Novel defects in collagen XII and VI expand the mixed Myopathy/Ehlers-Danlos syndrome spectrum

Tibbe Dhooge

Center for Medical Genetics Ghent

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Myopathic EDS

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Recessive and dominant mutations in *COL12A1* cause a novel EDS/myopathy overlap syndrome in humans and mice

Yaqun Zou[1], Daniela Zwolanek[2], Yayoi Izu[3], Shreya Gandhy[1], Gudrun Schreiber[4], Knut Brockmann[5], Marcella Devoto[6,7,8], Zuozhen Tian[9], Ying Hu[1], Guido Veit[3], Markus Meier[10], Jörg Stetefeld[10], Debbie Hicks[11], Volker Straub[11], Nicol C. Voermans[12], David E. Birk[3], Elisabeth R. Barton[9], Manuel Koch[2,*] and Carsten G. Bönnemann[1,*]

[1]Neuromuscular and Neurogenetic Disorders of Childhood Section, National Institute of Neurological Disord
Stroke, NIH, Bethesda, MD, USA, [2]Medical Faculty, Institute for Dental Research and Oral Musculoskeletal
Center for Molecular Medicine Cologne, Center for Biochemistry, University of Cologne, D-50931 Cologne,
[3]Department of Molecular Pharmacology and Physiology, University of South Florida, Tampa, FL, USA, [4]Clini
for Pediatric Neurology, Kassel, Germany, [5]Interdisciplinary Pediatric Center for Children with Developmenta
Disabilities, University Medical Center, Göttingen, Germany, [6]Division of Human Genetics and Department of
The Children's Hospital of Philadelphia, Philadelphia, PA, USA, [7]Department of Biostatistics and Epidemiology
School of Medicine, University of Pennsylvania, Philadelphia, PA, USA, [8]Department of Molecular Medicine, Ur
Sapienza, Rome, Italy, [9]Department of Anatomy and Cell Biology, School of Dental Medicine, University of Per
PA, USA, [10]Department of Chemistry, Microbiology, Biochemistry and Medical Genetics, University of Manitob
[11]Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK and [12]Department of Neuro
Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

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Mutations in the collagen XII gene define a new form of extracellular matrix-related myopathy

Debbie Hicks[1], Golara Torabi Farsani[1], Steven Laval[1], James Collins[2], Anna Sarkozy[1], Elena Martoni[3], Ashoke Shah[1], Yaqun Zou[4], Manuel Koch[5], Carsten G. Bönnemann[4], Mark Roberts[6], Hanns Lochmüller[1], Kate Bushby[1] and Volker Straub[1,*]

[1]MRC Centre for Neuromuscular Disease at Newcastle, Institute of Genetic Medicine, Newcastle, UK [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA [3]Department of Experimental and Diagnostic Medicine, University of Ferrara, Ferrara, Italy [4]NIH, National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA [5]Institute for Dental Research and Oral Musculoskeletal Biology, Centre for Biochemistry, University of Cologne, Cologne, Germany [6]Departments of Neurology and Neuropathology, Hope Hospital, Salford, UK

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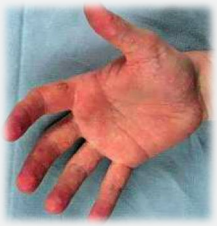
Myopathic EDS

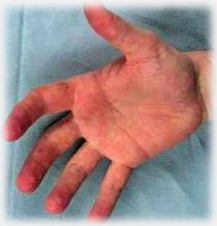


Bethlem myopathy

Ullrich congenital muscular dystrophy

Type VI collagen related myopathies

Myopathic EDS



Bethlem myopathy

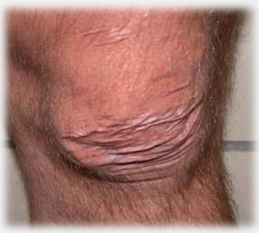
Ullrich congenital muscular dystrophy

Type VI collagen related myopathies

EDS

'myopathic EDS'

COL12A1



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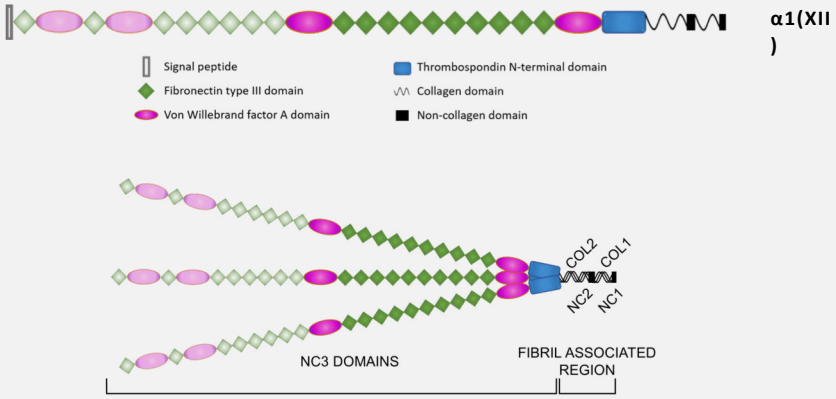
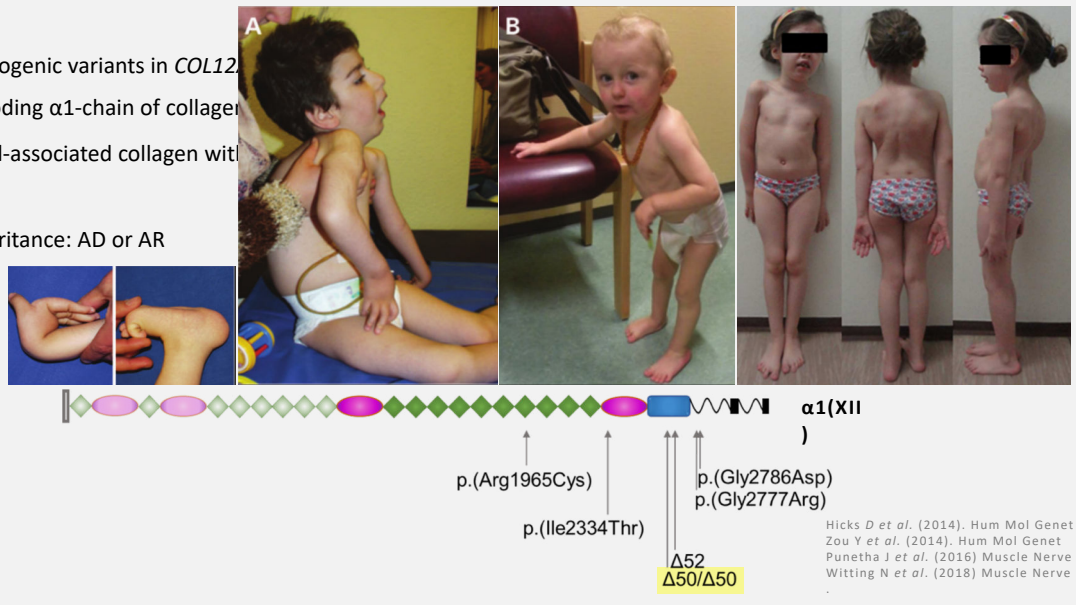
Myopathic EDS and collagen XII

- Pathogenic variants in *COL12A1*
- Encoding α1-chain of collagen XII
- Fibril-associated collagen with interrupted triple helices (FACIT)



Myopathic EDS and collagen XII

- Pathogenic variants in *COL12*
- Encoding α1-chain of collage
- Fibril-associated collagen wit
- Inheritance: AD or AR



Hicks *D et al.* (2014). Hum Mol Genet
Zou Y *et al.* (2014). Hum Mol Genet
Punetha J *et al.* (2016) Muscle Nerve
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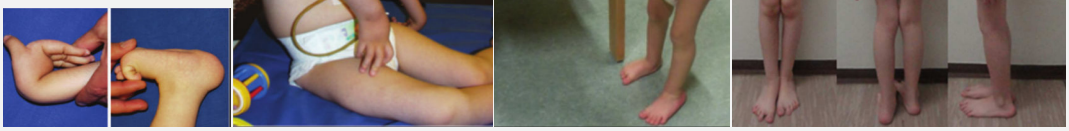

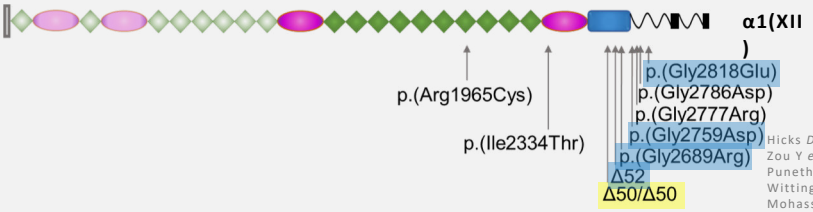

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Mohassel *et al.* (2019) Ann Clin Transl Neurol

Resolving unexplained *in house* EDS cases

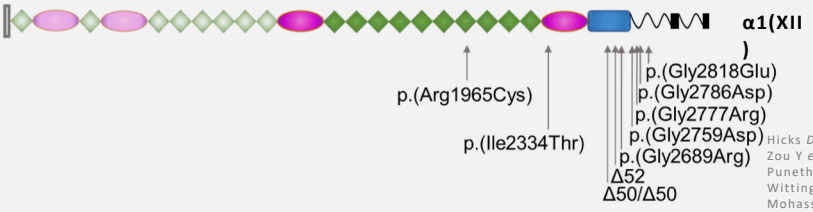
78 unresolved patients fulfilling the clinical criteria for myopathic EDS

Major criteria

1. Congenital muscle **hypotonia** and/or muscle atrophy, that improves with age
2. Proximal joint **contractures** (knee, hip, and elbow)
3. **Hypermobility** of distal joints

Minor criteria

1. Soft, doughy skin
2. Atrophic scarring
3. Motor developmental delay
4. Myopathy on muscle biopsy



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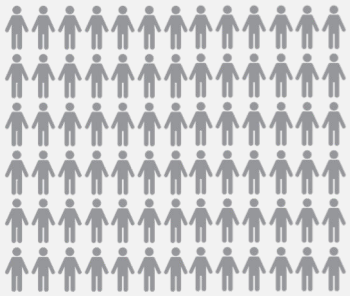
Resolving unexplained *in house* EDS cases



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Minor criteria

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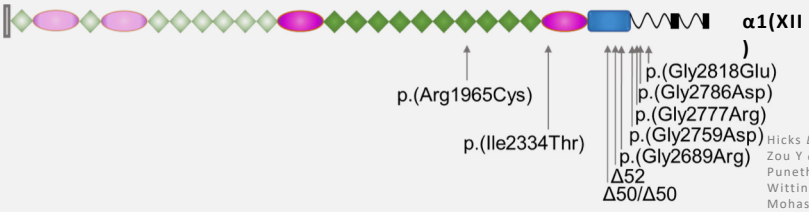
NGS panel sequencing

- *COL12A1*
- *COL6A1*
- *COL6A2*
- *COL6A3*



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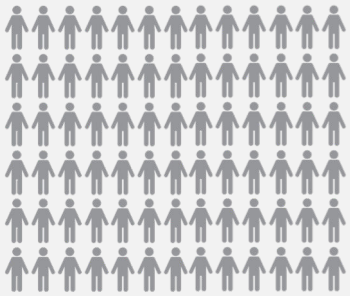
Resolving unexplained *in house* EDS cases



78 unresolved patients fulfilling the clinical criteria for myopathic EDS

NGS panel sequencing

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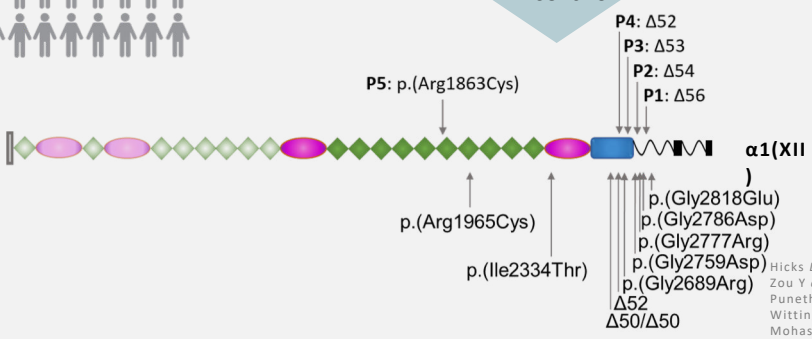

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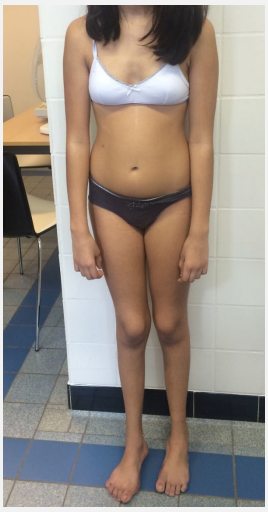
Clinical overview of *in house* mEDS patients

	COL12A1				
	Δ56	**Δ54**	**Δ53**	**Δ52**	**p.(R1863C)**
Age	4y	5y	13y	7y	18y
Early development	delay	delay	delay	delay	toe walking
Hypotonia	+	+	+	+	-
Muscle weakness	+	+	+	+	-
Contractures	+	-	+	+	progressive
Club feet	-	-	+	-	+
Joint hypermobility	generalized	generalized (7/9)	generalized (9/9)	distal	-
Hip dislocation	-	-	+	+	-
Pedes plani	+	+	-	+	-
Skin	soft	soft	soft, hyperextensible	soft	-
Facies	macrocrania	EDS-like	EDS-like	micrognathia	-

Clinical overview of *in house* mEDS patients

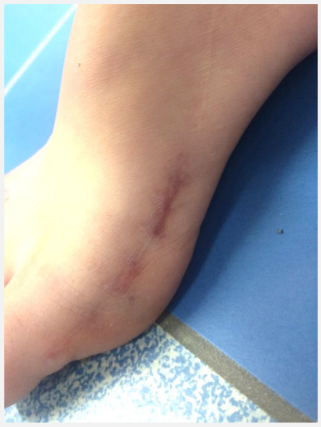


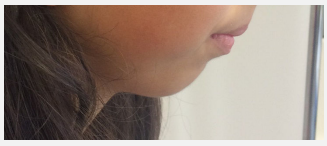
Major criteria

1. Congenital muscle **hypotonia** and/or muscle atrophy, that improves with age	5/7
2. (Proximal) joint **contractures** (knee, hip, and elbow)	5/7
3. **Hypermobility** of distal joints	2/7
Generalized joint hypermobility	5/7

Minor criteria

1. Soft, doughy skin	3/7
2. Atrophic scarring	1/7
3. Motor developmental delay	4/7
4. Myopathy on muscle biopsy	1/3
Mild skin hyperextensibility	1/7
Light blue sclerae	3/7
Micrognathia	2/7
High arched palate	2/7





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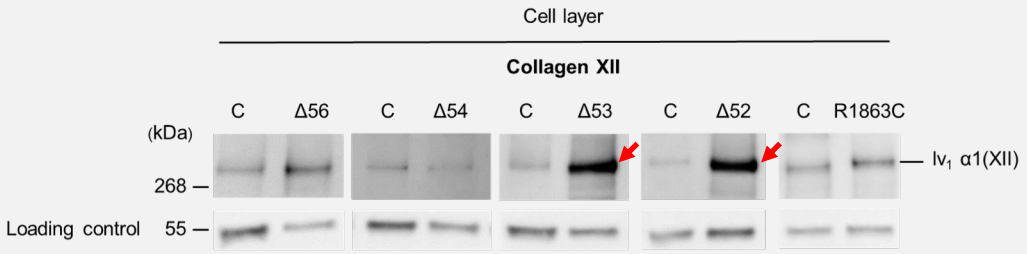
Intracellular accumulation of collagen XII in 2 patients



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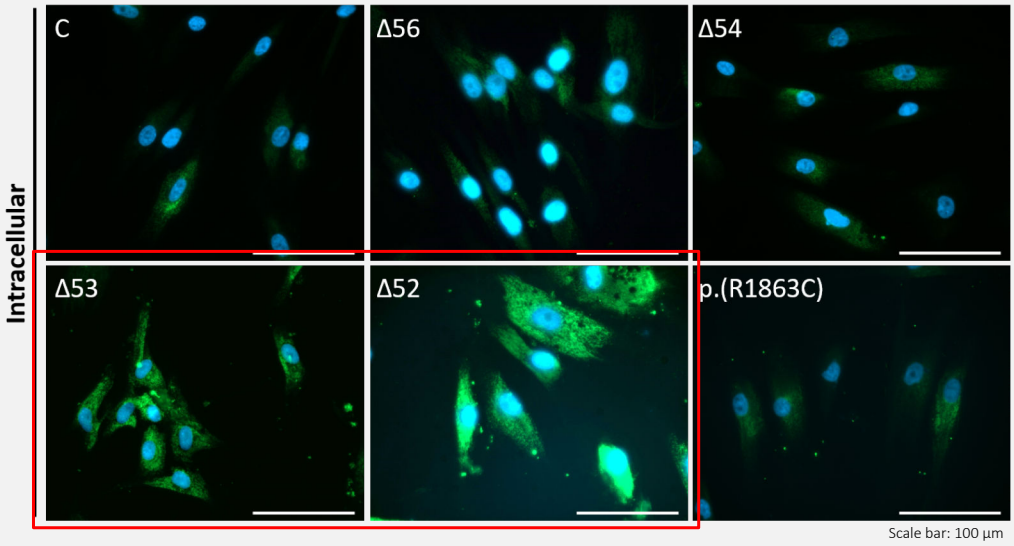

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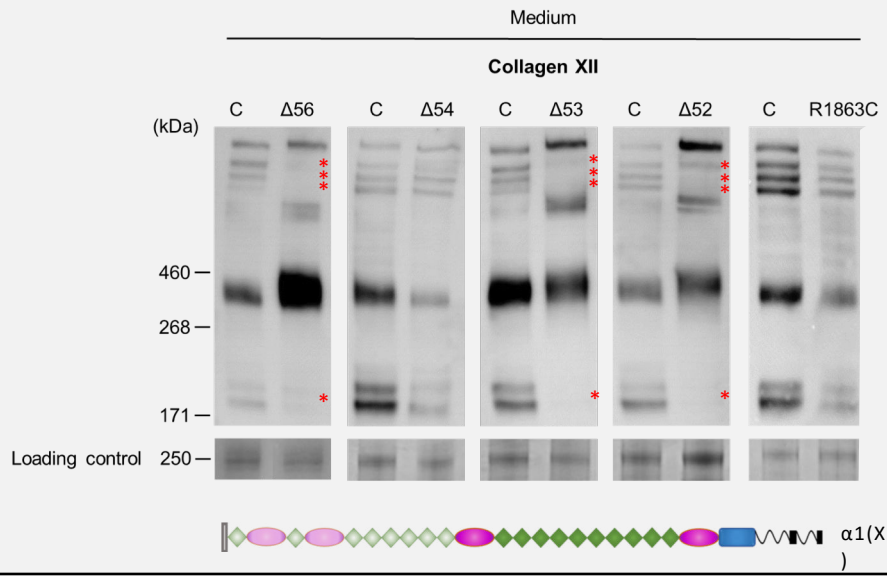
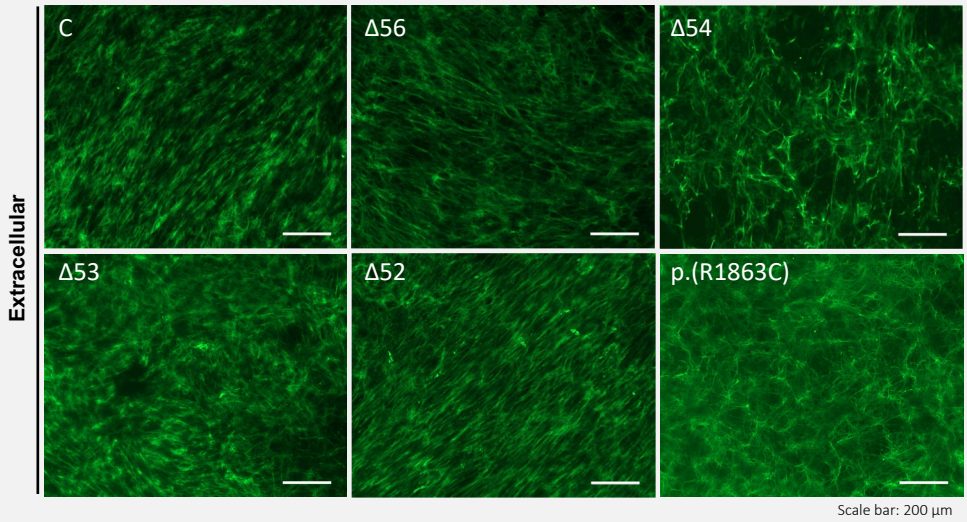
Aberrant secretion of collagen XII in 3 patients



Normal architecture of collagen XII



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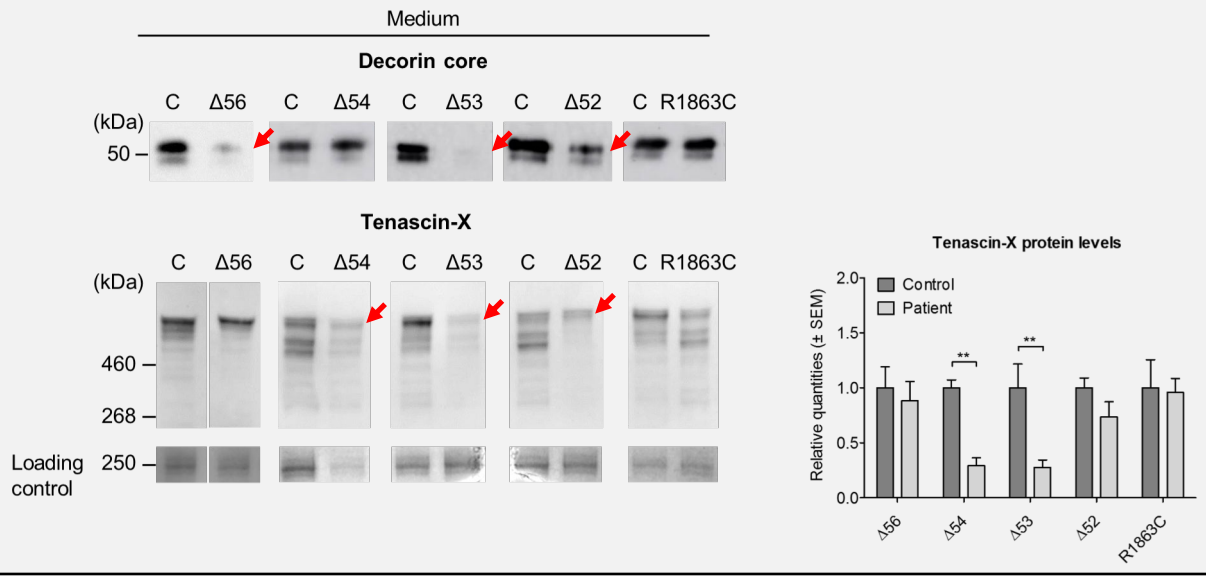
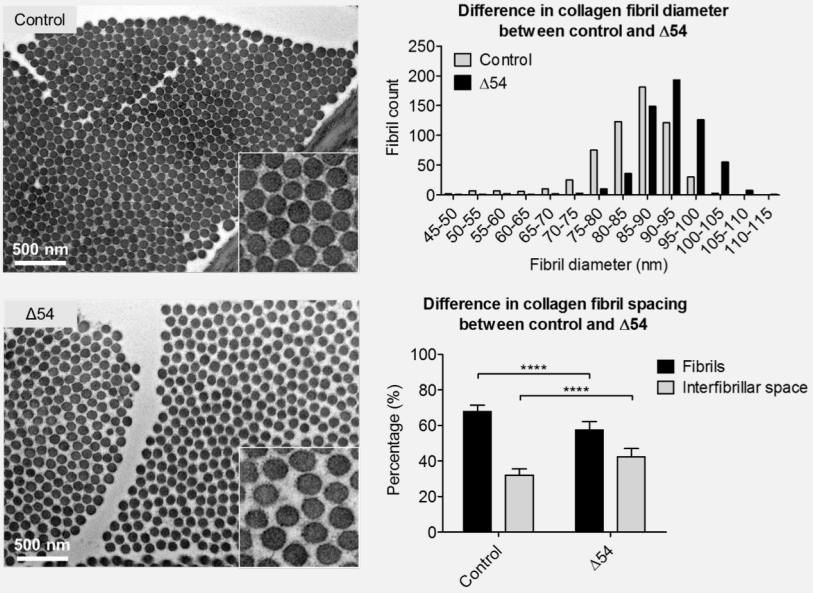
Variant-specific reduction of matrix proteins



Ultrastructural changes in Δ54 skin biopsy



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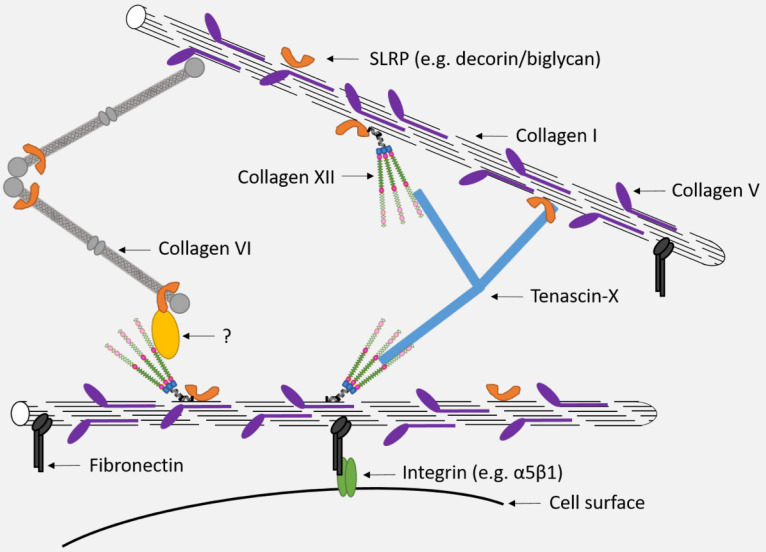
Variant-specific molecular effects



Myopathic EDS: clinical overlap

Difficult to distinguish between mEDS and myopathies

72/78 patients genetically unresolved

- Genetic heterogeneity

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Myopathic EDS

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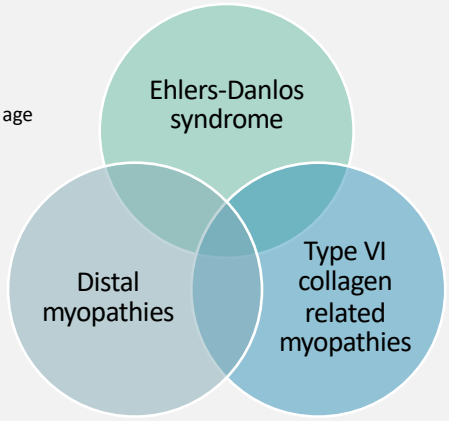

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Dr. Sofie Symoens
Prof. Dr. Fransiska Malfait

Referring physicians
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Prof. Dr. Florence Petit
Prof. Dr. Nathalie Goemans
Dr. Anne Destrée

TEM
Riet De Rycke

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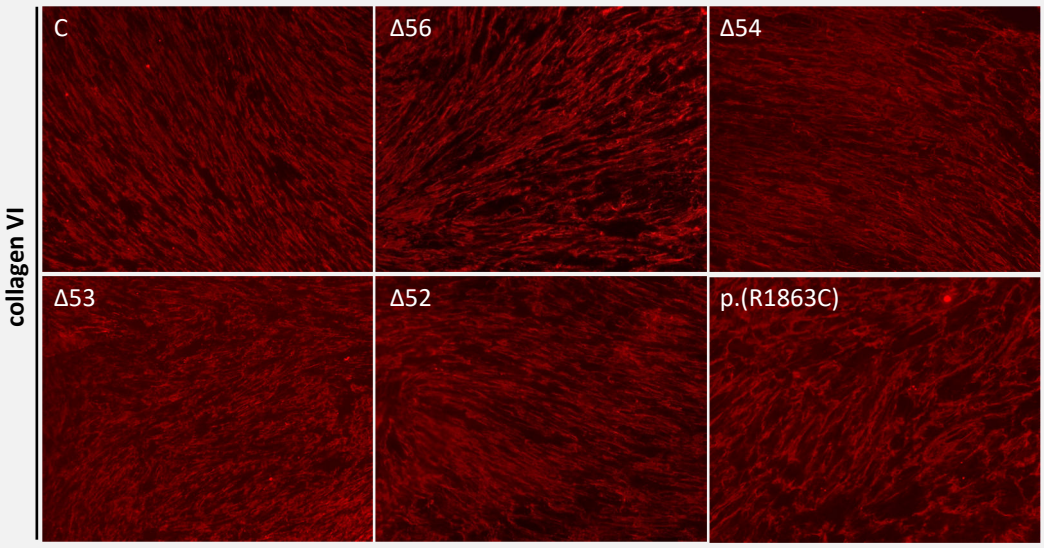
No differences in other interaction partners

Collagen I, V and VI and fibronectin normal



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