

MECHANISMS IN ACQUIRED CUTIS LAXA SHED LIGHT ON ELASTIC FIBER BREAKDOWN

BERT CALLEWAERT

CENTER FOR MEDICAL GENETICS, GHENT UNIVERSITY HOSPITAL



European
Reference
Networks



7th Cutis laxa days
Ghent, Feb 3, 2026

Cutis laxa: clinical hallmark

Heterogeneous group of connective tissue disorders characterized by redundant, loose, sagging and inelastic skin and variable systemic involvement

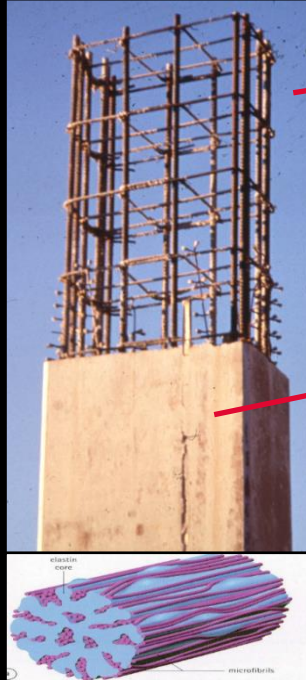


Cutis Laxa

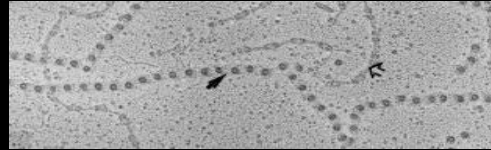


Hyperextensible skin
(Classical EDS)

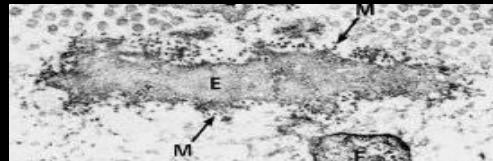
ELASTIC FIBERS



MICROFIBRIL



MICROFIBRIL + ELASTIN
= ELASTIC FIBER



Louis XIV
79 y – 72,3 years on the throne

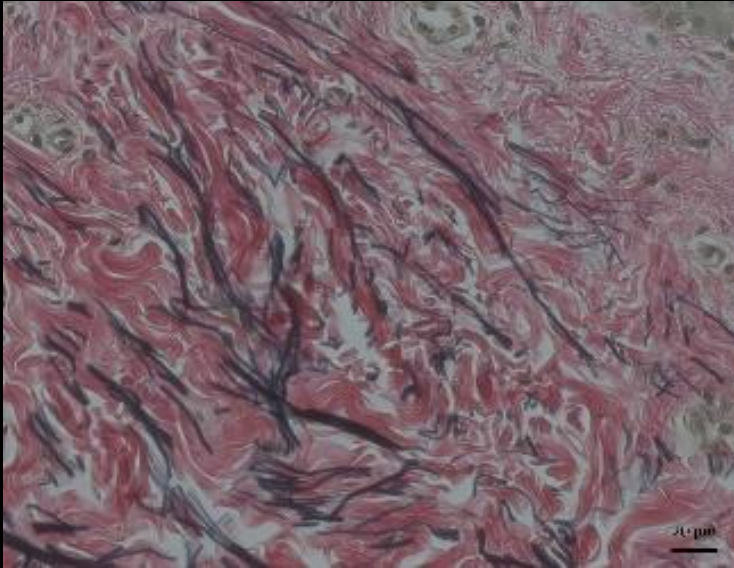
96 y – 70,5 years on the throne



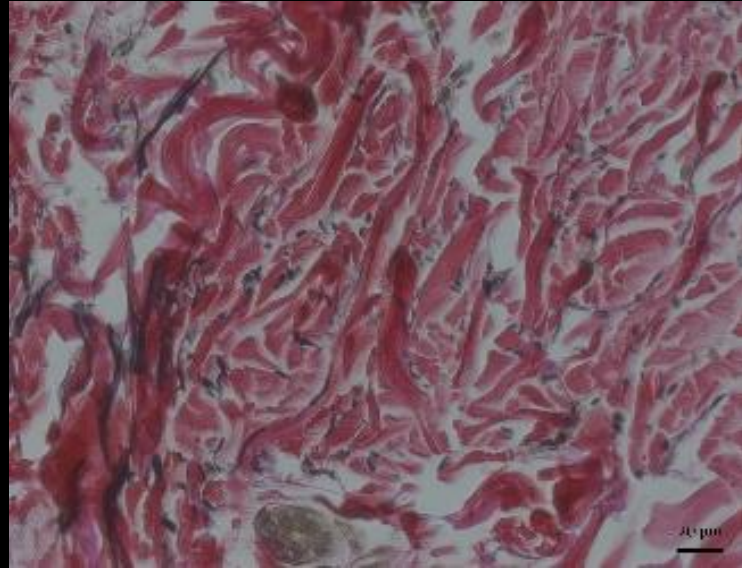
- Inherited EFD → synthesis and/or assembly of elastic fibers: Genetics
 - Acquired EFD → destruction of normal elastic fibers: Genetics - Environment
- Note: ageing process / emphysema / aortic dilatation

Cutis laxa: elastic fiber fragmentation

Control



ADCL





46 yo
Elastogenesis → Elastolysis

Elastic fiber degeneration: Acquired Cutis Laxa



10 years old



29 years old

Acquired Cutis Laxa: type 1



Type 1 Acquired cutis laxa:

- Genetic predisposition
- > females, young adulthood – middle aged
- Following erythema / inflammation
- Trunk/lower half of face → limbs (months – years)
- Trigger
 - Infectious
 - Toxic (drugs (penicillin, penicillamine, isoniazide)
 - Paraneoplastic (MGUS, MM)
 - Insect bites
 - fillers, surgery, ...
- Systemic risk
 - Emphysema
 - Aortic root dilatation
 - Bladder diverticula

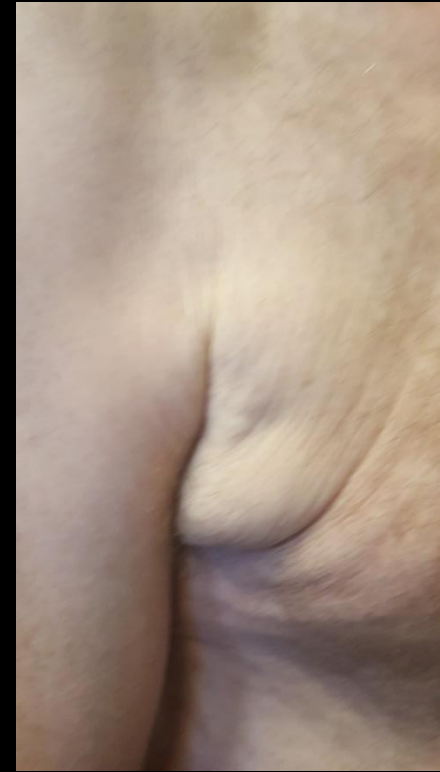
- 39 years
- 32 yrs :
Progressive cutis laxa
 - Following erythema
 - Initially on the trunk
- Progressive joint pain
(mechanical pain)
- Etiology ?



Elastic fiber degeneration: Acquired Cutis Laxa

- 49 years
- Adolescence: FESS
- 45 yrs: Progressive cutis laxa
 - Following erythema
 - Initially on the trunk
- Progressive joint pain
(mechanical pain)
- Monoclonal gammopathy
(MGUS)





Progressive emphysema

Acquired Cutis Laxa: type 2

Type 2 Acquired CL or Marshall syndrome

- inflammatory dermatitis with neutrophilic component (mostly urticarial or papular eruptions)
- Followed by loss of skin elasticity over the inflammatory area.
- Localized



(a) left shoulder



(b) neck



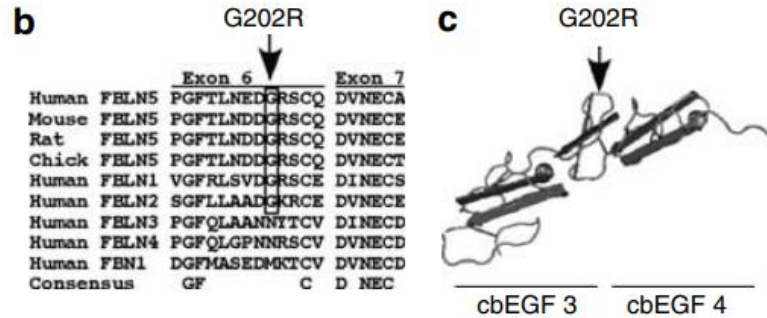
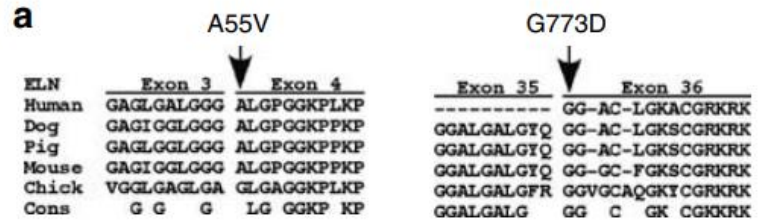
Acquired Cutis Laxa: Ghent Cohort (n=15) Cutis laxa gene panel: normal Literature: ascertainment bias	M/F	8/7
	Mean age of onset	37
	Trigger	
	Neutrophilic dermatosis	1
	Medication	0
	Malignancy	2
	Infection	0
	Hyperthyroidism	2
	Surgery	1
	Extension of involvement	
	Generalized	7
	Localized	5
	Preceding inflammation/erythema	6
	Progression in time	6
	Pulmonary (COPD)	2
	Cardiovascular	0
	Osteoarticular features	
	Joint pain	4
	Gastrointestinal features	0
	Urogenital features	0
	Neurological features	0

Acquired Cutis Laxa: type 1

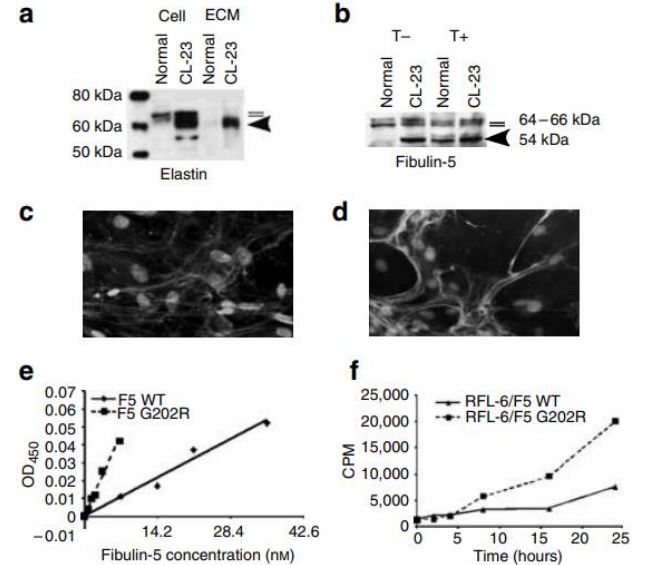
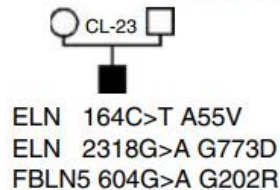


Figure 1. Development of cutis laxa. The patient, shown here at the age of 12 years, was first seen with an inflammatory condition characterized by erythematous papules affecting the entire skin including (a) the legs and (b) the arms. Six months later, he developed generalized cutis laxa (c) characterized by marked sagging and wrinkling of the skin.

Acquired Cutis Laxa: genetics ?



d ELN 164C>T A55V ELN 2318G>A G773D
FBLN5 604G>A G202R



GNOMAdv4.0

17/800 000
6861/800 000
340/800 000

Acquired Cutis Laxa: Ghent Cohort

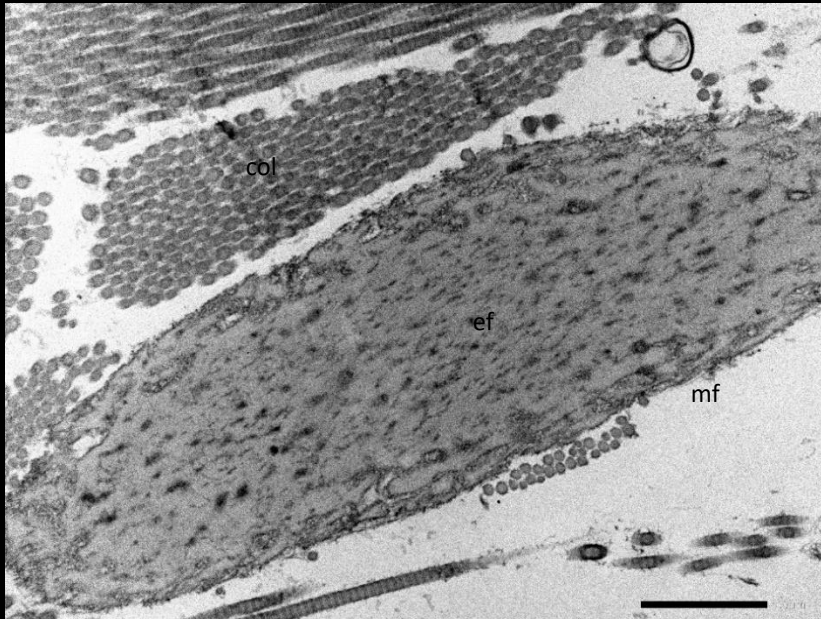
Diagnostic handles (1)



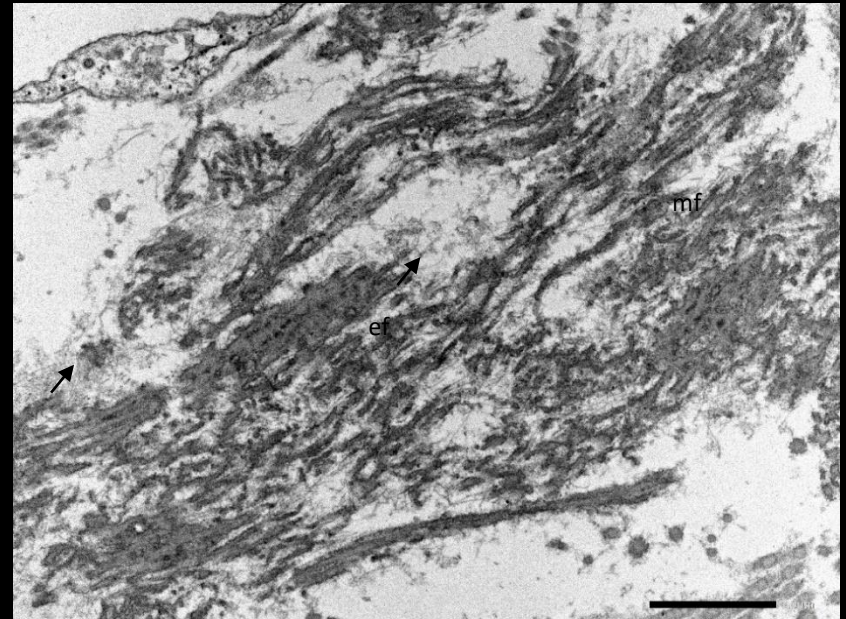
Acquired Cutis Laxa: Ghent Cohort

Diagnostic handles (2)

Non-affected skin



Affected skin

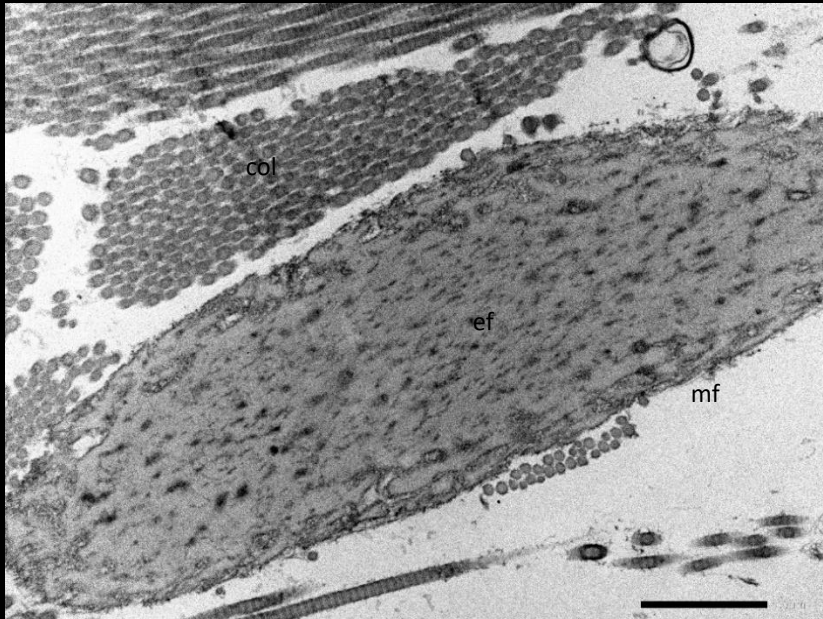


Scalebar 2 μ m

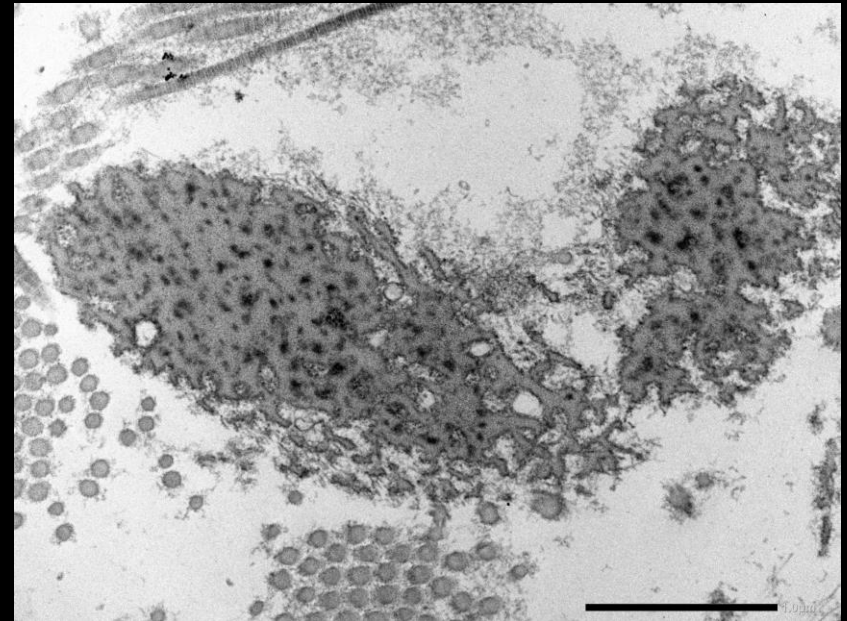
Acquired Cutis Laxa: Ghent Cohort

Diagnostic handles (2)

Non-affected skin



Affected skin (inflammation)

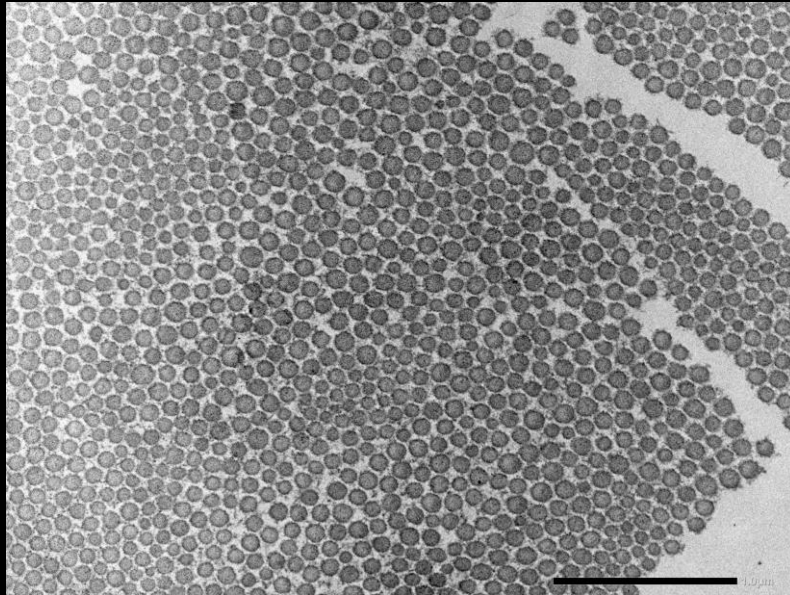


Scalebar 2 μ m

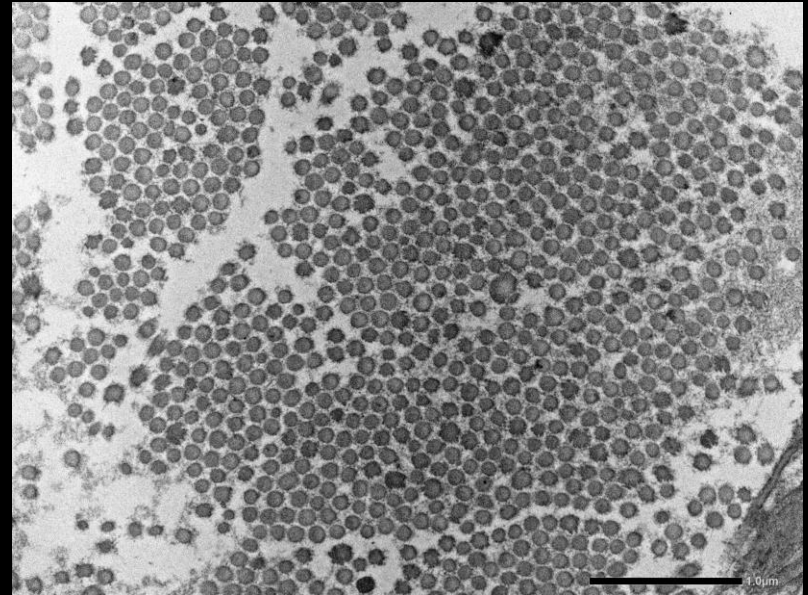
Acquired Cutis Laxa: Ghent Cohort

Diagnostic handles (2)

Non-affected skin



Affected skin



Scalebar 2 μm

Acquired Cutis Laxa: Ghent Cohort

Diagnostic handles (2)

Inflammatory condition



changes to how white blood cells react ?
Epigenetics ?

Acquired Cutis Laxa: Ghent Cohort

Diagnostic handles (1)

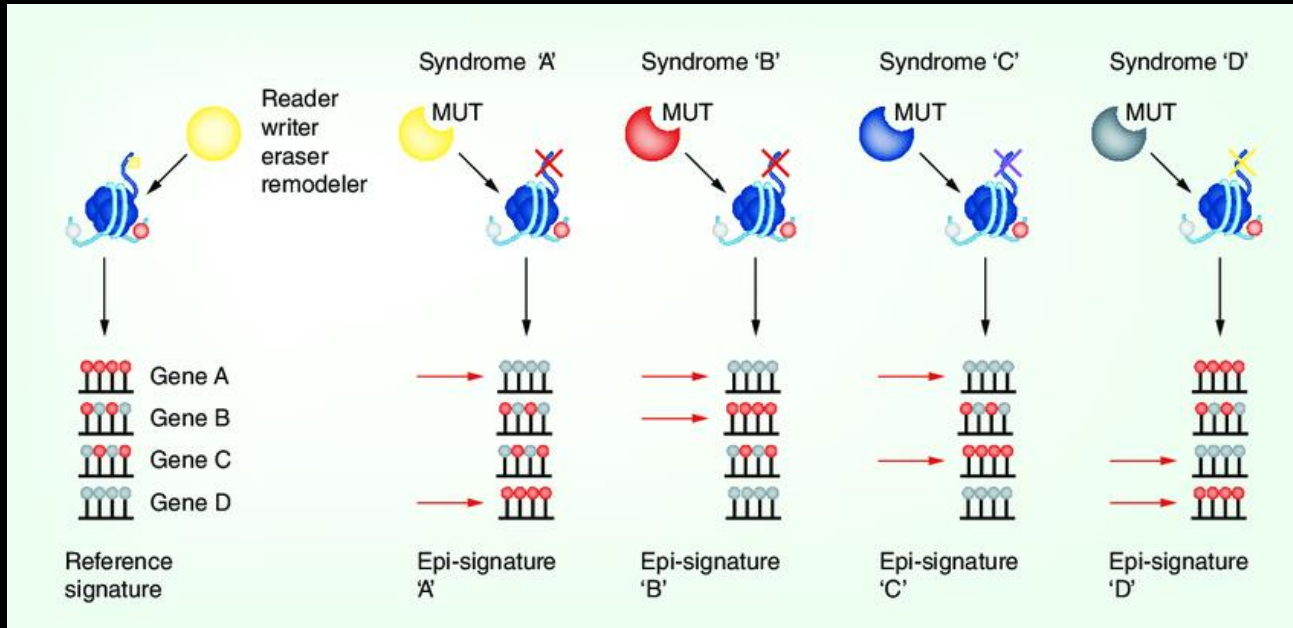


Other guests
(environment, pathogenic
variants)



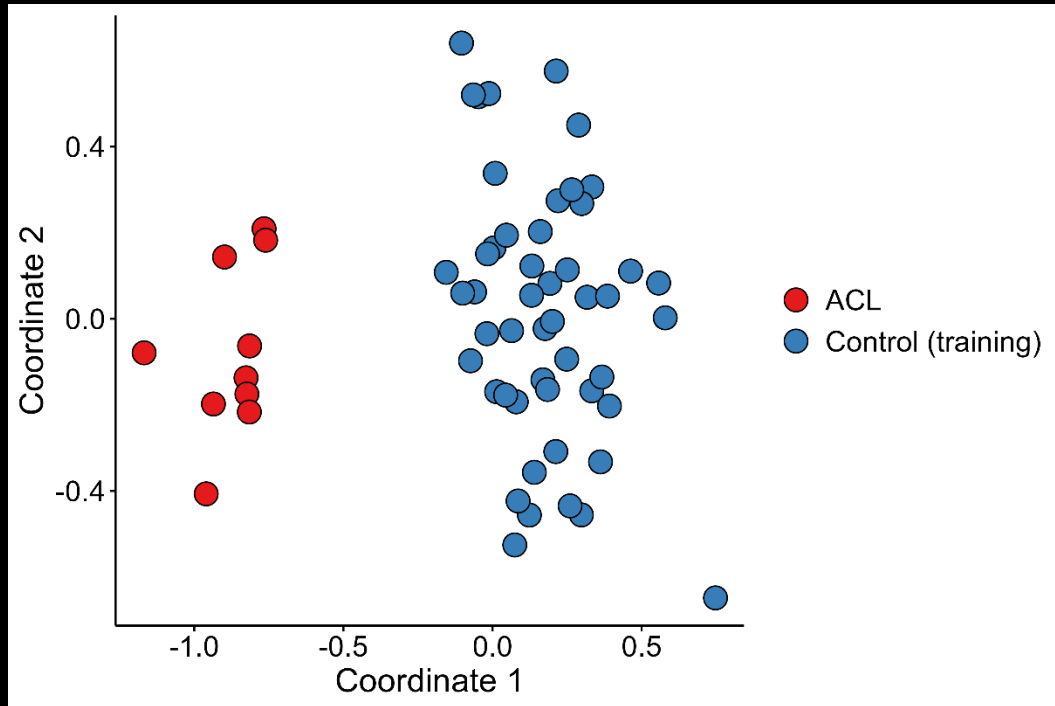
Acquired Cutis Laxa: Ghent Cohort

Diagnostic handles (2)



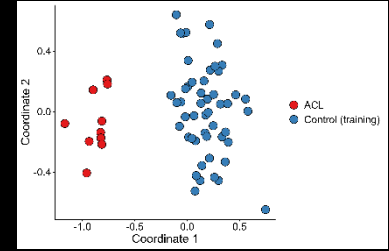
Acquired Cutis Laxa: Ghent Cohort

Diagnostic handles (1)



Acquired Cutis Laxa: Ghent Cohort

GO analysis



Description	GeneSet ratio	p-value
wound healing	15/405	2,70139E-05
response to wounding	16/535	0,000189435
vascular wound healing	3/22	0,001467083
regulation of guanylate cyclase activity	2/6	0,001629212
MDA-5 signaling pathway	2/10	0,003245668
neurotransmitter transport	8/197	0,003250394
angiogenesis involved in wound healing	3/31	0,003814341
positive regulation of receptor internalization	3/25	0,004513285
platelet aggregation	4/70	0,005067551
intermediate filament cytoskeleton organization	4/92	0,005173909

Acquired Cutis Laxa: type 1

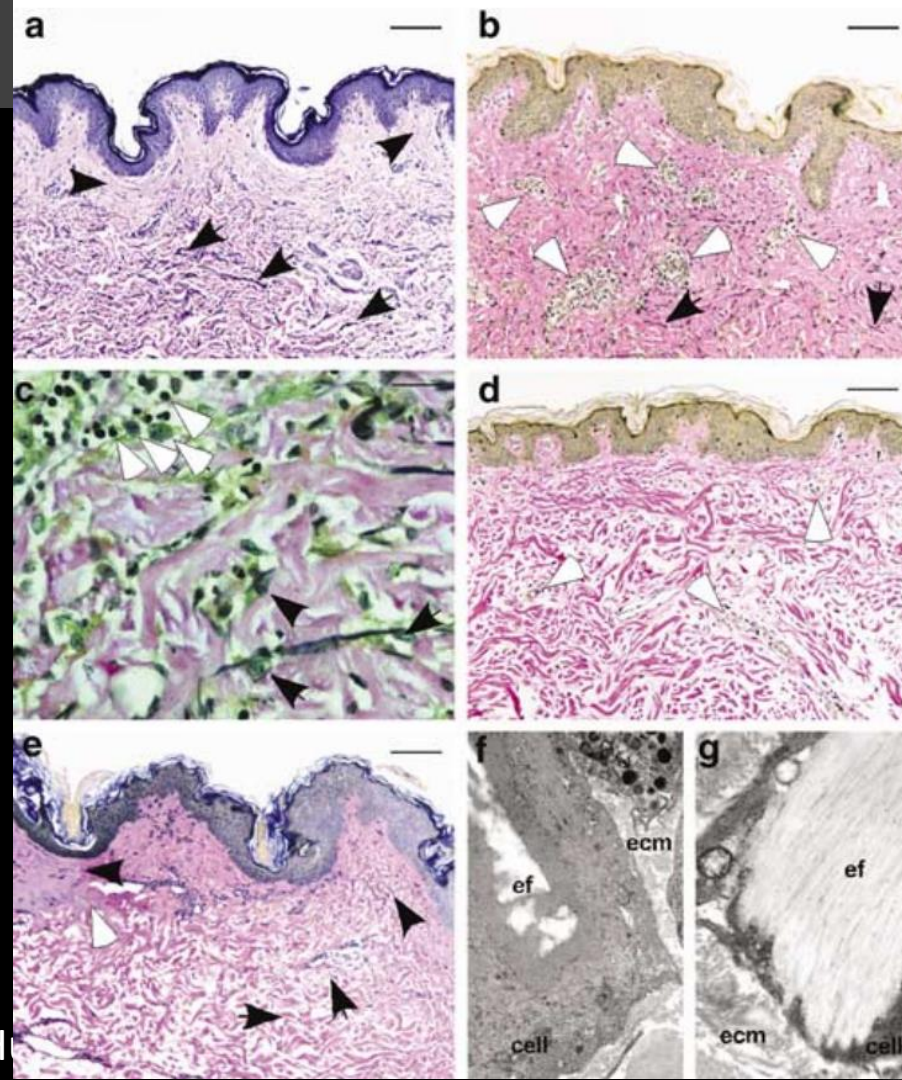


Figure 1. Development of cutis laxa. The patient, shown here at the age of 12 years, was first seen with an inflammatory condition characterized by erythematous papules affecting the entire skin including (a) the legs and (b) the arms. Six months later, he developed generalized cutis laxa (c) characterized by marked sagging and wrinkling of the skin.

Acquired Cutis Laxa: type 1



Figure 1. Development of cutis laxa. The patient, shown here at the age of 12 years, was first seen with an inflammatory condition characterized by erythematous papules affecting the entire skin including (a) the legs and (b) the arms. Six months later, he developed generalized cutis laxa (c) characterized by marked sagging and wrinkling of the skin.



RNA SEQ AFFECTED VS. NON-AFFECTED SKIN

Differential expression of genes implied in

- elastin degradation
- Cell motility and adhesion
- Cartilage maintenance
- Inflammation
- Protein degradation

Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Antigen processing-Cross presentation	4 / 109	0.009	2.54e-05	0.005	3 / 23	0.002
RUNX1 regulates transcription of genes involved in differentiation of keratinocytes	2 / 8	6.79e-04	7.83e-05	0.008	1 / 8	5.37e-04
Assembly of collagen fibrils and other multimeric structures	3 / 61	0.005	1.27e-04	0.008	4 / 26	0.002
Endosomal/Vacuolar pathway	2 / 12	0.001	1.75e-04	0.008	1 / 4	2.69e-04
Trafficking and processing of endosomal TLR	2 / 13	0.001	2.06e-04	0.008	2 / 7	4.70e-04
Transcriptional regulation by RUNX1	4 / 206	0.017	2.94e-04	0.009	2 / 132	0.009
Collagen formation	3 / 90	0.008	3.95e-04	0.011	25 / 77	0.005
Degradation of the extracellular matrix	3 / 140	0.012	0.001	0.018	9 / 105	0.007
Regulation of activated PAK-2p34 by proteasome mediated degradation	2 / 50	0.004	0.003	0.018	1 / 2	1.34e-04
Cross-presentation of soluble exogenous antigens (endosomes)	2 / 50	0.004	0.003	0.018	1 / 6	4.03e-04
Class I MHC mediated antigen processing & presentation	4 / 386	0.033	0.003	0.018	4 / 48	0.003



(a) left shoulder



(b) neck



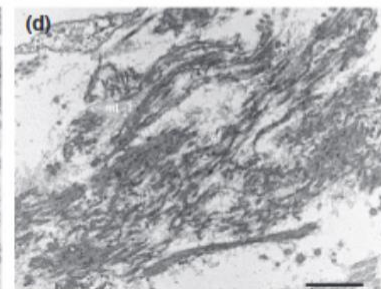
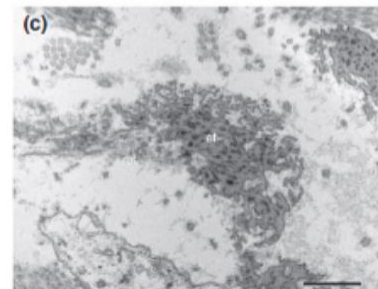
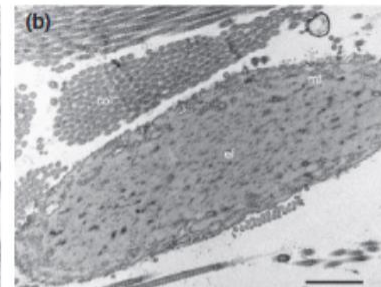
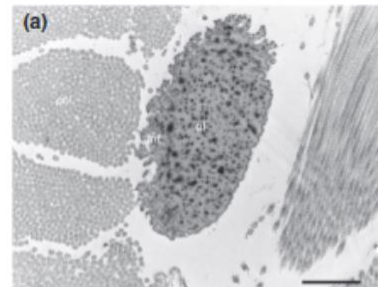
(e) 2018, after 6 months adalimumab



(f) 2020, after 2 years adalimumab

control

Non affected skin

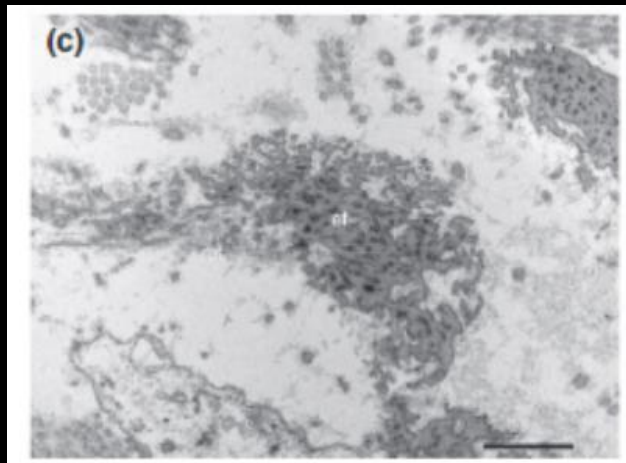


Early stage

Late stage

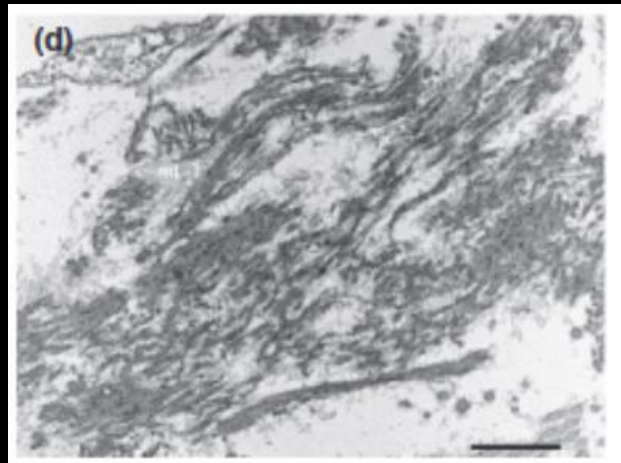
40 mg Adalimumab
SC/week

Early stage



Inflammation ↑
T-Cell ↑
CTSV ↑

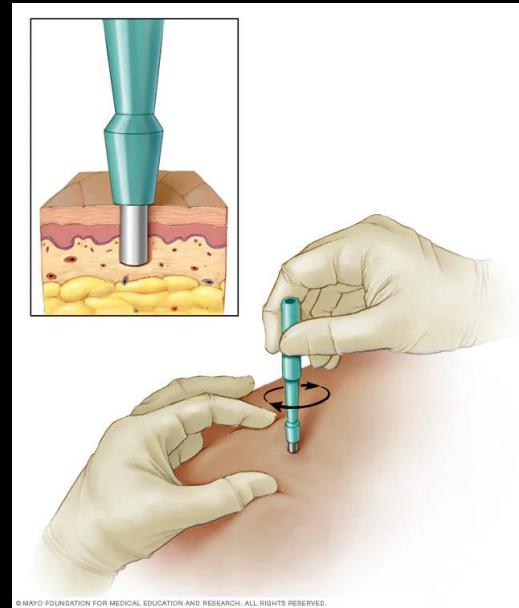
Late stage



APC ↑

Take home

- ✓ EF morphology, pathophysiology and clinical presentation are intrinsically linked
- ✓ Inflammatory responses / autoimmunity result in EF degradation
- ✓ Infiltration of immune cells is a hallmark of EF degradation in ACL
- ✓ New clues to EF degradation
- ✓ Samples are needed for research
 - with novel techniques, resampling may be needed too
 - skin biopsies (EM, fibroblasts, RNA, single cell)
 - Blood (DNA, methylooom, proteomics, extracellular vesicles...)





CALLEWAERTGENOMICSLAB
FROM RARE TO CARE

Aude Beyens
Wouter Steyaert
Maxim Verlee
Michiel Vanhooydonck
Lore Pottie
Lisa Caboor
Karolien Aelbrecht
Sofie Symoens
Patrick Sips

Cologne, Germany
Gerhard Sengle
Berlin, Germany
Björn Fischer-Zimzak
Göttingen, Germany
Uwe Kornak
Pittsburg, USA
Zsolt Urban
Paris, France
Christine Bodemer
Smail Hadj-Rabia
Perth, Australia
Fiona McKenzie
Istanbul, Turkey
Elif Yilmaz
Alper Gezdirici
Sehime Temel
Nijmegen, The Netherlands
Ron Wevers
Tatjana Gardeitchik
London, Canada
Bekim Sadikovich

Referring physicians All families !!!

