Biology and natural history of Ehlers-Danlos syndromes: types with vascular complications

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VGS, October 3, 2025, Portland, OR

Disclosures

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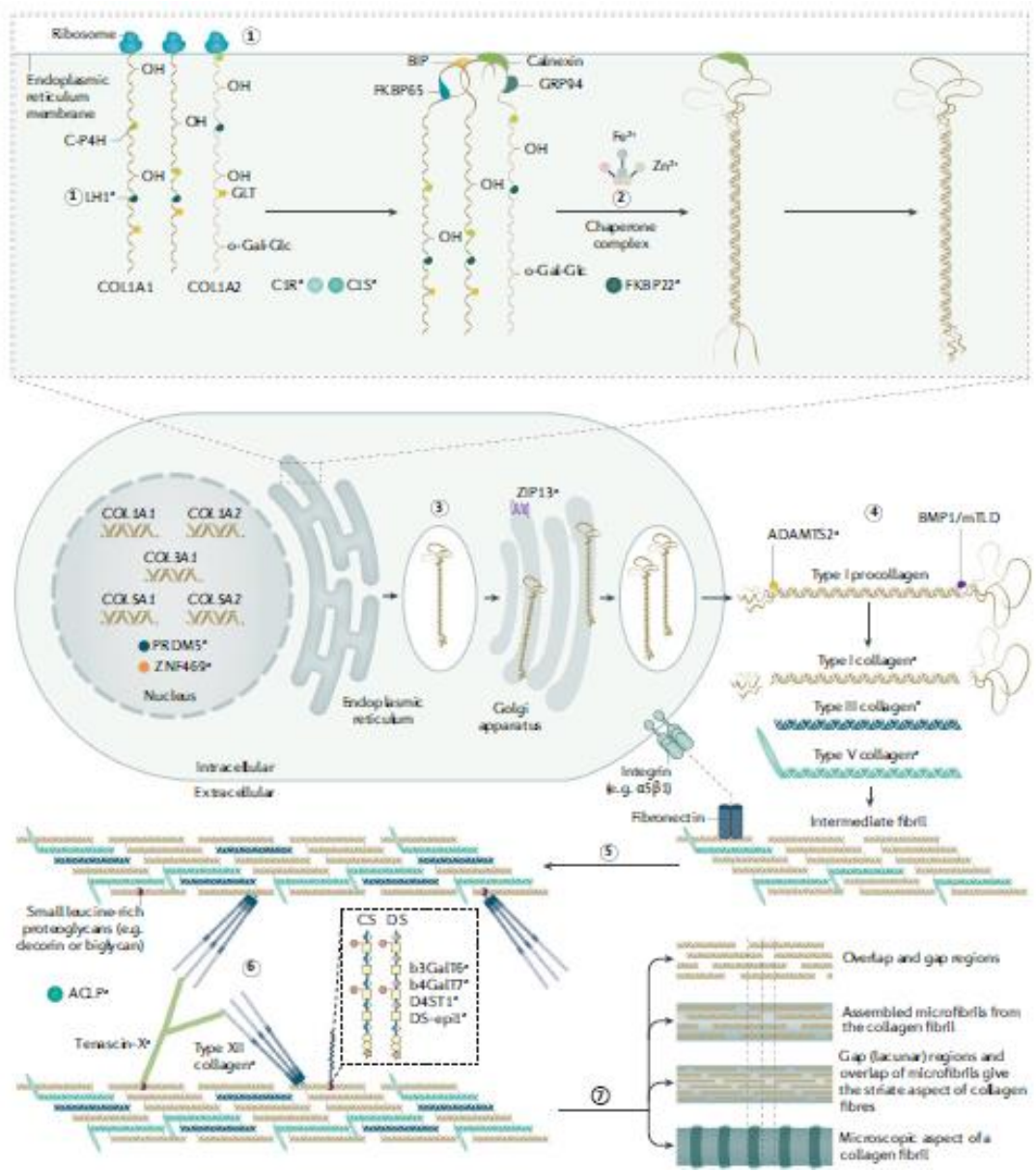
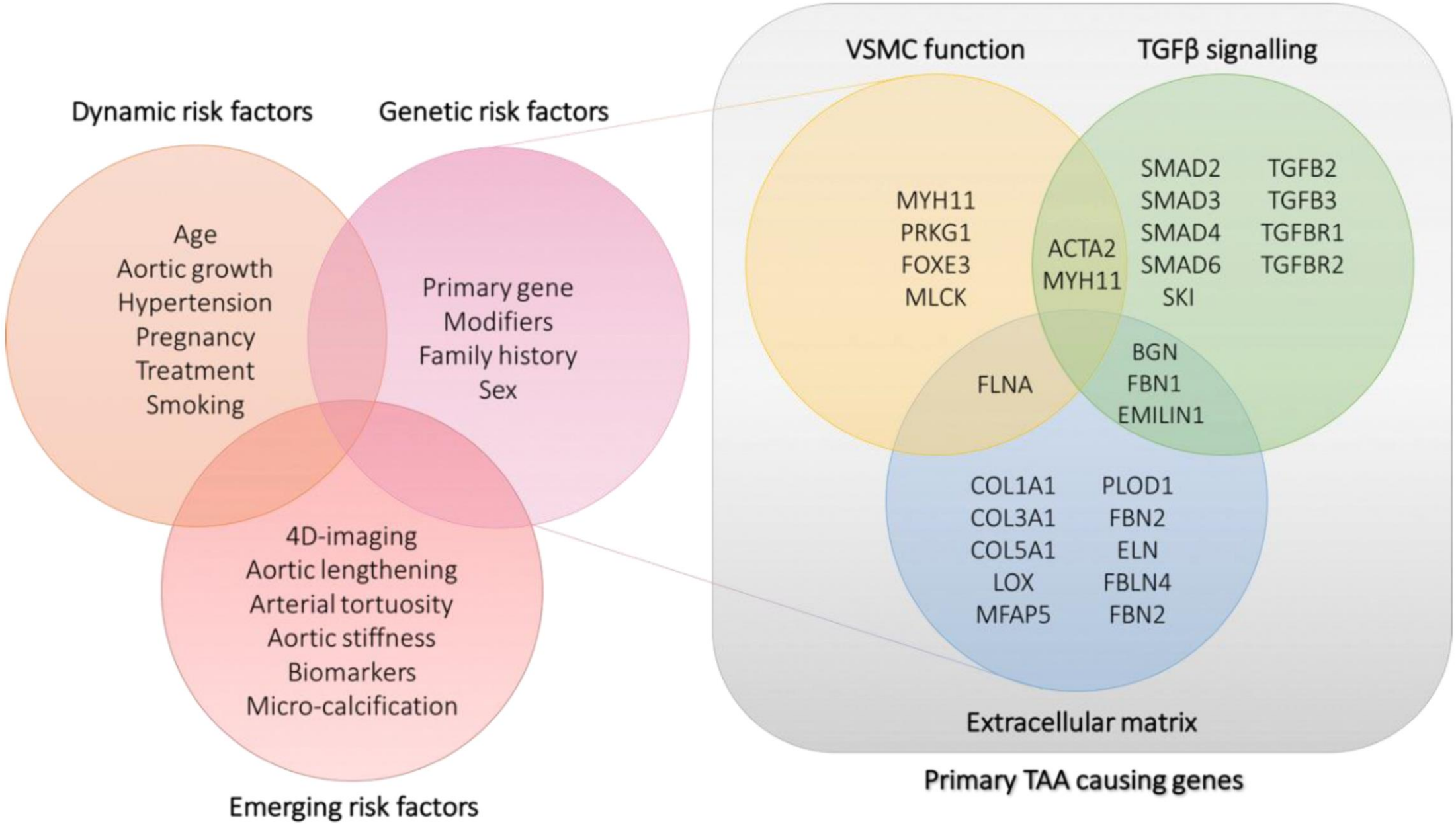
https://thevedsmovement.org/

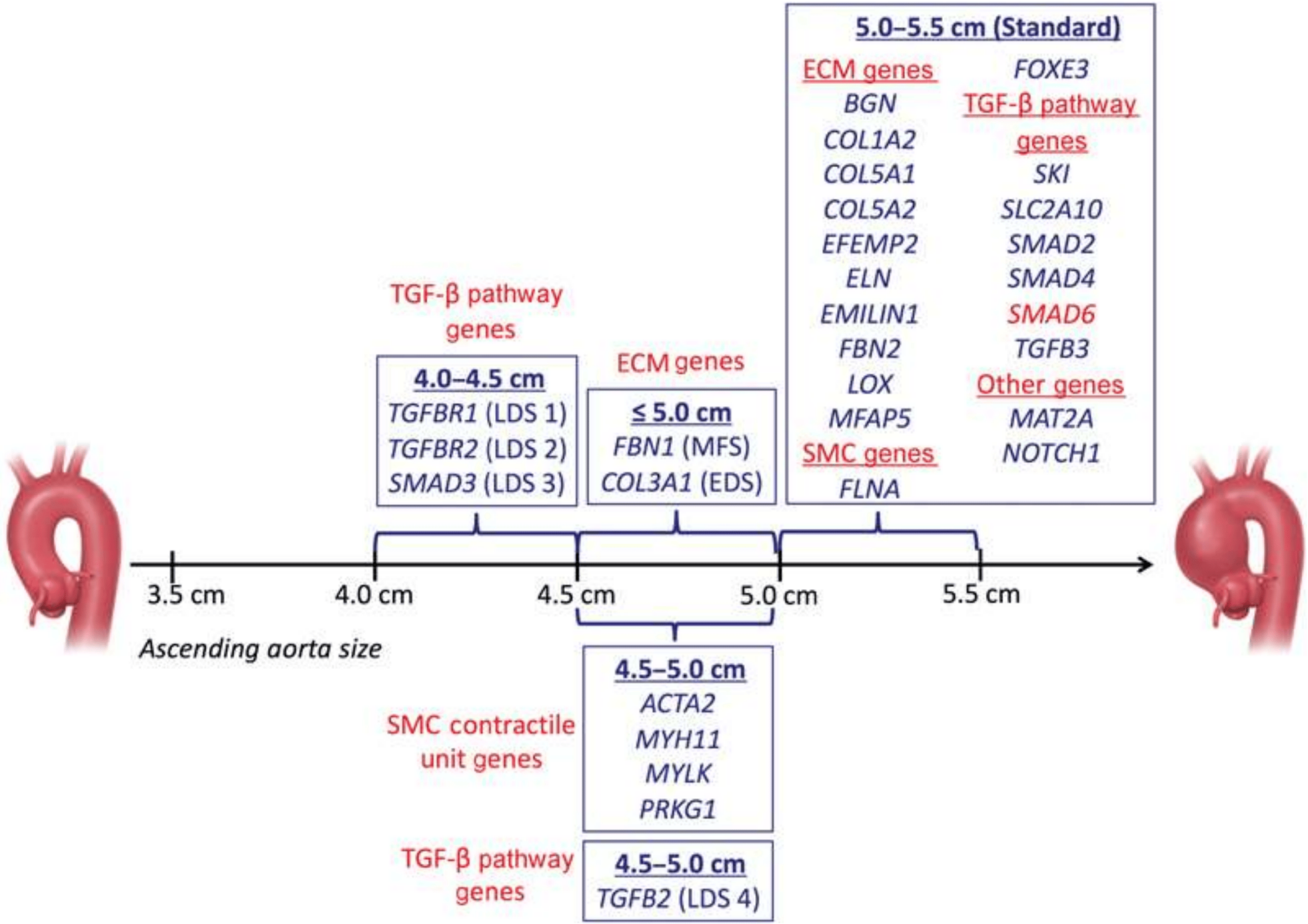
https://translucentone.blog/2020/02/29/the-movement/

Name of EDS Subtype	***IP****	***Genetic Basis***	***Protein Involved***
Classical EDS (cEDS)	AD	Major: *COL5A1, COL5A2*	Type V collagen
		Rare: *COL1A1* c.934C>T, p.(Arg312Cys)	Type I collagen
Classical-like EDS (clEDS)	AR	*TNXB*	Tenascin XB
Cardiac-valvular EDS (cvEDS)	AR	*COL1A2* (biallelic mutations that lead to *COL1A2* NMD and absence of pro α2(I) collagen chains)	Type I collagen
Vascular EDS (vEDS)	AD	Major: *COL3A1*	Type III collagen
		Rare: *COL1A1* c.934C>T, p.(Arg312Cys) c.1720C>T, p.(Arg574Cys) c.3277C>T, p.(Arg1093Cys)	Type I collagen
Hypermobile EDS (hEDS)	AD	Unknown	Unknown
Arthrochalasia EDS (aEDS)	AD	*COL1A1, COL1A2*	Type I collagen
Dermatosparaxis EDS (dEDS)	AR	*ADAMTS2*	ADAMTS-2
Kyphoscoliotic EDS (kEDS)	AR	*PLOD1*	LH1
		FKBP14	FKBP22
Brittle cornea syndrome (BCS)	AR	*ZNF469*	ZNF469
		PRDM5	PRDM5
Spondylodysplastic EDS (spEDS)	AR	*B4GALT7*	ß4GalT7
		B3GALT6	ß3GalT6
		SLC39A13	ZIP13
Musculocontractural EDS (mcEDS)	AR	*CHST14*	D4ST1
		DSE	DSE
Myopathic EDS (mEDS)	AD or AR	*COL12A1*	Type XII collagen
Periodontal EDS (pEDS)	AD	*C1R*	C1r



Malfait et al, Nature Genetics Review


Dynamic risk factors
Genetic risk factors
Age
Aortic growth
Hypertension
Pregnancy
Treatment
Smoking
Primary gene
Modifiers
Family history
Sex
4D-imaging
Aortic lengthening
Arterial tortuosity
Aortic stiffness
Biomarkers
Micro-calcification
Emerging risk factors
(A)
VSMC function
TGFβ signalling
MYH11
PRKG1
FOXE3
MLCK
ACTA2
MYH11
SMAD2
SMAD3
SMAD4
SMAD6
SKI
TGFB2
TGFB3
TGFBR1
TGFBR2
FLNA
BGN
FBN1
EMILIN1
COL1A1
COL3A1
COL5A1
LOX
MFAP5
PLOD1
FBN2
ELN
FBLN4
FBN2
Extracellular matrix
Primary TAA causing genes
(B)

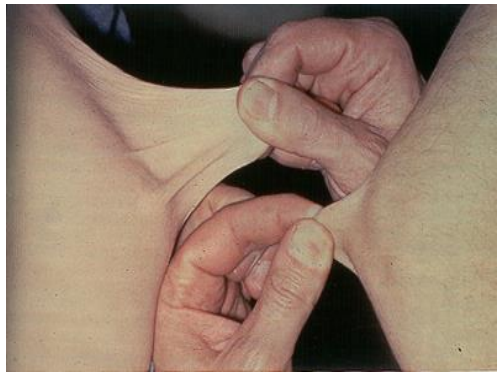

5.0–5.5 cm (Standard)
ECM genes
FOXE3
BGN
TGF-β pathway genes
COL1A2
COL5A1
SKI
COL5A2
SLC2A10
EFEMP2
SMAD2
ELN
SMAD4
EMILIN1
SMAD6
FBN2
TGFB3
LOX
Other genes
MFAP5
MAT2A
SMC genes
NOTCH1
FLNA
TGF-β pathway genes
4.0–4.5 cm
TGFBR1 (LDS 1)
TGFBR2 (LDS 2)
SMAD3 (LDS 3)
ECM genes
≤ 5.0 cm
FBN1 (MFS)
COL3A1 (EDS)
3.5 cm
4.0 cm
4.5 cm
5.0 cm
5.5 cm
Ascending aorta size
4.5–5.0 cm
ACTA2
MYH11
MYLK
PRKG1
SMC contractile unit genes
TGF-β pathway genes
4.5–5.0 cm
TGFB2 (LDS 4)

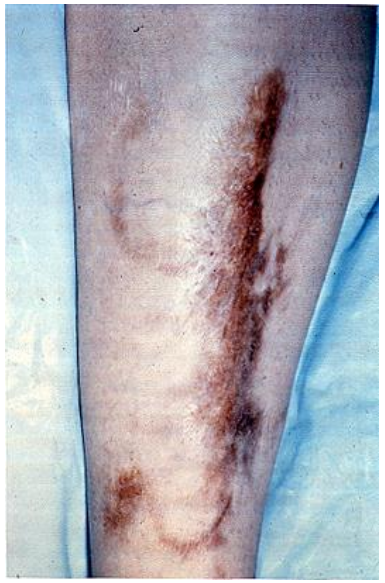
Three types of EDS have vascular events

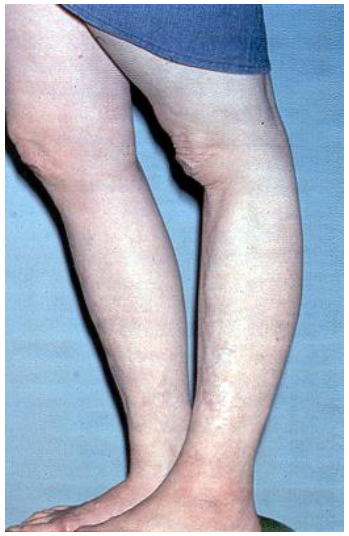
Classical EDS—*COL5A1*, *COL5A2*

Kyphoscoliotic EDS—*PLOD1* and *FKBP14*

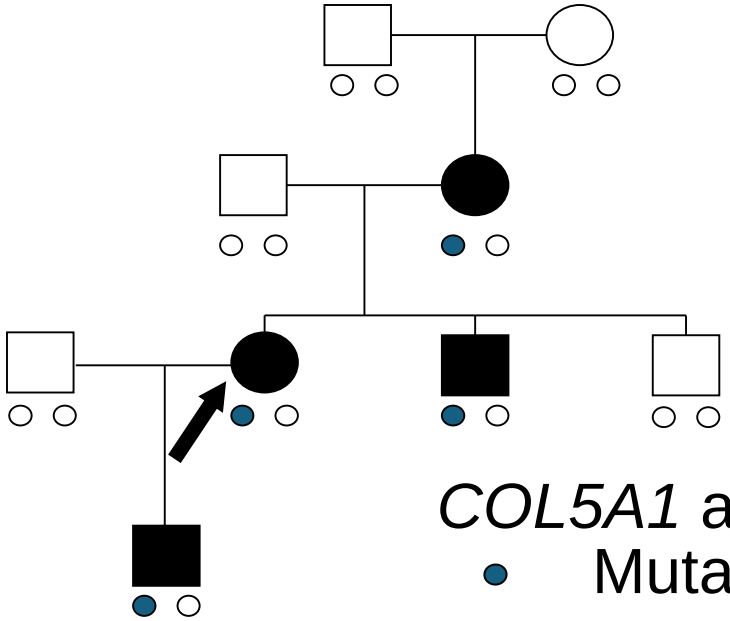
Vascular EDS—*COL3A1*







EDS type I



Frequency—uncommon
perhaps 1/25-50,000

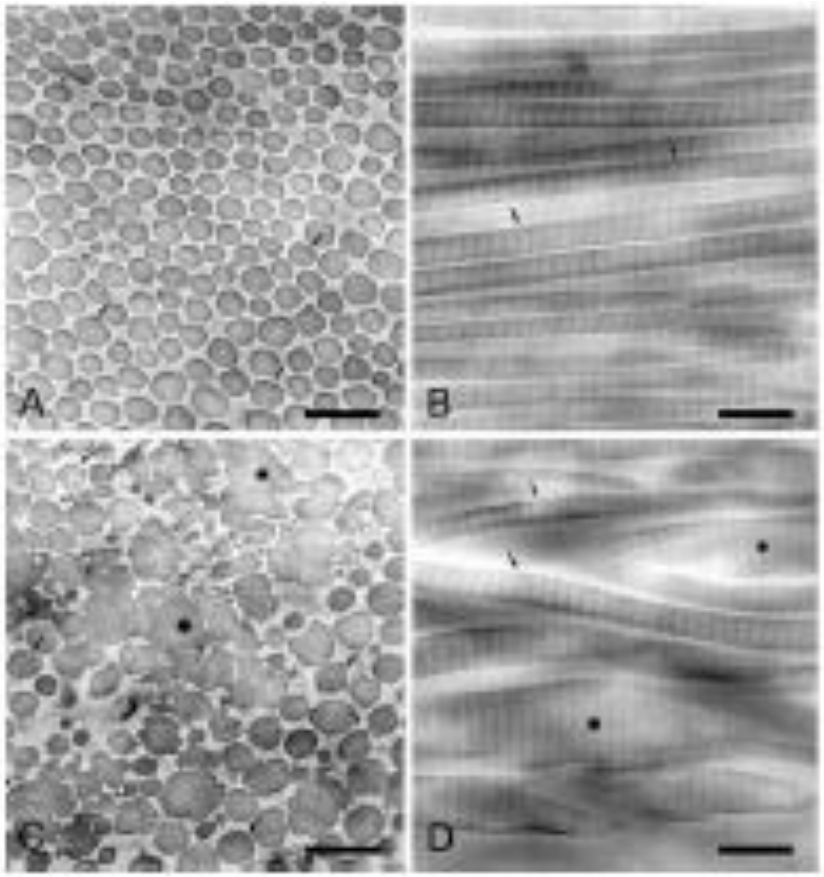
COL5A1 alleles

- Mutation
- No mutation

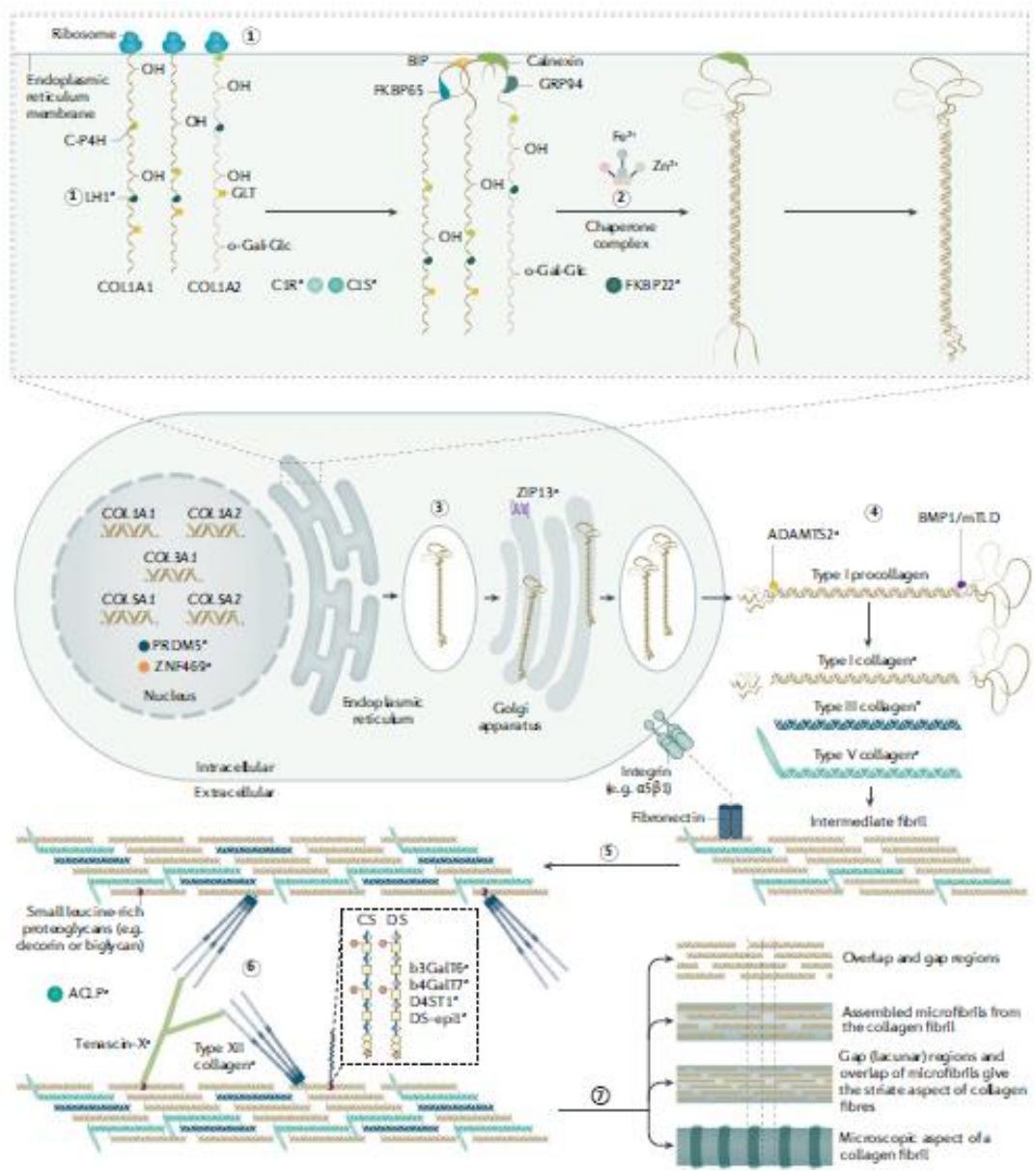
Mice with a nonsense mutation in one COL5A1 allele.

+/+

+/-



Wenstrup et al. J Biol Chem 279:63331-63384, 2005



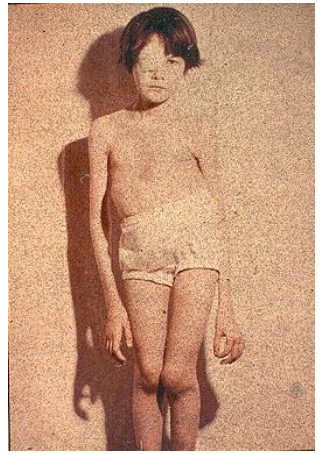
Malfait et al, Nature Genetics Review

Diagnostic confirmation of EDS type I

Heterozygosity for mutation in the type V collagen genes: *COL5A1* and *COL5A2*

Kyphoscoliotic EDS (EDS type VI)

- Ocular scoliotic or kyphoscoliotic type
- EDS type VI
  - Marked joint laxity
  - Intractable scoliosis
  - Soft, velvety skin
  - Ocular globe fragility
  - Keratoconus
  - Autosomal recessive inheritance due to biallelic pathogenic variants in *PLOD1* (lysyl hydroxylase)



Major long term issue

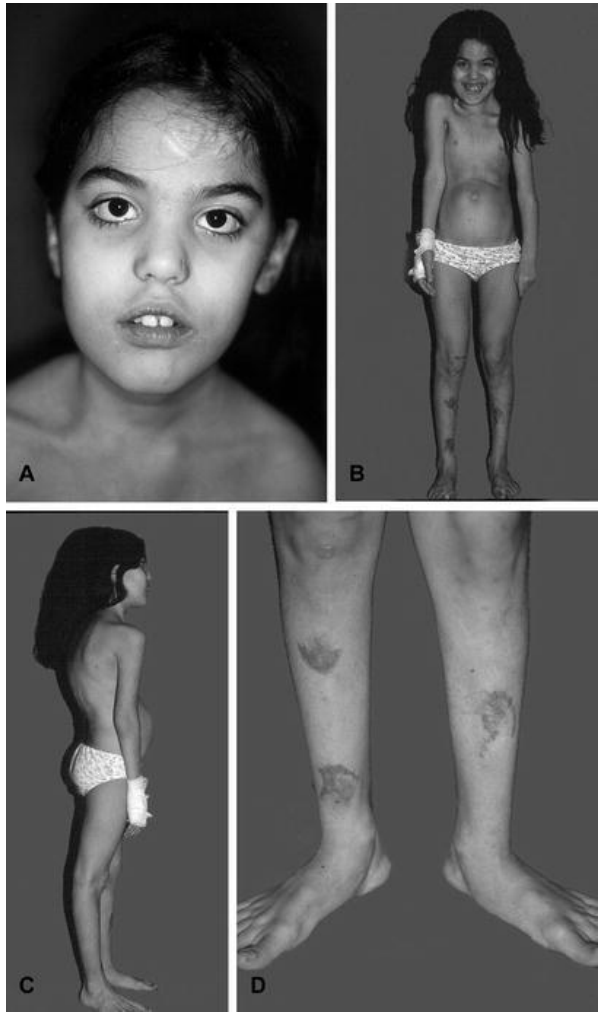
Arterial dissection

Hearing loss for *FKBP14*-related

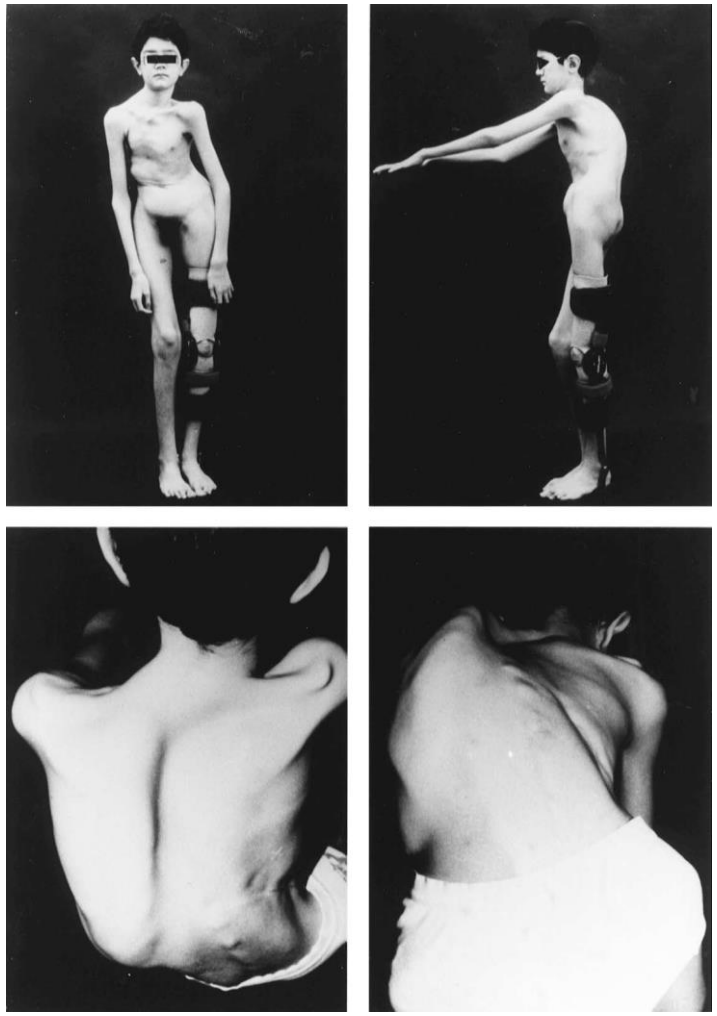
Surveillance and Treatment

Uncertain

Some mutations in *PLOD1* may respond to vitamin C



Brunk et al
Eur J Pediatr 163:214-217, 2004



Heim et al. Acta Paediatr 87:708-710, 1998

FKBP14 related EDS

FIG. 1. Photographs of the patient throughout life: (a) non-dysmorphic facies at birth; (b) some facial elongation and hypotonia notable at 6 months; (c) hypotonia and kyphoscoliosis evident at 1 year; (d) non-dysmorphic appearance at 2 years; (e) neck appears short due to kyphoscoliosis, long fingers at 6 years; (f) deformation of chest due to kyphoscoliosis, low muscle mass, long fingers at 10 years; (g) low muscle mass and short stature at 15 years; (h) long thin face, prominent brows, and low muscle mass at 19 years; (i) facial features less gaunt at 30 years; (j) profile showing kyphoscoliosis, pectus carinatum, and short stature at 35 years; (k) and (l) similar facial and physical features at 42 years.

FKBP14 related EDS

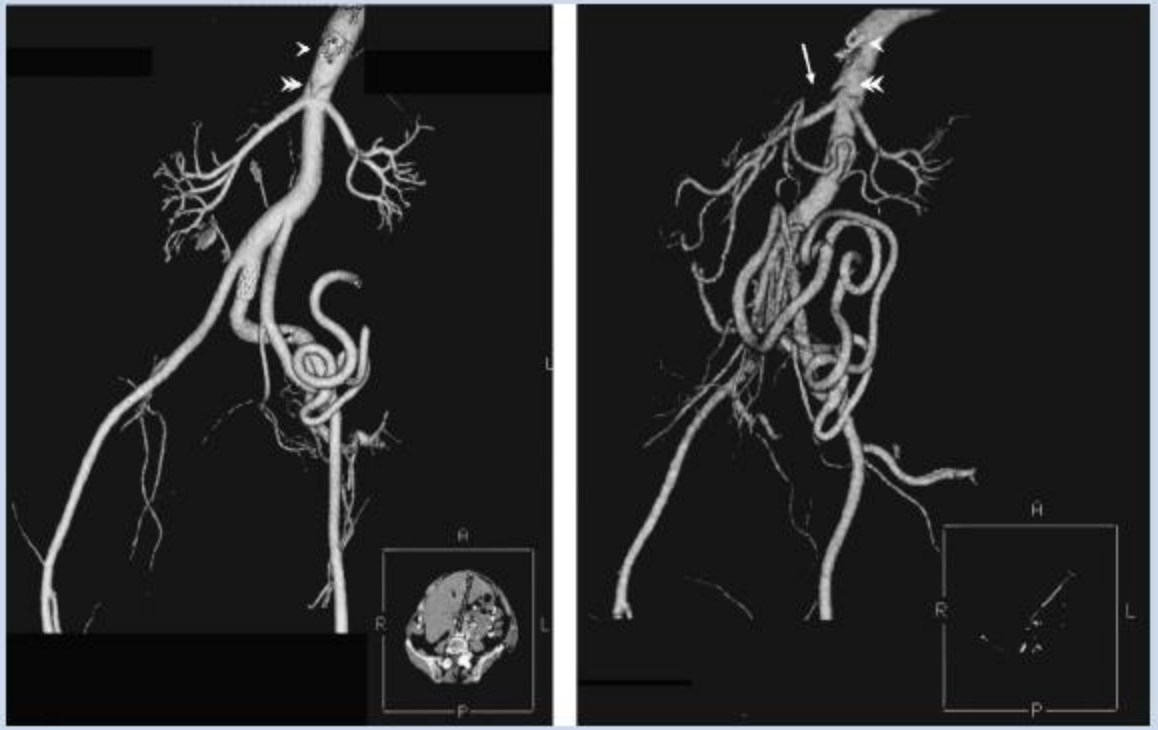
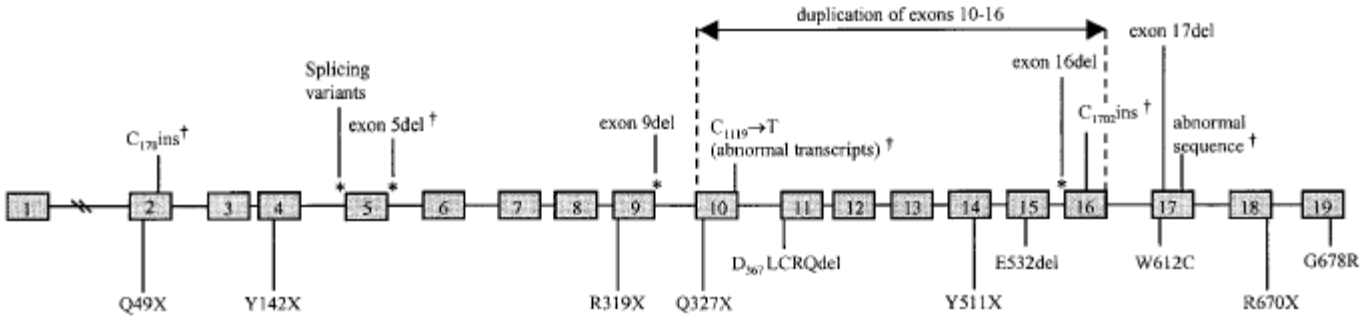


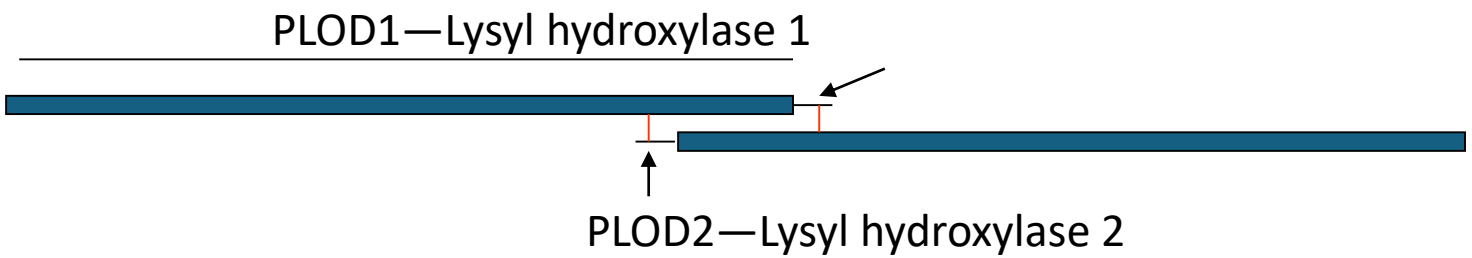
FIG. 2. CTA 3D reconstructions of abdominal vasculature. A: Tortuosity and enlargement of IMA with occlusion of celiac artery with stent (single arrowhead) and occlusion of the SMA (double arrowhead). Also note stent in left iliac artery. B: Repeat imaging 9 months later demonstrating complete occlusion of SMA (double arrowhead) with retrograde filling distal to occlusion (arrow). Occlusion of celiac artery with stent (single arrowhead) persists. IMA is markedly enlarged and tortuous.

EDS type VI

Autosomal recessive, mutations in *PLOD1* which encodes lysyl hydroxylase, vitamin C is a co-factor

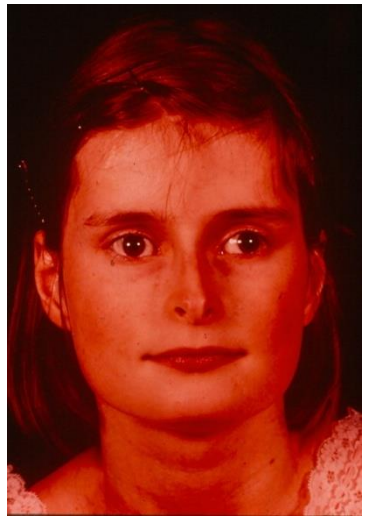
Rare, frequency unknown, about 40-50 reported





Vascular Ehlers-Danlos Syndrome (EDS type IV) Clinical Features

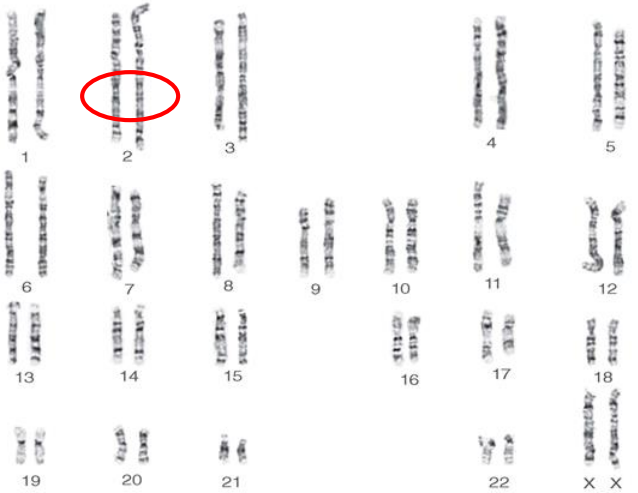
- “Characteristic” facies
  - Thin nose
  - Thin lips
  - Attached lobes
  - Sometimes tight skin over the face
- Visible venous pattern; bruising
- Small joint hypermobility
- Normal scar formation

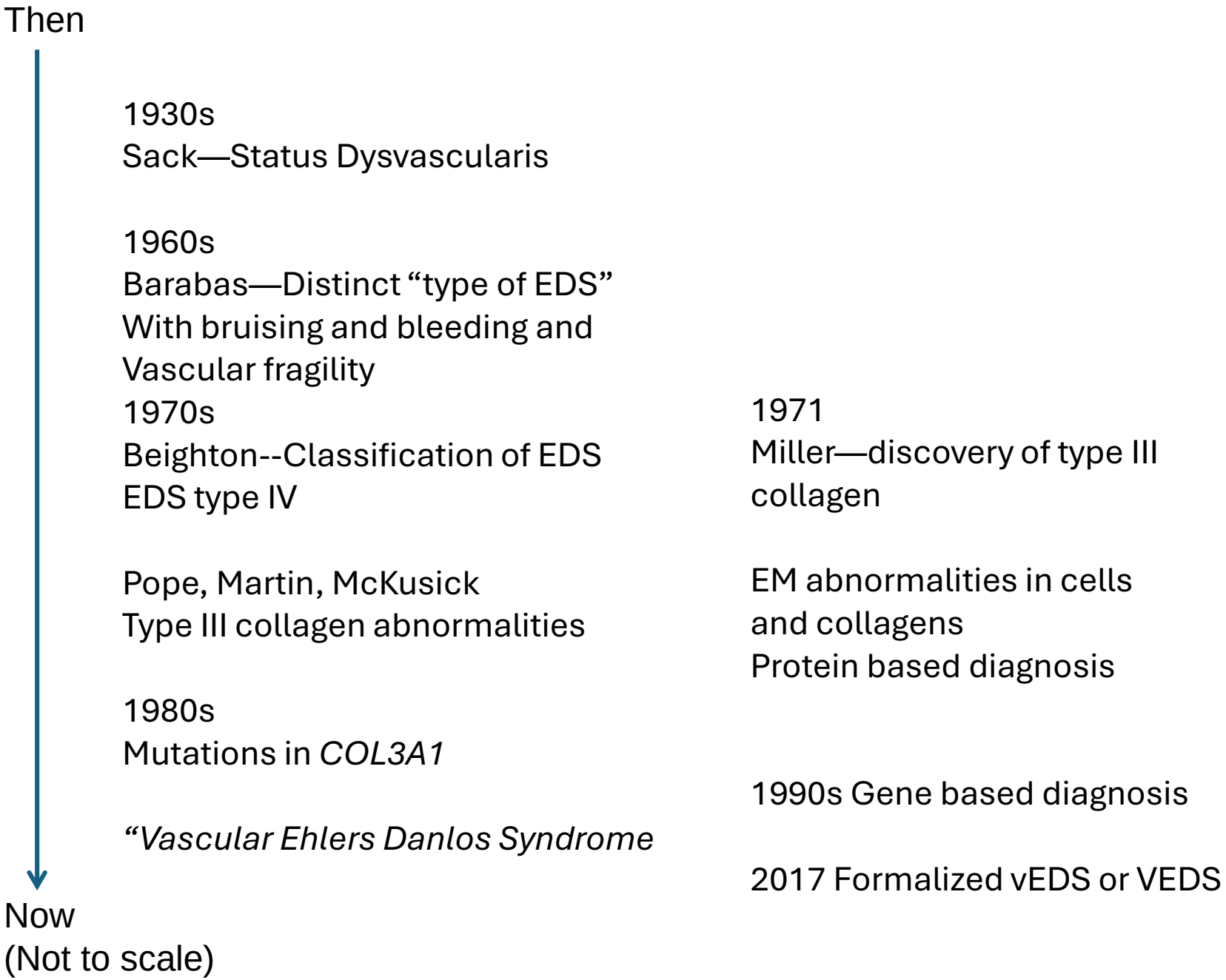



SCANDINAVIA LEGACY
CO
TON
FIELD

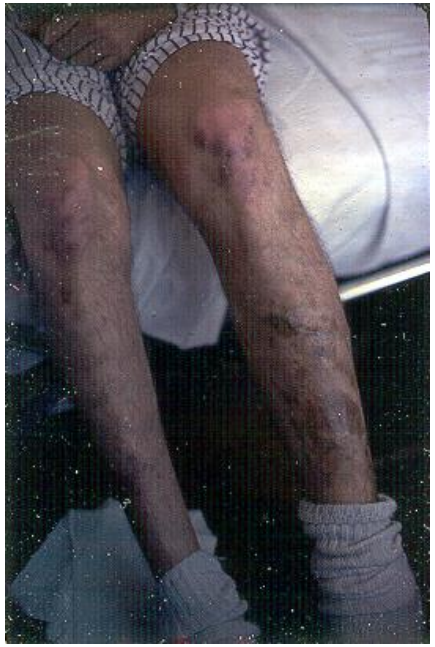
Vascular EDS results from heterozygous pathogenic alterations in *COL3A1*, a gene located on chromosome 2.

COL3A1 encodes the chains of type III collagen, a major component of arterial and bowel walls.



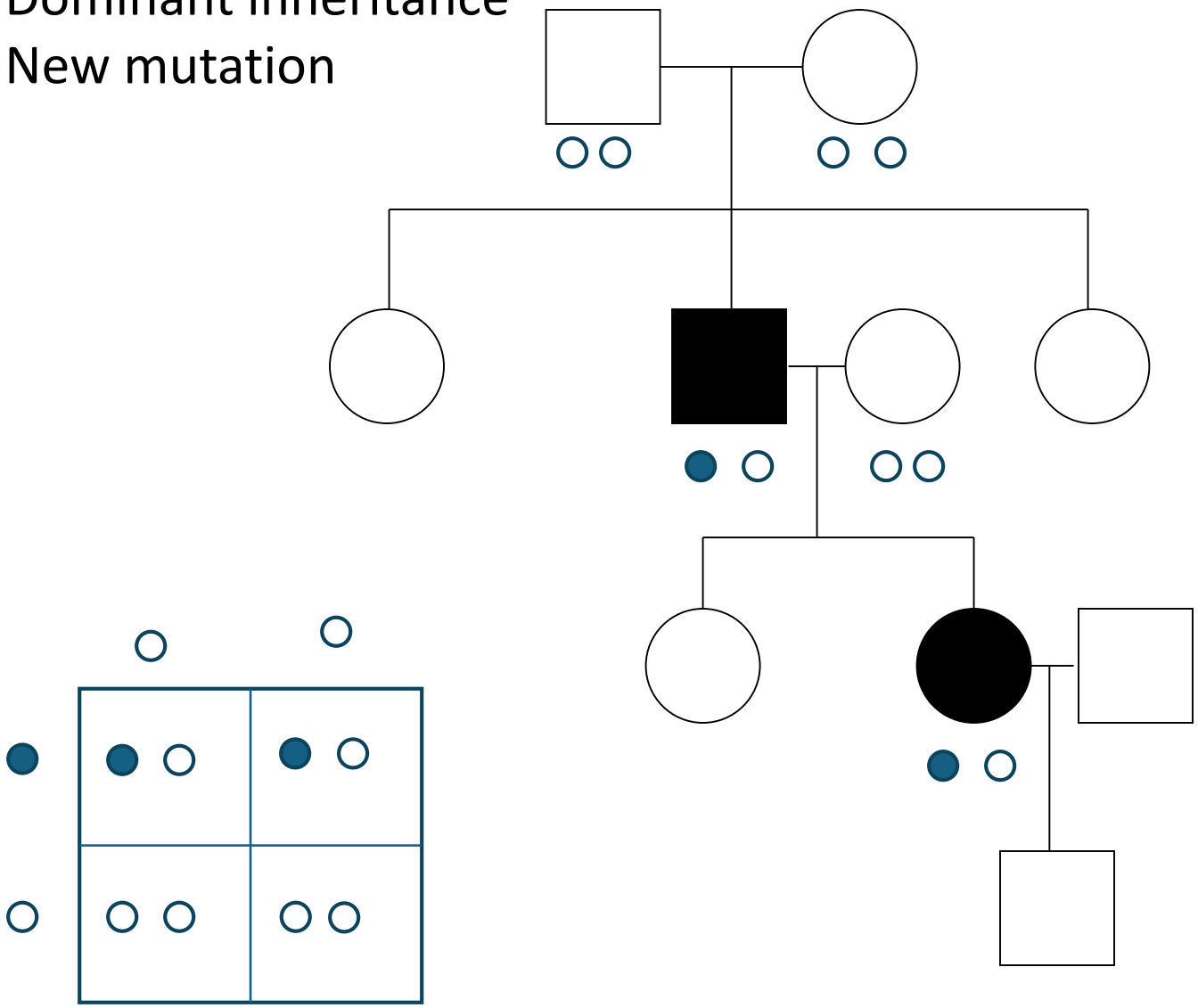

Then
1930s
Sack—Status Dysvascularis
1960s
Barabas—Distinct “type of EDS”
With bruising and bleeding and
Vascular fragility
1970s
Beighton--Classification of EDS
EDS type IV
Pope, Martin, McKusick
Type III collagen abnormalities
1980s
Mutations in *COL3A1*
“Vascular Ehlers Danlos Syndrome
1971
Miller—discovery of type III
collagen
EM abnormalities in cells
and collagens
Protein based diagnosis
1990s Gene based diagnosis
2017 Formalized vEDS or VEDS
Now
(Not to scale)

Darren

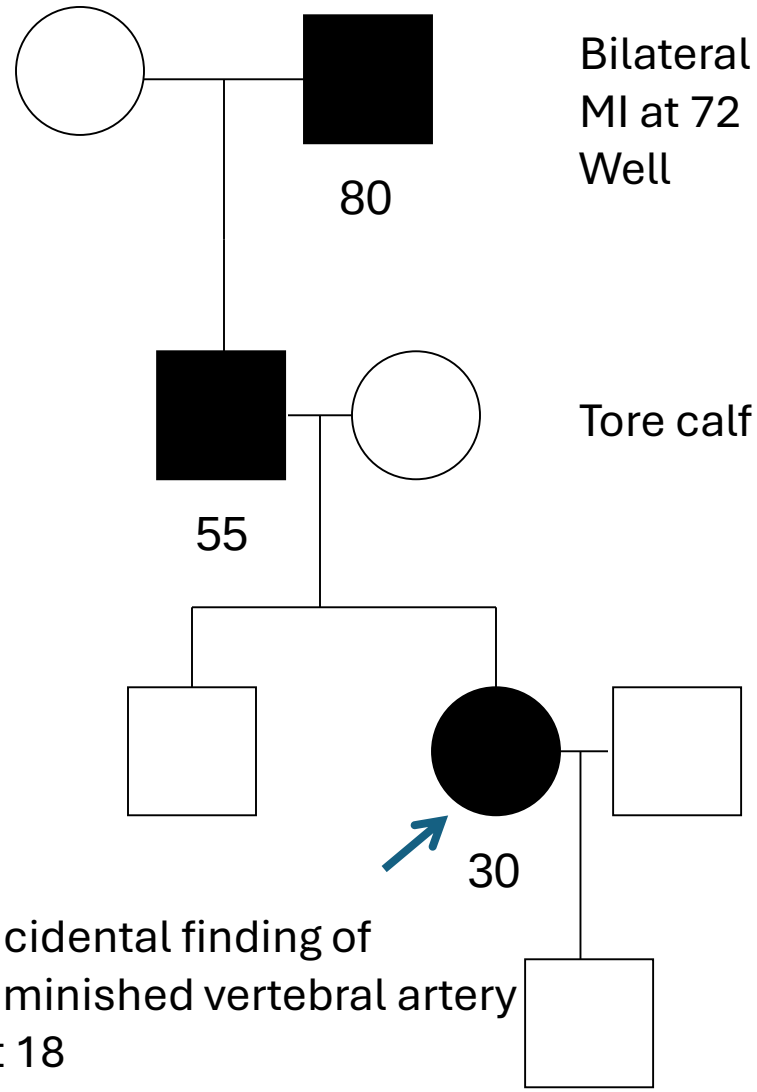


Birth	6	12	22	28	32	35
Club foot	Bowel rupture	Tibial bleed	Keratoconus Corneal transplant	Stroke	Brachial Artery tear	Colonic rupture DEATH

Dominant inheritance
New mutation



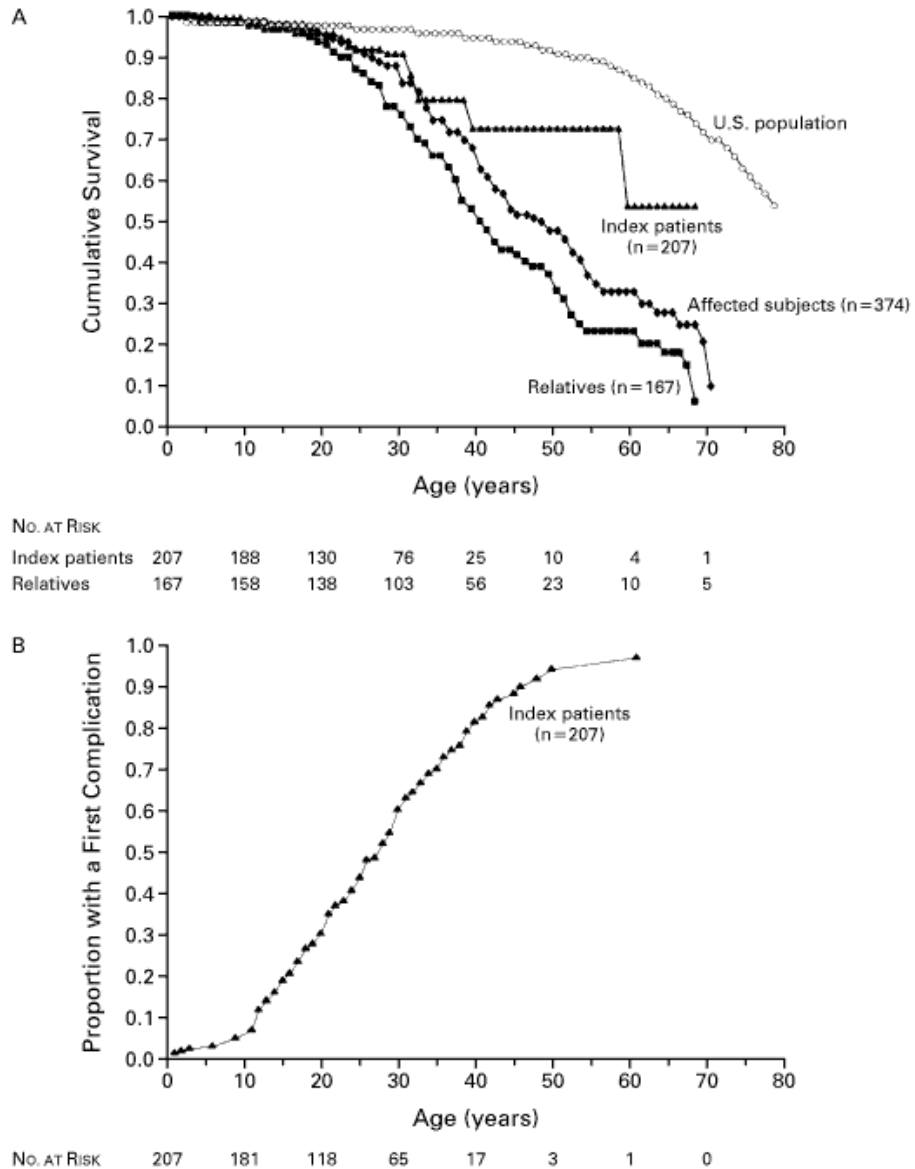
Kelly



Bilateral knee replacements at 70
MI at 72
Well

Tore calf muscle descending Mt. Rainier at 40

Incidental finding of diminished vertebral artery at 18
Normal pregnancy and delivery at 29



From Pepin et al, NEJM March 8, 2000

Major complications

Spontaneous pneumothorax
Bowel rupture—usually sigmoid colon
Arterial dissection/rupture
Carotid-cavernous sinus fistula
Pregnancy—rare uterine rupture
Pulmonary nodules with hemoptosis

History

Family history

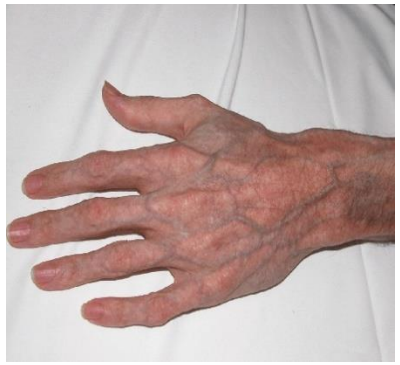
Talipes equinovarus (club foot)
Congenital hip dislocation
Hypermobility of small (and large) joints
Bruising

Spontaneous pneumothorax
Tendon and muscle rupture
Gingival recession and gingival fragility
Early-onset varicose veins (under age 30 and nulliparous if female)

Bowel rupture (sigmoid colon)
Aneurysms, dissections, or ruptures
Characteristic facial appearance

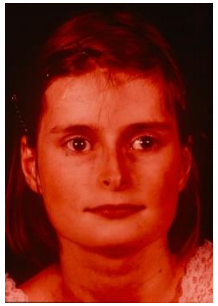
“Do you sleep with your eyes open?”

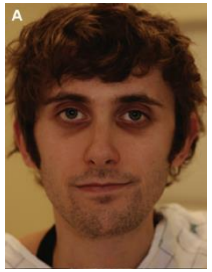
Clinical Examination



Shake hands

- Does the skin seem thin, old
- Are the joints lax/soft
- Can you see vessels
- Are the fingers tapered
- Is there wrinkling on the palms and fingers

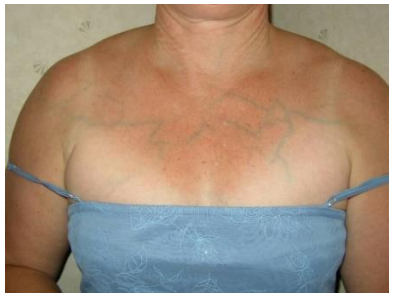




Look at the face

- Is the hair fine and thin
- Thin nose
- Thin lips
- Visible veins on forehead
- Gingival recession/fragility
- Eyes recessed or prominent, pigmentation of skin

Clinical Examination

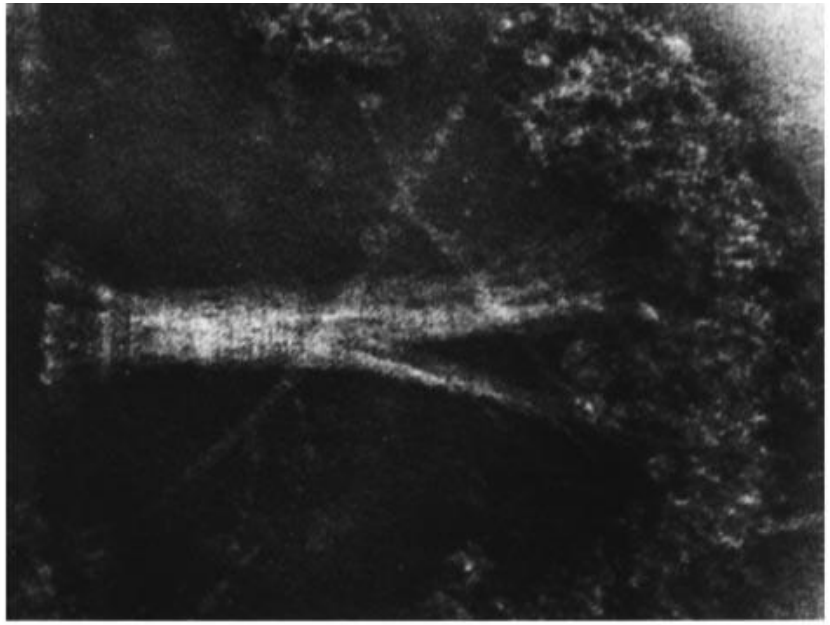


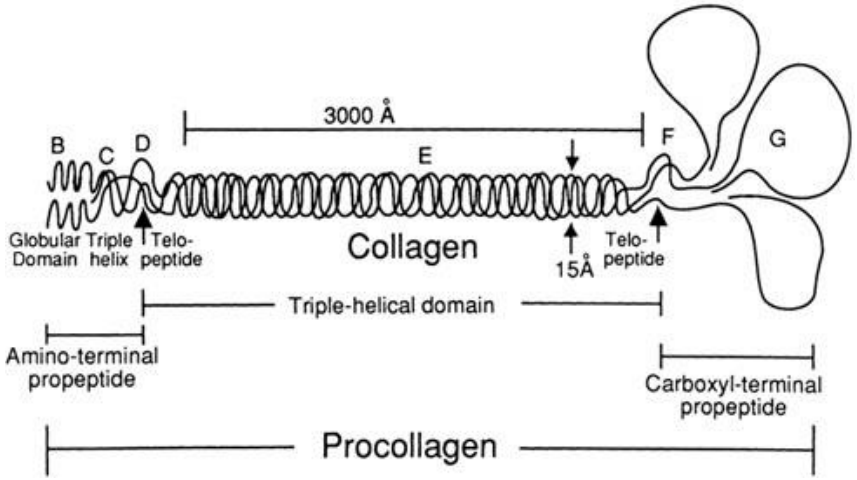
Examine the skin
- Does the skin seem thin, old
- Easily visible veins
- Bruises
- Is the skin extensible or soft
- Are scars normal or abnormal
- Is there heme pigment from old bruises

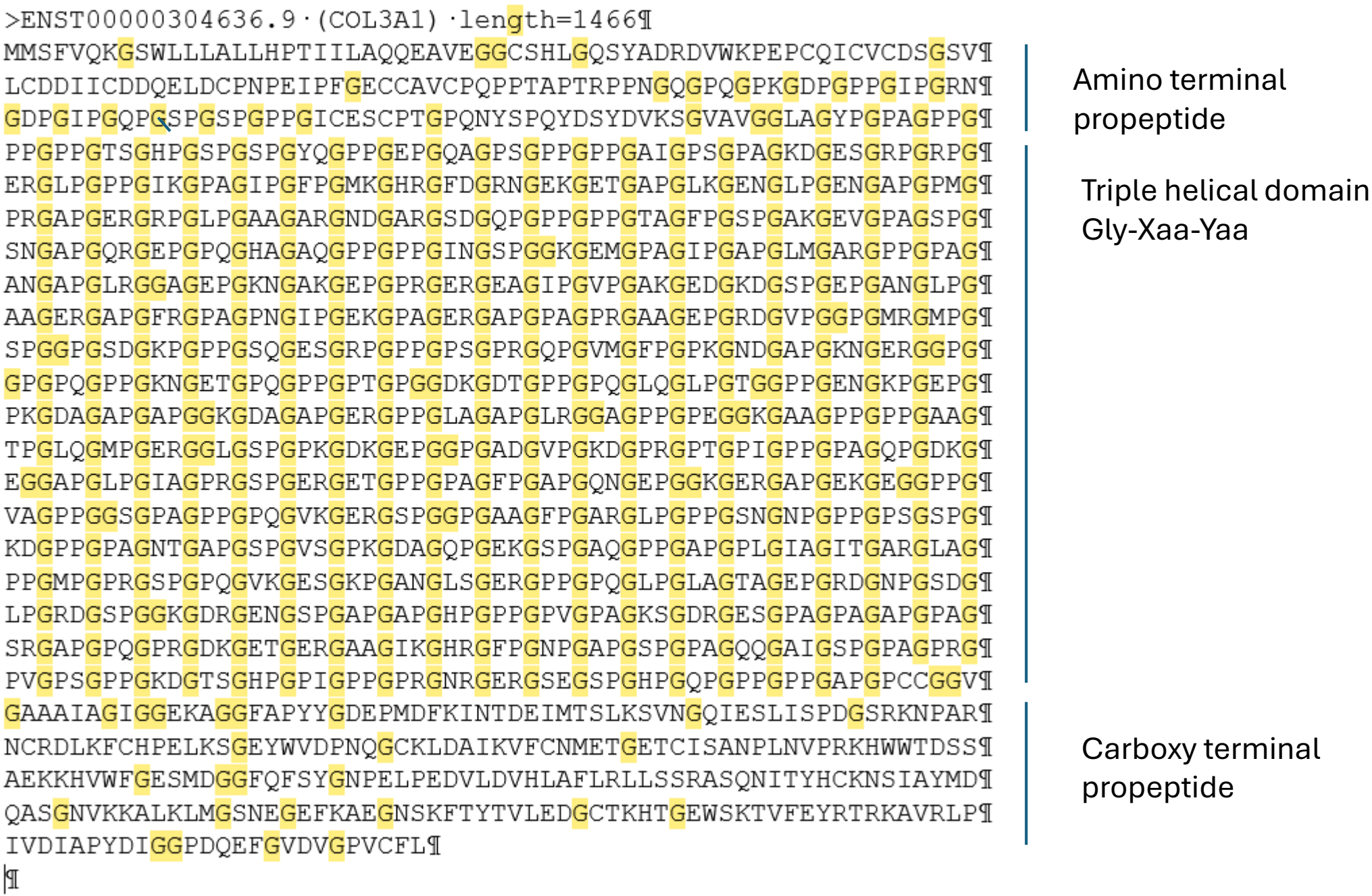
Joints
- Is joint mobility normal
- Small joints (hands) vs. large joints

Abdomen/Chest
- Listen for murmurs, bruits

Approaching the 45th Anniversary of the Discovery of Type III Collagen



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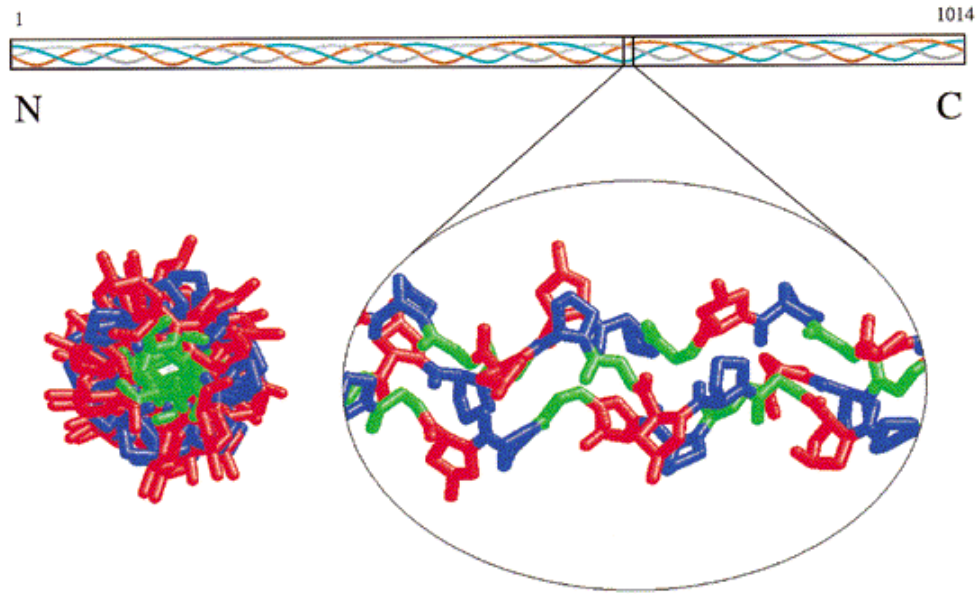
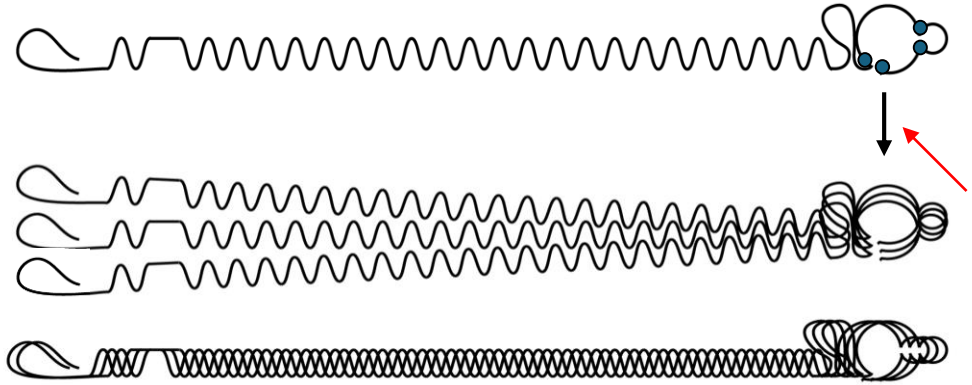
Amino terminal propeptide
Triple helical domain Gly-Xaa-Yaa
Carboxy terminal propeptide



Buevich et al, Biochemistry 39:4299-4308, 2000

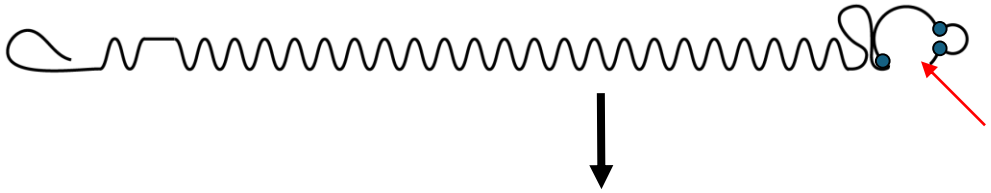
Half-normal amounts of type III procollagen molecules despite mutant mRNA stability

50% normal
proα1(III) chains



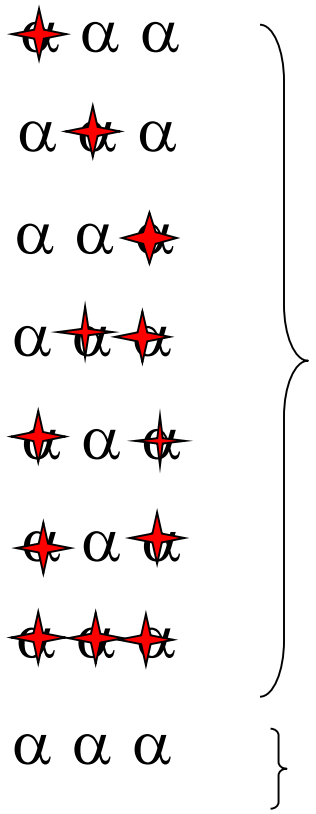
50% normal type III
procollagen

50% truncated
proα1(III) chains



proα1(III) degraded

Dominant negative effect of structurally abnormal proα1(III) chains



7/8 of type III procollagen molecules are **abnormal**

1/8 of type III procollagen molecules are **normal**

Survival is affected by mutation type and molecular mechanism in vascular Ehlers–Danlos syndrome (EDS type IV)

Melanie G. Pepin, MS[1], Ulrike Schwarze, MD[1], Kenneth M. Rice, PhD[2], Mingdong Liu, PhD[2], Dru Leistritz, MS[1] and Peter H. Byers, MD[1,3]

Genet Med advance online publication 12 June 2014

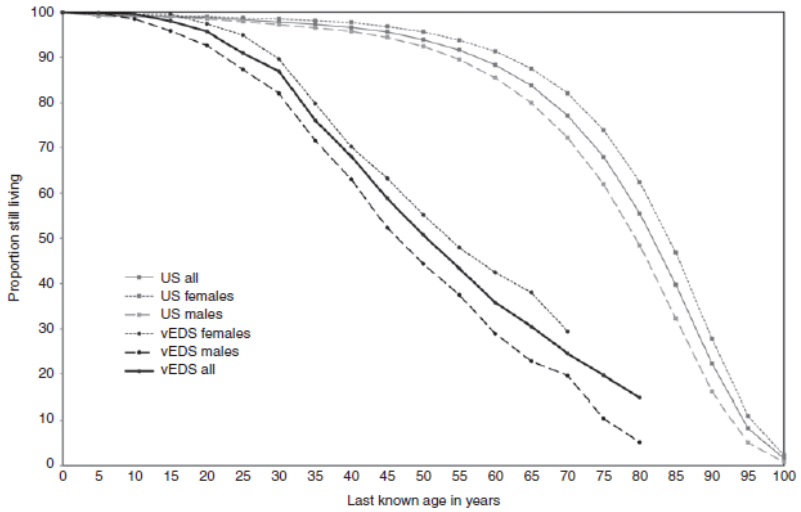


Figure 1 Kaplan–Meier survival curve comparing vascular Ehlers–Danlos syndrome (vEDS) study population to 2008 US population.

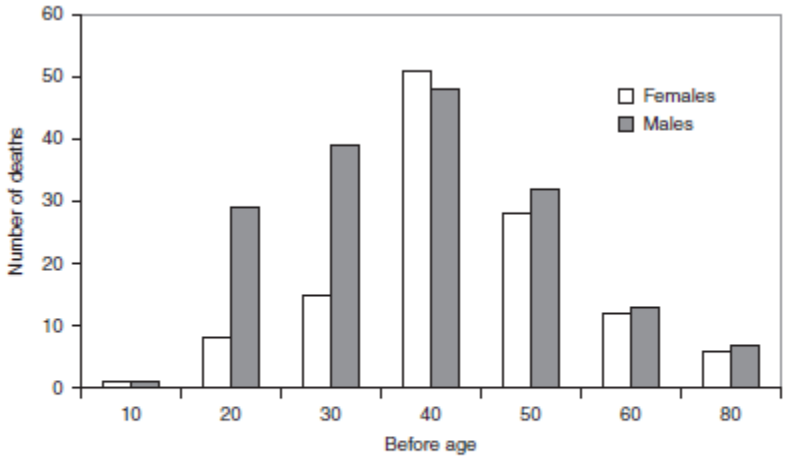
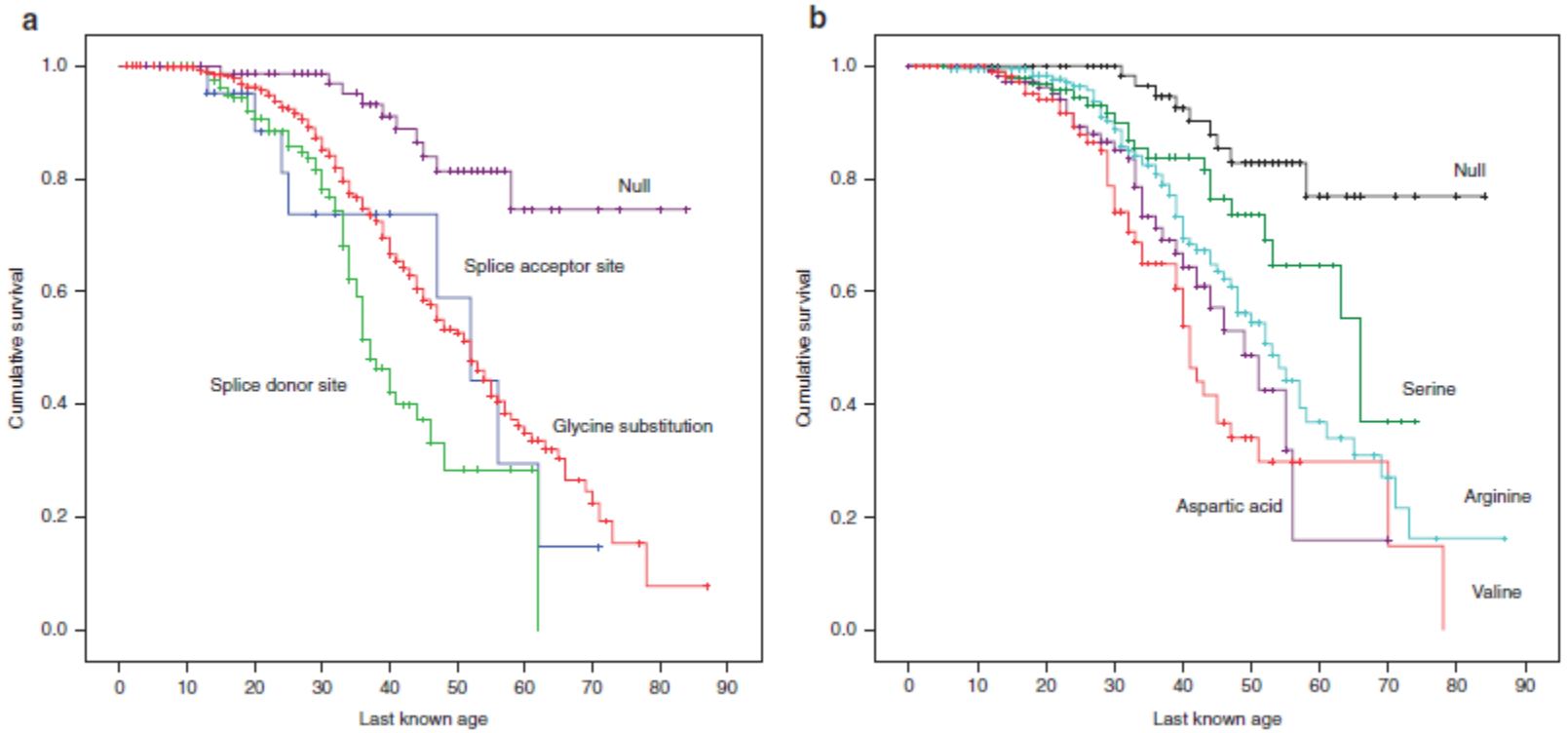


Figure 2 Number of deaths by decade in males and females of vascular Ehlers–Danlos syndrome study population.

Survival is affected by mutation type and molecular mechanism in vascular Ehlers–Danlos syndrome (EDS type IV)

Melanie G. Pepin, MS[1], Ulrike Schwarze, MD[1], Kenneth M. Rice, PhD[2], Mingdong Liu, PhD[2], Dru Leistritz, MS[1] and Peter H. Byers, MD[1,3]



Pregnancy-related deaths and complications in women with vascular Ehlers–Danlos syndrome

Mitzi L. Murray, MD, MA[1,2], Melanie Pepin, MS[1], Suzanne Peterson, MD[3] and Peter H. Byers, MD[1,2]

Genet Med advance online publication 12 June 2014

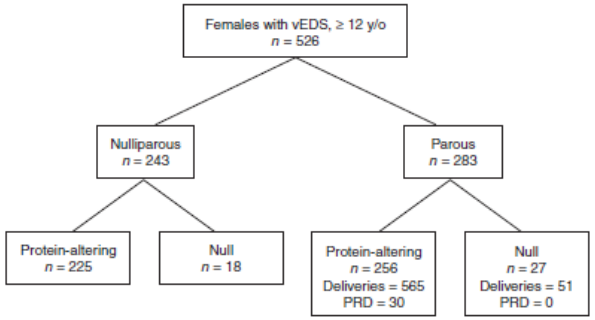


Figure 1 Ascertainment of females with vEDS from a pedigree review, divided by parity and mutation type. PRD, pregnancy-related death; vEDS, vascular Ehlers–Danlos syndrome.

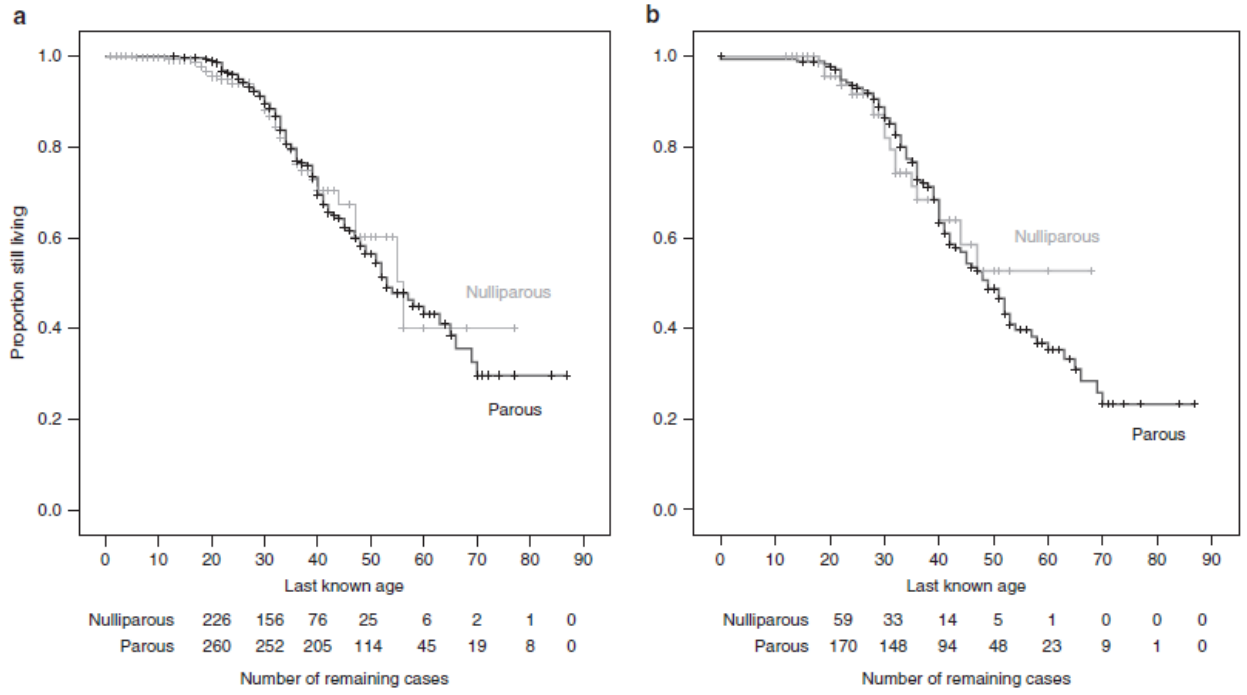
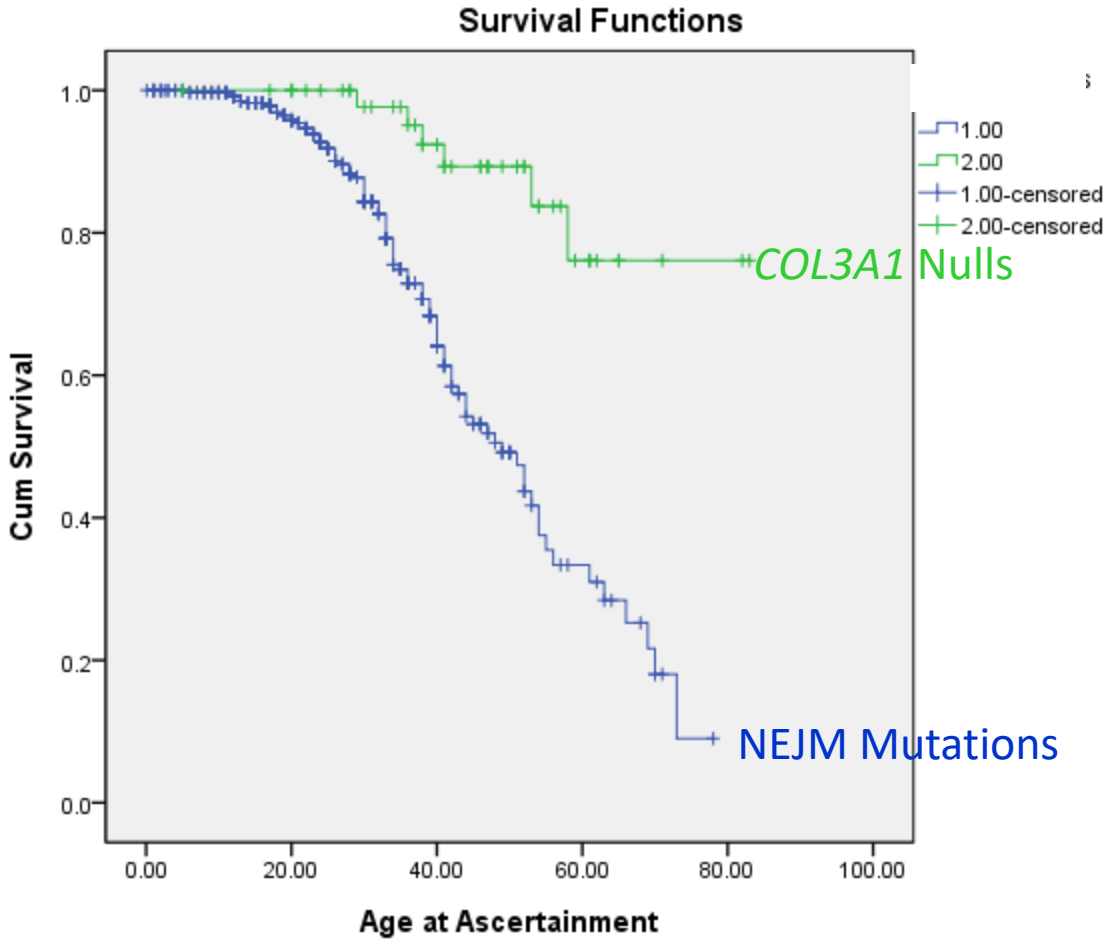


Figure 2 Kaplan–Meier estimates. (**a**) Overall survival of 526 parous ($n = 283$) and nulliparous ($n = 243$) women of reproductive age with vEDS; (**b**) overall survival in parous ($n = 179$) and nulliparous ($n = 86$) affected female relatives of probands with vEDS. vEDS, vascular Ehlers–Danlos syndrome.

Kaplan-Meier Survival Curve

Index Patients and Relatives



Treatment

Medical

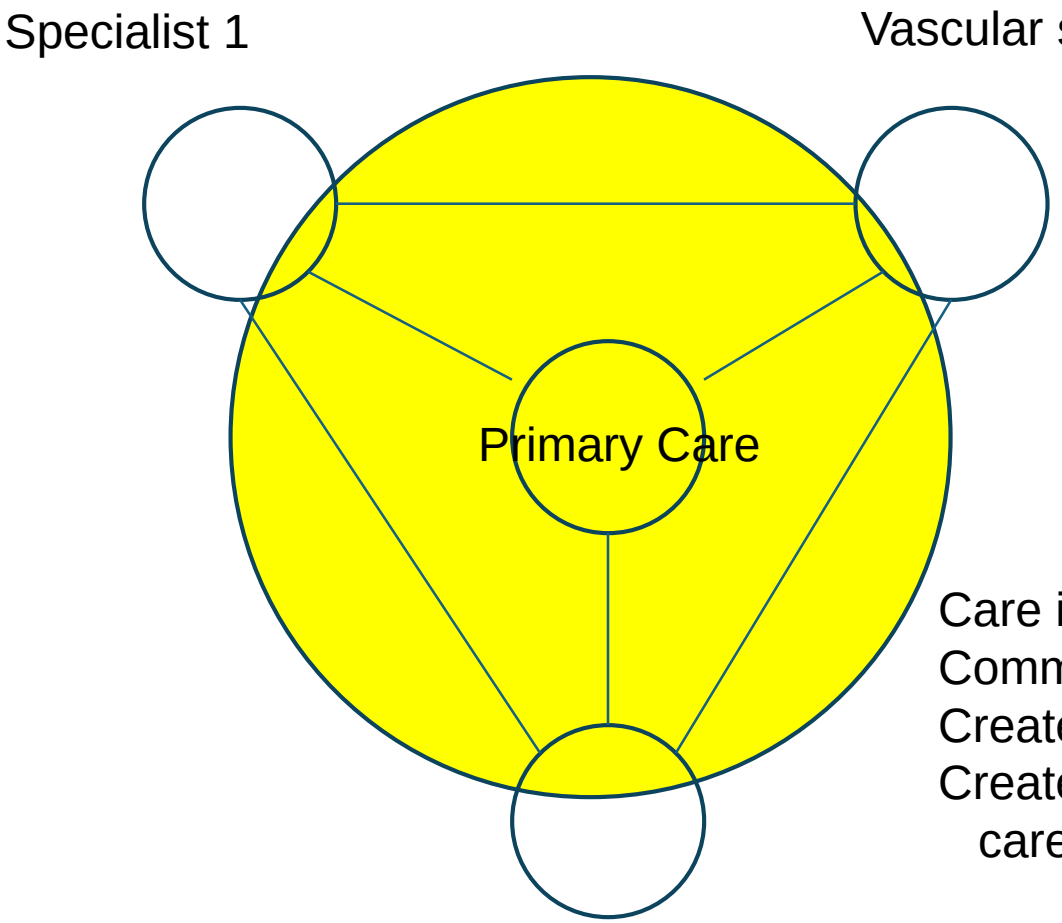
- Surveillance
- Blood pressure control
- Anticoagulation after dissection to maintain flow

Surgical

- Endovascular stent
- Invasive surgery if necessary

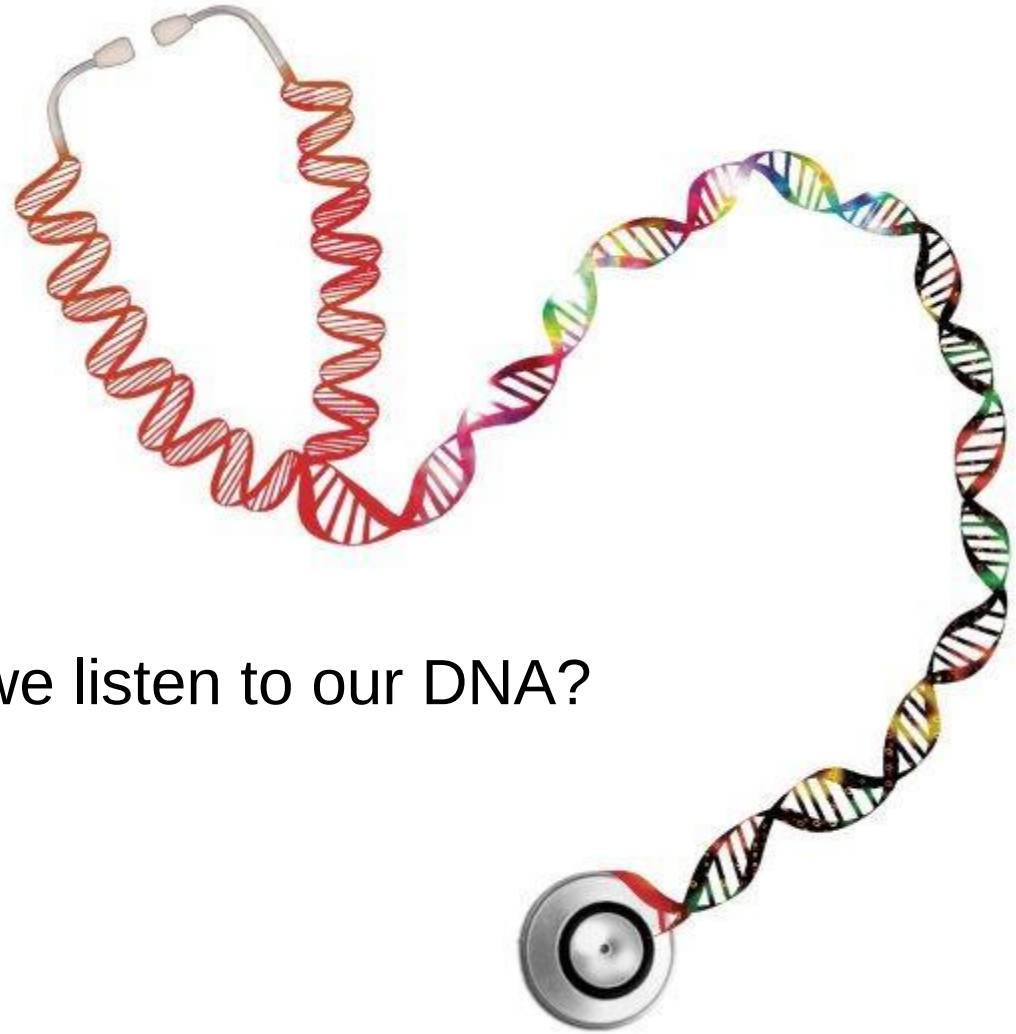
- Planned hypotension and judicious volume depletion after surgical intervention

Identify and create care team



Care is local
Communication is vital
Create plan for ordinary care
Create plan for extraordinary care

Help comes from around the world



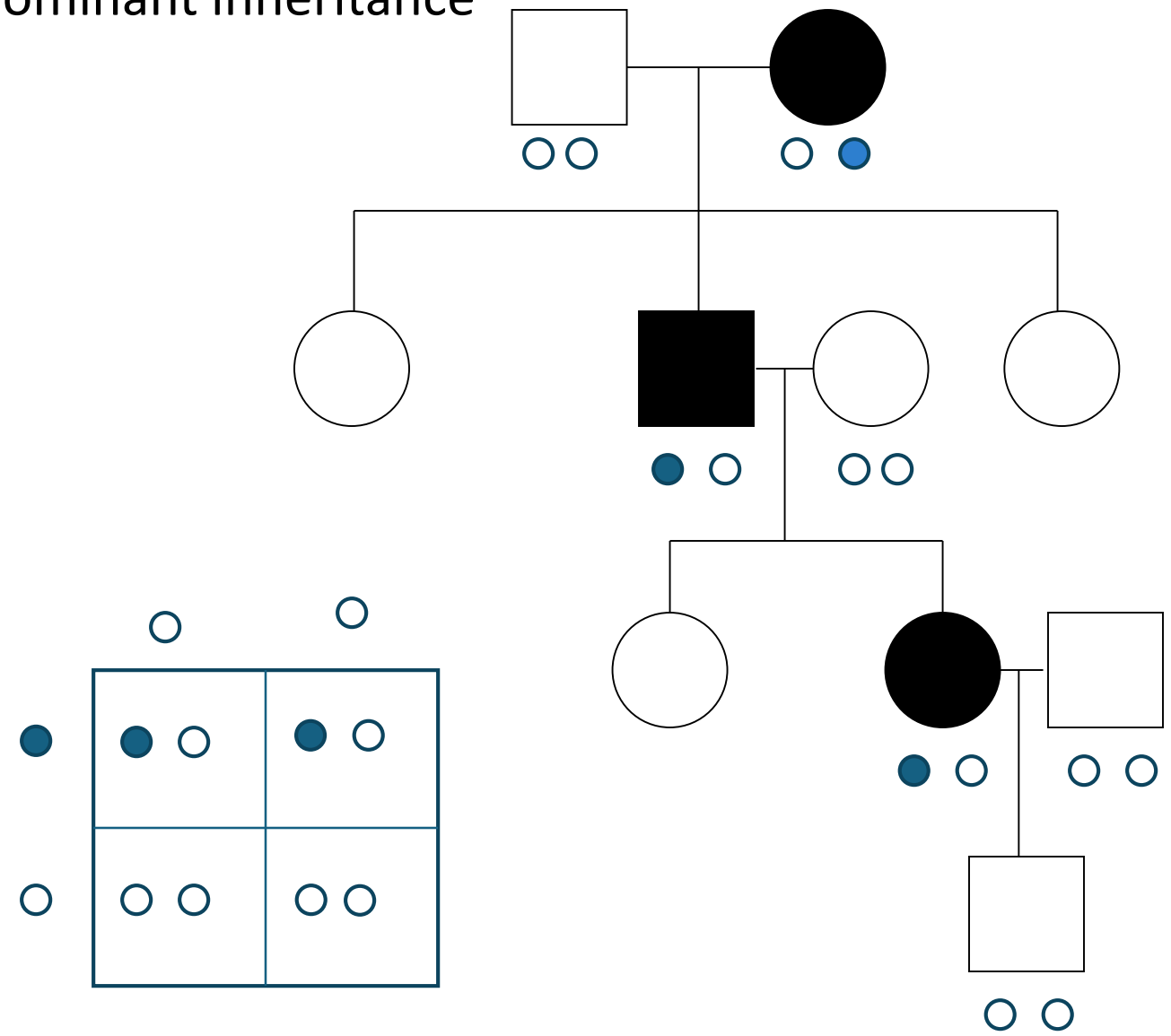
How can we listen to our DNA?

Thank you

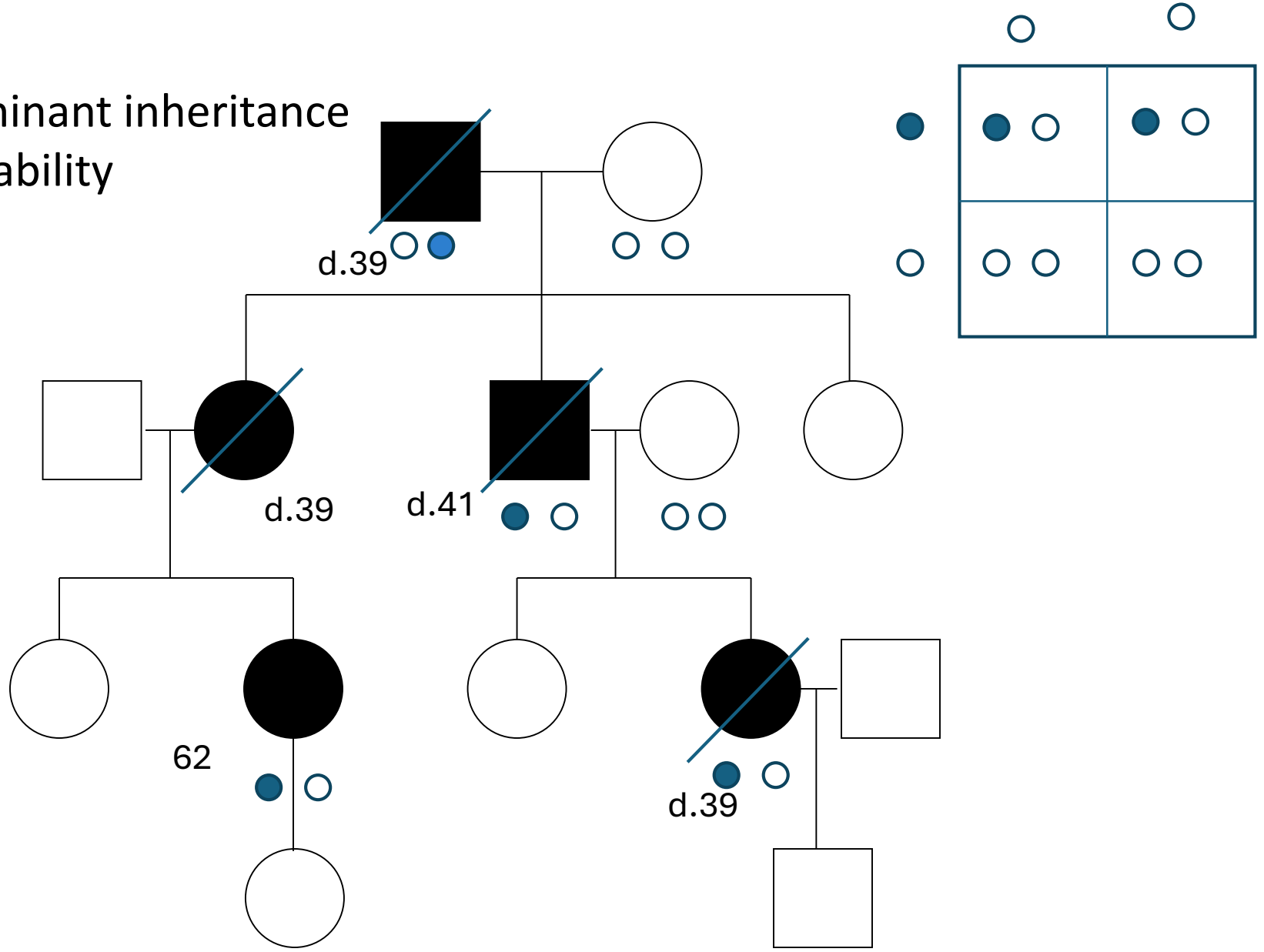
Contact:

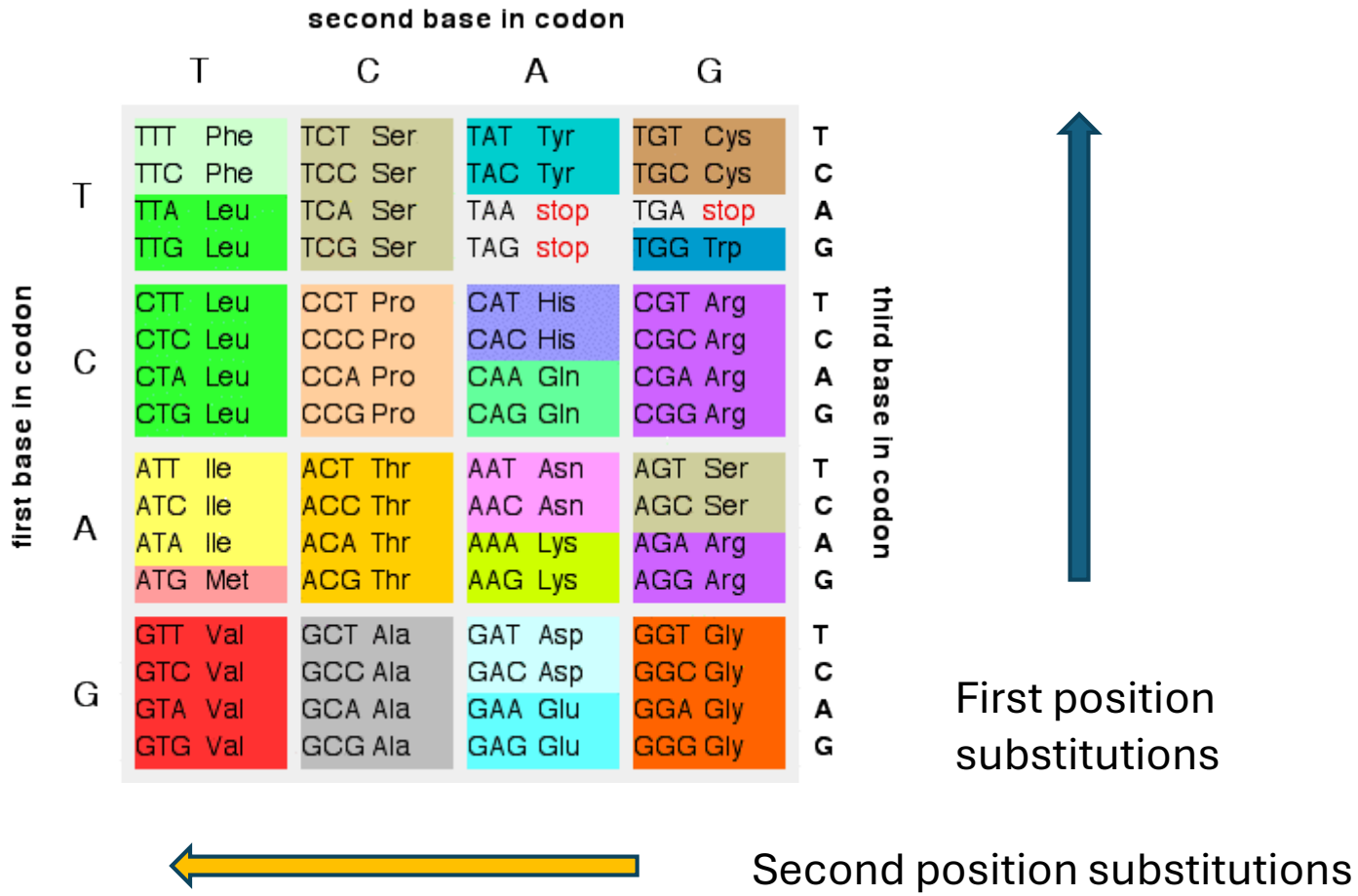
E-mail: pbyers@uw.edu
Phone: 206-512-0650

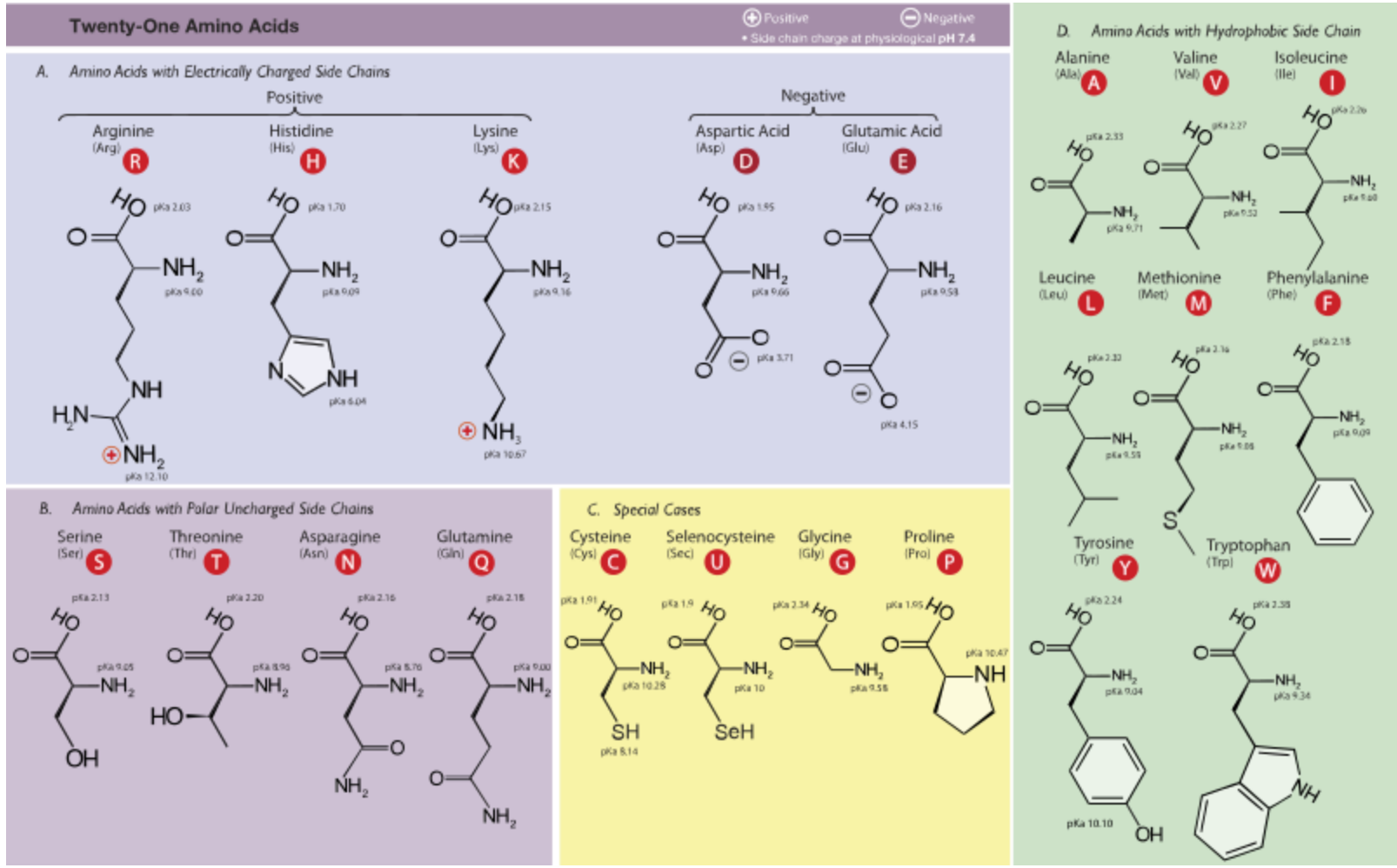
Dominant inheritance



Dominant inheritance
Variability




second base in codon
T
C
A
G
first base in codon
third base in codon
T
C
A
G
TTT Phe
TTC Phe
TTA Leu
TTG Leu
TCT Ser
TCC Ser
TCA Ser
TCG Ser
TAT Tyr
TAC Tyr
TAA stop
TAG stop
TGT Cys
TGC Cys
TGA stop
TGG Trp
CTT Leu
CTC Leu
CTA Leu
CTG Leu
CCT Pro
CCC Pro
CCA Pro
CCG Pro
CAT His
CAC His
CAA Gln
CAG Gln
CGT Arg
CGC Arg
CGA Arg
CGG Arg
ATT Ile
ATC Ile
ATA Ile
ATG Met
ACT Thr
ACC Thr
ACA Thr
ACG Thr
AAT Asn
AAC Asn
AAA Lys
AAG Lys
AGT Ser
AGC Ser
AGA Arg
AGG Arg
GTT Val
GTC Val
GTA Val
GTG Val
GCT Ala
GCC Ala
GCA Ala
GCG Ala
GAT Asp
GAC Asp
GAA Glu
GAG Glu
GGT Gly
GGC Gly
GGA Gly
GGG Gly
First position substitutions
Second position substitutions


Twenty-One Amino Acids
Positive
Negative
• Side chain charge at physiological pH 7.4
A. Amino Acids with Electrically Charged Side Chains
Positive
Negative
Arginine (Arg) R
Histidine (His) H
Lysine (Lys) K
Aspartic Acid (Asp) D
Glutamic Acid (Glu) E
B. Amino Acids with Polar Uncharged Side Chains
Serine (Ser) S
Threonine (Thr) T
Asparagine (Asn) N
Glutamine (Gln) Q
C. Special Cases
Cysteine (Cys) C
Selenocysteine (Sec) U
Glycine (Gly) G
Proline (Pro) P
D. Amino Acids with Hydrophobic Side Chain
Alanine (Ala) A
Valine (Val) V
Isoleucine (Ile) I
Leucine (Leu) L
Methionine (Met) M
Phenylalanine (Phe) F
Tyrosine (Tyr) Y
Tryptophan (Trp) W

Pregnancy

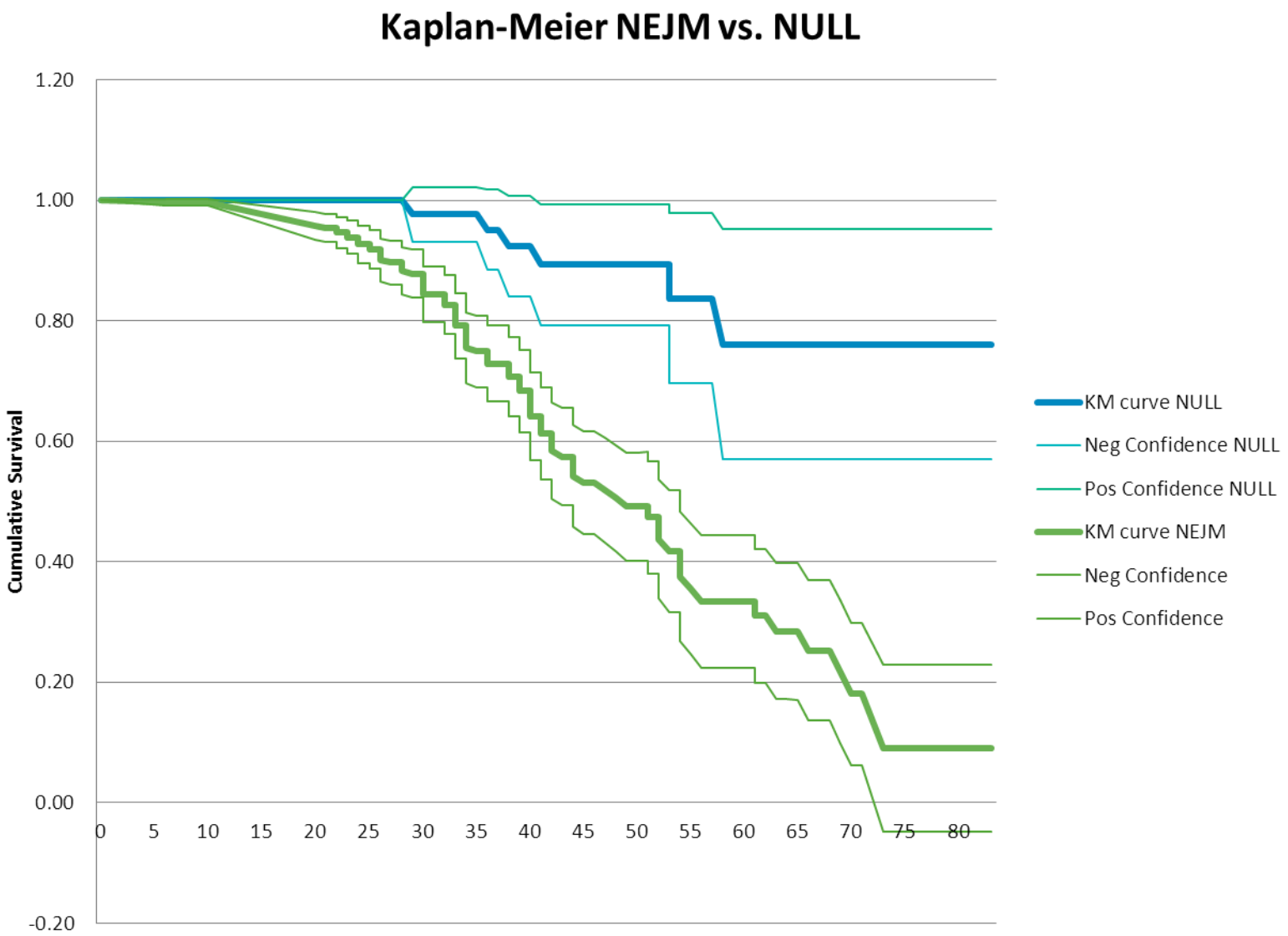
Don’t get pregnant because you will die

If you do get pregnant, terminate the pregnancy, or you will die

If you don’t terminate the pregnany, see someone else

BUT……

Supplemental Figure 1: Kaplan-Meier Curves and Confidence Intervals



*Non-overlapping confidence intervals are indicative of significance

Management and Treatment

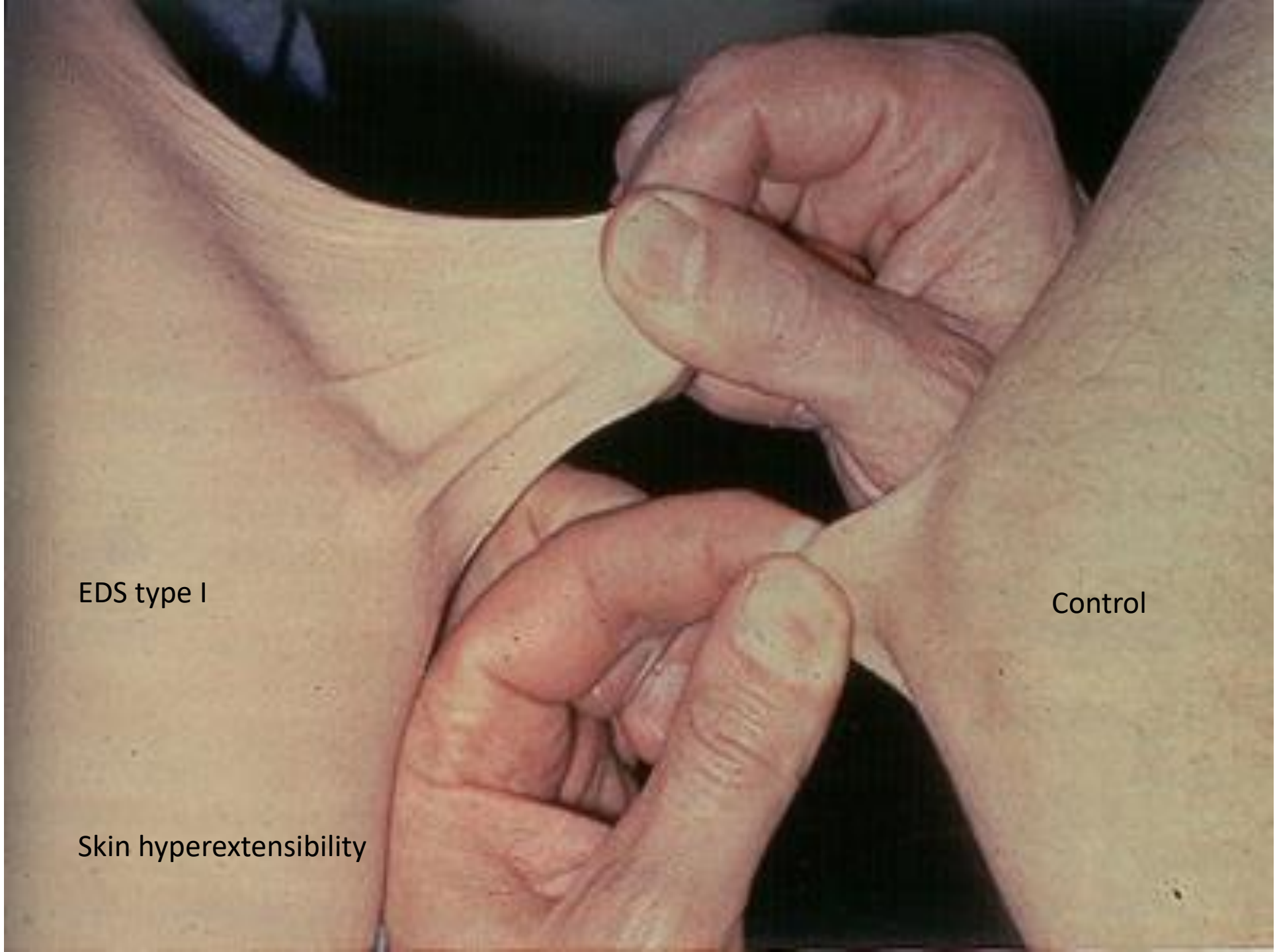
CARE TEAM

Disclosures

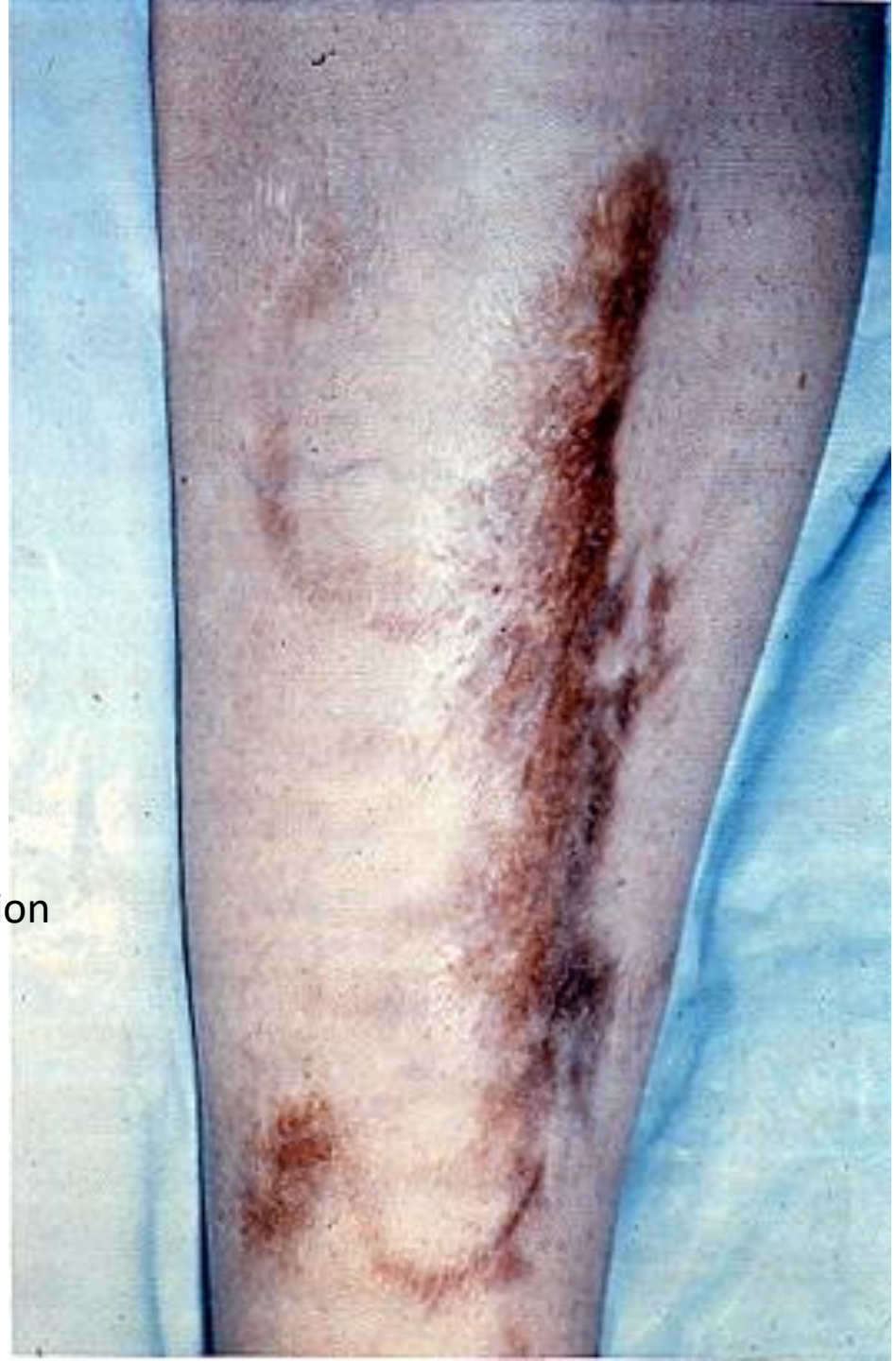
Director, Collagen Diagnostic Laboratory
University of Washington
Seattle, WA 98195

Studies, such as the ones shown here, provide partial salary support. I wish I owned stock in something that actually made money.

Other laboratories that do the studies:
Connective Tissue Gene Tests, Allentown, PA
Matrix DNA Diagnostics, Tulane, Invitae, Ambry, GeneDx, Prevention, etc


EDS type I
Control
Skin hyperextensibility

Cigarette paper scars
Heme pigment accumulation



Genu recurvatum
Large joint hypermobility