frequent bruising may raise questions about non-accidental trauma

Bruising

- Subjective abnormality of the skin texture is appreciable on exam (unusually soft, “doughy”)
- Molluscoid pseudotumors are fleshy lesions associated with scars, found over pressure points (e.g. elbow, fingers)

Molluscoid Pseudotumors

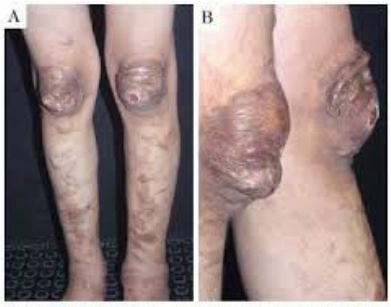


FIGURE 1(A,B): Clinical aspects showing scars on the patient's legs and pseudotumoral lesions on his knees

Clinical Considerations (3)

- Subcutaneous spheroids are small spherical hard bodies, frequently mobile and palpable on the forearms and shins. Spheroids may be calcified and detectable radiologically

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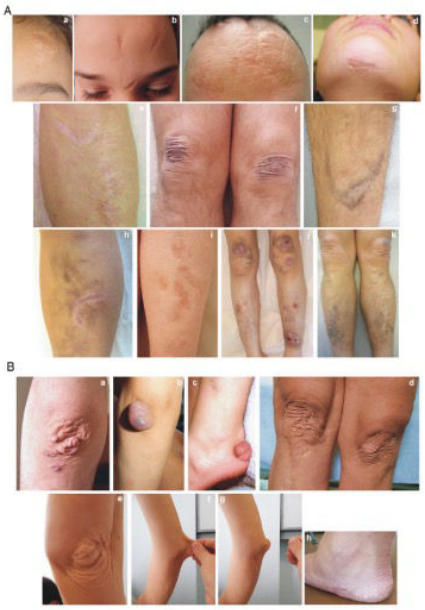
DOI: 10.1111/cge.13052

WILEY CLINICAL GENETICS

ORIGINAL ARTICLE

Spectrum of mucocutaneous, ocular and facial features and delineation of novel presentations in 62 classical Ehlers-Danlos syndrome patients

M. Colombi[1] | C. Dordoni[1] | M. Venturini[2] | C. Ciaccio[1] | S. Morlino[3] | N. Chiarelli[1] | A. Zanca[2] | P. Calzavara-Pinton[2] | N. Zoppi[1] | M. Castori[4] | M. Ritelli[1]



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Joint Hypermobility

- Joint hypermobility is assessed through the Beighton score.
- A score of 5 or more is considered indicative of generalized joint hypermobility in adults up to age 50
- After age 50, a score of 4 or more is considered positive.

Beighton Scale

Verification of Clinical Diagnosis

- Confirmatory DNA 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.

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RESEARCH ARTICLE

Human Mutation

OFFICIAL JOURNAL HGVS HUMAN GENOME VARIATION SOCIETY www.hgvs.org

Comprehensive Molecular Analysis Demonstrates Type V Collagen Mutations in over 90% of Patients with Classic EDS and Allows to Refine Diagnostic Criteria

Sofie Symoens,† Delfien Syx,† Fransiska Malfait, Bert Callewaert, Julie De Backer, Olivier Vanakker, Paul Coucke, and Anne De Paepe*

Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium

HUMAN MUTATION, Vol. 33, No. 10, 1485–1493, 2012

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Organ System Review

- Musculoskeletal
- Skin
- Cardiovascular
- Gastrointestinal
- Neurologic

Musculoskeletal

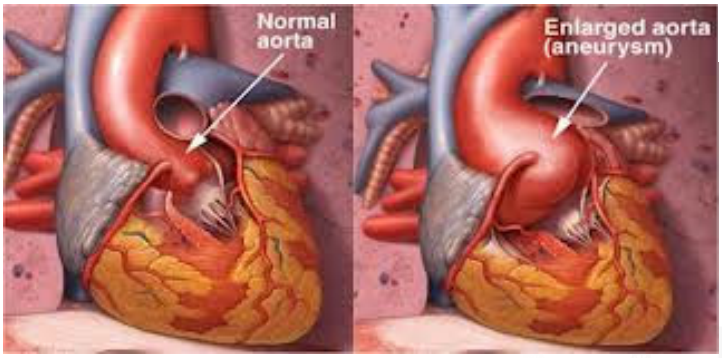
- Joint hypermobility
- Complications of joint hypermobility
- Mild muscle hypotonia
- Skeletal morphology alterations
- Increased bone fragility (osteopenia or osteoporosis)

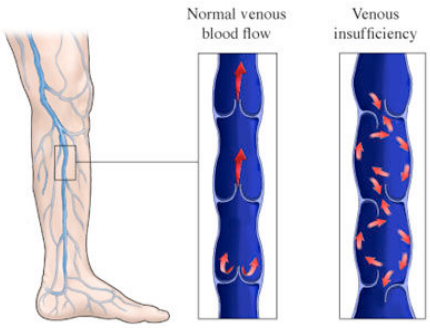
Skin

- Stretchy
- Soft, “doughy” texture
- Severe atrophic scarring
- Hemosideric scars over the shins and extensor surfaces of the forearm
- Easy bruising

Cardiovascular

- Aortic root dilation – mild; rarely progresses (Atzinger et al., 2011)
- Mitral valve prolapse – 6 % (Atzinger et al., 2011)
- Venous insufficiency

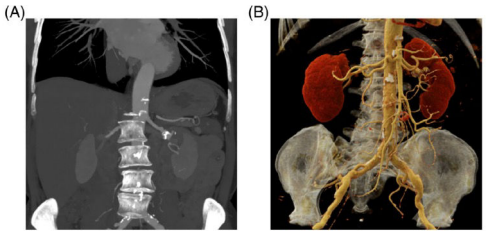




Cardiovascular Events

- Symoens et al., 2012 – 2 people with cEDS (of 102) had severe vascular events
- Monroe et al., 2015 – 3 members of a single family had catastrophic vascular events and COL5A1 p.Gly1537Val
  - Ruptured left subclavian artery (15) and celiac artery aneurysm (18), subarachnoid hemorrhage (43)
  - Right iliac artery rupture (34)
  - Renal artery tear (28)
- Yasuda et al., 2013 – superior mesenteric artery rupture (13)

Classical EDS with Vascular Fragility Caused by COL1A1 pArg312Cys



EDS subtype	Prevalence	References
Vascular EDS	72.0%	22
Classical EDS	0 to 2.2 %	2,3
COL1A1 p.Arg312Cys	18.8% (3/16)	15,16,18,20 and current case report

Malfait et al., 2007
Gaines et al., 2015
Columbi et al., 2017
Duong et al., 2019
Adham et al., 2019

Gastrointestinal

- Dysphagia
- Dyspepsia
- Gastro-esophageal reflux
- Hiatal hernia
- Irritable bowel syndrome
- Unspecified abdominal pain
- Constipation
- Diarrhea
- Rectocoele

Neurologic

- Pain
- Dysautonomia
- Headache
- Frequency of Chiari I, craniocervical instability, tethered cord as yet undefined.

Others

- Prolonged bleeding time
- Chronic fatigue syndrome
- Mast cell activation
- Giant bladder diverticuli

Management - Skin

- Avoidance of trauma
- Closure of wounds – plastic surgeon if possible
- Ascorbic acid (2 gm/day for adults)
- DDAVP may help to normalize bleeding time

Management - Muscloskeletal

- Physiotherapy
- Avoid high-impact activities
- Avoid excessive demonstrations of hypermobility
- A multi-disciplinary team is very helpful for management
- Ring splints, carefully considered b
- Bracing and orthotics may be helpful
- DEXA analysis

Management – Pain

- Neurological assessment in patients with symptoms suggestive of neuropathic pain/compression neuropathy
- Regular, light, non-weight-bearing exercise.
- Physical therapy for muscle relaxation
- Myofascial trigger point release
- Relaxation techniques - mindfulness-based stress reduction, biofeedback
- Counselling support including cognitive behavioral therapy
- Anti-inflammatory drugs and pain medications

Management - Cardiac

- Echocardiography to look for aortic root dilation and mitral valve prolapse.
- Aortic root size and mitral valve prolapse are increased in patients with classical EDS, but they tend to be of little clinical significance.
- Echo frequency in symptom-free adults frequency can be reduced (Atzinger et al., 2011).
- If echo is normal in adulthood no follow up is required (Malfait et al., 2010).
- Consider vascular imaging /aggressive blood pressure control if the patient has a glycine substitution identified near the C-terminal end of the triple helix, or on the basis of their family history (Monroe et al., 2015)

Management - Gastrointestinal

- Upper gastrointestinal endoscopy or 24 h pH-metry to evaluate reflux disease in symptomatic patients. Treatment with proton-pump inhibitor if needed
- Colonoscopy should be performed with care due to a possibly increased risk of mucosal bleeding
- Treatment of functional gastrointestinal complaints in EDS patients is problematic due to the absence of tailored strategies and frequent resistance to pharmacologic treatments at standard dosages/regimens.
- Patient education, including diet and nutritional advice, seems at the moment the most effective management tool

Management - Pregnancy

- Careful follow-up throughout pregnancy is warranted.
- Prematurity happens more often when the fetus is affected and is mainly due to premature rupture of the membranes
- Breech presentation is more common if the baby is affected, due to hypotonia

Disorder	Gene(s)	MOI	Clinical Features of This Disorder	
			Overlapping w/cEDS	Distinguishing from cEDS
Classic-like EDS (OMIM 606408)	*TNXB*	AR	• Skin hyperextensibility • Velvety skin • GJH • Easy bruising	• AR inheritance • Absence of atrophic scarring
Cardiac-valvular EDS (OMIM 225320)	*COL1A2*	AR	• Skin hyperextensibility • Atrophic scarring • Easy bruising • (Generalized) joint hypermobility	• AR inheritance • Severe progressive cardiac-valvular problems
Hypermobile EDS	Unknown	AD	• GJH • Soft, velvety skin • Mild skin hyperextensibility • Mild atrophic scarring	Absence of truly papyraceous &/or hemosiderotic scars
Arthrochalasia EDS (OMIM 130060, 617821)	*COL1A1* *COL1A2*	AD	• GJH • Skin hyperextensibility • Atrophic scarring • Easy bruising	Bilateral congenital hip dislocation
Dermatosparaxis EDS (OMIM 225410)	*ADAMTS2*	AR	• Soft, doughy skin texture • Atrophic scarring • Skin hyperextensibility • GJH	• Extreme skin fragility (usually > than in cEDS) • Redundant, almost lax, skin • Unusual craniofacial features • Postnatal growth restriction • AR inheritance
Kyphoscoliotic EDS	*PLOD1*	AR	• GJH • Skin hyperextensibility • Easy bruising • Atrophic scarring	Congenital muscle hypotonia
Kyphoscoliotic EDS w/myopathy & neurosensory hearing loss	*FKBP14*	AR	• GJH • Skin hyperextensibility • Easy bruising	• Congenital muscle hypotonia • Muscle atrophy • Congenital hearing impairment

Malfait et al., Gene Reviews, 2018

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THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 281, NO. 16, pp. 12888–12895, May 5, 2006

Murine Model of the Ehlers-Danlos Syndrome

*col5a1 HAPLOINSUFFICIENCY DISRUPTS COLLAGEN FIBRIL ASSEMBLY AT MULTIPLE STAGES**

Received for publication, October 24, 2005, and in revised form, January 23, 2006 Published, JBC Papers in Press, February 20, 2006, DOI 10.1074/jbc.M511528200

Richard J. Wenstrup‡¶, Jane B. Florer‡, Jeffrey M. Davidson§, Charlotte L. Phillips¶, Brent J. Pfeiffer¶, Diana W. Menezes‖, Inna Chervoneva**, and David E. Birk‖

The American Journal of Pathology, Vol. 185, No. 5, May 2015

ELSEVIER

The American Journal of PATHOLOGY

ajp.amjpathol.org

MUSCULOSKELETAL PATHOLOGY

Targeted Deletion of Collagen V in Tendons and Ligaments Results in a Classic Ehlers-Danlos Syndrome Joint Phenotype

Mei Sun,* Brianne K. Connizzo,† Sheila M. Adams,* Benjamin R. Freedman,† Richard J. Wenstrup,† Louis J. Soslowsky,† and David E. Birk*

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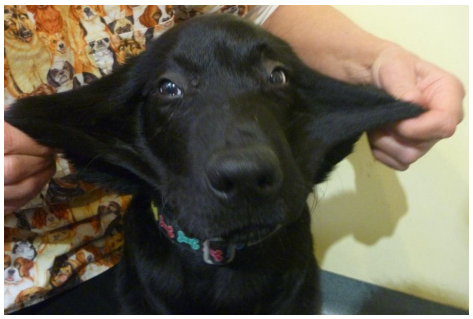
genes

MDPI

Article

Identification of Two Independent *COL5A1* Variants in Dogs with Ehlers–Danlos Syndrome

Anina Bauer [1,2], John F. Bateman [3,4], Shireen R. Lamandé [3,5], Eric Hanssen [4,6], Shannon G.M. Kirejczyk [7], Mark Yee [8], Ali Ramiche [9], Vidyha Jagannathan [1,2], Monika Welle [4,10], Tosso Leeb [1,2] and Fiona L. Bateman [3,11,*]



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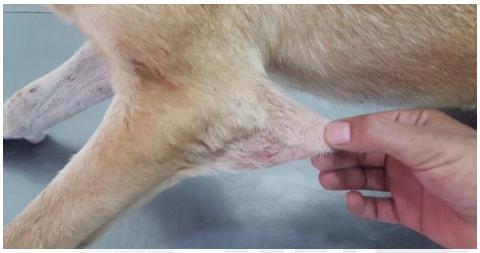

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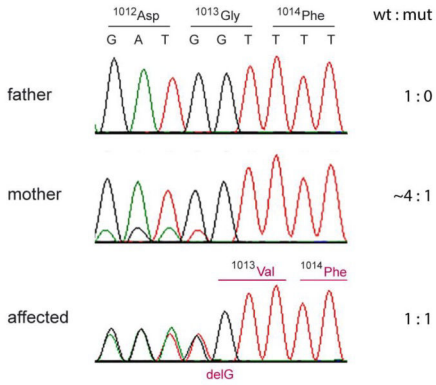

Bauer et al., Genes 2019

Thanks

- The Classical EDS committee

  Jessica M. Bowen
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  Fransiska Malfait
  Christina Schwarting

- Our patients and their families
- The Ehlers-Danlos Society