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

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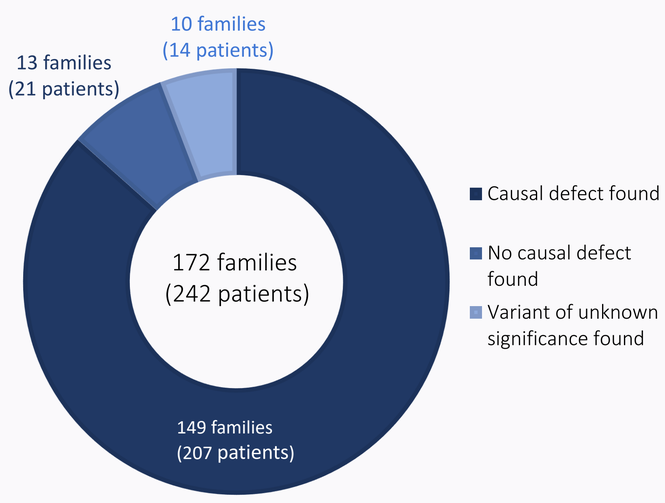
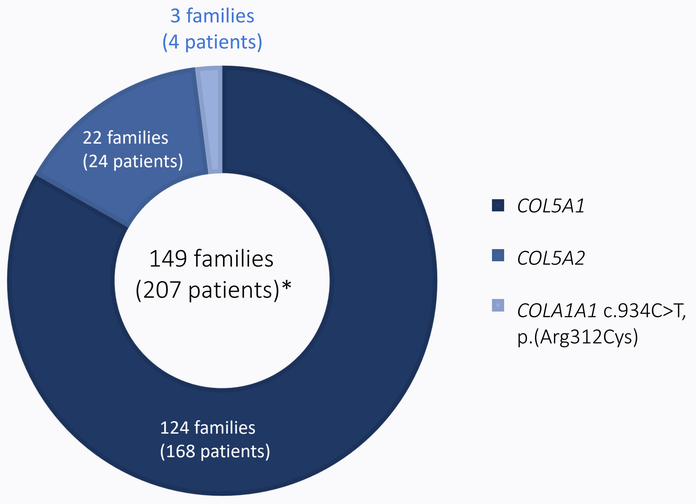
Introduction

Type V collagen is a minor fibrillar collagen with a broad tissue distribution. Reduced availability of type V collagen seems the major disease-causing mechanism of the classical subtype of Ehlers-Danlos syndrome (cEDS), an autosomal dominant heritable connective tissue disorder hallmarked by generalized joint hypermobility. Large gaps remain in our knowledge of this disease with few reports of large groups of patients and lack of in-depth characterization of the molecular defects. Also, there is still a subset of the patients in whom no molecular defect can be identified. We gathered and analyzed the data of 242 patients with a clinical suspicion of cEDS.

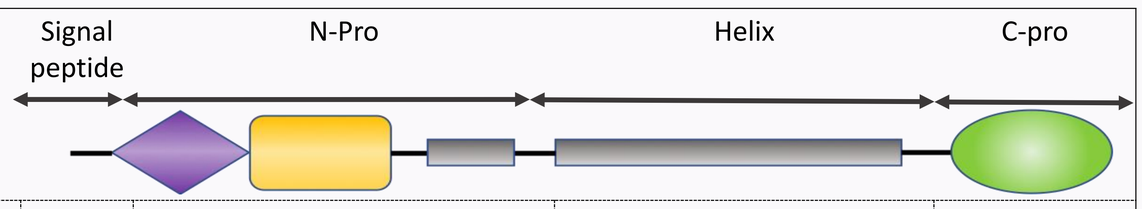
Patient cohort





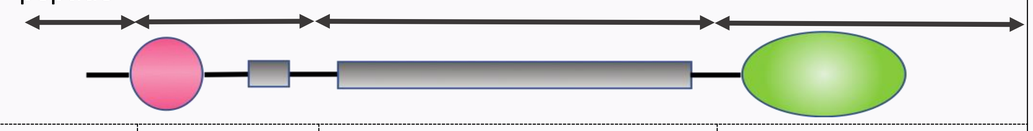
Molecular Characteristics

α1(V) (*COL5A1*)



	Signal peptide	N-Pro	Helix	C-pro
Glycine substitutions		2 (1 VUS)	9	1
In frame indels		6 (1 VUS)	3	2
Premature termination codons		16	38	5
Missense	2	2 (1 VUS)	(2 VUS)	2
Splice site unknown outcome	1	1 (1 VUS)	14 (2 VUS)	3
Multi exon deletion			2	

α2(V) (*COL5A2*)

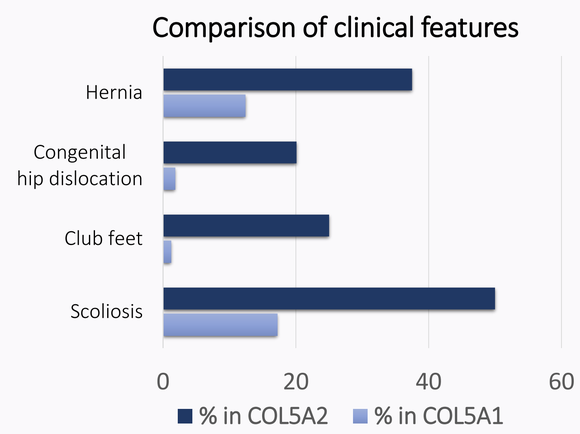


	Signal peptide	N-Pro	Helix	C-pro
Glycine substitutions			7	
In frame indels			12	
Missense		1		1 (1 VUS)
Splice site unknown outcome			(1 VUS)	
Multi exon deletion			1	

Thrombospondin type I domain · Von Willebrand factor type C domain · Variable domain · Collagen domain · C-propeptide

Clinical features of causal mutations

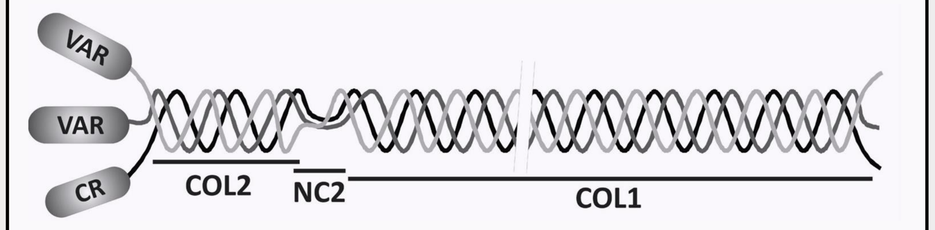
A degree of skin hyperextensibility, atrophic scarring and joint hypermobility is present in about 95% of the individuals with a causal defect. More than 90% of the patients have easy bruising, skin fragility, soft, doughy skin and complications of joint hypermobility. The presence of molluscoid pseudotumors and subcutaneous spheroids are relatively rare and unknown features, but function as highly diagnostic features when present.Individuals with causal variants in COL5A2 seem to be affected with a more severe/ complicated disease with a significant higher prevalence of club feet, hernia's of the abdominal wall, scoliosis and congenital hip dislocations.



Conclusion

The majority of the cEDS patients harbour mutations in *COL5A1;* only 15% of all causal defects are located in *COL5A2*. More than 50% of the pathological *COL5A1* mutations causes a premature termination codon. All pathological variants in *COL5A2* cause structural defects, mostly glycine substitutions. No premature termination codons have been identified in *COL5A2*. In about 5-10% of the patients with a clinical diagnosis of cEDS, no causal defect is found in *COL5A1/COL5A2.* Whole exome or whole genome sequencing can function as the next diagnostic step.

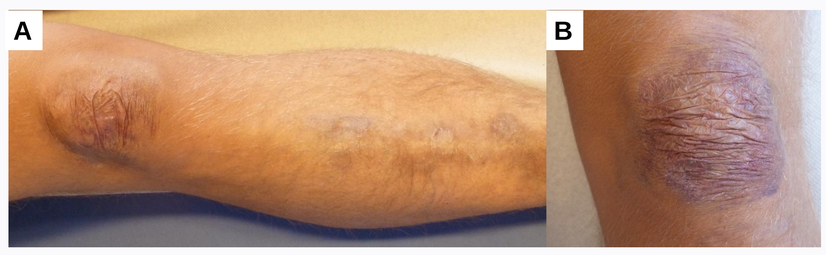
More than 95% of the patients with causal defects present with atrophic scarring, hyperextensible skin and joint hypermobility. Patients harboring defects in *COL5A2* seem to have a more severe phenotype. Defects in type V collagen do not seem te be associated with severe vascular complications. Patients with the specific *COL1A1* c.934C>T, p.(Arg312Cys) mutation on the other hand may present as cEDS but seem to have a propensity to arterial rupture.



Type V collagen is mainly found as the $\alpha1(V)_2\alpha2(V)$ heterotrimer which assembles with type I collagen into heterotypic type I/V collagen fibrils. The α1 chain is coded by *COL5A1* and the α2 chain is coded by *COL5A2.* The type V collagen helix is buried within the type I collagen fibril and its N-propeptide projects through the gap zone of the type I collagen regulating collagen fibril diameter and interacting with other components.

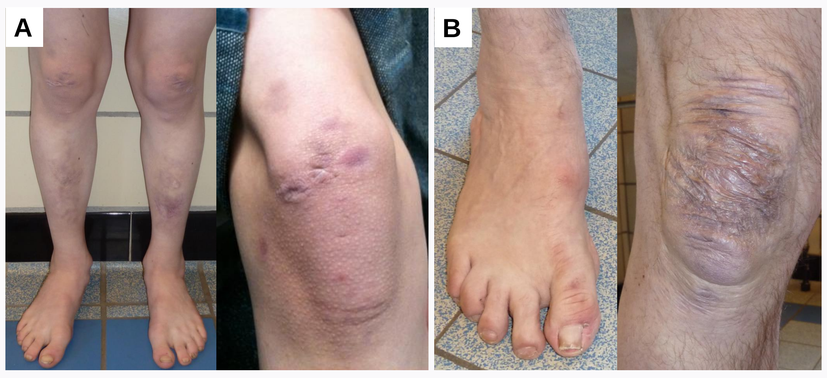
Case 1: causal defect in *COL5A1*

Patient with nonsense mutation in *COL5A1* (c.3769C>T; p.(Arg1257*)) displaying atrophic scarring (A,B) and sequelae of ecchymoses (A). Furthermore, he displayed typical hallmarks of cEDS with joint hypermobility and skin hyperextensibility.



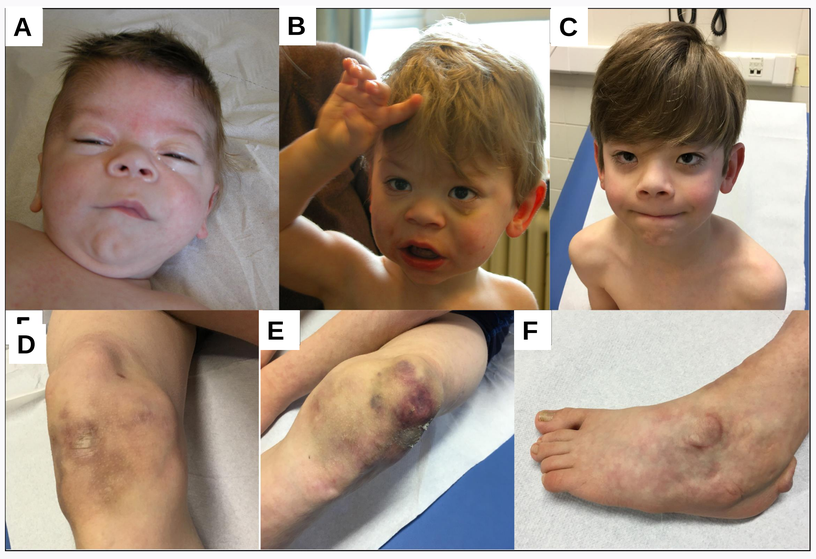
Case 2: no causal defect found

Family (B is the proband, A is the daughter of B) with clinical suspicion of cEDS in whom no defect in *COL5A1/COL5A2* could be identified. Affected family members present with atrophic scarring, easy bruising, molluscoid pseudotumors, joint hypermobility and skin hyperextensibility. Single gene sequencing of *COL5A1* and *COL5A2* failed to identify a causal defect. Whole exome sequencing is ongoing.



Case 3: fading boundaries

Whole exome sequencing revealed a de novo splice site defect in *COL5A2*, c.2031+1G>T in a boy with a clinical suspicion of Ehlers-Danlos syndrome, dermatosparaxis type (dEDS). He was a floppy infant with a club foot and an umbilical hernia. Height and weight always remained <p10. He suffers from joint dislocations due to generalized joint hypermobility. His skin is hyperextensible and fragile with easy bruising. There are multiple widened atrophic scars, molluscoid pseudotumors and sequelae of ecchymoses. Facial features are reminiscent of dEDS with swollen eyelids at birth and epicanthic folds. Pictures at the age of 4 months (A), 2 (B) and 10 (C,D,E,F) years.



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