Ehlers-Danlos: a invisible disease

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What is Ehlers-Danlos?

Group of inherited connective tissue disorder

- Affect collagen and extracellular matrix (ECM)

Known since 1901

3 main features:

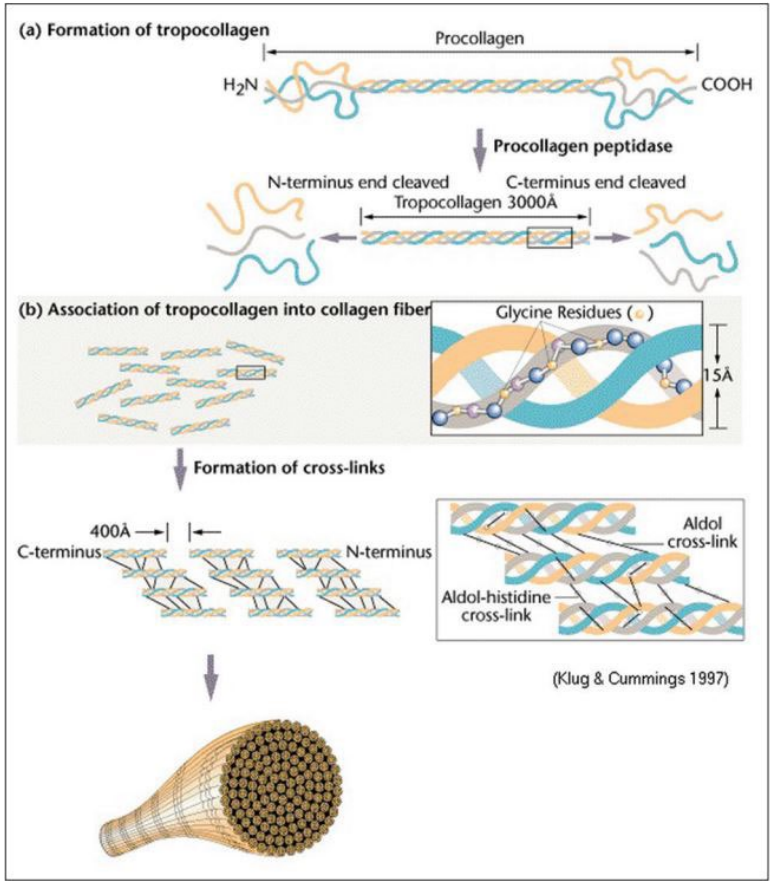
- Joint hypermobility
- Skin hyperextensibility
- Tissue fragility

Composed of 13 differents subtypes

- Hypermobile-type Ehlers-Danlos syndrome (hEDS)

Prevalence of the disease

- 1/5000 people worldwide
- Recent study in Wales, UK: 1/500



Collagen

Triple helical conformation made of 3 alpha chains.

Collagen fibrils made by self-assembly

Cross-linking occurs between adjacent tropocollagen.

Why is collagen important ?

Table 1: Types of collagen

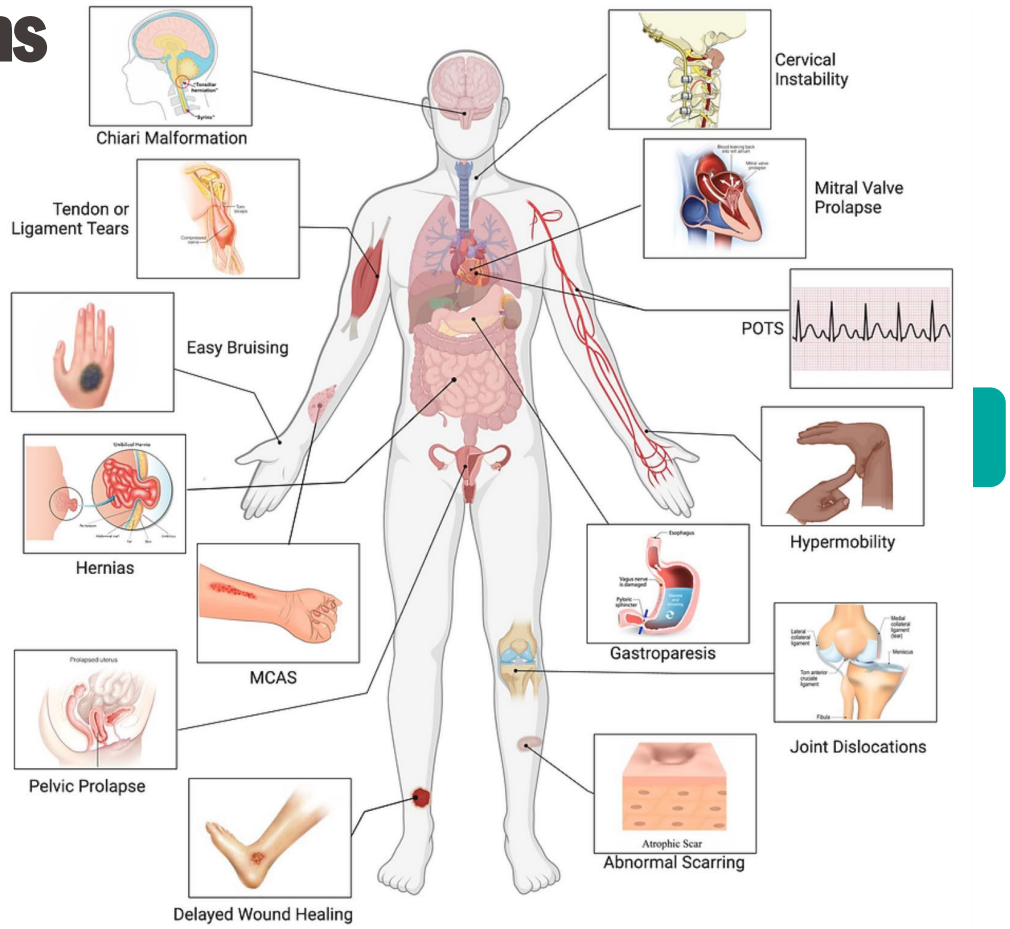
Type	Gene name	Chains	Characteristic features	Tissue distribution	Major function
I	Col1A1 Col1A2	α1(I) 3 α1(I) 2	Most abundant collagen	Abundant in skin, bone dentin cementum, tendons, ligaments and most connective tissue	Provides tensile strength to connective tissue
II	Col2A1	α1(II) 3	Forms hetrofibrils with colix	Cartilage, vitreous humor, intervertebral disk	Provides tensile strength to connective tissue
III	Col3A1	α1(III) 3	Abundant in elastic tissue	Embryonic connective tissue, pulp, skin, blood vessels, lymphoid tissue	Provides tensile strength to connective tissue
V	Col5A1 Col5A2 Col5A3	α1(V) 2 α2(V)	Forms the core of Type I fibrils. Binds to DNA heparin sulfate, thrombospondin, heparin, and insulin	Basal lamina, blood vessels, ligaments, skin, dentin, periodontal tissues	Provides tensile strength to connective tissue
XI	Col1A1 Col1A2	α1XII α2XI α3XII	Forms core of Type II fibrils	Cartilage, vitreous humor, placenta	Provides tensile strength, controlling lateral growth of Type II fibrils
XXIV	Col24A1	α11(XXIV) 3	Displays structural features unique to invertebrates fibrillar collagen	Bone cornea	Regulation of Type I fibrinogenesis
XXVII	Col27 A1	α1(XXVII) 3	Presence of triple helix imperfection	Cartilage, eye ear, lungs	Association of Type II fibrils
VI	COL6A1, A2, A3	α1(VI) α2(VI) α3(VI)	Highly disulfide crosslinked	Ligaments, skin, placenta, cartilage	Bridging between cells and matrix
XII	COLI3A1	α1(XIII) 3	Single transmembrane domain	Epidermis, hair follicle, cell surface	Cell matrix, cell to cell adhesion
XXV	COL25A1	α1(XXV) 3	Extracellular domain deposited in β amyloid plaques	Neurons	Neuron adhesion
XV	COL 15A1	α1(XV) 3	Contains antiangiogenic factor	Epithelial and endothelial basement membranes	Stabilizes skeletal muscle cells and microvessels
IX	COL9A1	α1(IX)	Interacts with glycosaminoglycans in cartilage	Cartilage, vitreous humor	Attaches functional groups to surface of Type II fibrils
XIV	COL 14A1	α1(XIV) 3	Associated with Type I	Widespread in many connective tissue	Modulates fibril interactons
XXVI	COL26A1	α1(XXVI) 3	Disulfide bonds are made into N-terminal noncollagenous domain	Developing and adult testis and ovary	Unknown
IV	COL4A1	α1(IV) 2	Interaction with Type IV, laminin, nedogen, integrin	Basal laminae	Structural network of basal lamina together with proteoglycans and laminin, nedogen, integrin
VIII	COLBA1	α1(VIII) 2		Cornea, endothelium	Tissue support, porous network
X	COL 10A1	α1(X) 3		Hypertrophic zone of cartilage growth plate	Calcium binding
VII	COL7A1	α1(VII) 3	Forms bundles made of dimmers anchored in anchoring plaques and basal lamina	Epithelium (skin, mucosa)	Strengthens epithelial-connective tissue junction

- Form the major part of ECM
- Most abundant protein in the body
- Different types of collagen
- Help maintain the structural integrity of tissues

A constellation of symptoms

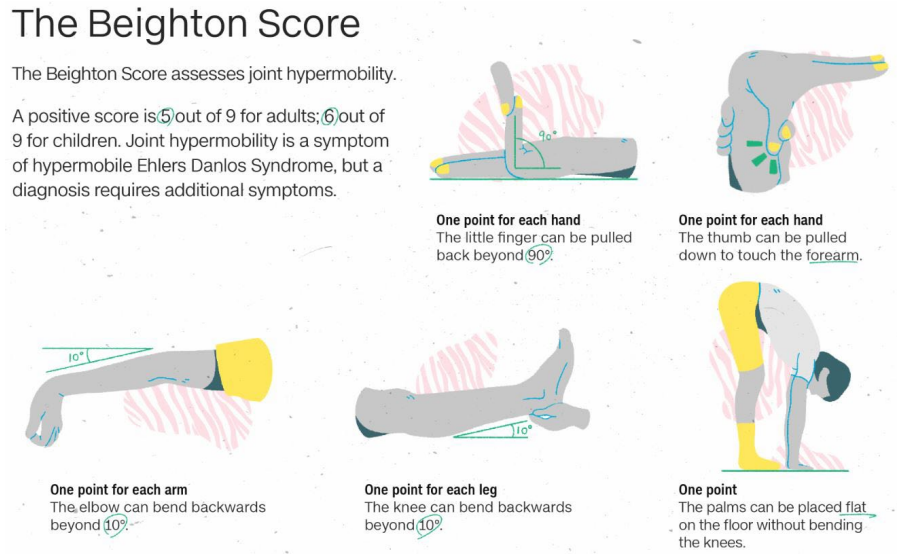
Neurological

Pro



Diagnostic

- Unlike other EDS, there is no genetic test for hEDS.
- 3 criteria:
  1. Assess generalized joint hypermobility
     - 5-Points quizz: at least 2 positive answers



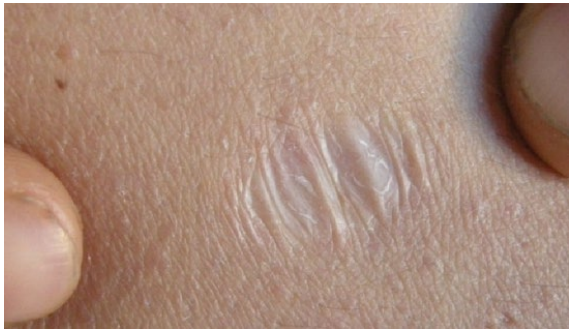
1. Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2. Can you now (or could you ever) bend your thumb to touch your forearm?
3. As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?
4. As a child or teenager did your shoulder or kneecap dislocated on more than one occasion?
5. Do you consider yourself double-jointed?

Diagnostic

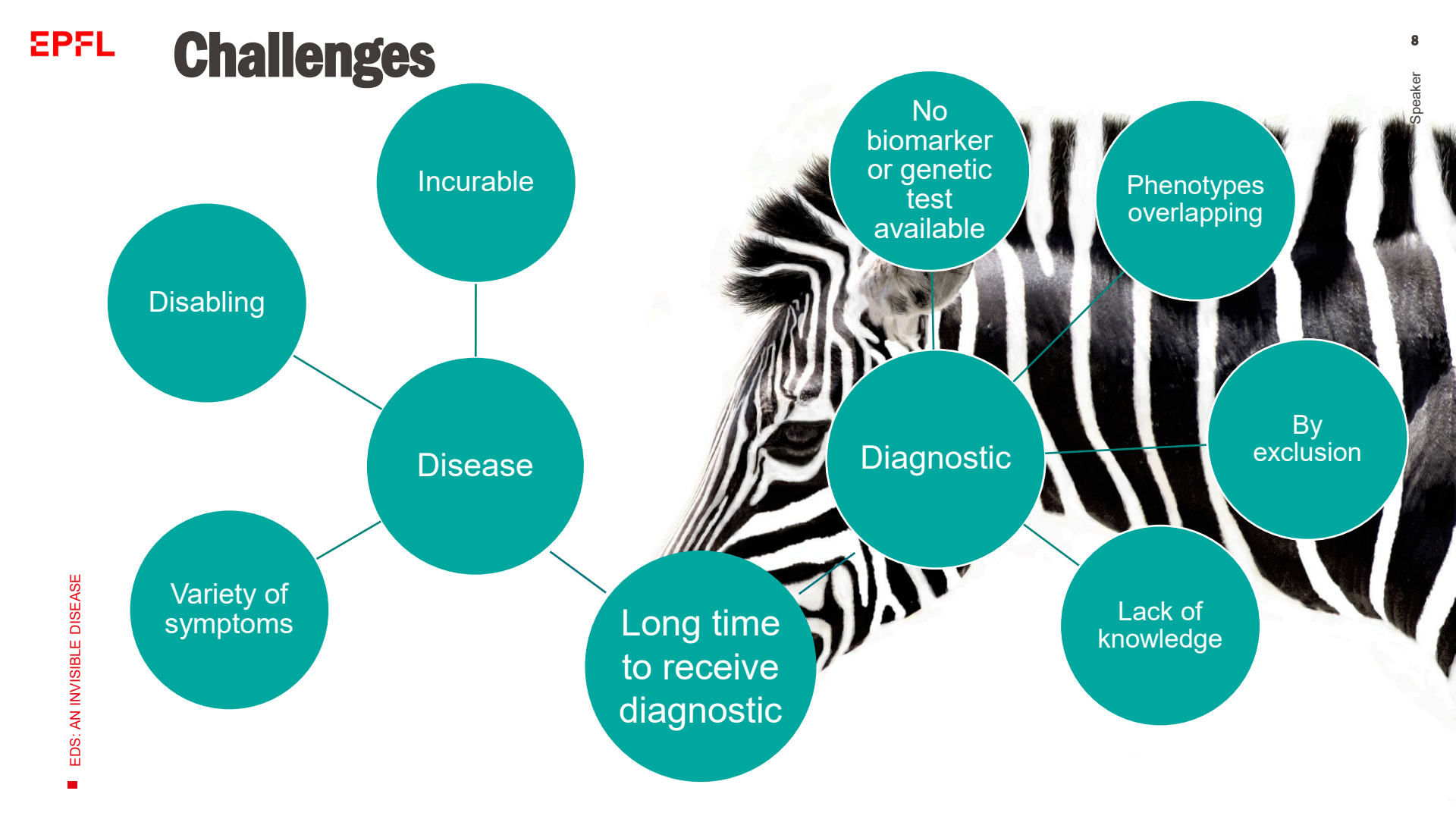
2. Fullfilled 2 or more of the following:
   - At least 5 of systemic manifestations
   - Positive family history
   - Muscoskeletal complications

3. Fullfilled all of the following:
   - Absence of unusual skin fragility
   - Exclusion of other connective tissue disorders
   - Exclusion of alternate diagnosis that include joint hypermobility

- Biospy possible but not always concluant



Challenges


Incurable
Disabling
Disease
Variety of symptoms
Long time to receive diagnostic
No biomarker or genetic test available
Phenotypes overlapping
Diagnostic
By exclusion
Lack of knowledge

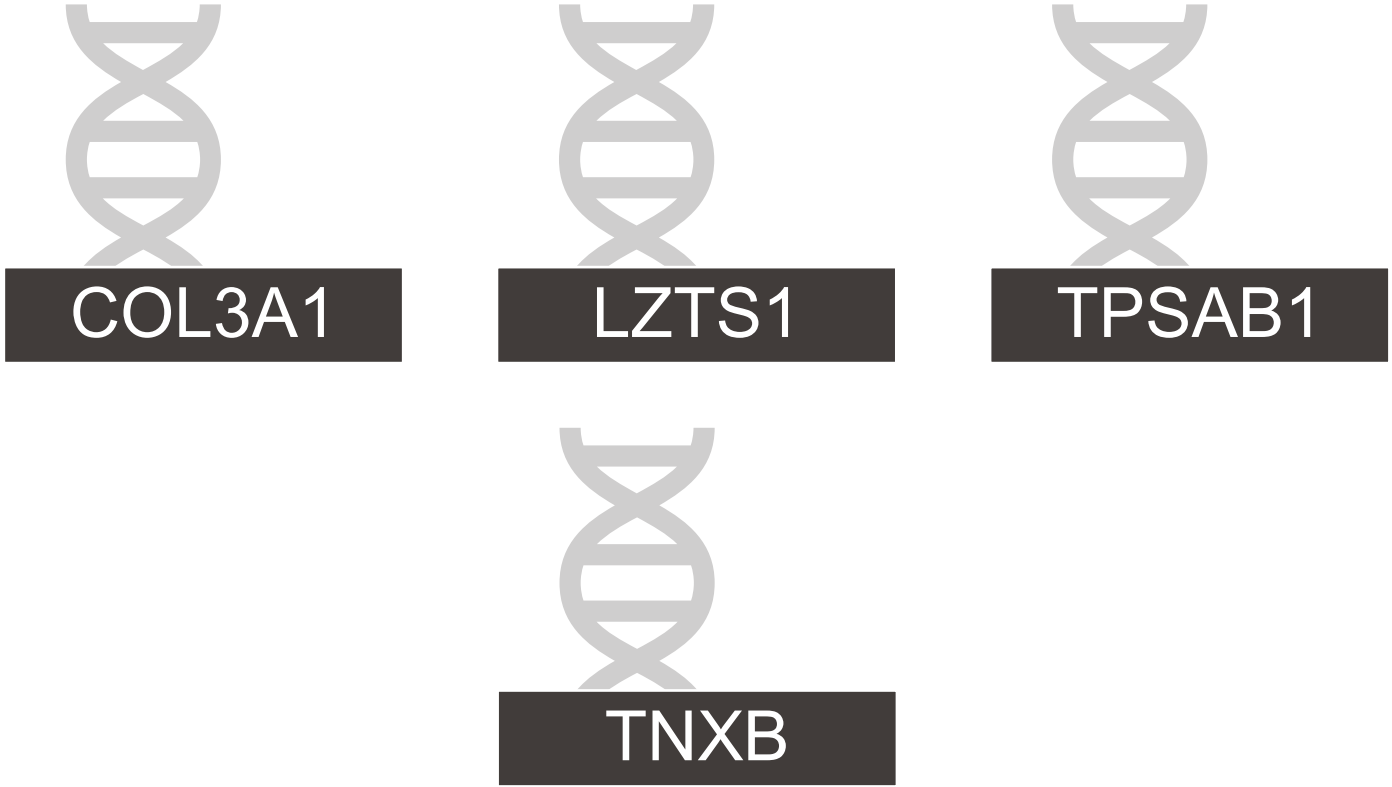
The role of genetics

Table I. Clinical Classification of the Ehlers-Danlos Syndromes, Inheritance Pattern, and Genetic Basis

	Clinical EDS subtype	Abbreviation	IP	Genetic basis	Protein
1	Classical EDS	cEDS	AD	Major: *COL5A1*, *COL5A1*	Type V collagen
				Rare: *COL1A1*	Type I collagen
				c.934C>T, p.(Arg312Cys)	
2	Classical-like EDS	clEDS	AR	*TNXB*	Tenascin XB
3	Cardiac-valvular	cvEDS	AR	*COL1A2* (biallelic mutations that lead to *COL1A2* NMD and absence of pro α2(I) collagen chains)	Type I collagen
4	Vascular EDS	vEDS	AD	Major: *COL3A1*	Type III collagen
				Rare: *COL1A1*	Type I collagen
				c.934C>T, p.(Arg312Cys)	
				c.1720C>T, p.(Arg574Cys)	
				c.3227C>T, p.(Arg1093Cys)	
5	Hypermobile EDS	hEDS	AD	Unknown	Unknown
6	Arthrochalasia EDS	aEDS	AD	*COL1A1, COL1A2*	Type I collagen
7	Dermatosparaxis EDS	dEDS	AR	*ADAMTS2*	ADAMTS-2
8	Kyphoscoliotic EDS	kEDS	AR	*PLOD1*	LH1
				FKBP14	FKBP22
9	Brittle Cornea syndrome	BCS	AR	*ZNF469*	ZNF469
				PRDM5	PRDM5
10	Spondylodysplastic EDS	spEDS	AR	*B4GALT7*	β4GalT7
				B3GALT6	β3GalT6
				SLC39A13	ZIP13
11	Musculocontractural EDS	mcEDS	AR	*CHST14*	D4ST1
				DSE	DSE
12	Myopathic EDS	mEDS	AD or AR	*COL12A1*	Type XII collagen
13	Periodontal EDS	pEDS	AD	*C1R*	C1r
				C1S	C1s

IP, inheritance pattern; AD, autosomal dominant; AR, autosomal recessive, NMD, nonsense-mediated mRNA decay.

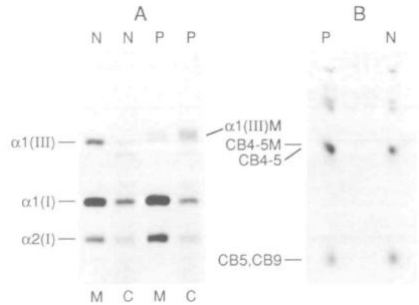
Potential gene mutation candidates for hEDS

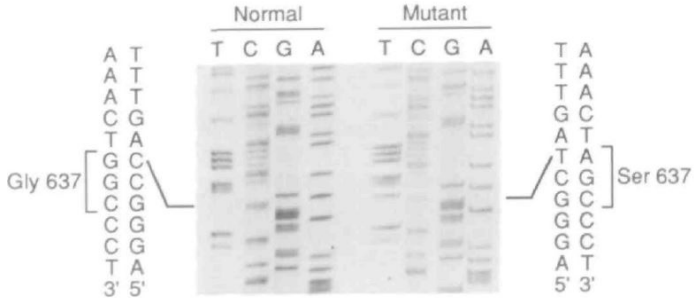


Candidate 1:

COL3A1

- Mutation observed in one family with hEDS (5 individus)
- Cultured fibroblasts showed reduced secretion of overmodified type III collagen.
- Usually associated with Vascular-type EDS
- Too few mutations in this region were studied and no other report of similar case.





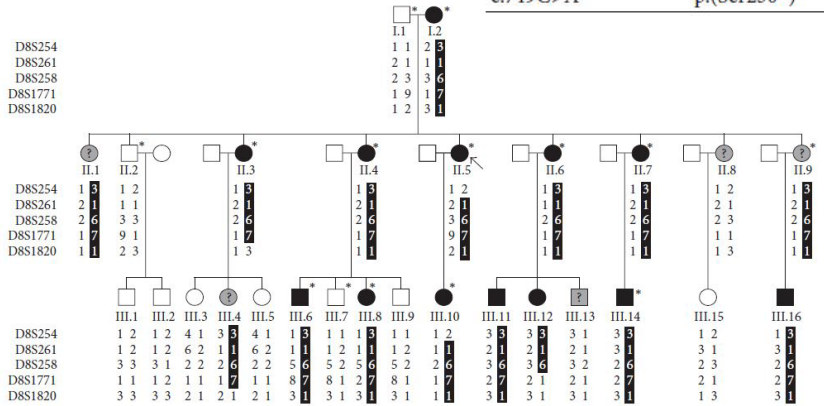
Candidate 2:

LZTS1

- Chromosome locus identified on 8p22-8p21.1, in multigenerational Belgian family (13 individus)

- Culture of fibroblast and RNA sequencing by genome wide linkage and whole exome sequencing

cDNA	Protein	SIFT	PolyPhen-2	Align GVGD	Mutation Taster
c.633C>A	p.(His211Gln)	Tolerated	Probably damaging	C0	Disease-causing
c.49C>G	p.(His17Asp)	Tolerated	Probably damaging	C0	Disease-causing
c.1585C>T	p.(Arg529Trp)	Deleterious	Probably damaging	C0	Disease-causing
c.749C>A	p.(Ser250*)	—	—	—	—



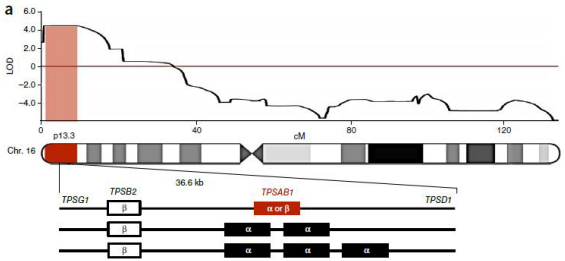
- Role in modulating gene transcription

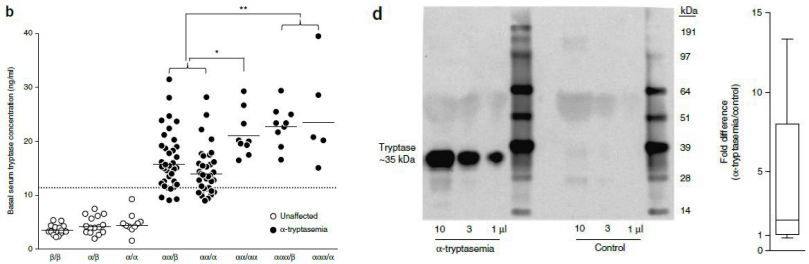
- No conclusive evidence of exact function.

Candidate 3:

TPSAB1

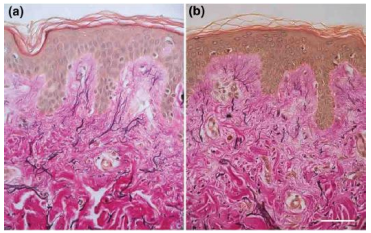
- Mutation observed in 35 families (96 individues)
- Culture of mast cells and RNA sequencing by linkage analysis of the exome sequence
- Elevated basal serum level tryptase associated with multisystem disorder, with joint hypermobility





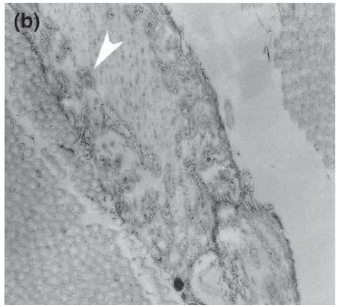
- Not all individuals fulfilled criteria for hEDS.
- Relatively common in general population.

Candidate 4:

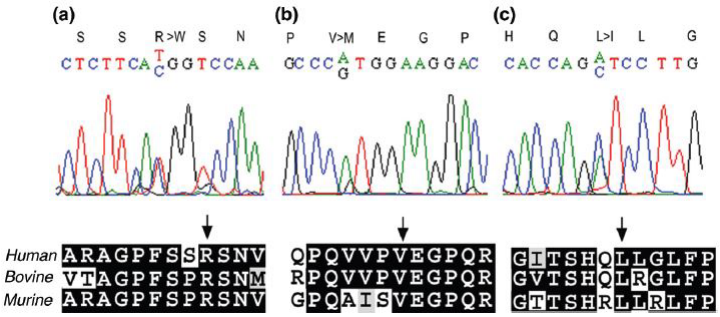


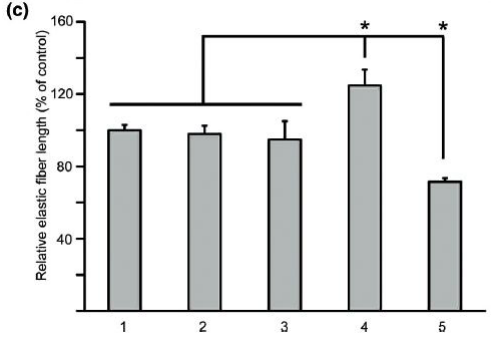
TNXB

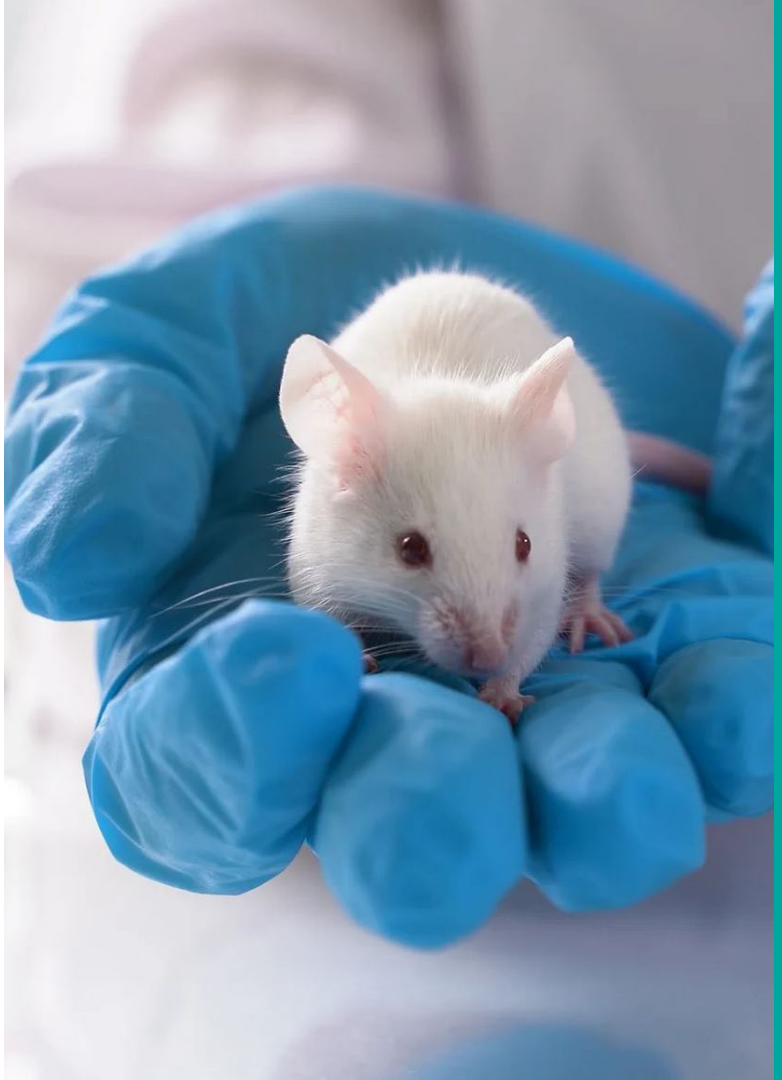
- Studied population of 24 patients
- Skin biopsy analysed by TEM and Tenascin-X encoding region sequenced



- Large ECM protein, responsible for collagen I deposition and maintaining homeostasis of ECM
- Tre substitutions:
  - Arg29Try
  - Val1195Met
  - Leu4033Ile







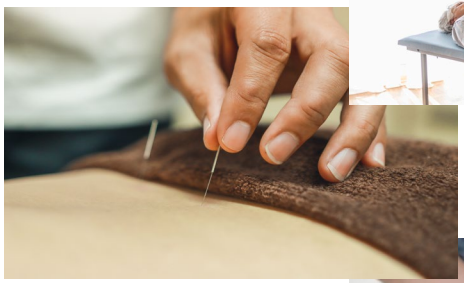
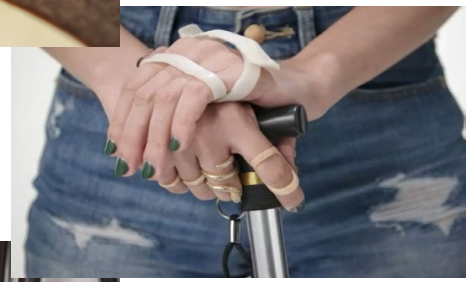
Current working models

Mouse models of EDS

Still working on the hEDS mouse model.

Current treatment

- Prevent and treat the symptoms:
- Physical therapy
  - Exercises
  - Posture reeducation
  - Osteopathic manipulative treatment
- Occupational therapy
  - Aids
  - Pain management strategies
- Acunpuncture
- Dietary modifications
- Drugs
  - Antihistamine, mab
  - Anti-inflammatory
- Surgery


Evolution of the field

The Ehlers-Danlos Syndromes

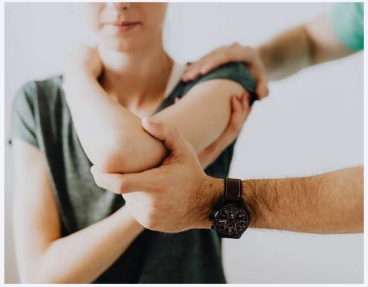
Ehlers-Danlos syndrome (EDS) is a group of genetic connective tissue disorders characterized by joint hypermobility, skin hyper-extensibility, and tissue fragility. There is phenotypic and genetic variation among the 14 subtypes. Professor Rodney Graham, a lead EDS expert, once said "No other condition in the history of modern medicine has been neglected in such a way as Ehlers-Danlos Syndrome."

The Norris lab is ready to change that.

Current EDS Initiatives

01
EDS/HSD Survey

EDS and HSD are related to a wide array of comorbid conditions, but comprehensive clinical overviews of these conditions are lacking in scientific literature. We are gathering a large data set of the multisystemic problems related to EDS and HSD to inform the direction of future research studies of EDS and HSD at the Norris Lab and beyond.

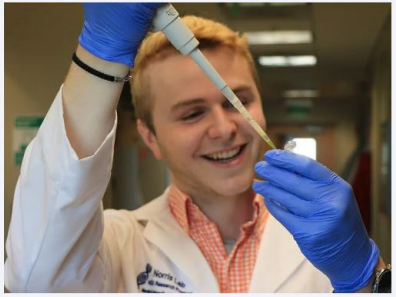


02
hEDS Genetic Registry

The Norris lab seeks to advance the understanding of hEDS through cutting-edge research into the genetic factors that underlie this complex condition. Through our comprehensive genetic registry and collaborative research efforts, we hope to improve diagnosis and treatment for individuals living with hEDS.

03
Ehlers-Danlos Mouse Models

Using state of the art CRISPR-Cas9 mediated genome editing, the Norris lab is working to develop mouse models of every subtype of Ehlers-Danlos. To advance the research into these diseases, we plan to make these mouse models available to other research institutions at no charge.



04
Patient-Scientist Initiative

The Norris lab belives that patients are the experts in their own diseases and has pioneered the "patient scientist" model of research. We offer multiple opportunities for students with hEDS who have an interest in research or medicine to gain experience in the lab.

Evolution of the field

- Personnalized medicine
- Identification of the mutation and biomarkers
- Understanding fundamentals principles of syndrom
- Diagnostic tools based on chemical/molecular manifestations more than clinical symptoms
- Effective or curative therapeutics

Impact on society

- Quicker diagnostic
- Confirmation by chemical/molecular testing.
- Better accuracy of diagnostic
- Better estimation of the prevalence
- Less surgeries needed
- Better quality of life
- Less frustration of the clinician

Thank you for your attention.

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