Delineating Ehlers-Danlos syndrome, the classical subtype: molecular and clinical characteristics of a large patient cohort

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Classical EDS: Historical background

Classical EDS as distinct type of EDS (Mitis – Gravis)
(Beighton et al., 1968)

→

First evidence of involvement of type V collagen in cEDS
mouse model with an in frame deletion in *COL5A2*
(Andrikopoulos et al,1995)

↓

Linkage of *COL5A1* in cEDS families
(Loughlin et al., 1995; Burrows et al, 1996)

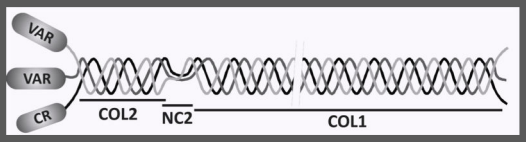
First reports of cEDS patients with mutations in *COL5A1*
(Nicholls et al., 1996; Wenstrup et al., 1996; De Paepe et al.,1997; Schwarze et al., 2000)

→

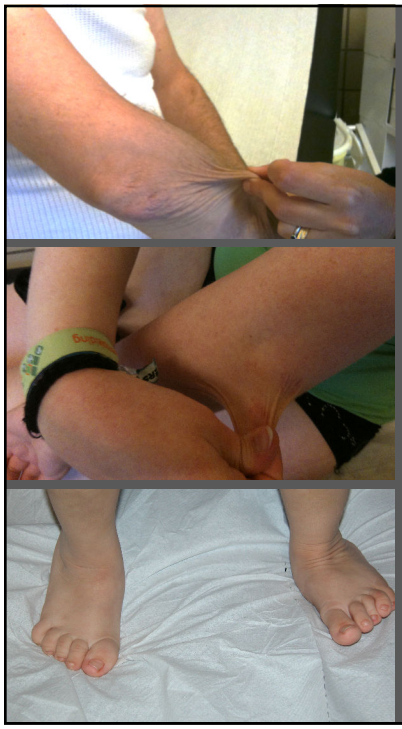
Pathogenic variants in either *COL5A1* or *COL5A2* in > 90%
(Symoens et al., 2011; Ritelli et al. 2013)

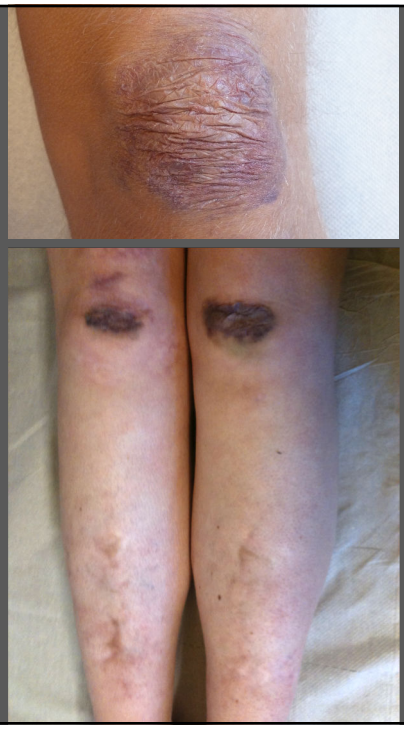
Type V collagen

- Minor fibrillar collagen - wide tissue distribution
- heterotrimer $[\alpha1(V)]_2\alpha2(V)$
  - α1(V) encoded by ***COL5A1***; α2(V) encoded by ***COL5A2***
- heterotypic type I/V collagen fibrils
- Regulation collagen fibril diameter - Interactions with ECM components



Symoens et al. 2012





Clinical criteria (2017)

1. **Skin hyperextensibility + Atrophic scarring**
2. **Joint hypermobility**

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
9. Family history of a first degree relative who meets clinical criteria

Malfait et al, 2017

Why this study?

Patient Selection

1995-2019

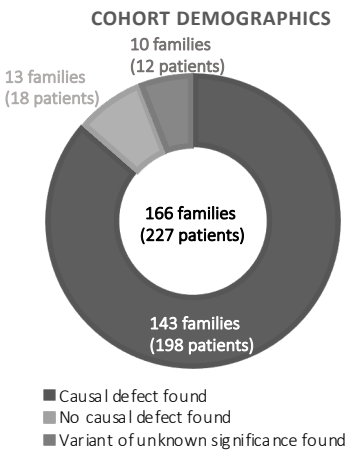
DNA samples from individuals with suspicion of cEDS were analyzed in our diagnostic connective tissue laboratory

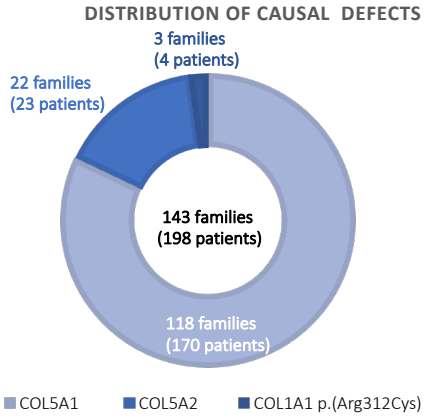
- physical examination at our center or an extensive clinical checklist
- Minimum set of 3 clinical criteria (Villefranche – 2017 criteria)

Inclusion: clinically diagnosed with cEDS in our center and all patients in whom a (likely) pathological variant was found

Methods

Patient cohort





COL5A1

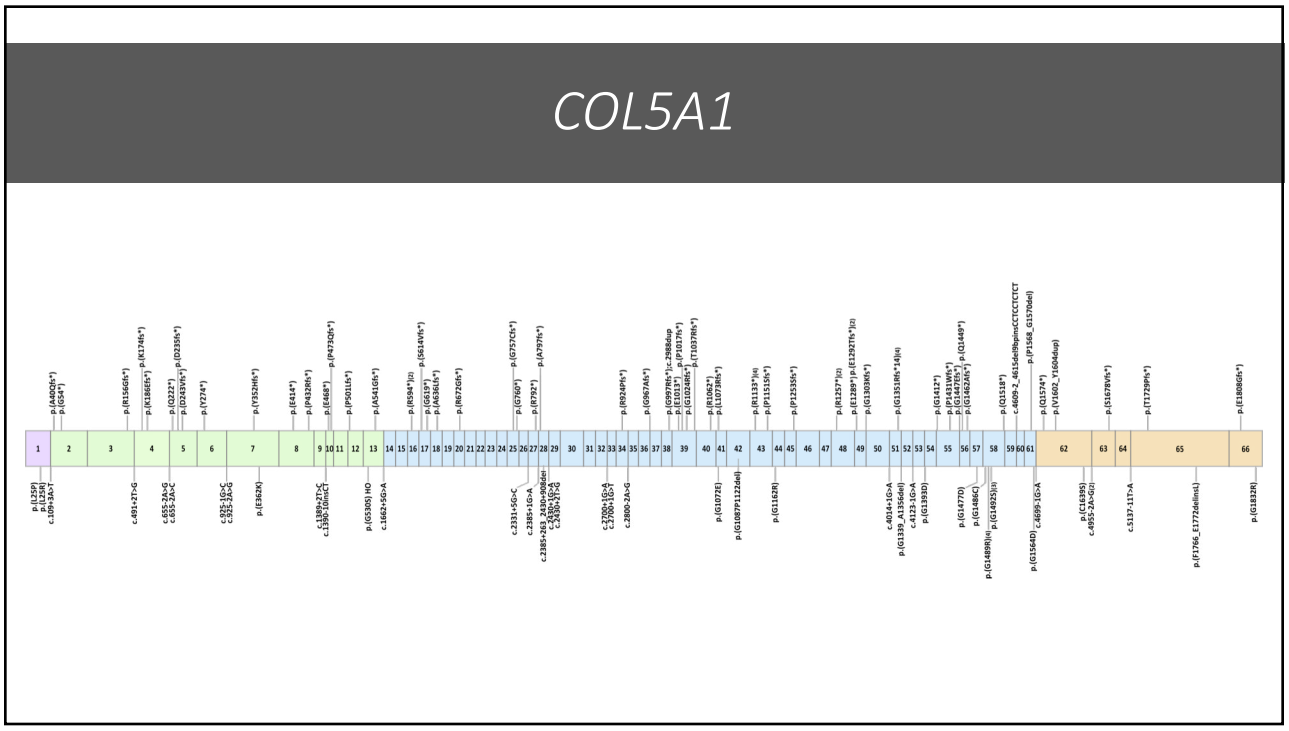
99 unique pathogenic variants

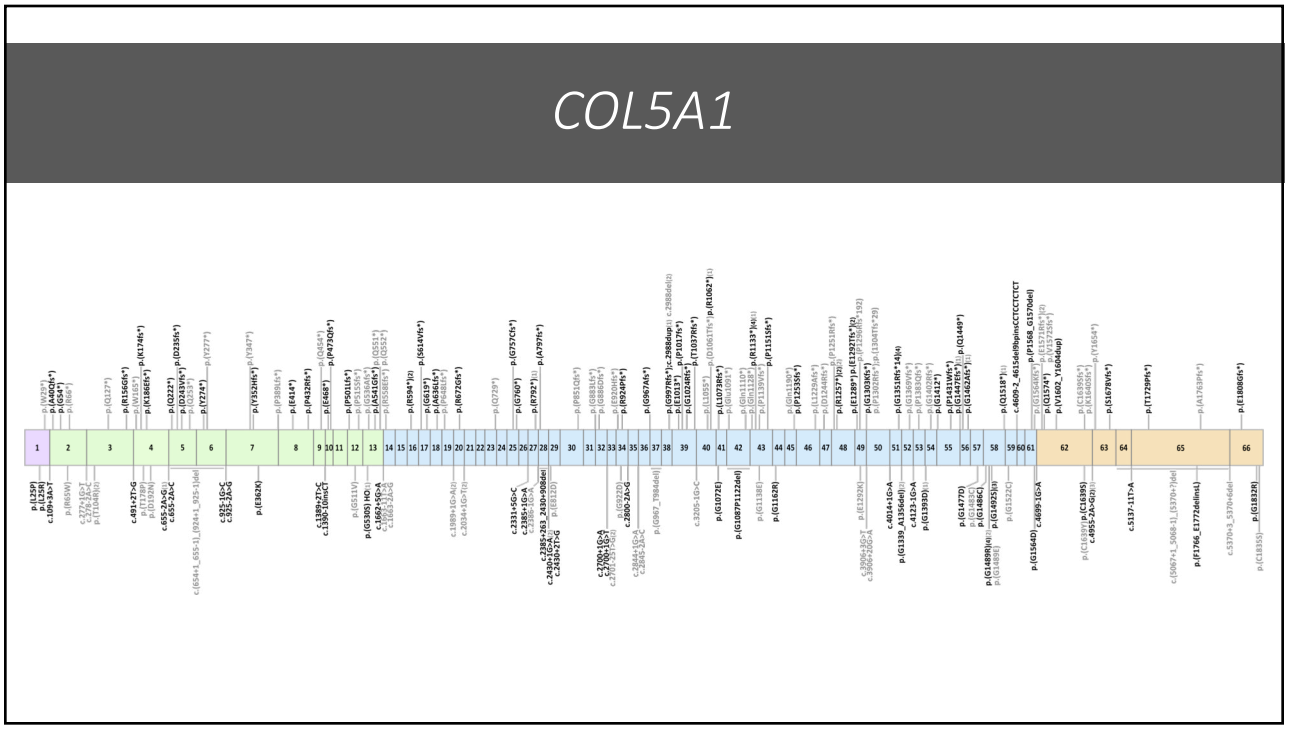
- >50% premature termination codons –> null alleles
- 27,8% structural defects

7 families with only null allele

8 variants of unknown significance

α1(V) (*COL5A1*)	Signal peptide	N-Pro	Helix	C-pro	Total
Glycine substitutions		(1 VUS)	9	1	10 (1 VUS)
In frame indels		5 (1 VUS)	3	3	11 (1 VUS)
Premature termination codons		17	35	4	56
Missense	2	1 (1 VUS)	(2 VUS)	2	5 (3 VUS)
Splice site unknown outcome	1	2 (1 VUS)	10 (2 VUS)	2	15 (3 VUS)
Multi exon deletion			2		2
Total	3	25 (3 VUS)	59 (4 VUS)	13	99 (8 VUS)





COL5A2

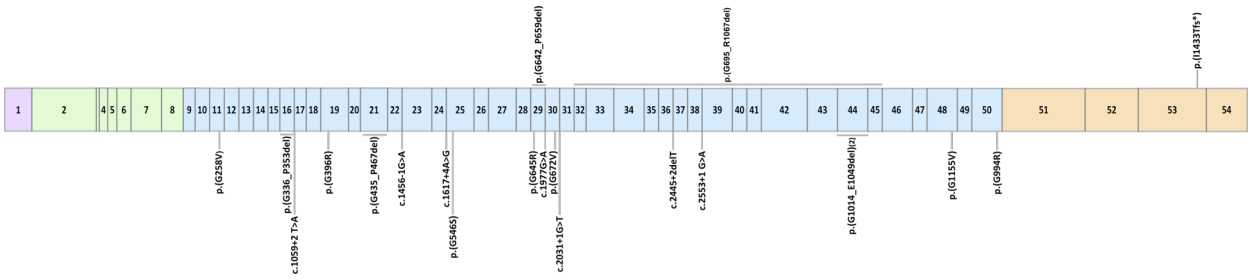
21 unique pathogenic variants

- All known pathogenic variants in *COL5A2* cause structural defects
- No null alleles

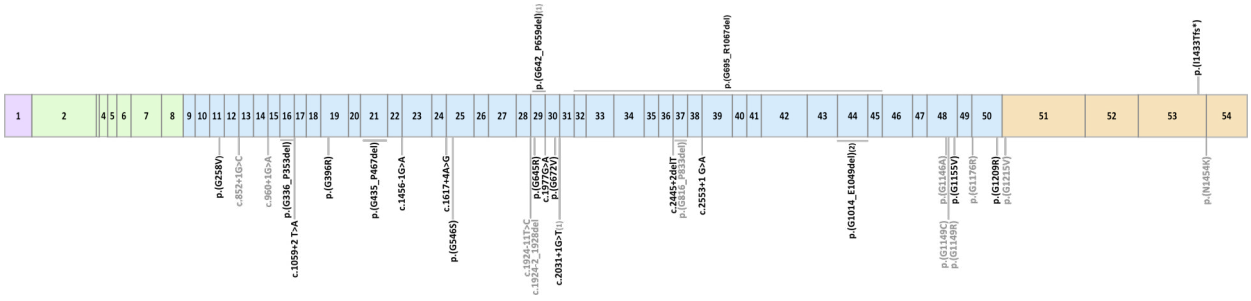
2 variants of unknown significance

α2(V) (*COL5A2*)	Signal peptide	N-Pro	Helix	C-pro	Total
Glycine substitutions			7		7
In frame indels			11		11
Out of frame indels				1	1
Missense				1 (1 VUS)	1 (1 VUS)
Splice site unknown outcome			(1 VUS)		(1 VUS)
Multi exon deletion			1		1
Total			21 (1 VUS)	2 (1 VUS)	21 (2 VUS)

COL5A2



COL5A2



Clinical features

Patients Evaluated in our center

Pathogenic variants

- Clinical criteria: median 2 major - 5 minor
- A degree of skin hyperextensibility, atrophic scarring in 95%
- Easy bruising, skin fragility, soft, doughy skin and complications of joint hypermobility in >90%
- Molluscoid pseudotumors and subcutaneous spheroids:
  - relatively rare and unknown features
  - highly diagnostic features when present.

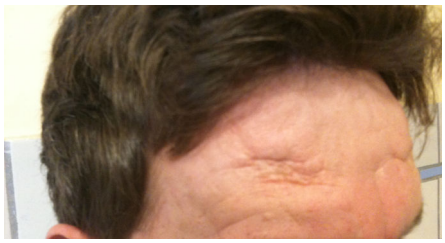
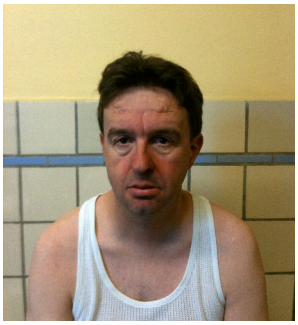
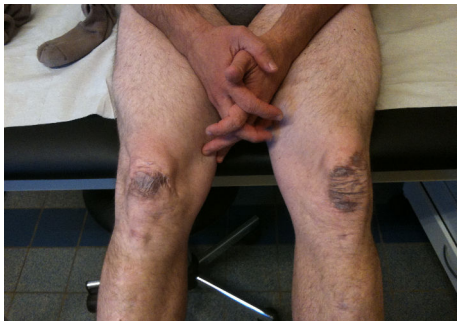
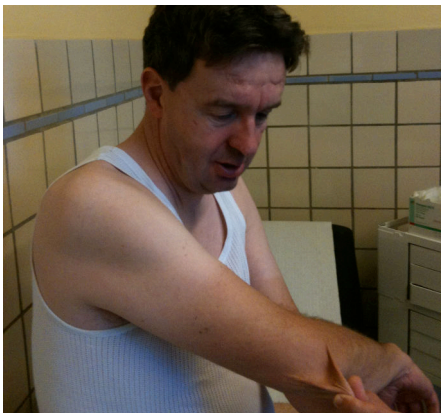
Clinical diagnosis + VUS

median major 1,5, 5,5 minor

Clinical Diagnosis + No defect

median 2 major, 5 minor

No significant differences between the 3 groups

Typical case (*COL5A1*)

Vascular complications in cEDS

COL5A1

3 individuals

1. p.(Gly1564Asp)
   - Rupture of mesenteric artery
     (De Leeuw et al. 2012)
2. p.(Gly619*)
   - Dissection of carotid artery
3. clinical diagnosis + VUS p.(Gly493Arg)
   - dissection of common hepatic artery + pseudoaneurysm of right hepatic artery

COL5A2

no known vascular complications

***COL1A1* p.(Arg312Cys)**

Our cohort

4 patients (3 families)

- dissection of right iliac artery (Malfait et al. 2007)

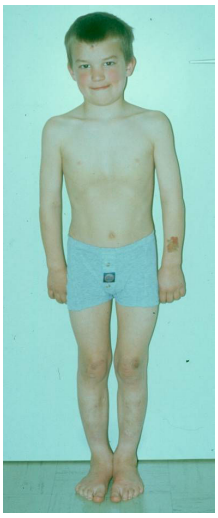
Literature

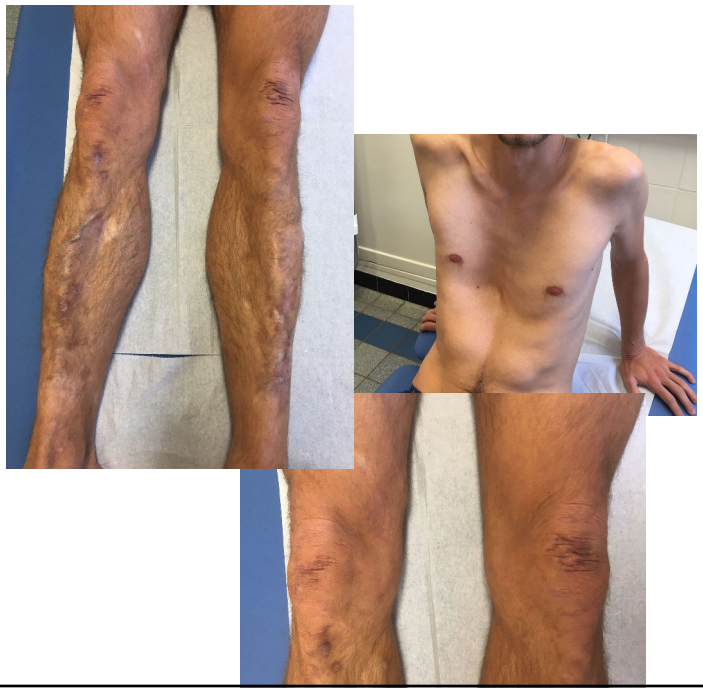
18 other patients (5 families) reported in literature

Total

21 patients

Life threatening vascular complications in 4 patients



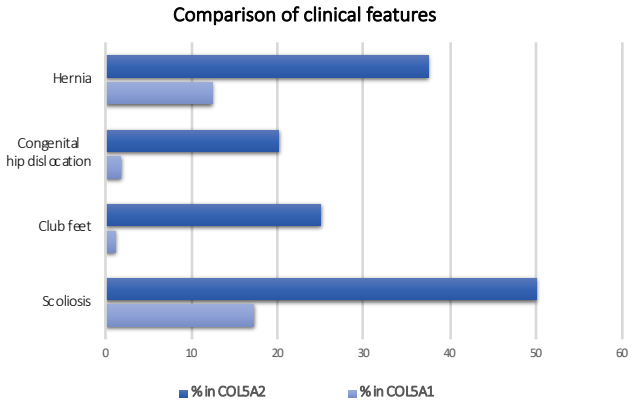


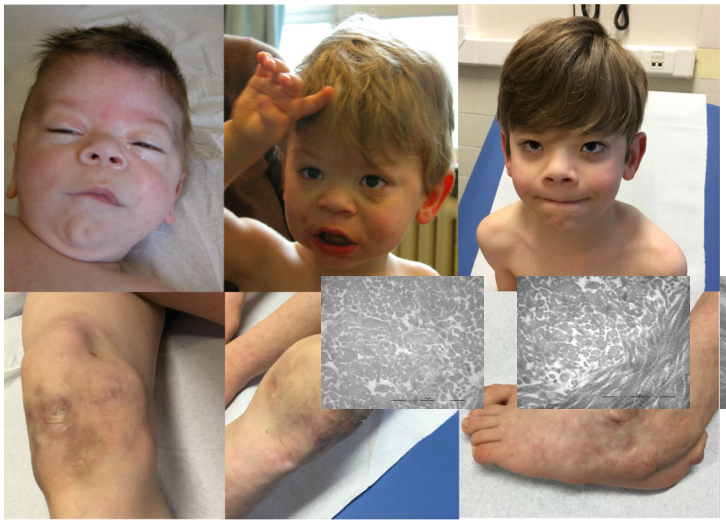
Genotype – phenotype correlations *COL5A1* vs *COL5A2*

- No difference in number of clinical criteria present

  (Fischer's Exact p-value= >0,99)

- causal variants in COL5A2 seem to cause a more severe disease





Clinical diagnosis of dermatosparaxis EDS

- Muscle hypotonia
- Club foot
- Umbilical hernia
- Soft, very fragile skin
- Atrophic scarring – hyperextensible skin
- Easy bruising
- severe joint hypermobility
- epicanthic folds, down slanting
- oral fissures, prominent lips
- alysis of the ADAMTS-2 gene
- defect
- Biochemical analysis of procollagens
- exome sequencing revealed a de novo splice site defect in COL5A2, c.2031+1G>T

Case Description

Conclusion

Largest cEDS cohort until today (227 patients)

Molecular

Pathogenic defects in 86%

- 83 % *COL5A1*
  - *>50% premature termination codons*
  - *30 % structural*
- 17 % *COL5A2*
  - *Structural defects*

Clinical

- Vascular complications are rare in cEDS
  - 20% of COL1A1 p.(Arg312Cys)
- COL5A2: more severe phenotype

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Questions?