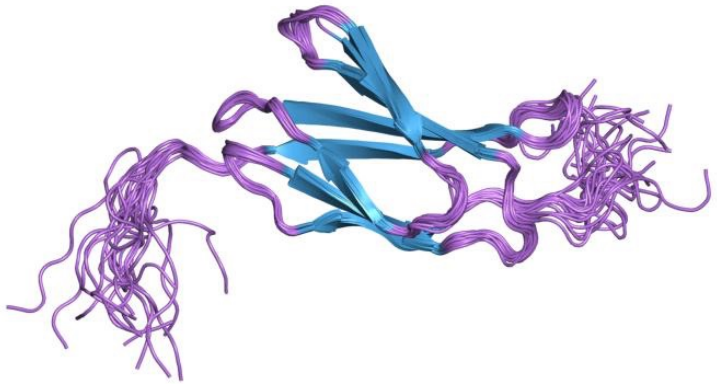


Classical Like Ehlers-Danlos syndromes

S. Demirdas, MD PhD
Department of Clinical Genetics, Erasmus Medical Center, Erasmus University, Rotterdam, the Netherlands

The Ehlers Danlos Society

clEDS

- Type 1
  - *TNXB* gene, Tenascin-X deficiency, AR inheritance
    - No atrophic scarring

- Type 2
  - *AEBP1* gene, ACLP deficiency, AR inheritance
    - Osteoporosis/-penia

Type 1 clEDS

Tenascin-X deficiency

1997

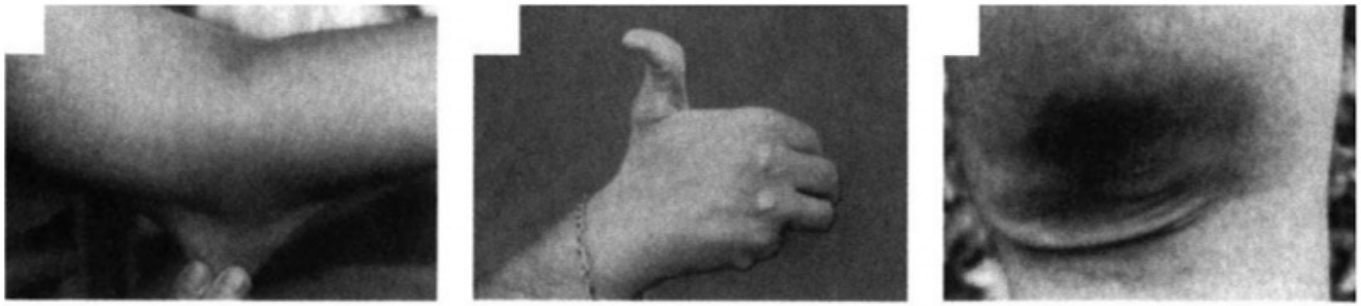
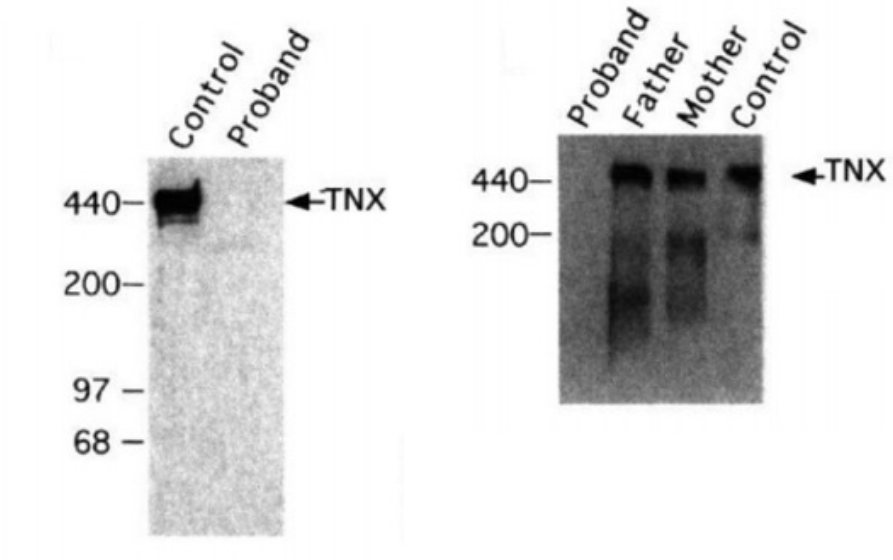


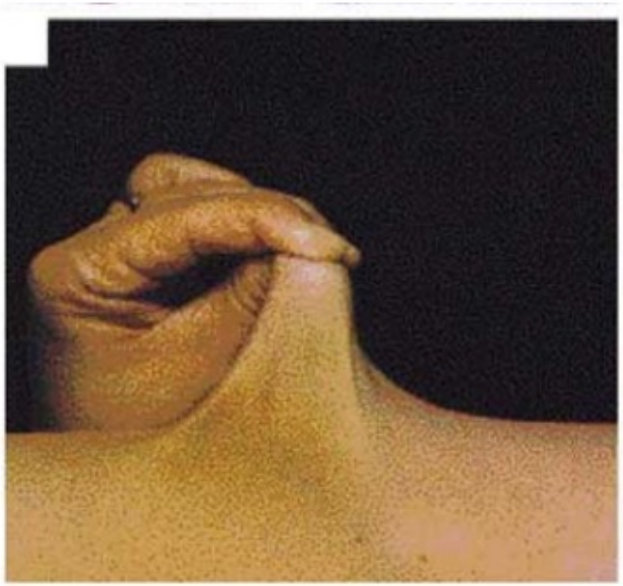
Fig. 1 Phenotype of the proband showing ***a***, hyperextensible skin; ***b***, hypermobility of the thumb; and ***c***, ecchymosis over the left knee obtained by depressing the clutch of an automobile. ***d***, Ultrastructural analysis of skin showed small collagen fibrils of normal shape (arrowheads). Fibril diameter

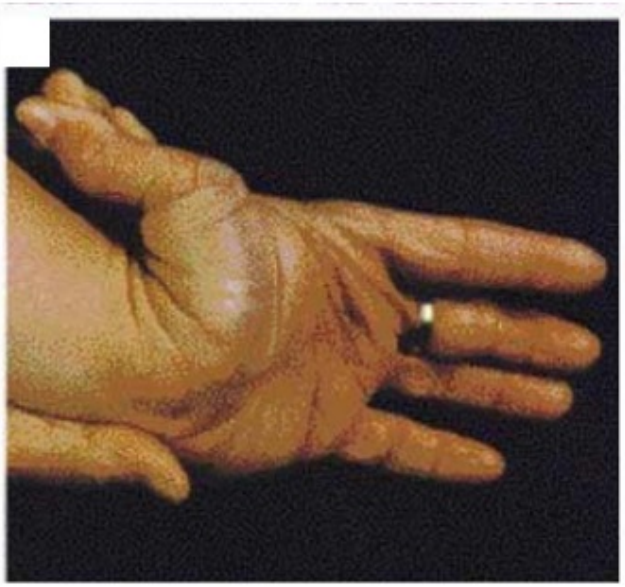


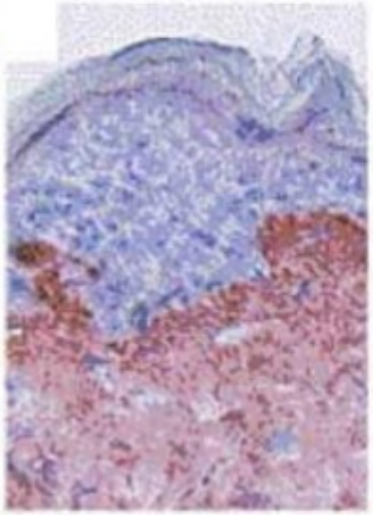
Male 26 years

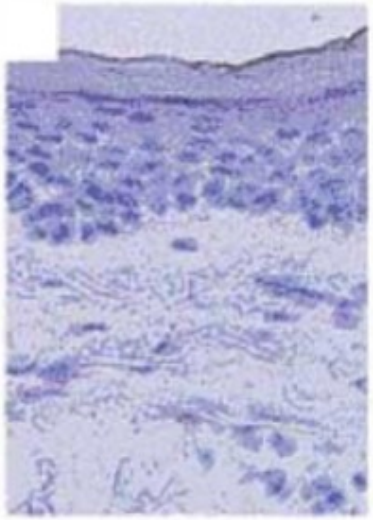
GH Burch et al, Tenascin-X deficiency is associated with Ehlers-Danlos syndrome, nature genetics volume 17 september 1997

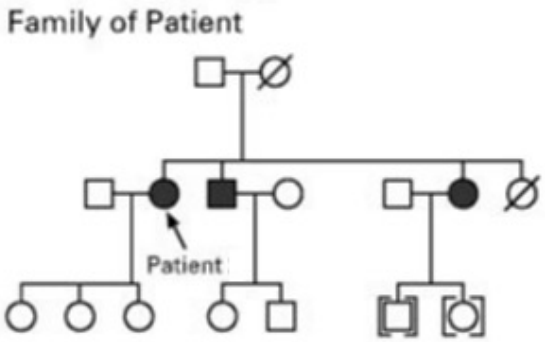
2001











J Schalkwijk et al, A Recessive Form of the Ehlers–Danlos Syndrome Caused by Tenascin-X Deficiency, N Engl J Med 2001; 345:1167-1175

Phenotype

clEDS is caused by a complete lack of Tenascin-X

an extra-cellular matrix protein (a glycoprotein)

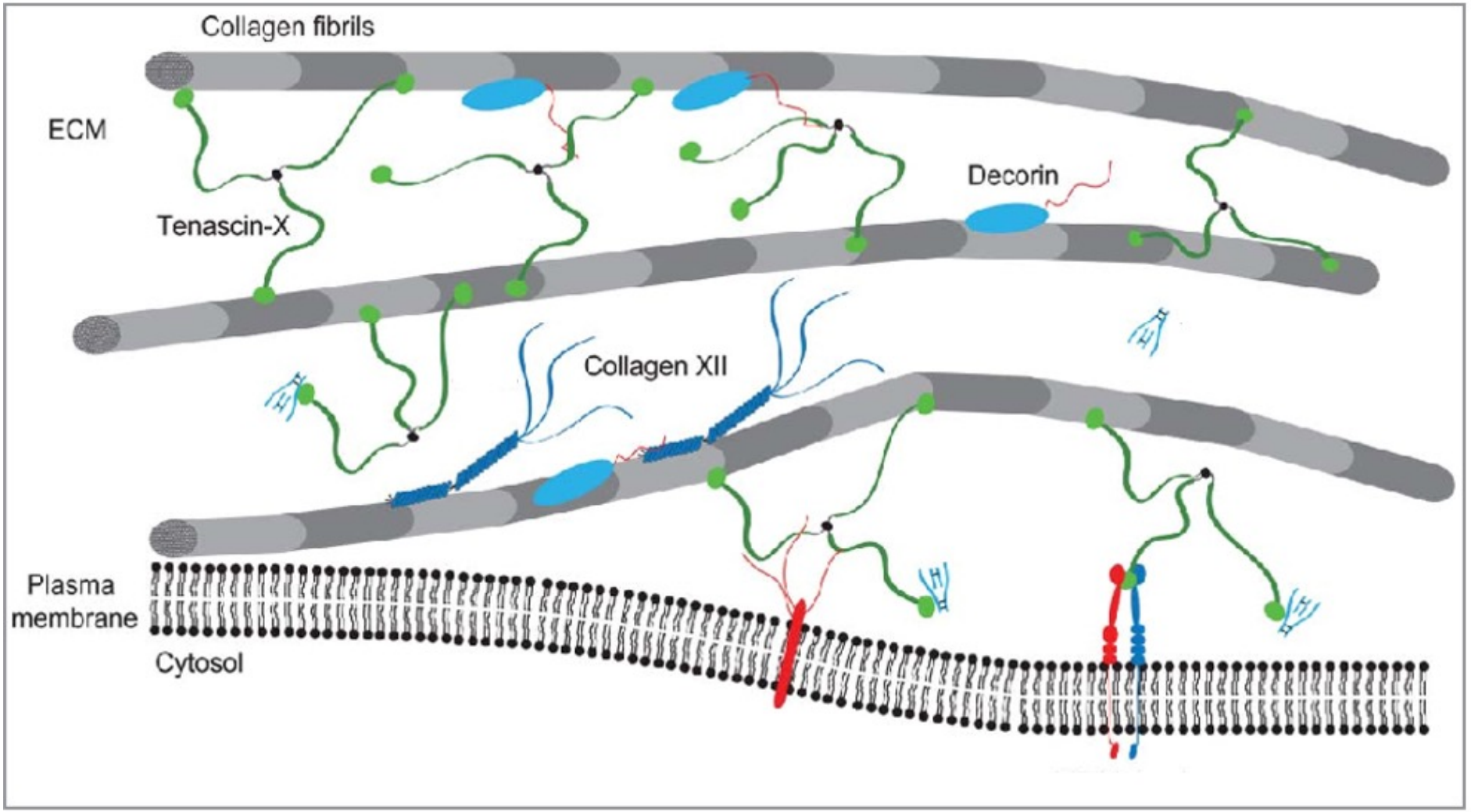
Differences with cEDS:

- Cause
- Inheritance pattern
- No atrophic scarring
- Distinctive toes/feet

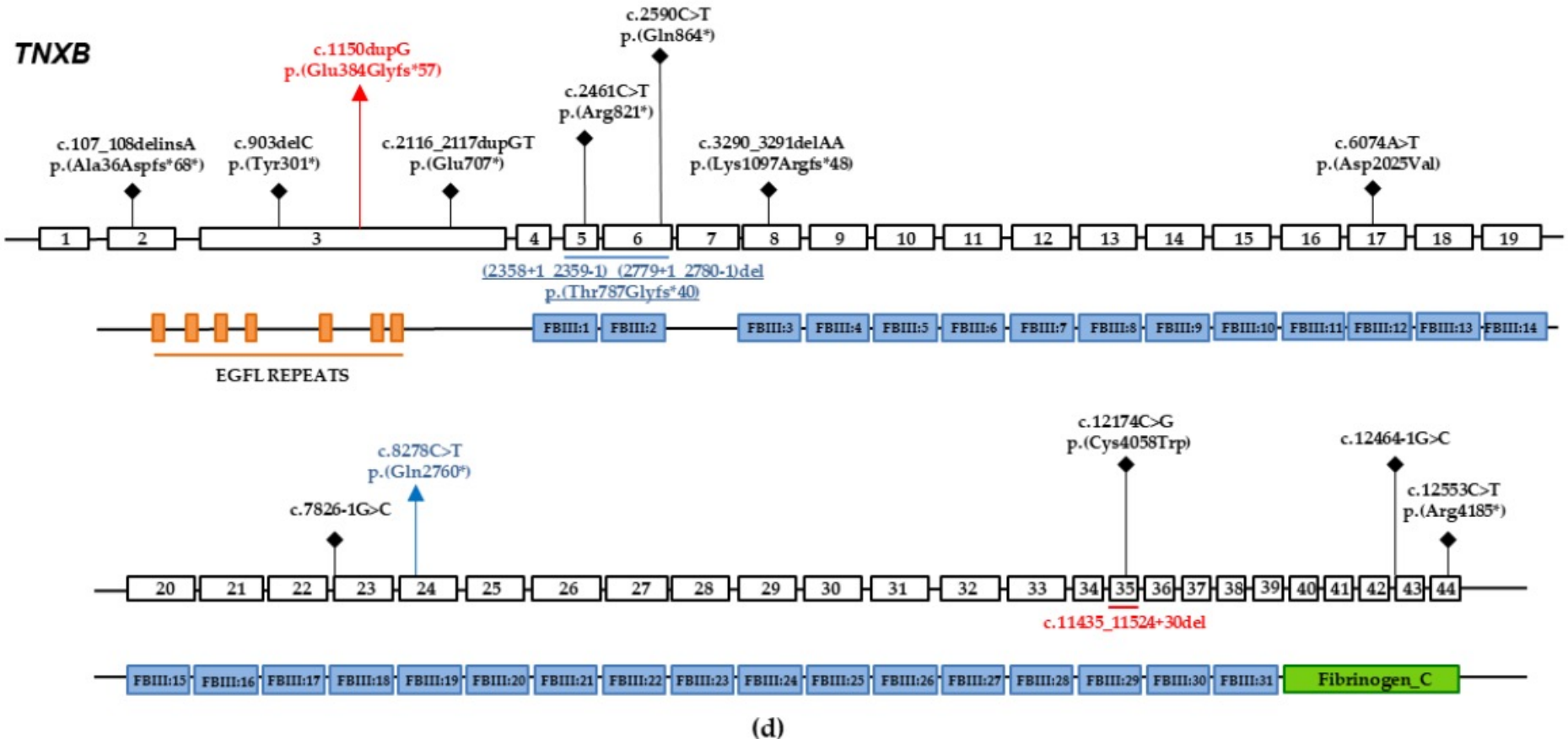
N = 51, published cases

https://zoom.nl/foto/portret/eversion---ehlers-danlos-syndrome.3092636.html

Tenascin X



U Valcourt et al,
Tenascin-X: beyond the architectural function
Cell Adh Migr. 2015;9(1-2):154-65



(d)

L Micale et al,
Novel TNXB Variants in Two Italian Patients with Classical-Like Ehlers-Danlos Syndrome,
Genes (Basel). 2019 Dec; 10(12): 967

Major Criteria

- Skin hyperextensibility, with velvety skin texture and absence of atrophic scarring
- Hypermobile small/large joints with or without recurrent dislocations (most commonly shoulder and ankle)
- Easy bruising skin, spontaneous ecchymoses

Minor Criteria

- Mild proximal and distal muscle weakness
- Axonal polyneuropathy
- Atrophy of muscles in hands and feet

- Foot deformities: broad/plump forefoot, brachydactyly with excessive skin; pes planus; hallux valgus; piezogenic papules.
- Acrogeric hands, mallet finger(s), clinodactyly, brachydactyly
- Edema in the legs in absence of cardiac failure

- Vaginal/uterus/rectal prolapse

Diagnosis

- Minimal criteria suggestive for clEDS:

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

- Confirmatory molecular testing is **obligatory** to reach a final diagnosis.

2001

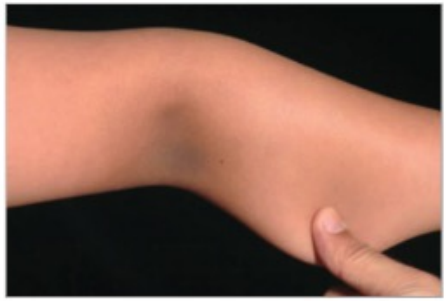


Fig 1. Soft, dough-like skin texture in association with skin hyperextensibility.

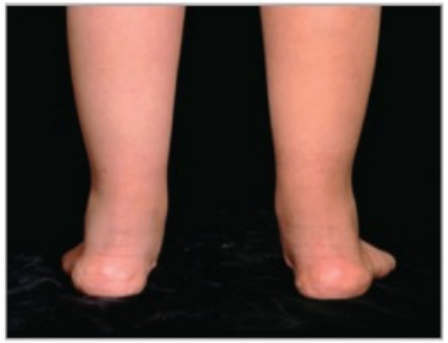


Fig 2. Pes planus with marked piezogenic papules.

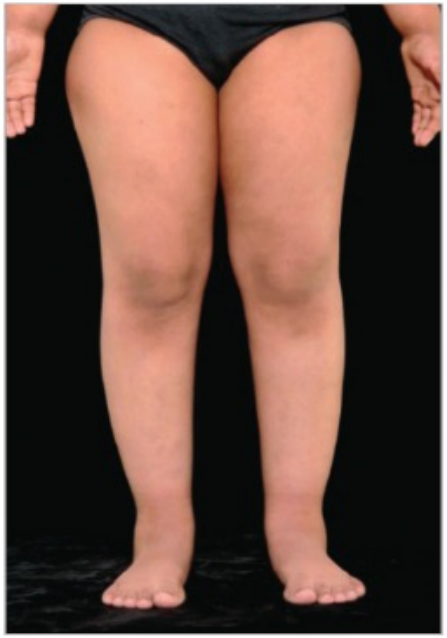


Fig 3. Marked absence of scarring on the lower limbs.

Male 7 years

Table 1 Relative values of serum tenascin-X levels

Type	%	95% CI
Mean (n = 20)[a]	100	151–49
Child	0	–
Father	64	–
Mother	45	–

[a]The mean serum values of 20 volunteers was set at 100%. The parents showed intermediate serum values in keeping with heterozygotes. The proband had no detectable levels of serum tenascin-X in keeping with an autosomal recessive trait. CI, confidence interval.

M O'Connel et al,
Tenascin-X deficiency and Ehlers–Danlos syndrome: a casereport and review of the literature,
Br J Dermatol. 2010 Dec;163(6):1340-5

CLINICAL GENETICS An International Journal of Genetics, Molecular and Personalized Medicine

Clin Genet 2017: 91: 411–425
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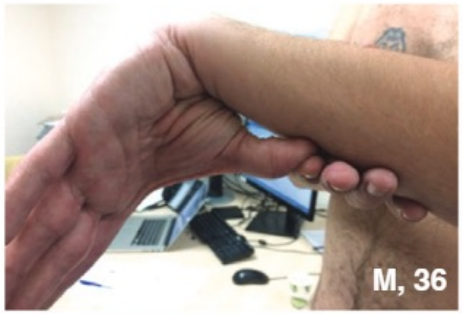
CLINICAL GENETICS
doi: 10.1111/cge.12853

Original Article

Recognizing the tenascin-X deficient type of Ehlers–Danlos syndrome: a cross-sectional study in 17 patients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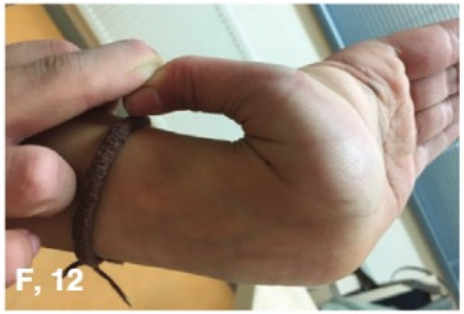
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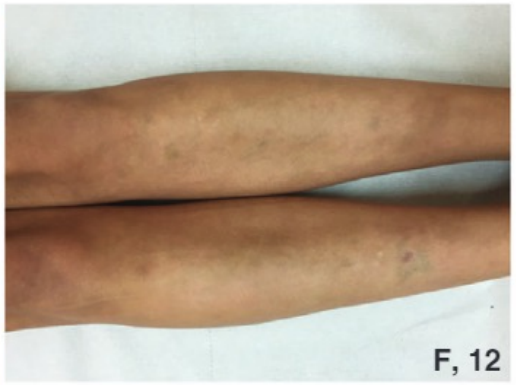
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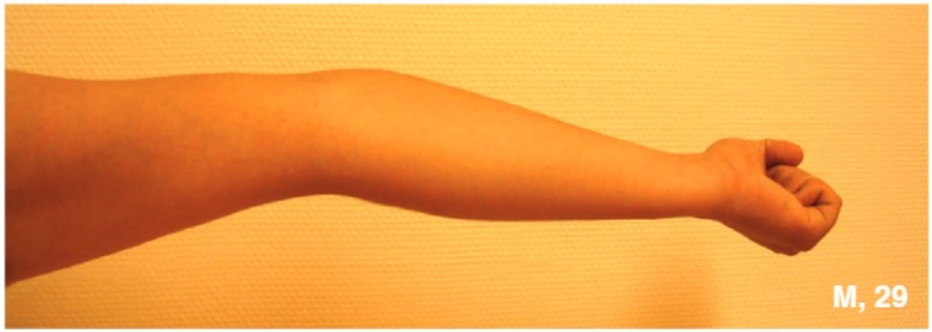
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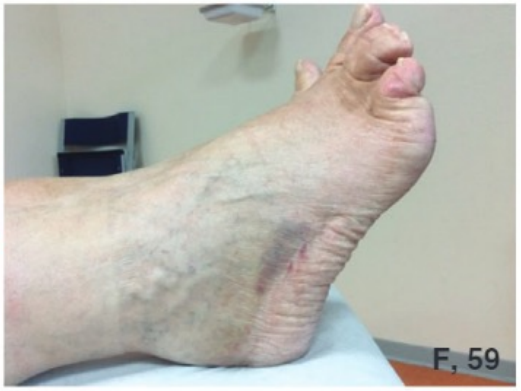
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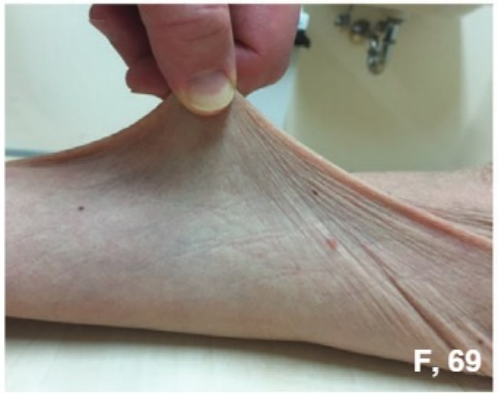
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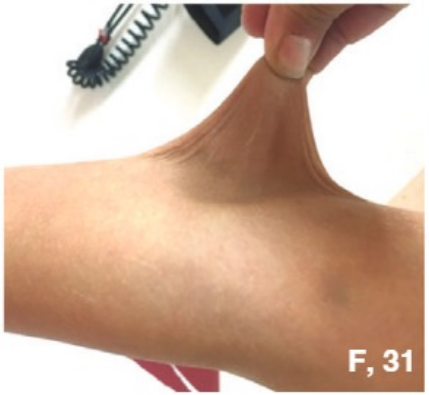
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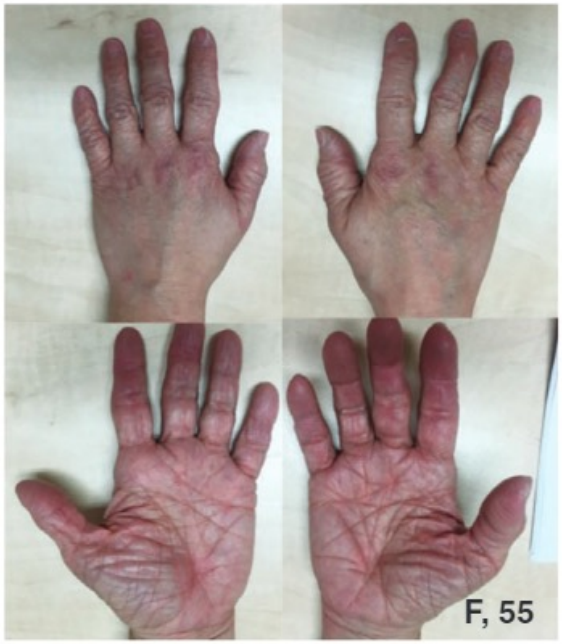
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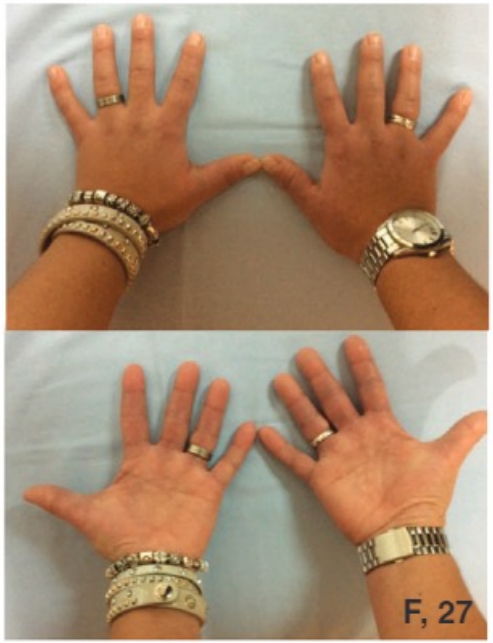
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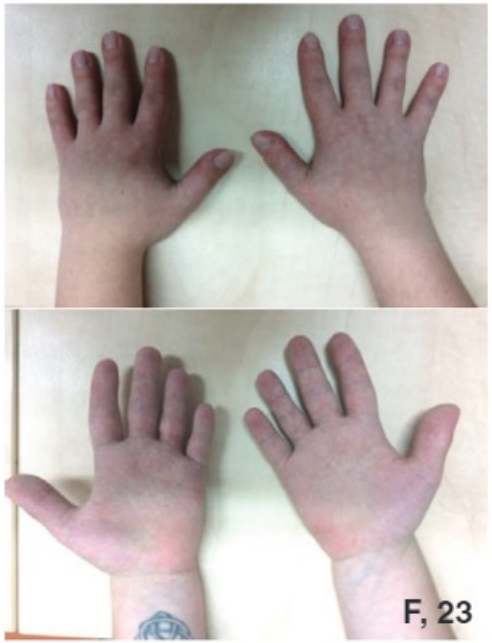
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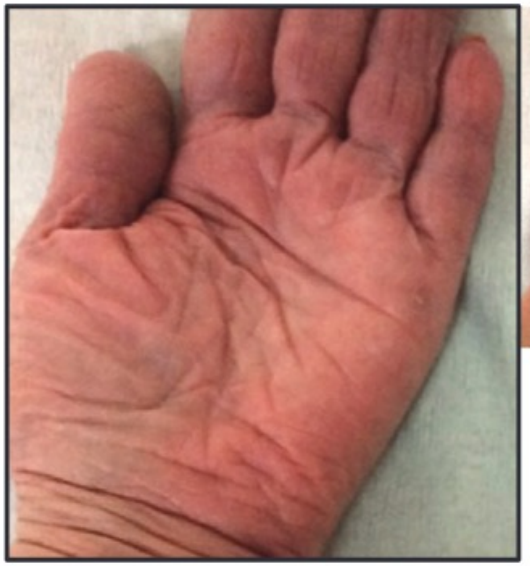

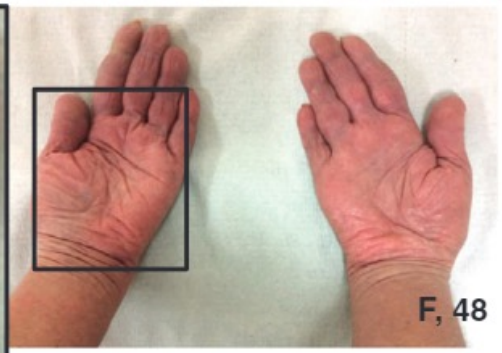
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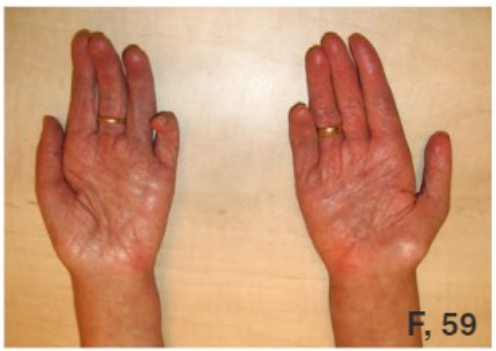
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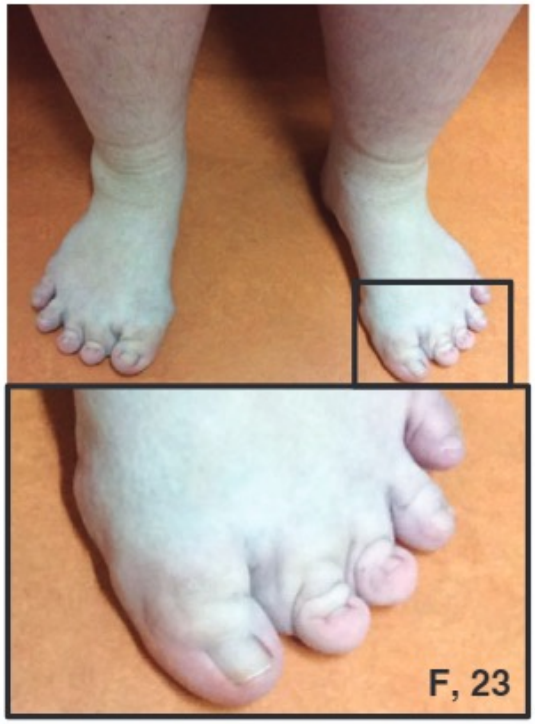
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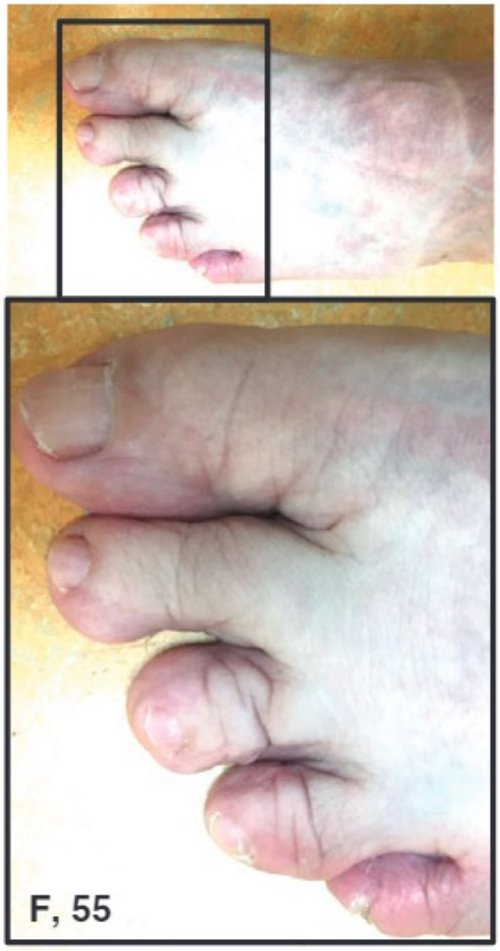
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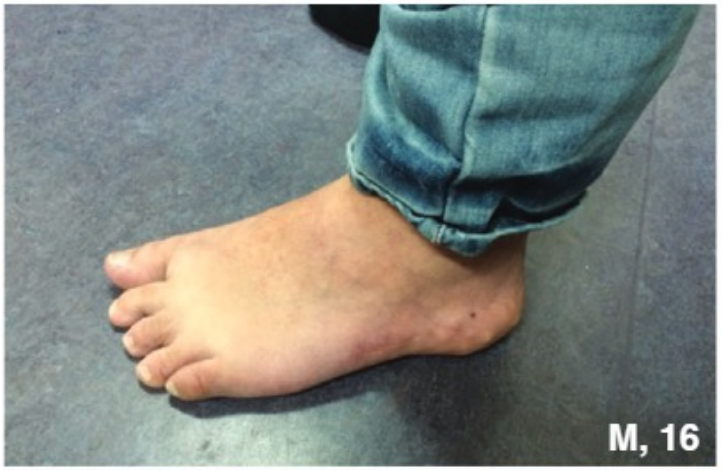
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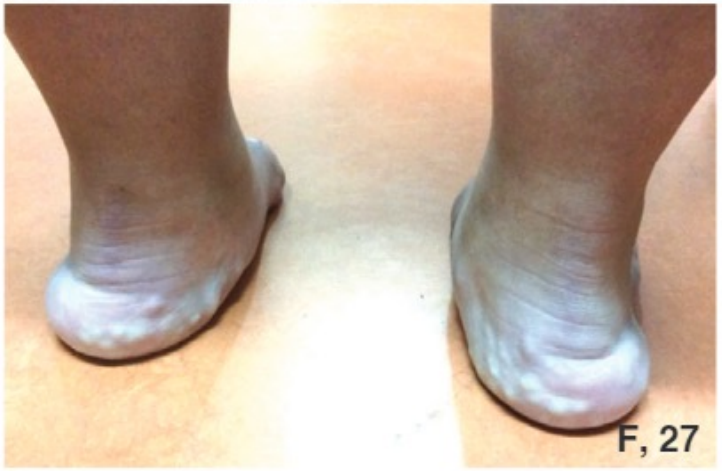
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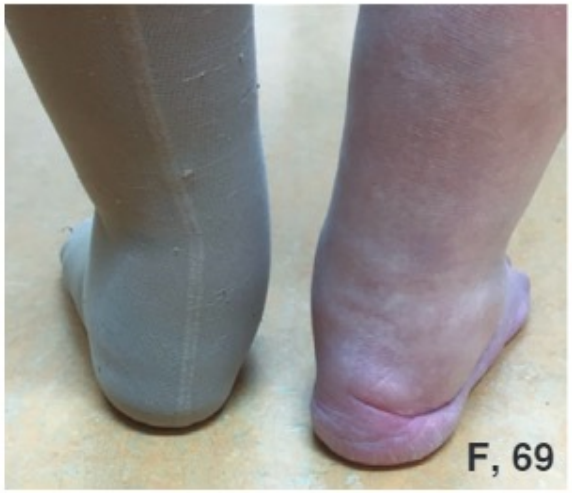
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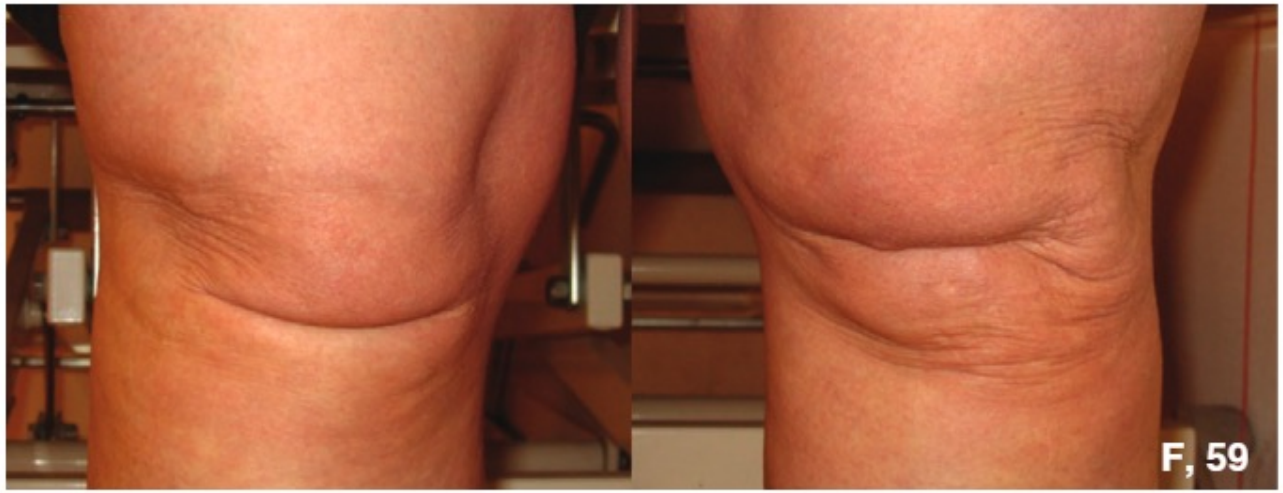
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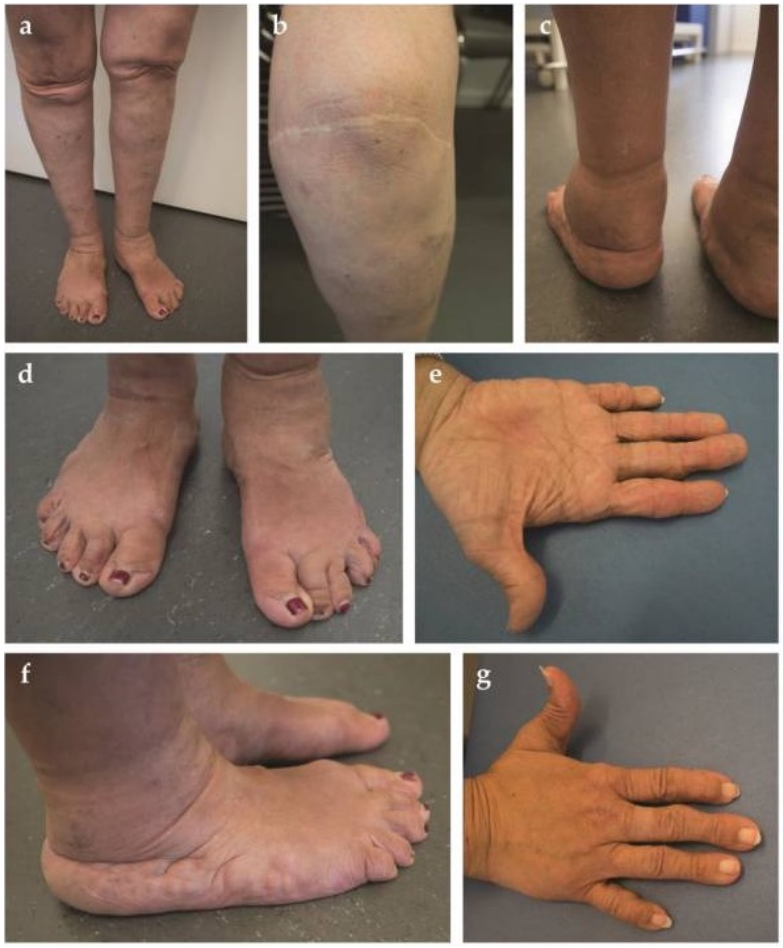
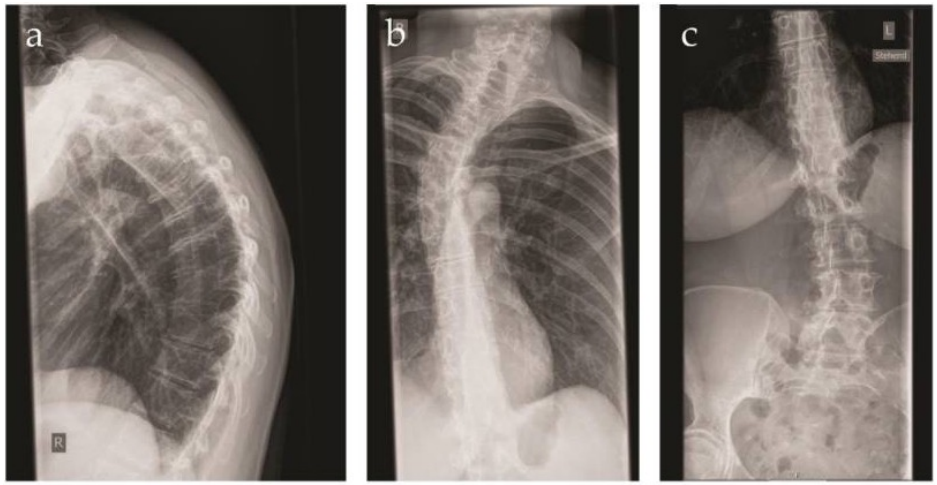
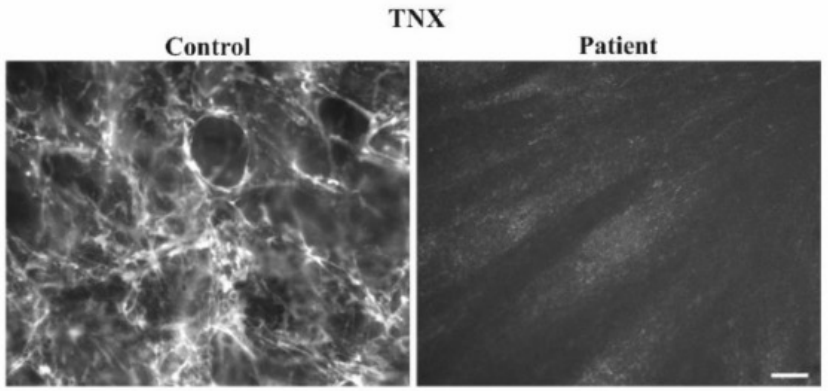
2019





Female 41 years



D Rymen et al,
Clinical and Molecular Characterization of Classical-Like Ehlers-Danlos Syndrome Due to a Novel TNXB Variant, Genes (Basel). 2019 Nov; 10(11): 843.

2020

Genetics inMedicine | ARTICLE

Classical-like Ehlers–Danlos syndrome: a clinical description of 20 newly identified individuals with evidence of tissue fragility

Claire Green, MSc[1], Neeti Ghali, MD[2], Rhoda Akilapa, BMBS, BMedSci[2], Chloe Angwin, MBBS[2], Duncan Baker, FRCPath (Dip), BSc[3], Marion Bartlett, MSc[2], Jessica Bowen, MSc[1], Angela F. Brady, PhD[2], Joanna Brock, BSc[3], Erin Chamberlain, MSc[4], Harveer Cheema, BSc[3], Vivienne McConnell, MD[5], Renarta Crookes, BSc[3], Hanadi Kazkaz, FRCP[6], Diana Johnson, BM, MD[1], F. Michael Pope, MD[7], Anthony Vandersteen, PhD[4], Glenda Sobey, MBChB, FCDerm[1] and Fleur S. van Dijk, MD, PhD[2]

Erasmus MC
University Medical Center Rotterdam

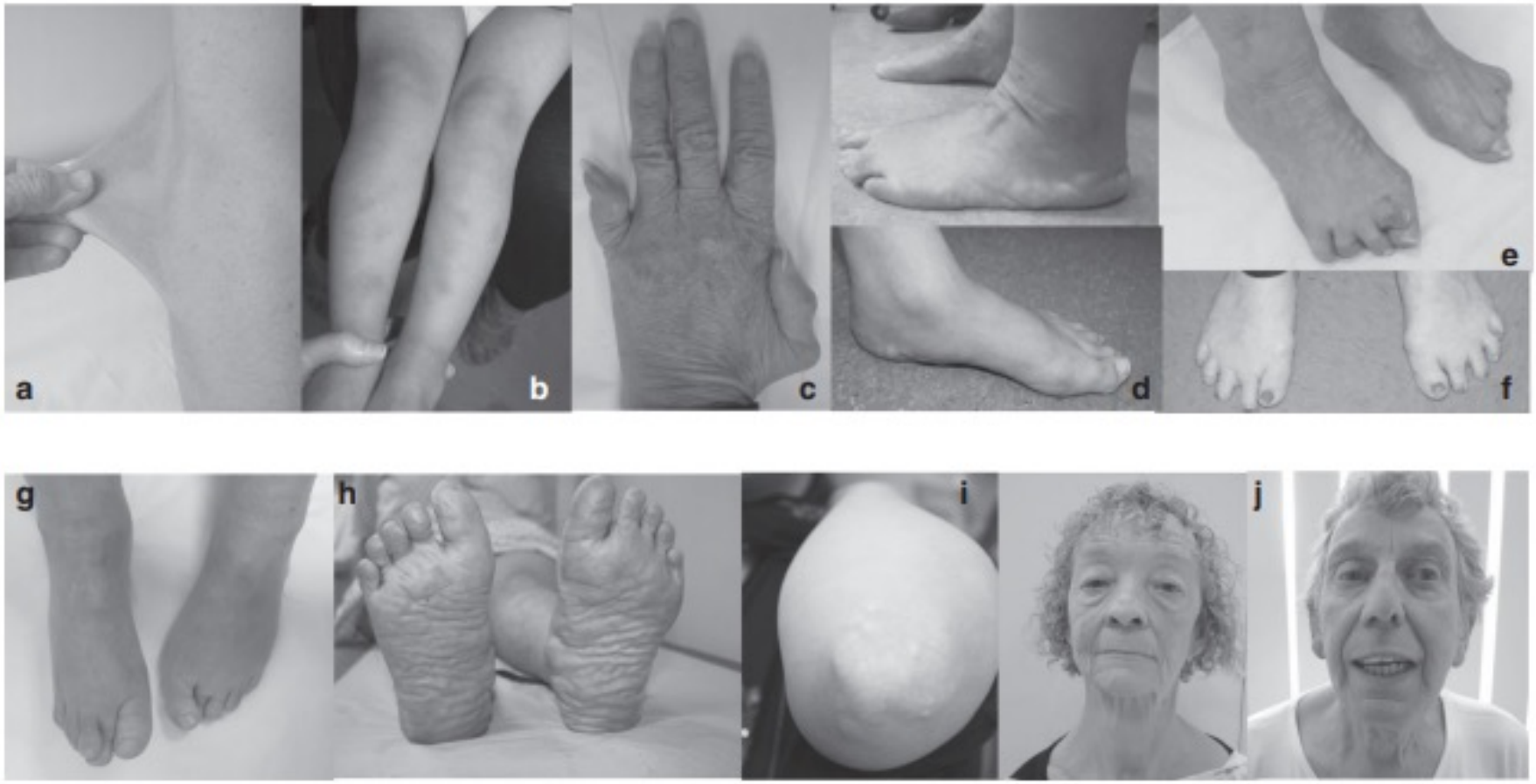


Fig. 1 Frequent and/or remarkable features in patients with classical-like Ehlers–Danlos syndrome (clEDS). **a** Skin hyperextensibility. **b** Easy bruising and spontaneous ecchymoses in a child with TN-X deficiency; a suspicion on nonaccidental injury was raised. **c** Wrinkled skin with deformation of thumbs and fingers due to joint hypermobility and repetitive dislocations. **d** Fat pads on soles of feet and piezogenic pedal papules. **e** Foot deformations with hallux valgus and over and underlapping toes in P3 at the age of 62 years. **f** Broad forefeet with short toes. **g** Foot deformations with hallux valgus and over and underlapping toes in P1 at the age of 55 years. **h** Skin wrinkling on soles of feet. **i** Subcutaneous spheroids on elbow. **j** Clinical photographs of patients P3 and P6 showing no specific dysmorphic features but sagging of the skin in 62-year-old P3 and to a milder degree in 68-year-old P6.

GI-tract

fragility of the gastrointestinal tract. We propose a predisposition to tissue fragility in patients with clEDS, in particular of the gastrointestinal tract and emphasize the importance of counseling with regard to the risk of gastrointestinal complications. We suggest caution when considering invasive gastrointestinal procedures and to avoid these interventions if possible. We recommend careful selection of analgesic medication in view of elevated risks of diverticulitis and diverticular bleeding in users of aspirin or NSAIDs. We advise carrying a medic alert card with information about clEDS including reported gastrointestinal fragility. We recommend

Working group

Netherlands

- **N.C. Voermans**, MD PhD, Neuromuscular neurologist, Radboudumc, Nijmegen
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- **E. Dulfer**, MD, clinical genetics department, university medical center Groningen
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Erasmus MC
University Medical Center Rotterdam

Type 2 clEDS

AEBP1 gene

bi-allelic pathogenic variants

2016

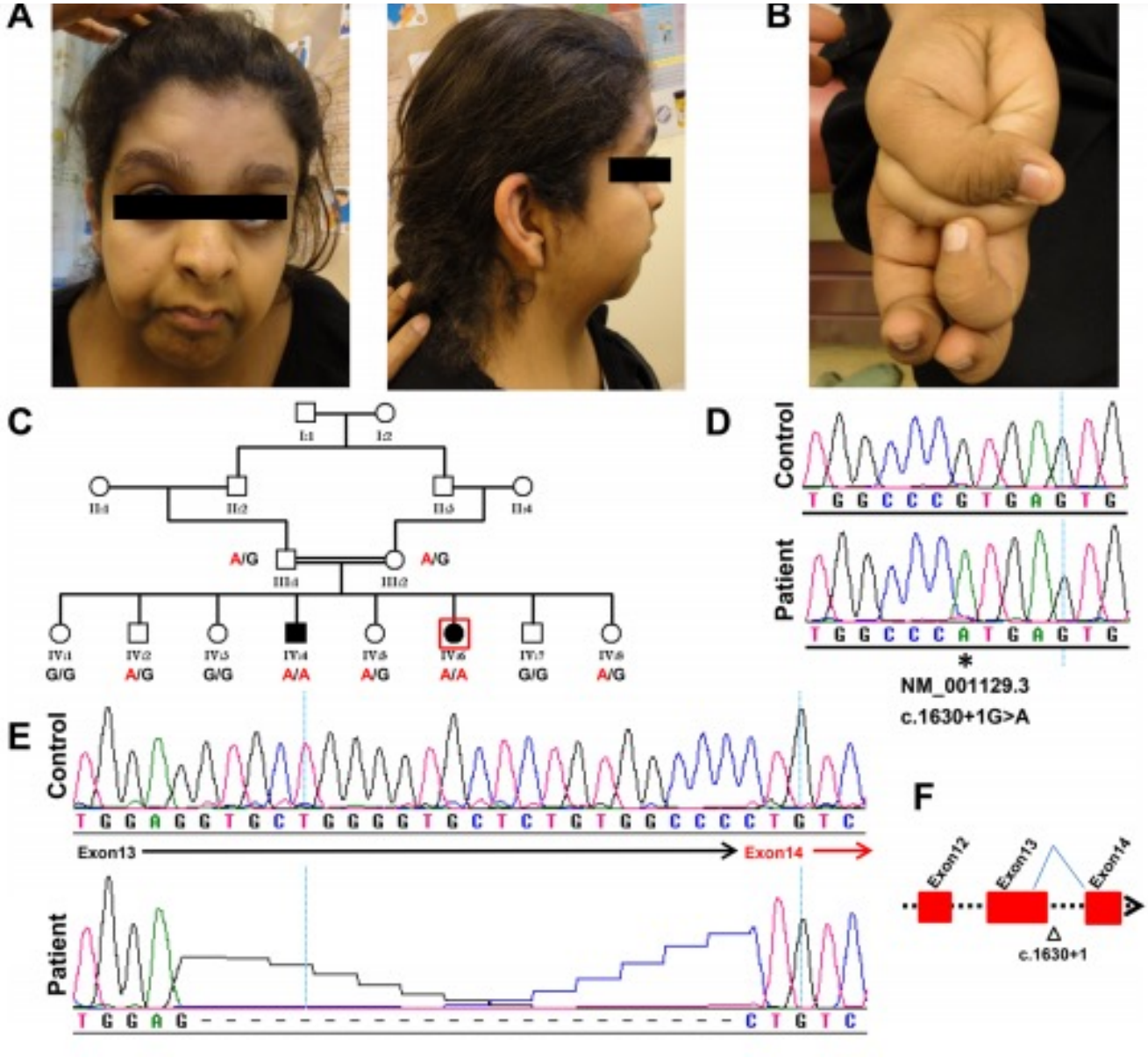
Table 1 Summary of clinical and molecular findings in our EDS-like cohort

Family ID	Phenotype
Family 1 ID: 14DG1601 (2 affected individuals)	Severe skin and joint laxity with dislocations of the hips, knees and ankles, severe osteopenia and Klippel–Feil anomaly, facial dysmorphism (low posterior hairline, bilateral ptosis, sagged face (with soft redundant skin), large ears, a narrow palate, abnormal dental alignment and webbed neck)

Gene	Mutation
AEBP1	NM_001129.3: c.1630+1G>A Homozygous

Alazami *et al*: DOI 10,1007/s00439-016-1660-z

Alazami *et al*: DOI 10.1007/s00439-016-1660-z



F, 12 yo

Phenotype

clEDS type 2 is caused by loss of function of the ACLP protein:
loss of unction bi-allelic variants in *AEBP1* gene

Differences with cEDS:

- Cause
- Inheritance pattern
- Cutis laxa
- Osteopenia/-porosis

N = 9, published cases

Overlap with cEDS, vEDS, kEDS and msEDS

https://zoom.nl/foto/portret/eversion---lers-danlos-syndrome.3092636.html

Phenotype

- Cutaneous
  - Hyperextensibility
  - Delayed wound healing
  - Fragility, easy bruising, atrophic scarring
  - Redundant skin (elastin?), acrogeria, ptosis
  - Thin and translucent
  - Umbilical, ventral, inguinal hernia

- Musculoskeletal
  - Generalized Joint Hypermobility, dislocations
  - Early onset osteopenia/osteoporosis
  - (Kypho)Scoliosis (often), pectus excavatum (N=2)
  - Foot deformities: pes planus, hallux valgus, toe deformities

Phenotype

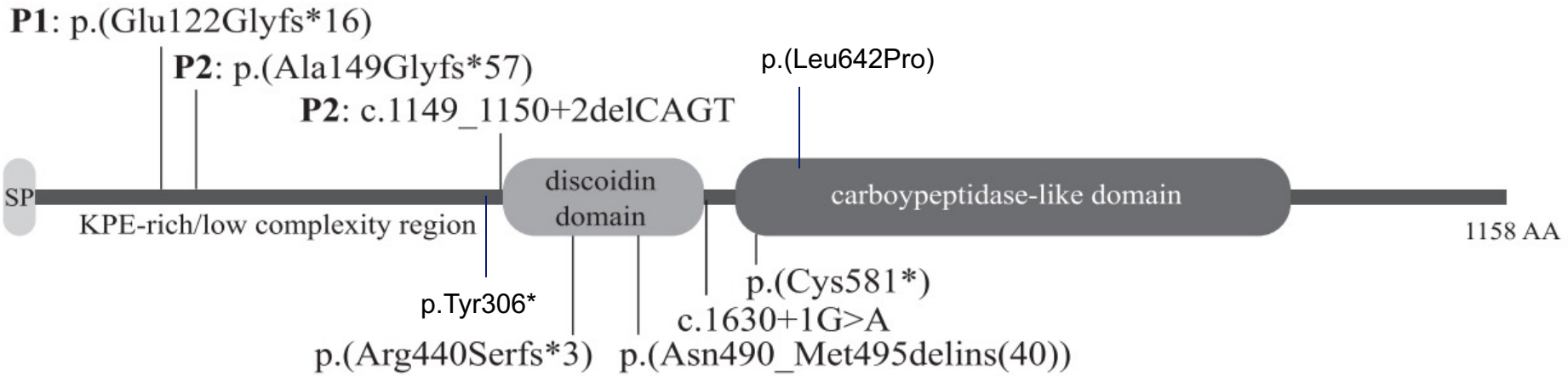
- Cardiovascular
  - Mitral valve prolapse and/or insufficiency
  - One male adult patient with progressive aortic root dilation
  - Varices at a young age

- Gastrointestinal
  - One male patient (same as above) had spontaneous bowel rupture
  - Motility problems

Phentotype

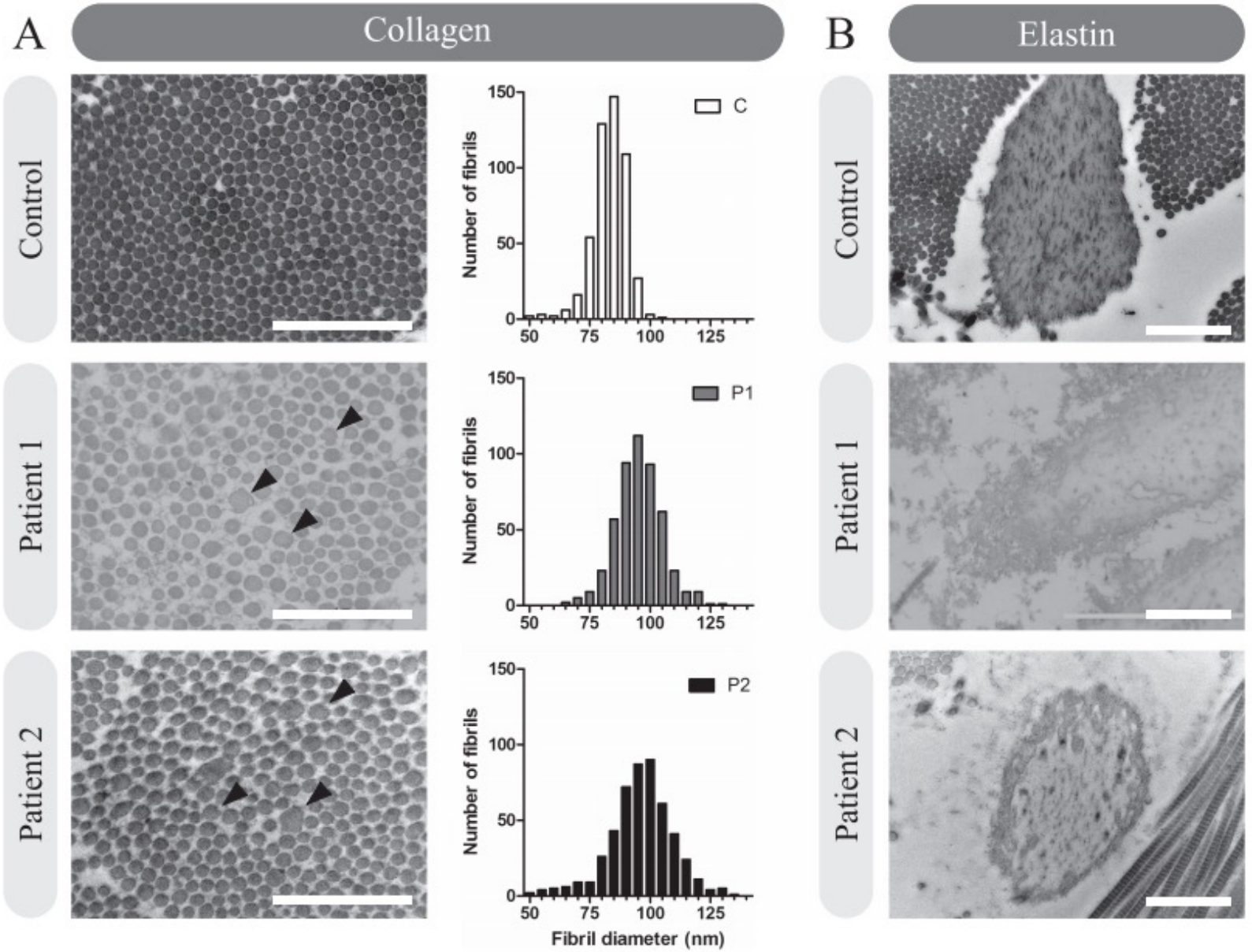
- Other
  - Myopia, astigmatism
  - Alopecia (N=3)
  - Dental involvement (N=3, one female patient loss of all teeth age 14 years)
  - Cryptorchidism (2/5 males)
  - Spontaneous pneumothorax (N=1)

AEBP1 gene



Syx *et al* 2019: DOI 10.1093/hmg/ddz024

Ultrastructural appearance

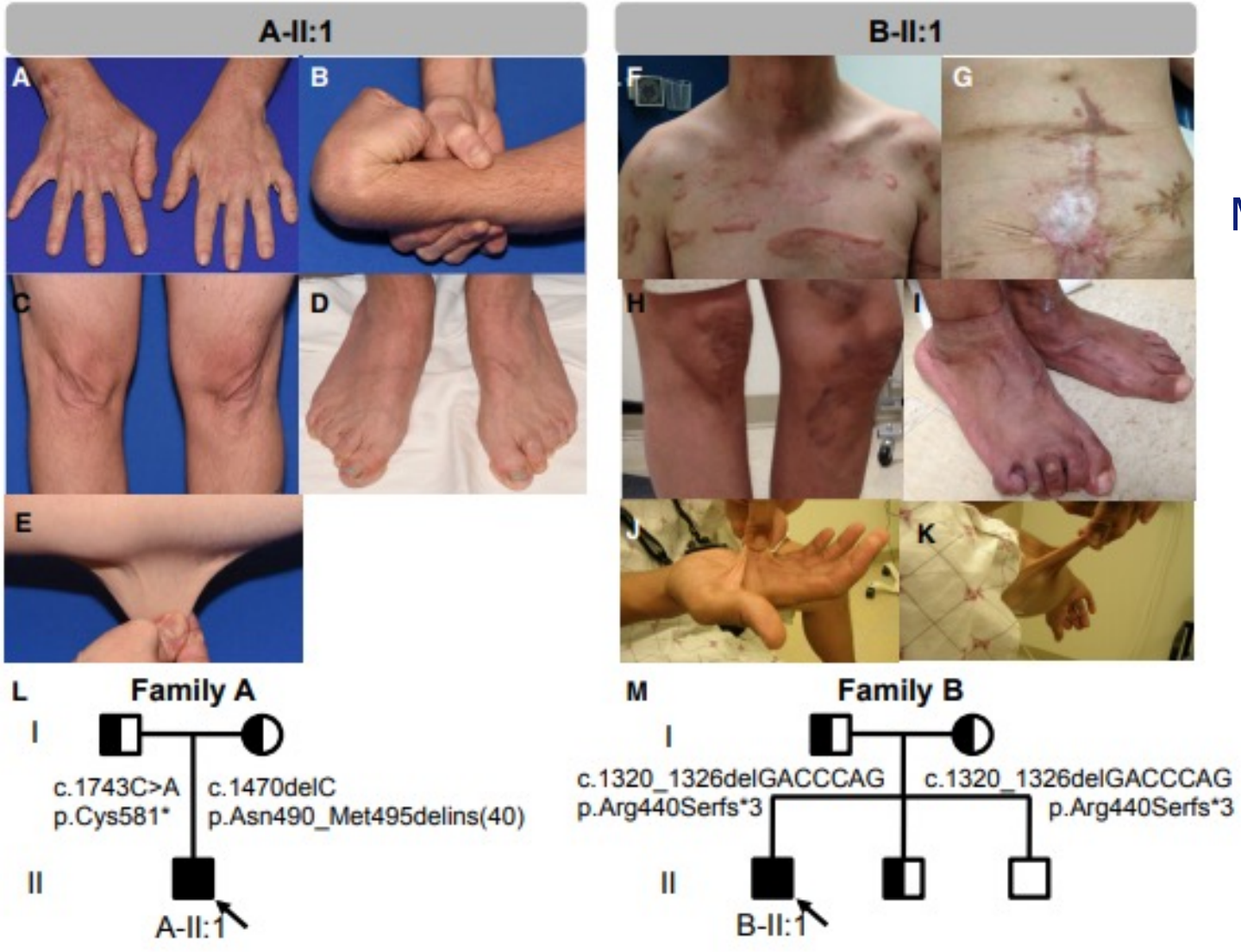


Syx *et al* 2019:
DOI
10.1093/hmg/ddz024

2018

Blackburn *et al*: DOI 10.1002/ajmg.a.60679

M, 35 yo

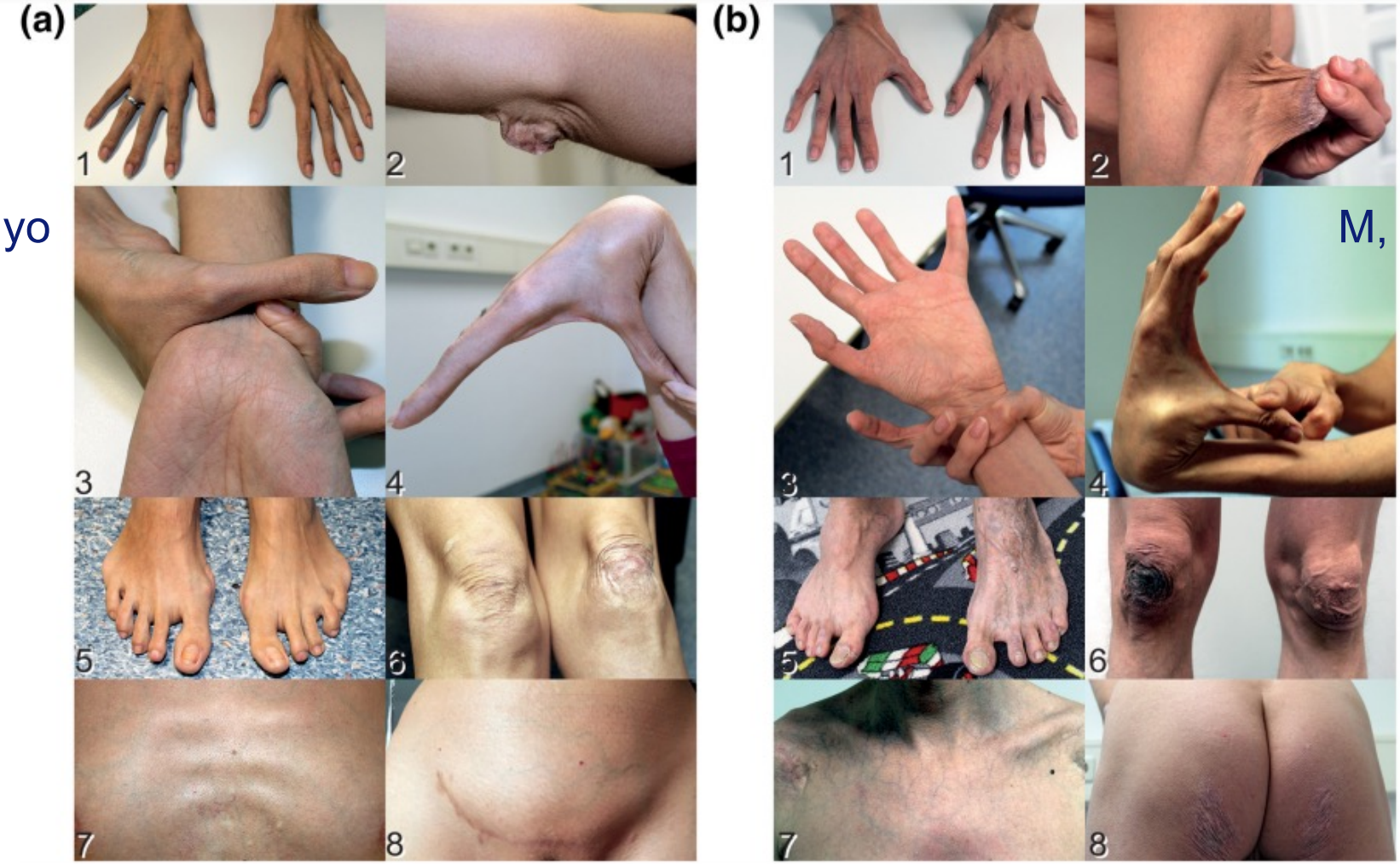


M, 33 yo

Figure 1. Clinical Features of Individuals with *AEBP1* Mutations

2018

F, 39 yo



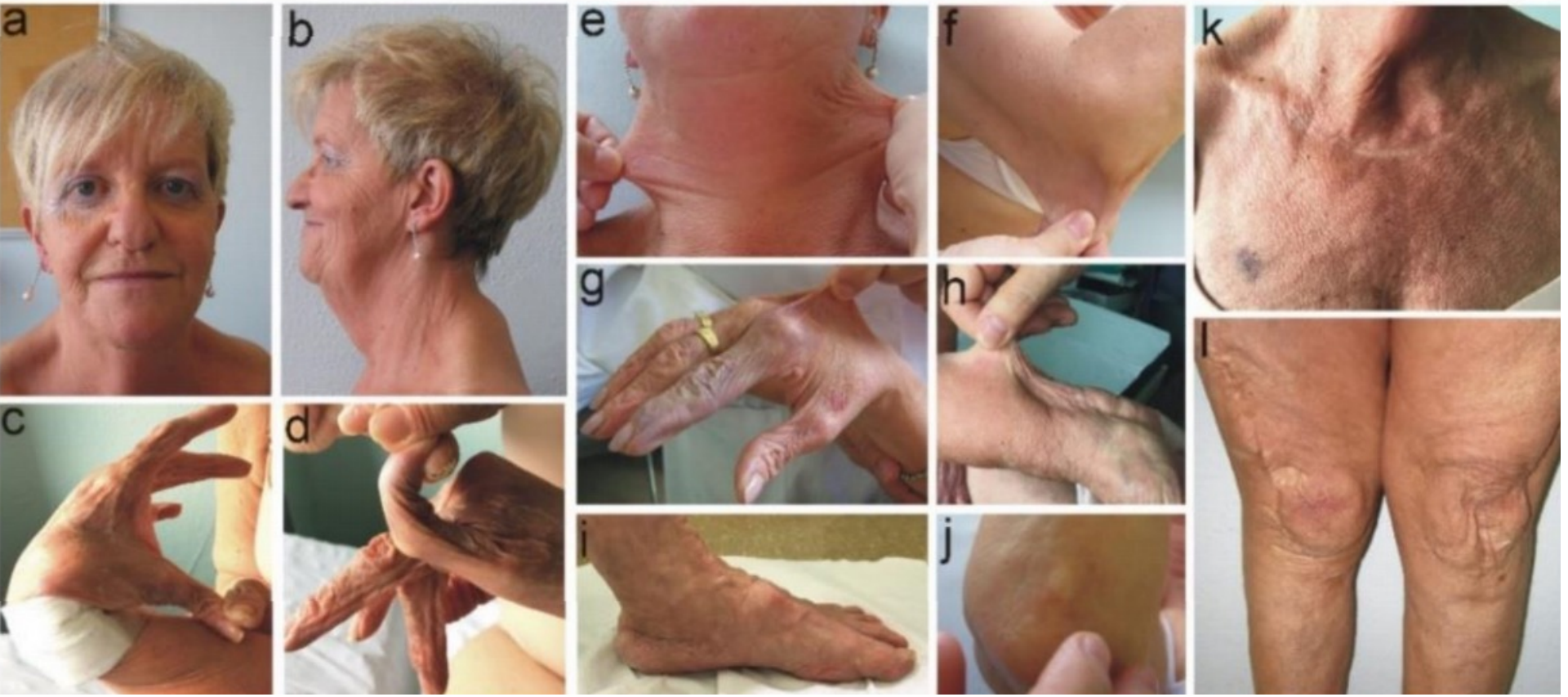
M, 38 yo

FIGURE 1 Clinical features of individual D-II:1 at age 39 years (a) and her brother (D-II:2) at age 38.5 years (b). Arachnodactyly (A1, B1), positive bilateral wrist sign (A3, B3). Passive flexion of thumbs to the forearm (A4, B4). Redundant skin of elbows, knees and buttocks (A2, A6, B2, B6, B8). Pes planus and sandal gap (A5, B5). Prominent superficial veins in the chest region (A7, B7). Poor wound healing and atypical scarring of the skin (A8, B8)

Hebebrand *et al*: DOI 10.1002/ajmg.a.60679

2019

Ritelli *et al*: DOI 10.3390/genes10020135



F, 53 yo

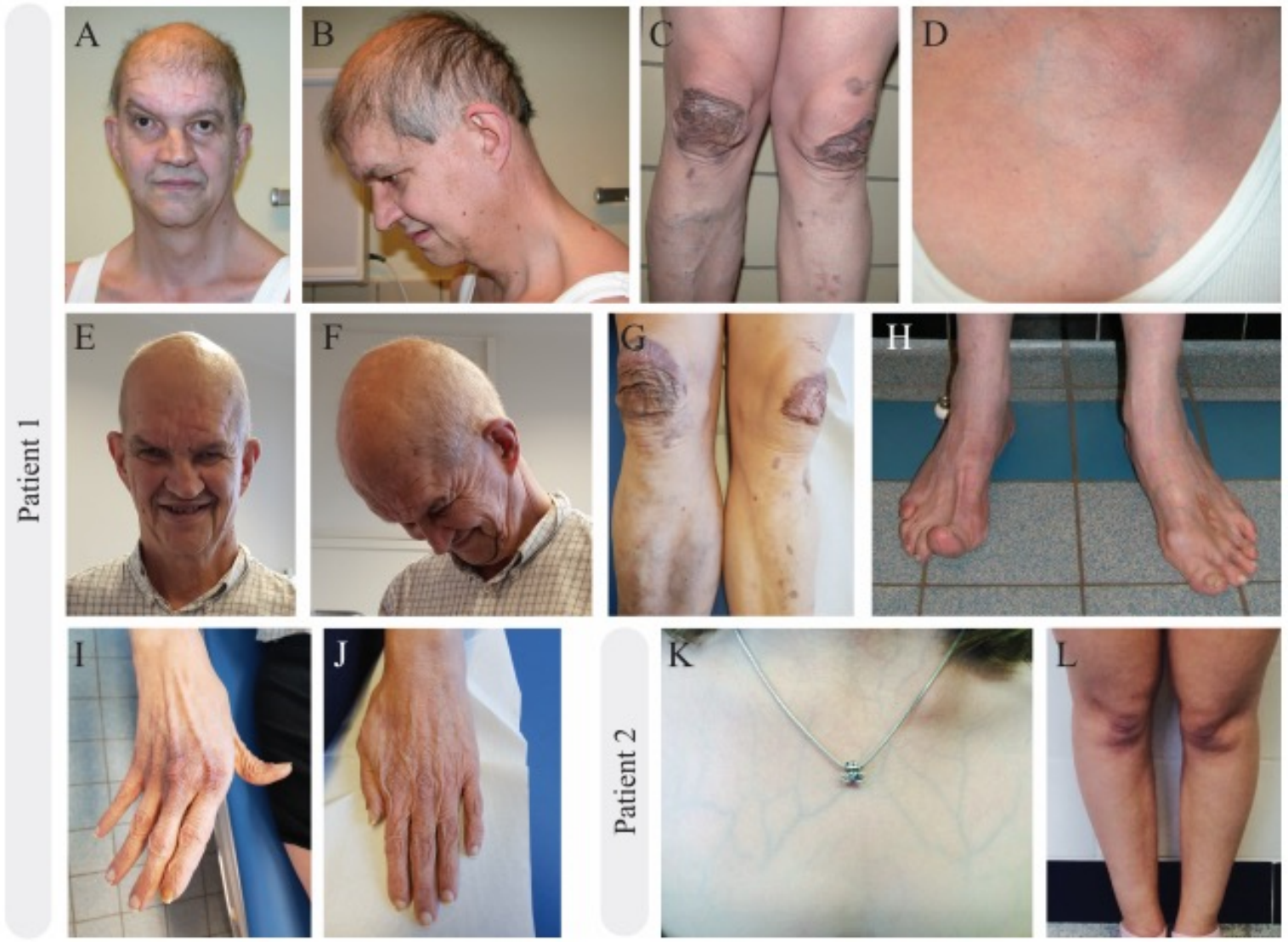
***AEBP1*: c.1925T>C, p.(Leu642Pro)**
NM_001129.4, NP_001120.3

2019

Figure 1

patient 1 at the age of 50 years (A–D and H) or 58 years (E–G, I and J)

patient 2 at the age of 21 years (K and L): female



Syx *et al*: DOI 10.1093/hmg/ddz024

clEDS

- Type 1
  - *TNXB* gene, Tenascin-X deficiency, AR inheritance
    - No atrophic scarring

- Type 2
  - *AEBP1* gene, ACLP deficiency, AR inheritance
    - Osteoporosis/-penia

Time for Q&A

https://www.etsy.com/listing/643748008/eds-ehlers-danlos-syndrome-acrylic