Cutis laxa: A Novel Classification And General Management Guidelines

Bert Callewaert, MD, PhD
Center for Medical Genetics, Ghent University Hospital

CTD teaching day
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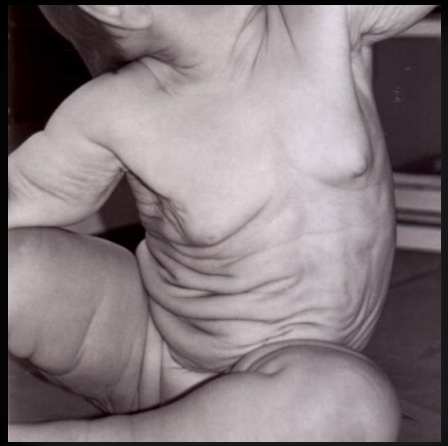
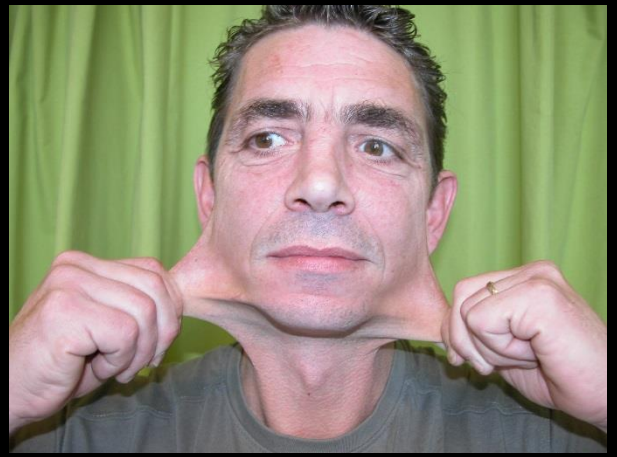
London North West
University – NHS Trust

Cutis laxa: clinical hallmark

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



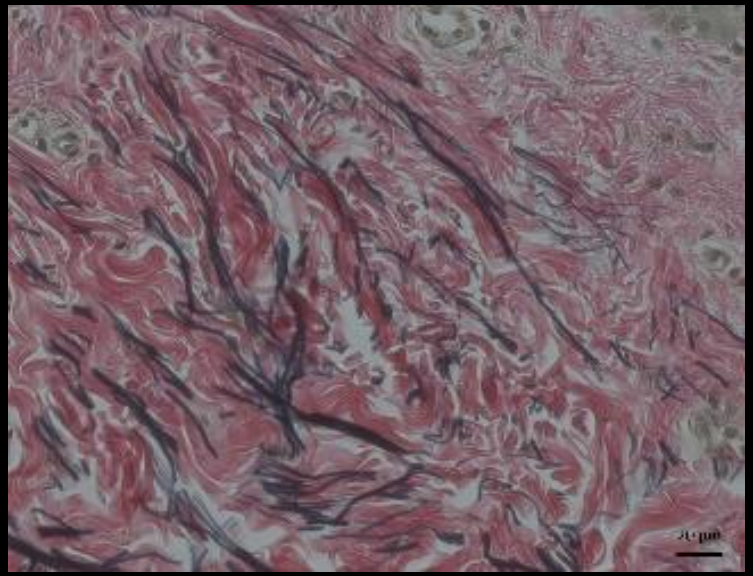
Cutis Laxa



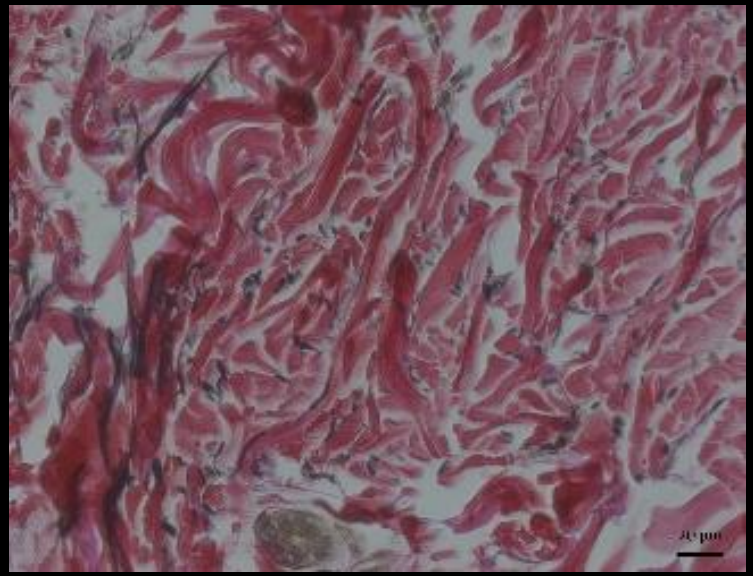
Hyperextensible skin
(Classic EDS)

Cutis laxa: elastic fiber fragmentation

Control

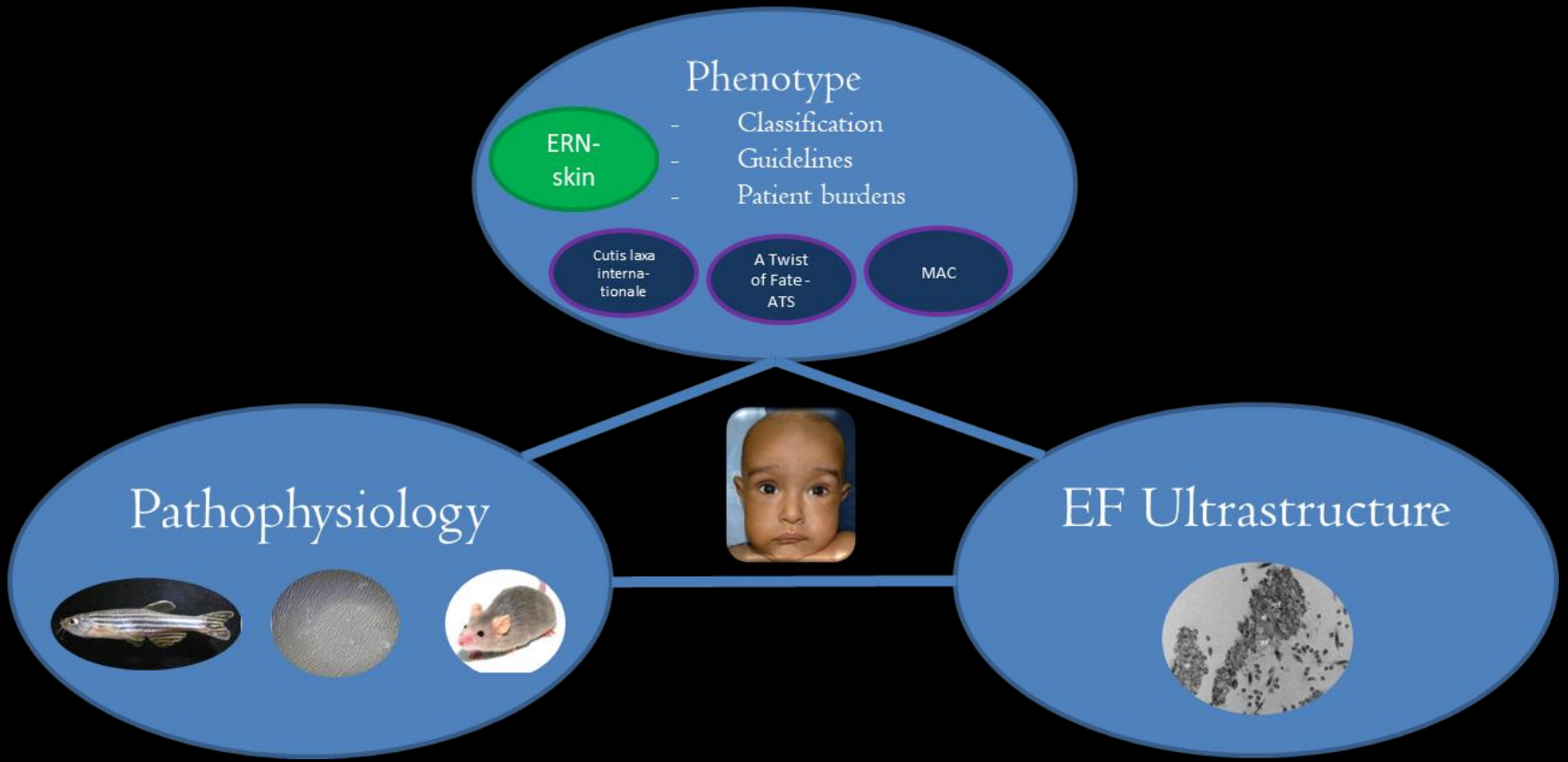


ADCL



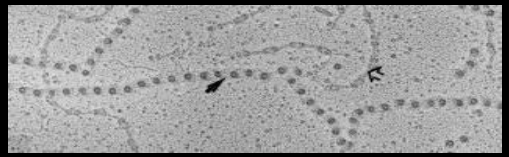
Callewaert et al, 2010

Cutis laxa: Classification

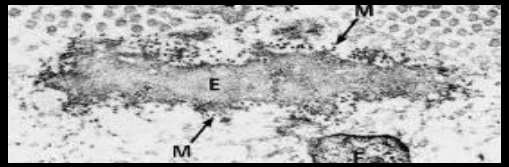


Elastic Fibers

MICROFIBRIL



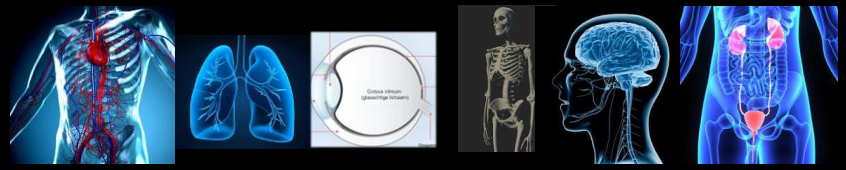
MICROFIBRIL + ELASTIN
= ELASTIC FIBER

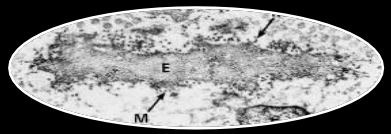


- Inherited EFD → synthesis and/or assembly of elastic fibers: Genetics
- Acquired EFD → destruction of normal elastic fibers: Genetics - Environment

  Note: ageing process / emphysema / aortic dilatation

Cutis laxa: diverse presentations





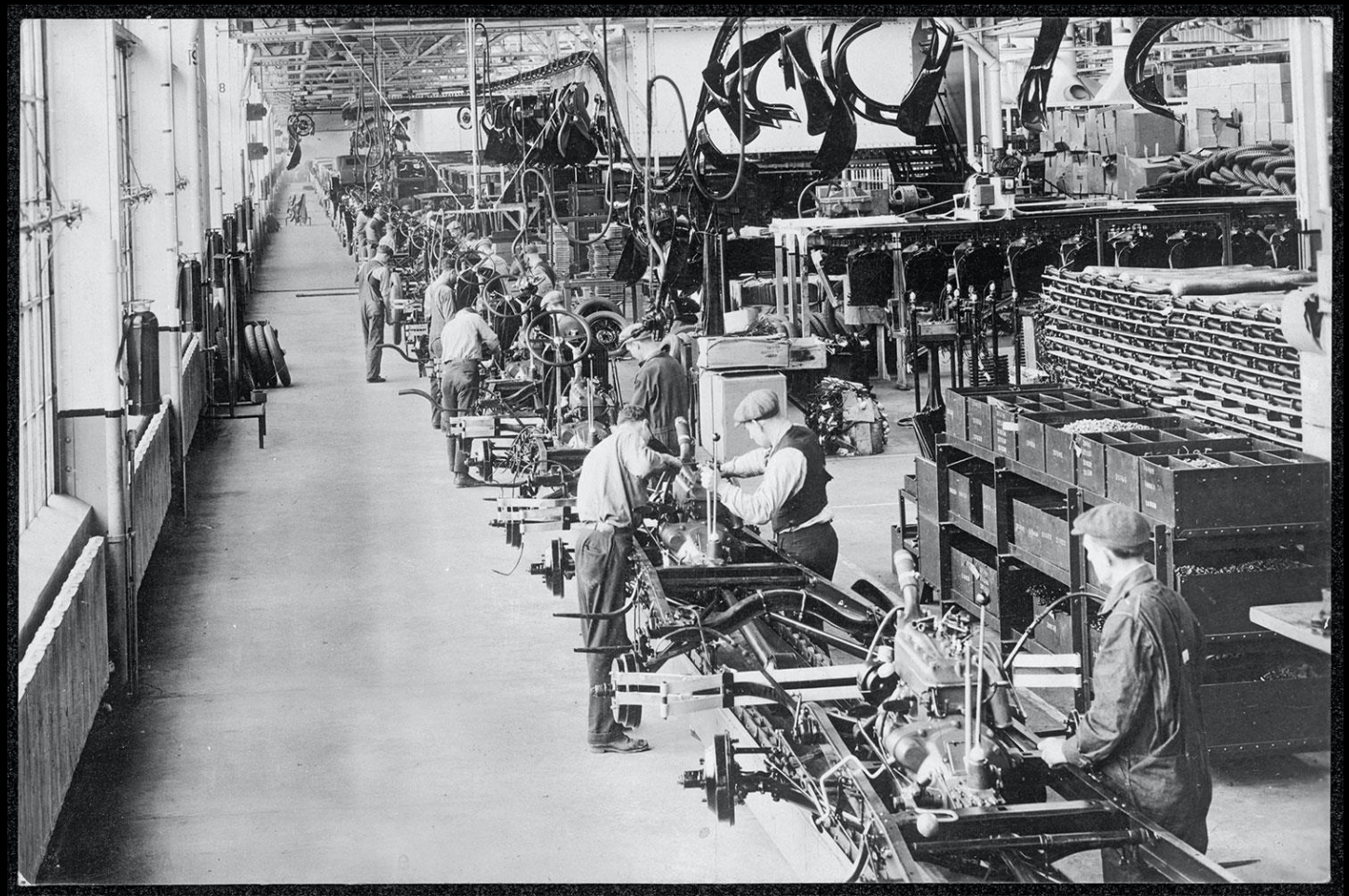
Mendelian disease

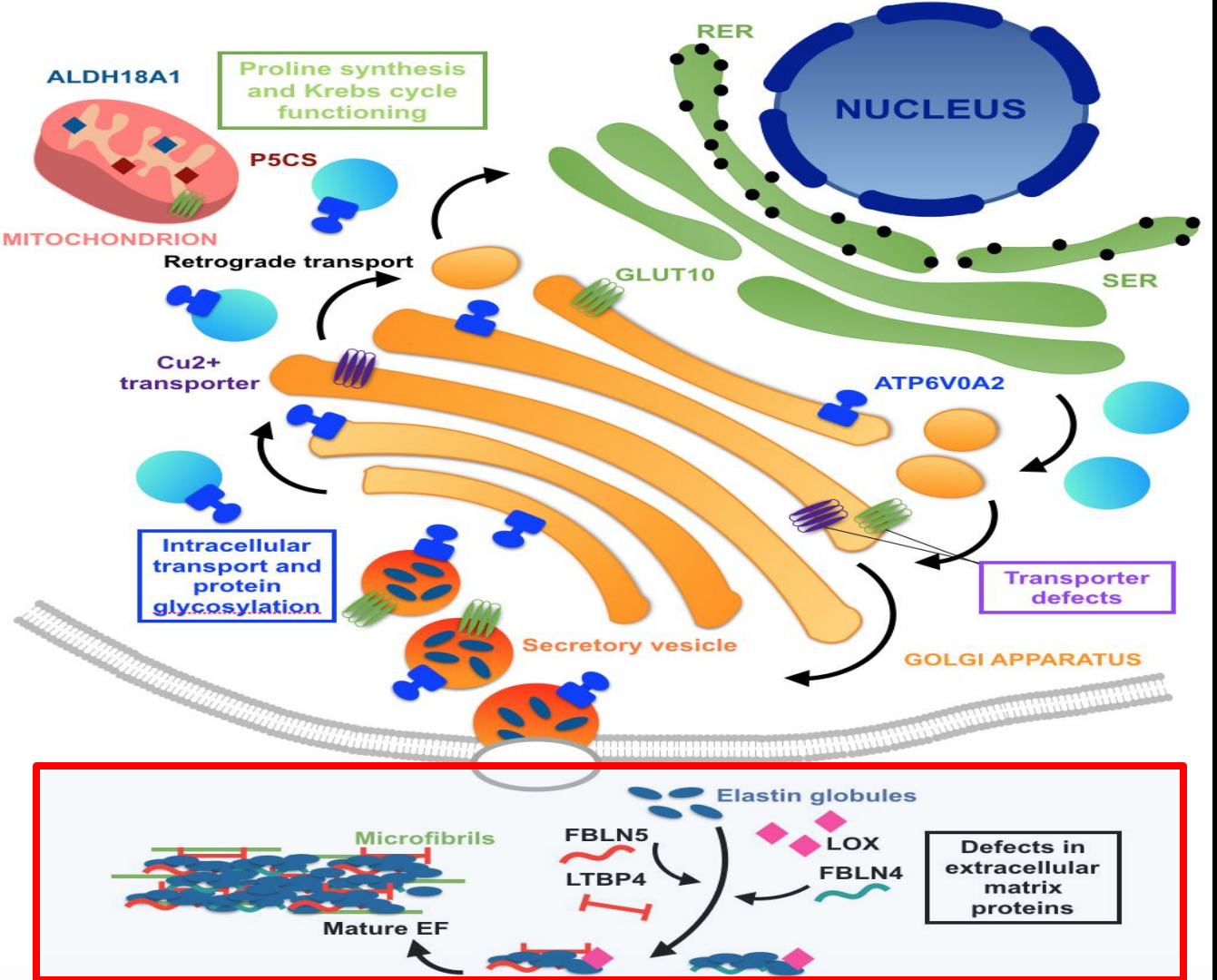
Genomic variability

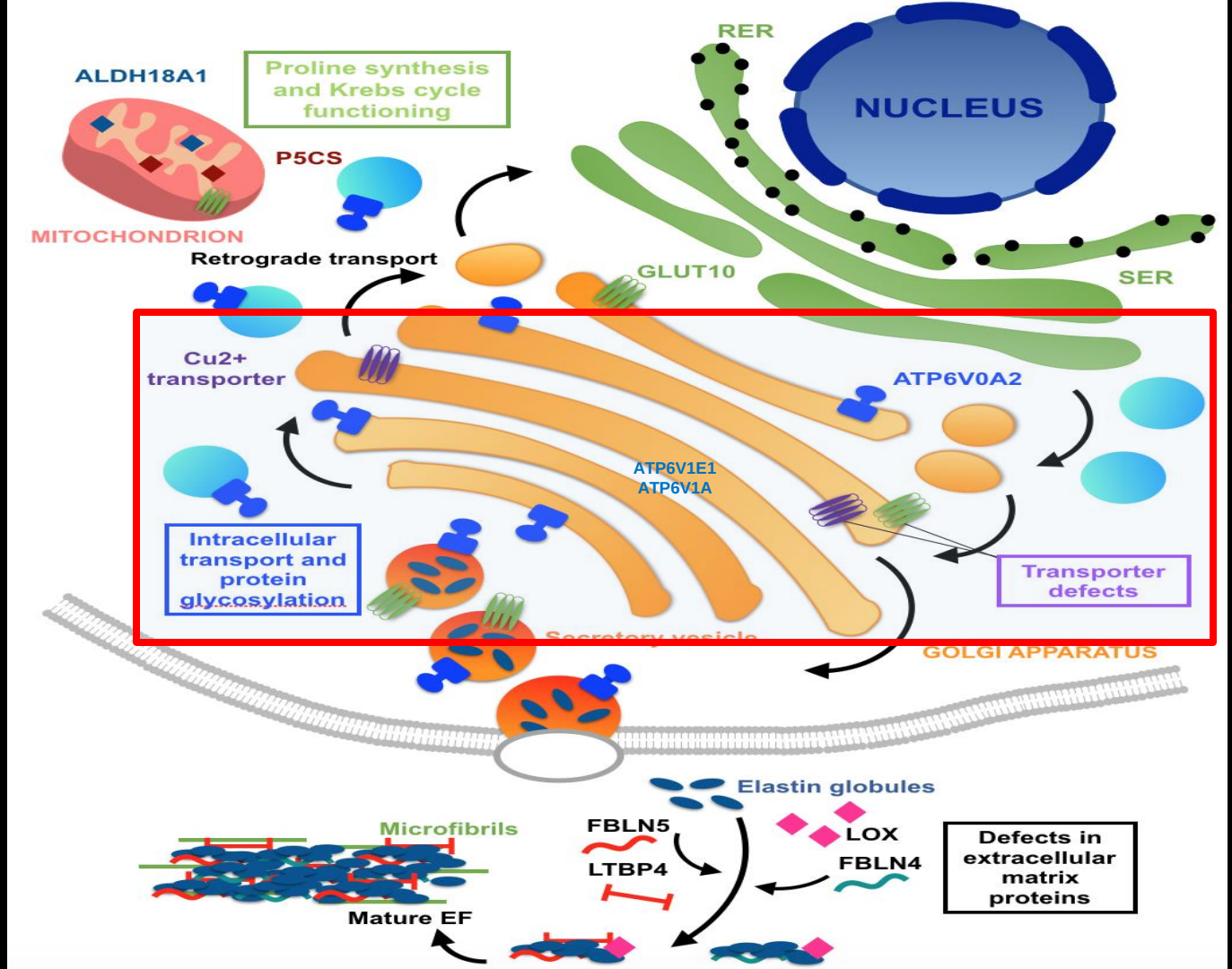
Environment influences

Elastic fiber
Acquired disease

Why are there so many presentations in cutis laxa?




ALDH18A1
Proline synthesis and Krebs cycle functioning
P5CS
MITOCHONDRION
RER
NUCLEUS
SER
Retrograde transport
GLUT10
Cu2+ transporter
ATP6V0A2
Intracellular transport and protein glycosylation
Transporter defects
Secretory vesicle
GOLGI APPARATUS
Elastin globules
Microfibrils
FBLN5
LOX
LTBP4
FBLN4
Mature EF
Defects in extracellular matrix proteins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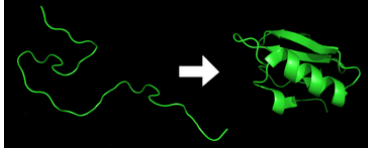
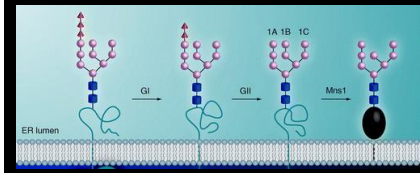
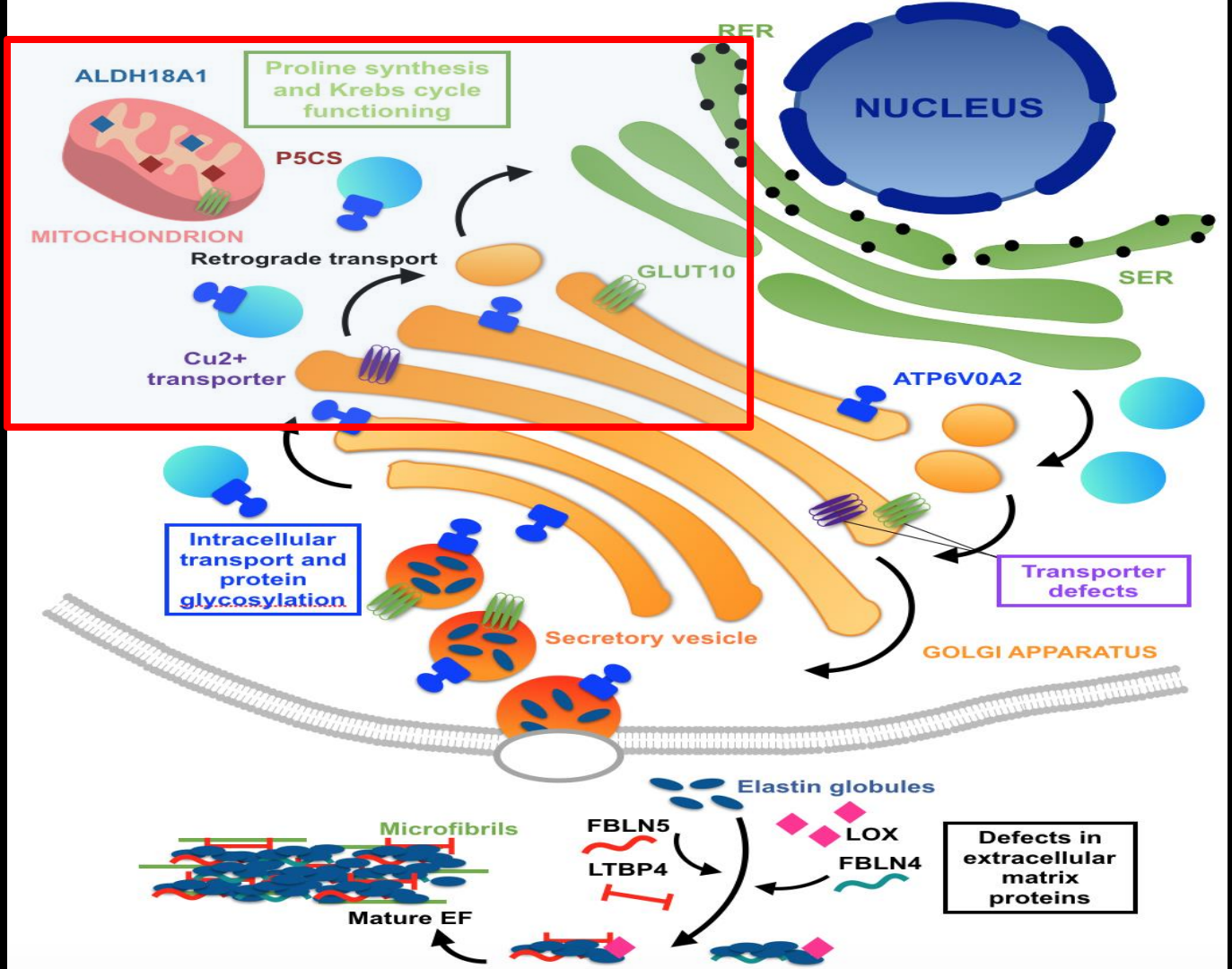



1A 1B 1C
GI
GII
Mns1
ER lumen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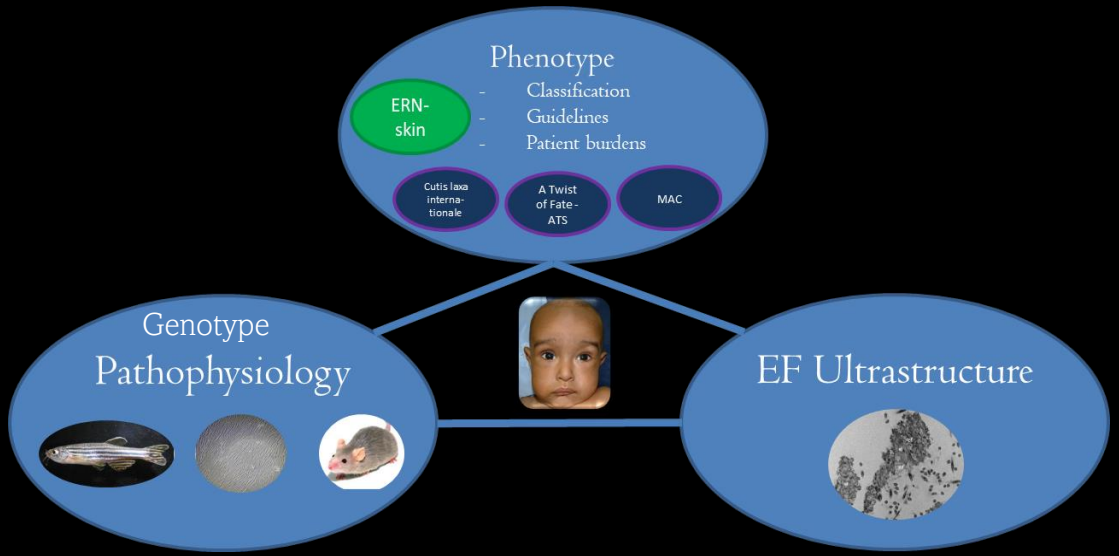
Cutis laxa: Classification in progress…

Cutis laxa:
> 40 OMIM entries

Main clinical manifestation

Major Criteria

Minor Criteria



Own database (185)

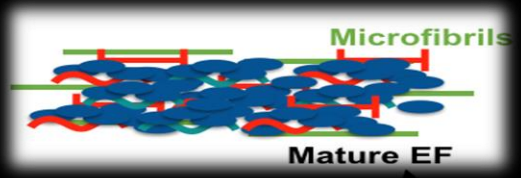
↓

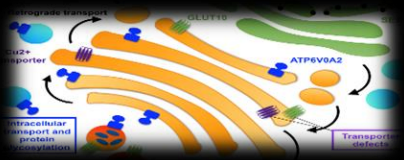
Systematic review: 840 cases

Cutis laxa: a meaningful classification

Main clinical manifestation

- Prominent Connective tissue features
  - Tortuosity
    - *SLC2A10*
    - *EMILIN1*
    - *FBLN4*
    - *LOX*
  - Emphysema
    - *LTBP4*
    - *FBLN5*
  - Skin
    - *ELN*
  - Bone
    - *LTBP1*
- Neurological
  - No IUGR/SGA
    - *ATP6V0A2*
    - *ATP6V1E1*
    - *ATP6V1A*
    - *ATP6AP1*
    - *(NBAS)*
    - *ATP7A*
    - *(COG7)*
    - *(RIN2)*
    - *GORAB*
  - IUGR/SGA
    - *ALDH18A1*
    - *PYCR1*
    - *ECHS1*
    - *TALDO1*





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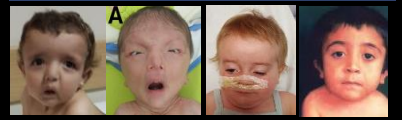
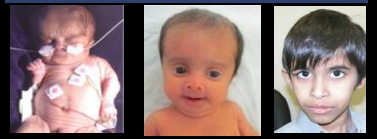
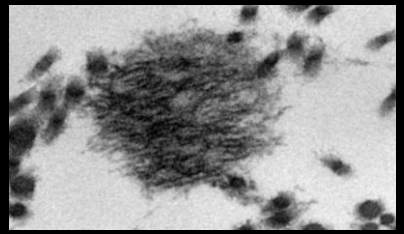
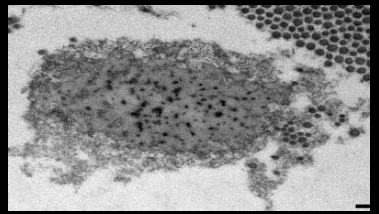
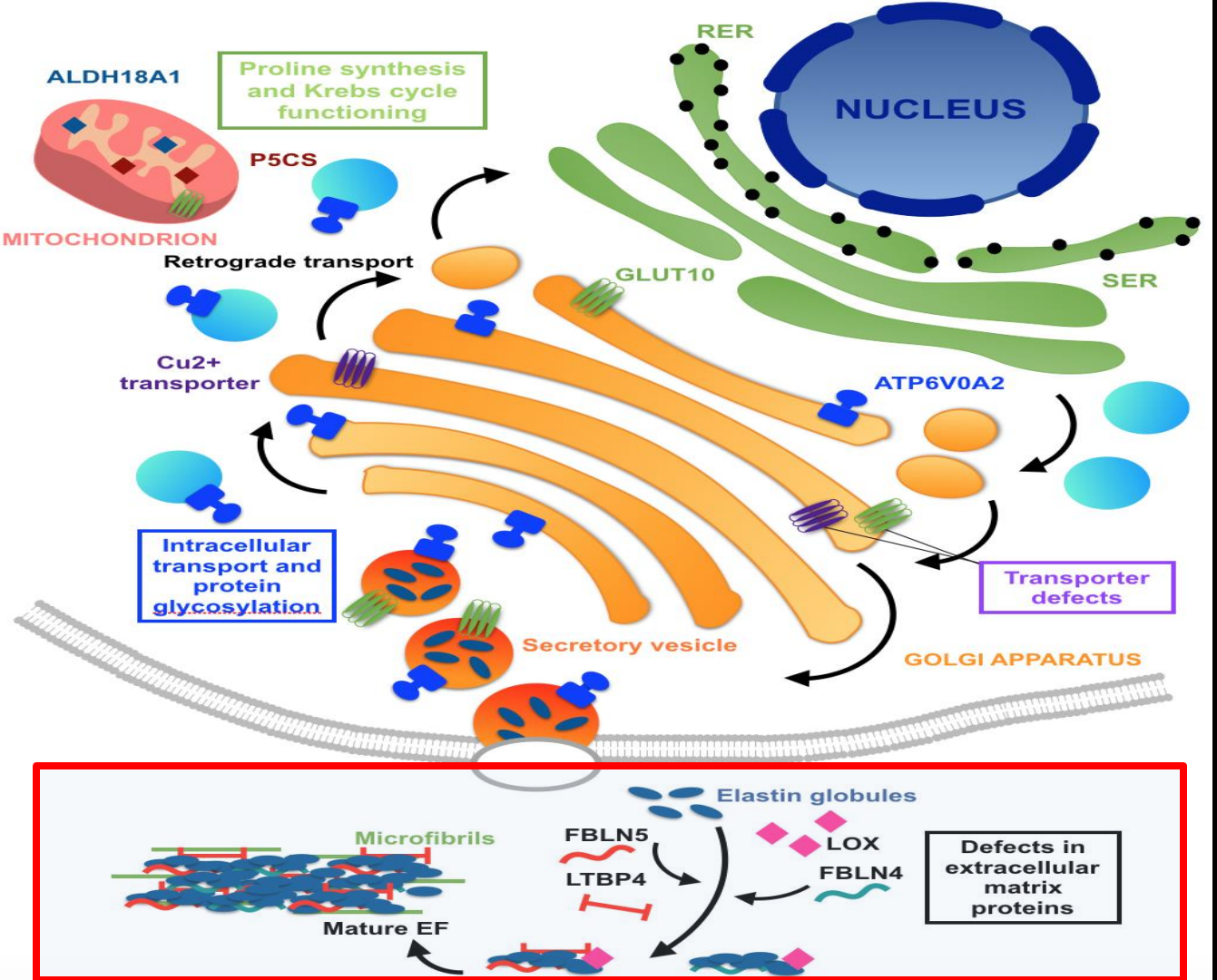





Correct classification 95% ~ Management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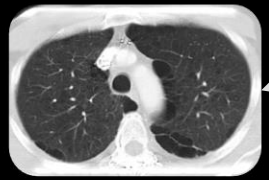
Pulmonary/arterial involvement

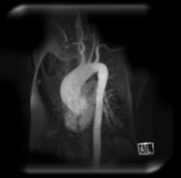


"Cutis laxa + Emphysema"

- *FBLN5* (type Ia)
- *LTBP4* (type Ic)

"Benign"

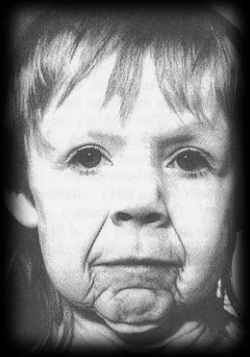
- *ELN* (ADCL t1)

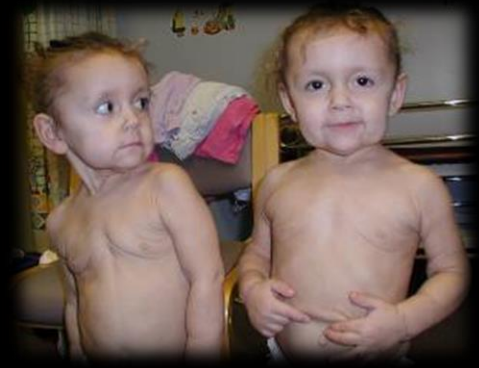


"Cutis laxa + Arterial tortuosity"

- *FBLN4* (type Ib)
- *SLC2A10:* Arterial tortuosity syndrome

Generalized cutis laxa – "benign" (ADCL tI)





BUT:

ARD ~ 55%

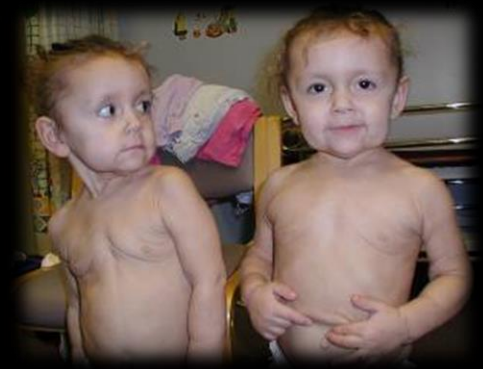
Emphysema ~ 35%

Callewaert et al, 2011

Hadj-Rabia, Callewaert et al, 2013

Pulmonary/arterial involvement

Generalized cutis laxa – "benign"



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      A   G   Q   F   P   L   G   G   V   A   A   R
WT:   GCC GGG CAG TTC CCA CTT GGA GGA GTG GCA GCA AGA
MT:   GCC GGG CAG TTC CCA CTT GGA GGA GTG GCA GCA AGA
      A   G   Q   F   P   L   G   G   V   A   A   R

      P   G   F   G   L   S   P   I   F   P   G   G
WT:   CCT GGC TTC GGA TTG TCT CCC ATT TTC CCA GGT GGG
MT:   CCT GGC TTC GGA TTG TCT CCC ATT TTC CZG GTG GGG
      P   G   F   G   L   S   P   I   F   Q   V   G

      A   C   L   G   K   A   C   G   R   K   R   K
WT:   GCC TGC CTG GGG AAA GCT TGT GGC CGG AAG AGA AAA
MT:   CCT GCC TGG GGA AAG CTT GTG GCC GGA AGA GAA AAT
      P   A   W   G   K   L   V   A   G   R   E   N

      *
WT:   TGA
MT:   GAg ctt cct agg acc cct gac tca cga cct cat caa
      D   L   P   R   T   P   D   S   R   P   H   Q

MT:   cgt tgg tgc tac tgc ttg gtg gag aat gta aac cct
      R   W   C   Y   C   L   V   E   N   V   N   P

MT:   ttg taa
      L   *
```

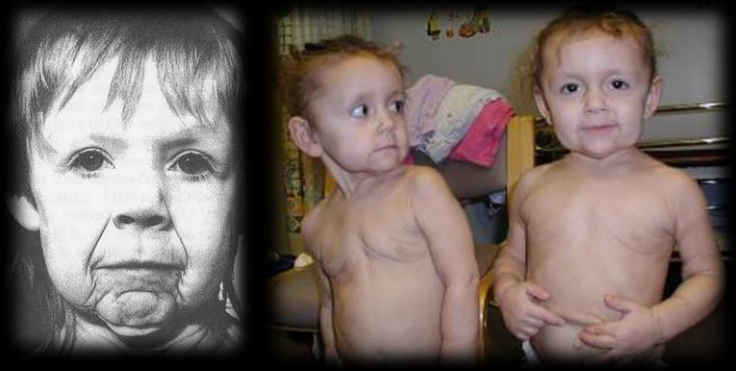
C-terminal frameshift mutations in *ELN*

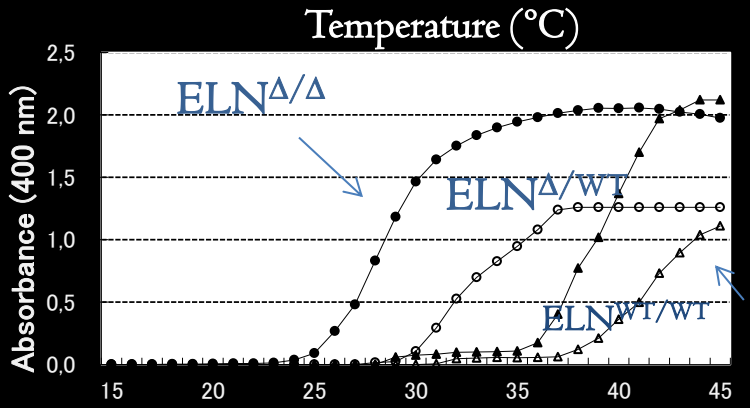
→ elongated protein

→ C-terminal missense sequence.

Callewaert et al, 2011

Generalized cutis laxa – "benign"





C-terminal frameshift mutations in *ELN*
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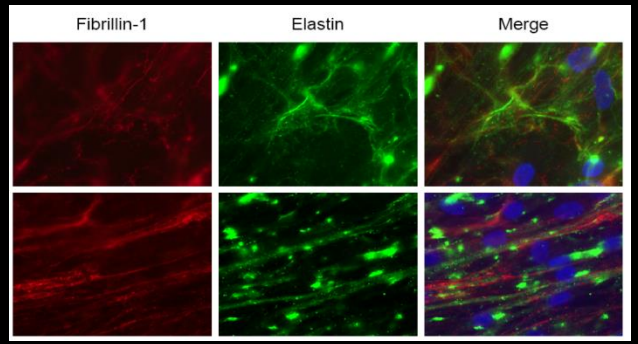
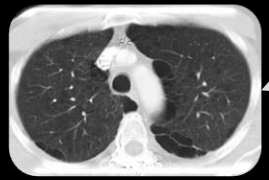


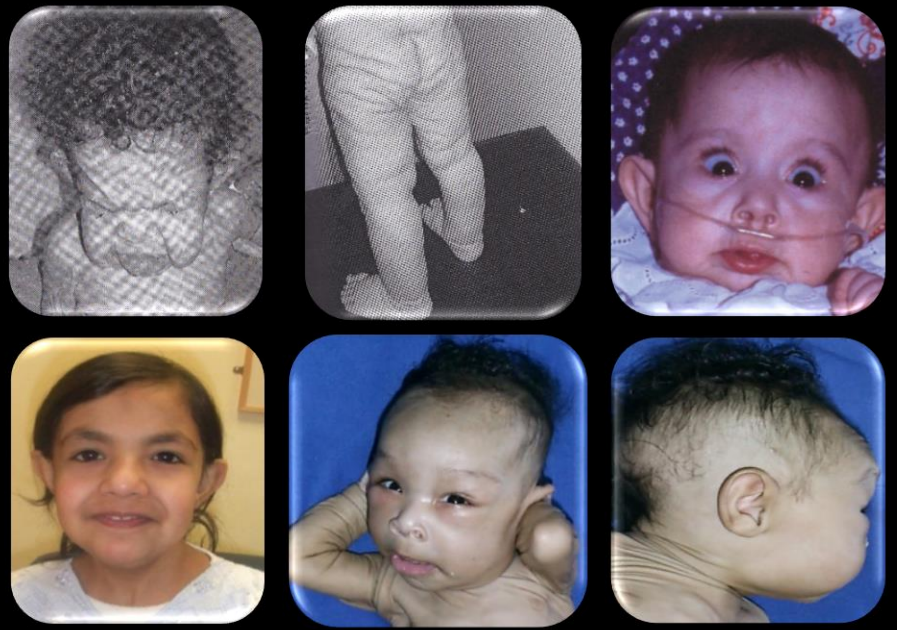
Callewaert et al, 2011

Pulmonary/arterial involvement



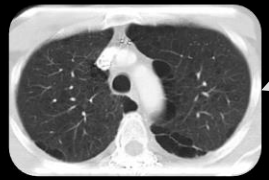
"Cutis laxa + Emphysema"

- *FBLN5* (type Ia)
- *LTBP4* (type Ic): URDS



Callewaert et al, 2013
Loeys et al, 2006

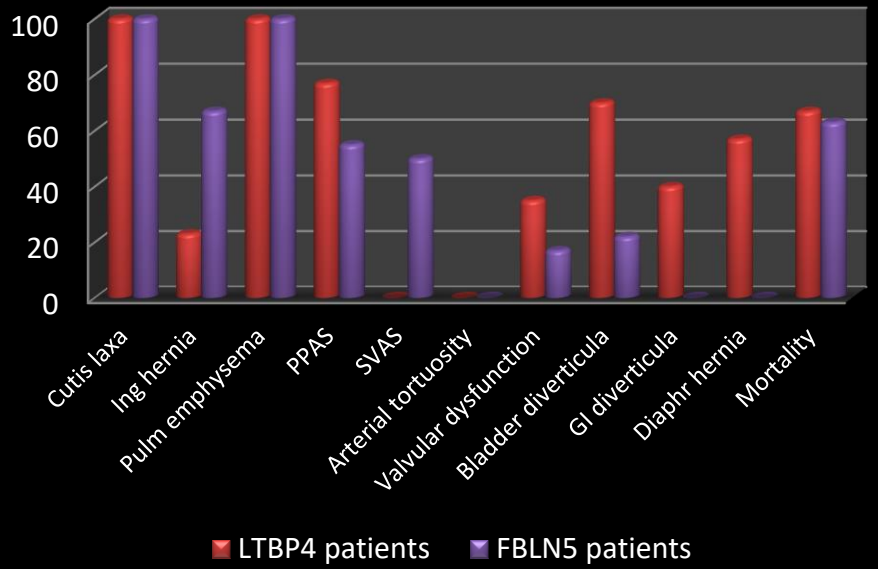
Pulmonary/arterial involvement



"Cutis laxa + Emphysema"

- *FBLN5* (type Ia)
- *LTBP4* (type Ic): URDS

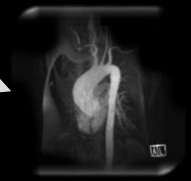
GI / GU diverticula

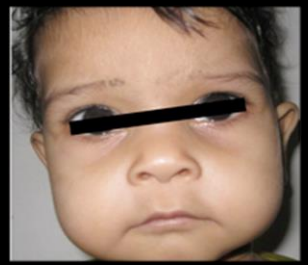


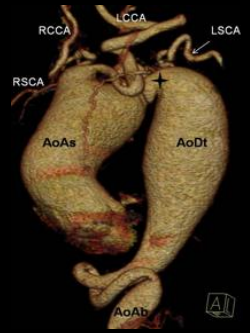
Callewaert et al, 2013

Pulmonary/arterial involvement

Callewaert et al, 2008
Renard, Callewaert, et al, 2011
Kappanayil et al, 2012







"Cutis laxa + Arterial tortuosity"

- *FBLN4* (type Ib)
- *SLC2A10:* Arterial tortuosity syndrome

Pulmonary/arterial involvement

Callewaert et al, 2008
Renard, Callewaert, et al, 2011
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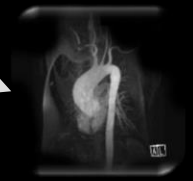
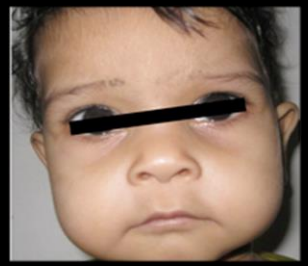
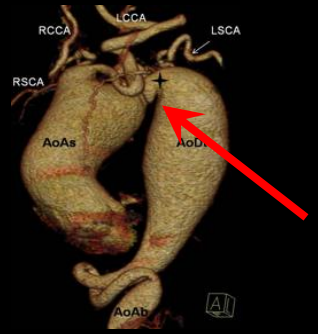




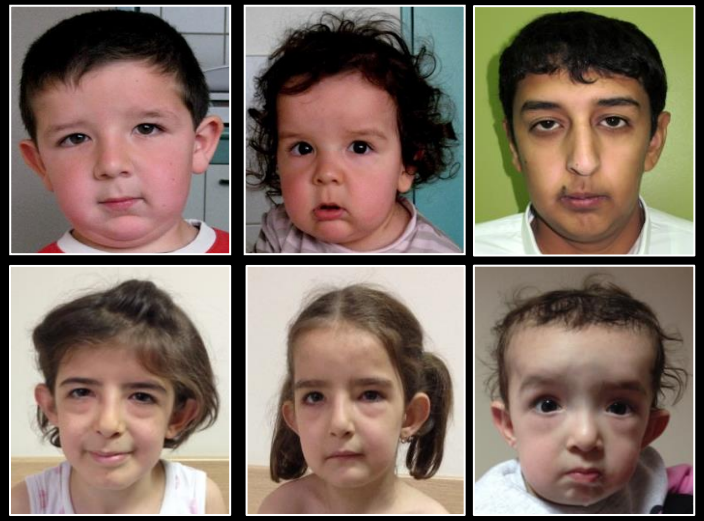


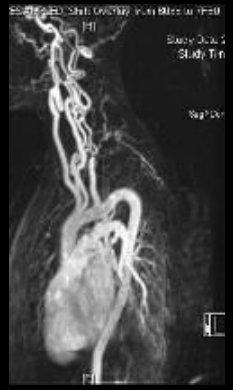
"Cutis laxa + Arterial tortuosity"

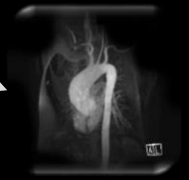
- *FBLN4* (type Ib)
  - *Tortuosity, coA (isthmus)*
  - *Aneurysms*
  - *Osteopenia*
  - *Marfanoid skeletal features*

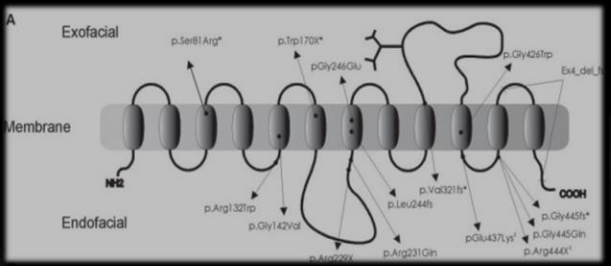
Pulmonary/arterial involvement

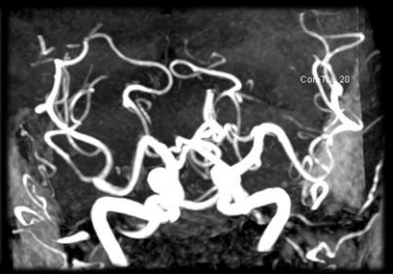
Callewaert et al, 2008
Beyens et al, 2018







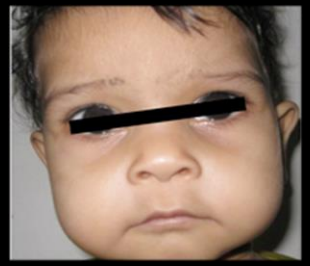


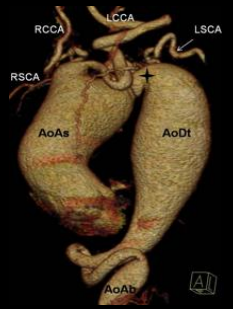


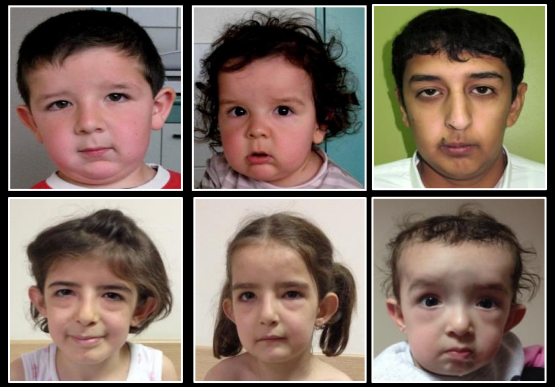
“Cutis laxa + Arterial tortuosity”

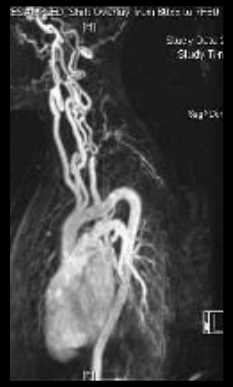
- *SLC2A10:* Arterial tortuosity syndrome
  - No dissections, but ischemic complications (CNS, kidney, bowel)
  - Diaphragmatic hernia
  - IRDS
  - Corneal thinning

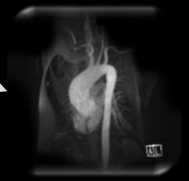
Pulmonary/arterial involvement











"Cutis laxa + Arterial tortuosity"

FBLN4

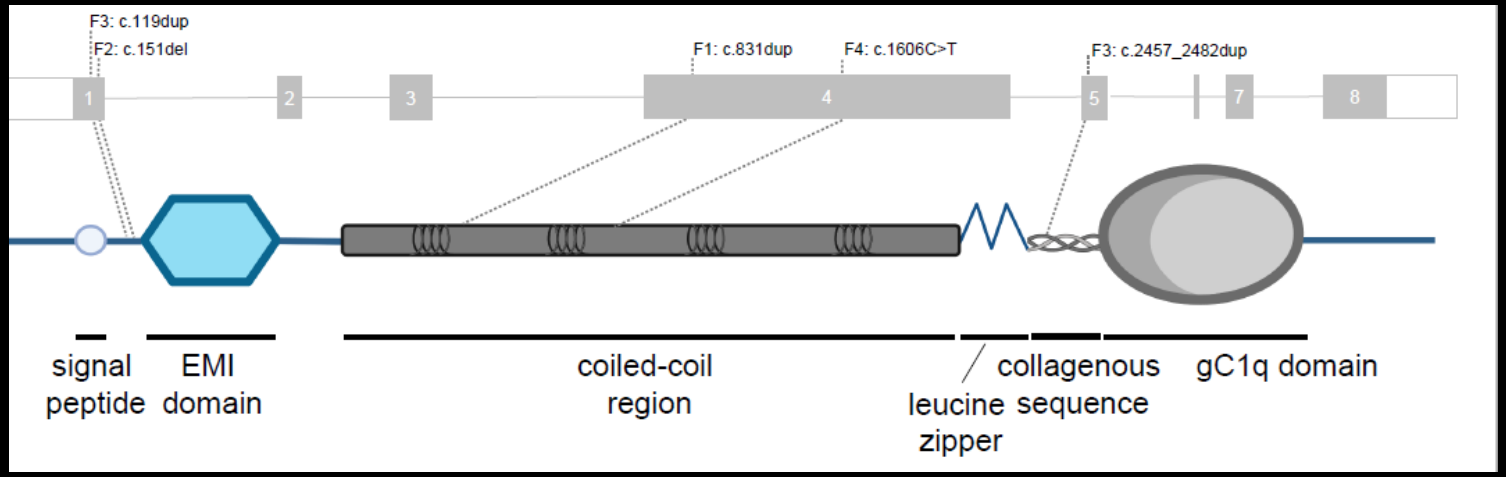
Prevalence

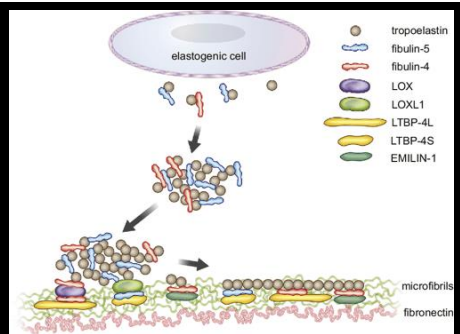
Aneuryms/dissections
Cardioresp. failure

SLC2A10

Novel entity: *EMILIN1* loss-of-function mutations

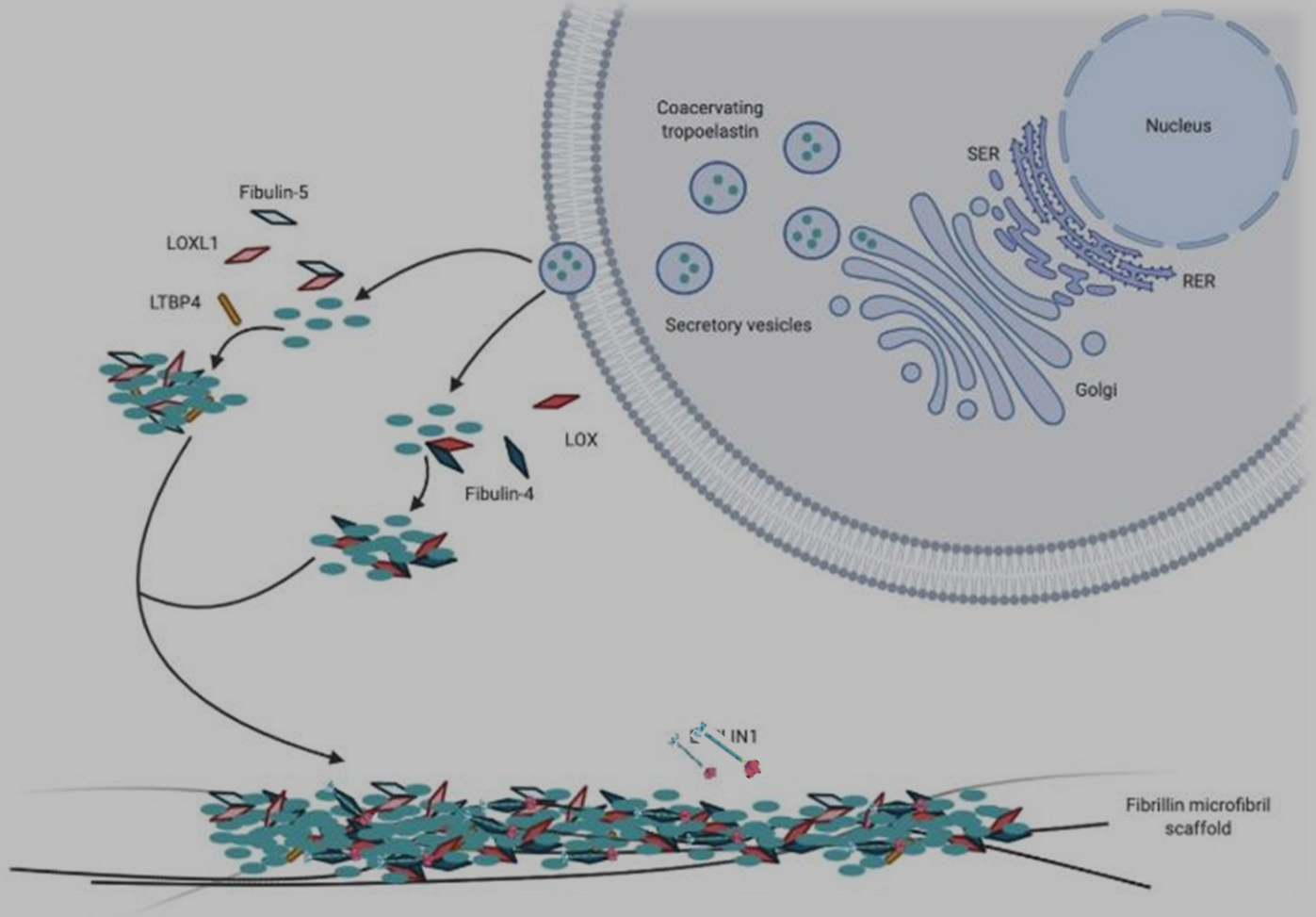
Unexplained **arterial tortuosity** and **fractures** ~ **resembling *FBLN4* related CL**





Adamo et al, 2022

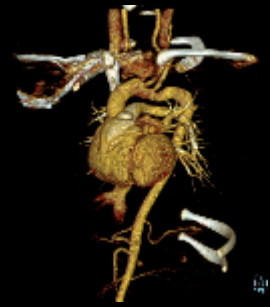
Role in extracellular matrix functioning

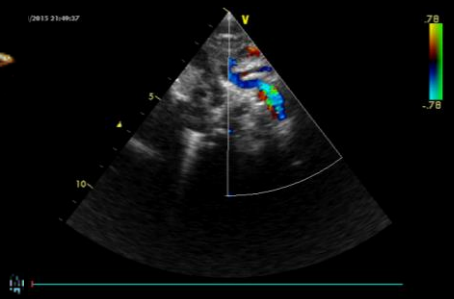


Schiavinato et al., 2016
Schiavinato et al., 2017

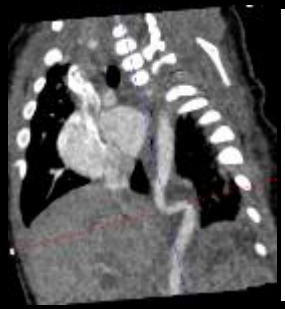
Cardiovascular imaging

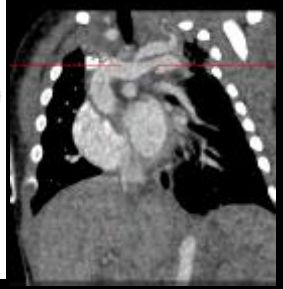
Family 1



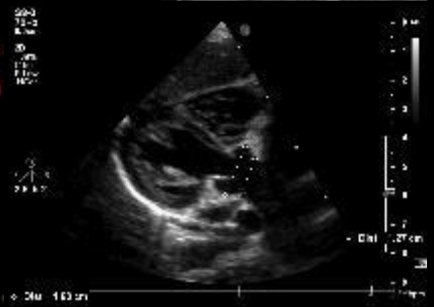


Family 2





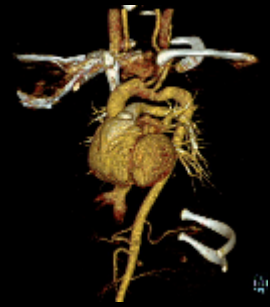
Family 3

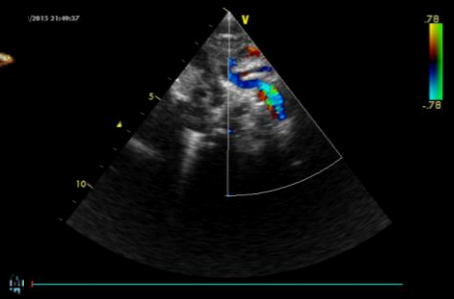


Tortuosity	4/4
ARD	2/4
Stenoses	1/4
Abnormal implantation of aortic branches	2/4

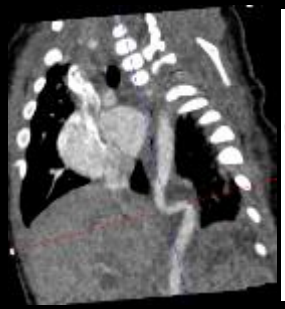
Cardiovascular imaging

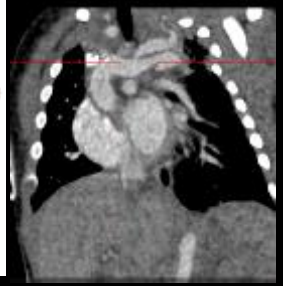
Family 1



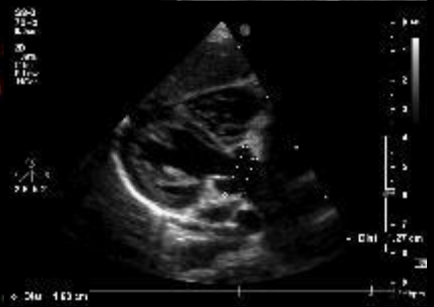


Family 2



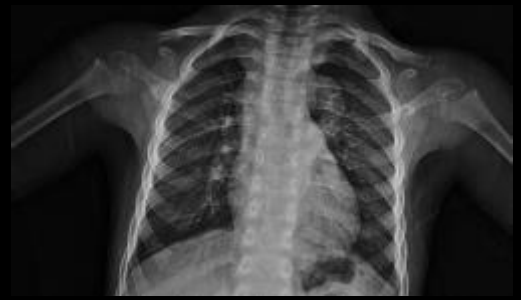


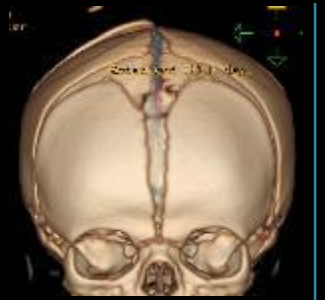
Family 3



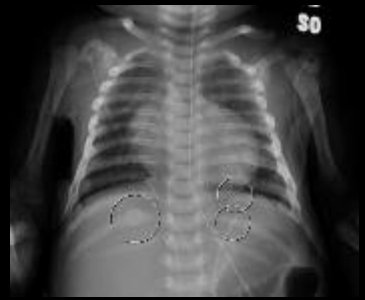
Skeletal imaging

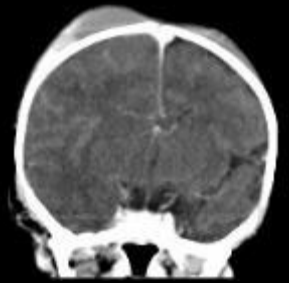
Family 1





Family 2

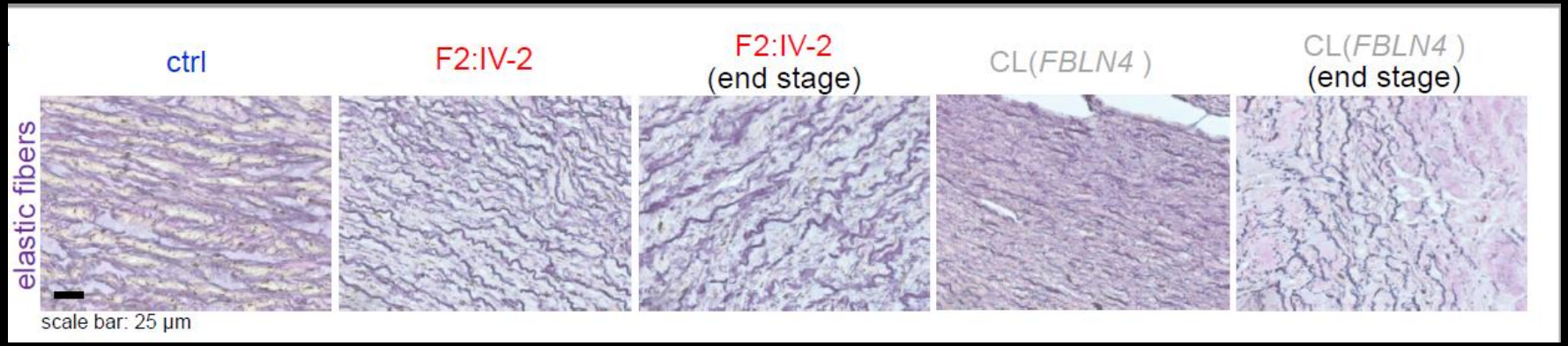




Family 3

Fractures	3/4
>> neonatal	
parietal	
ribs	
limbs	

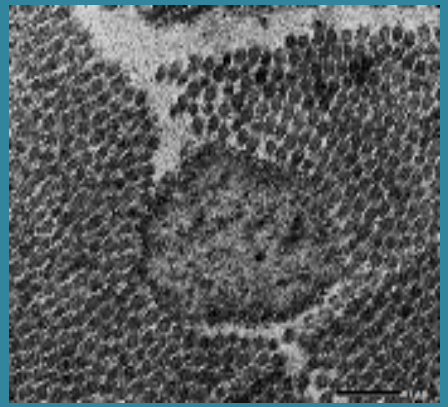
Histological analysis of *EMILIN1* deficient aortic tissue



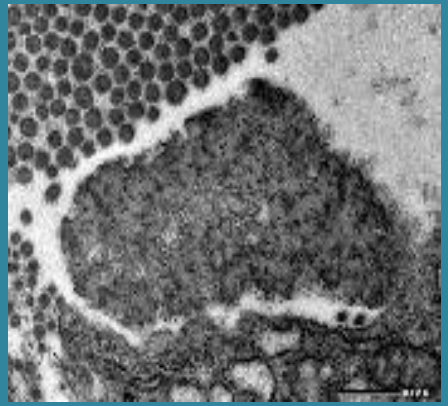
Aortic tissue of *EMILIN1* or *FBLN4* deficient individuals shows severe medial degenerative changes

Ultrastructural evaluation of *EMILIN1* or *FBLN4 deficient* human skin

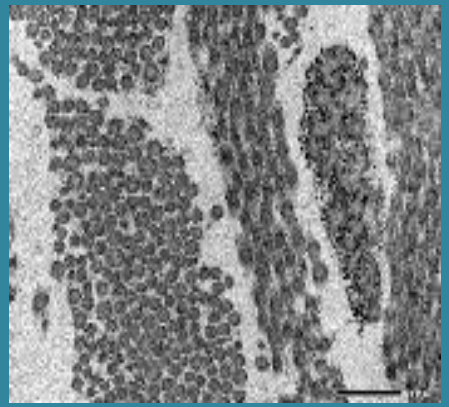
Control



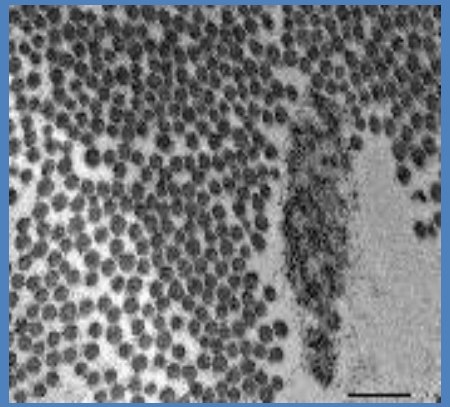
F3:II-1



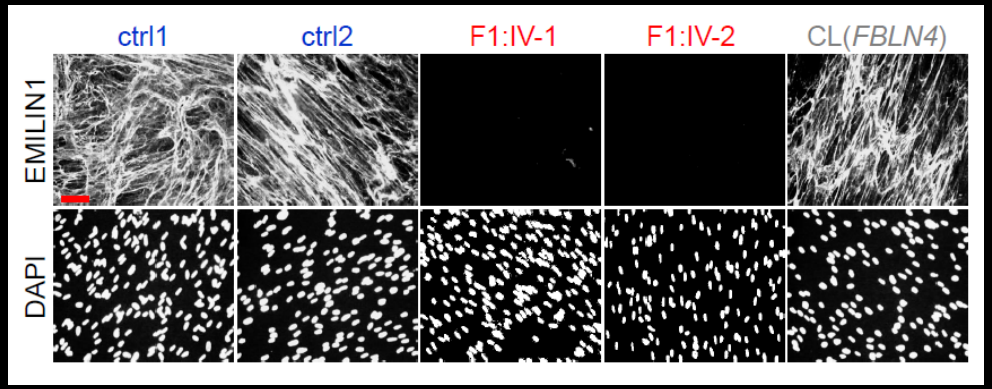
F1:II-1

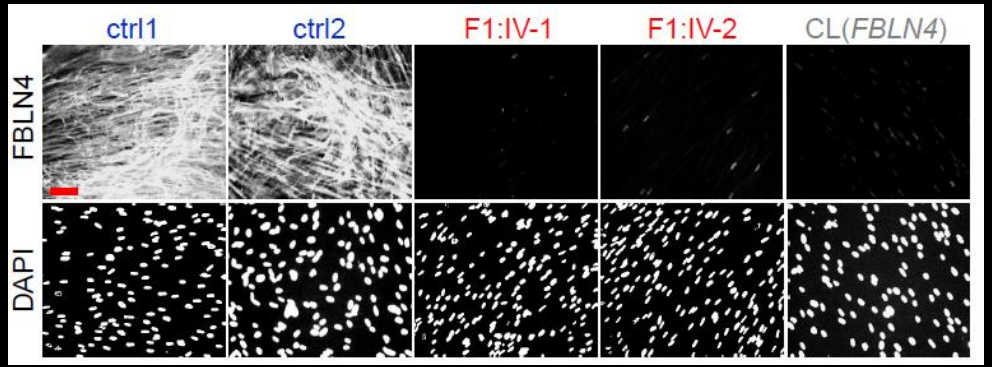


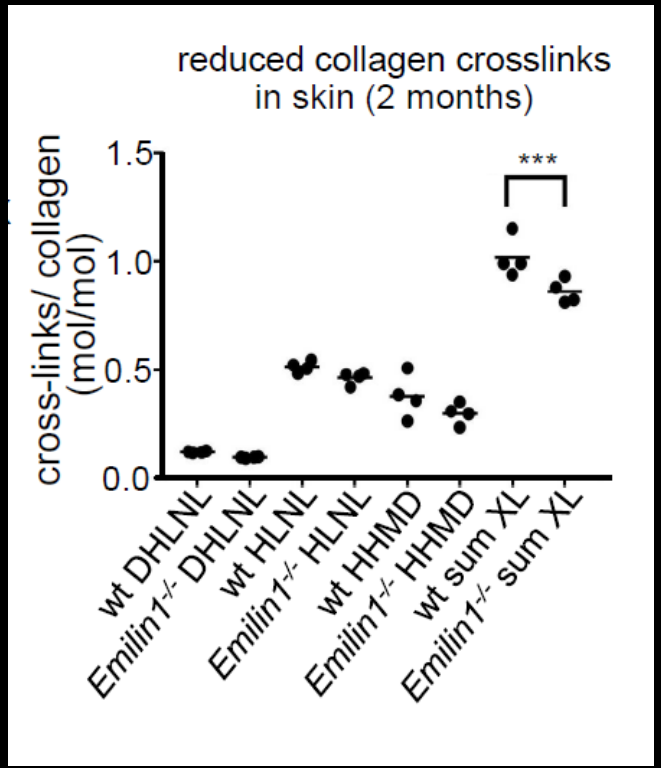
FBLN4



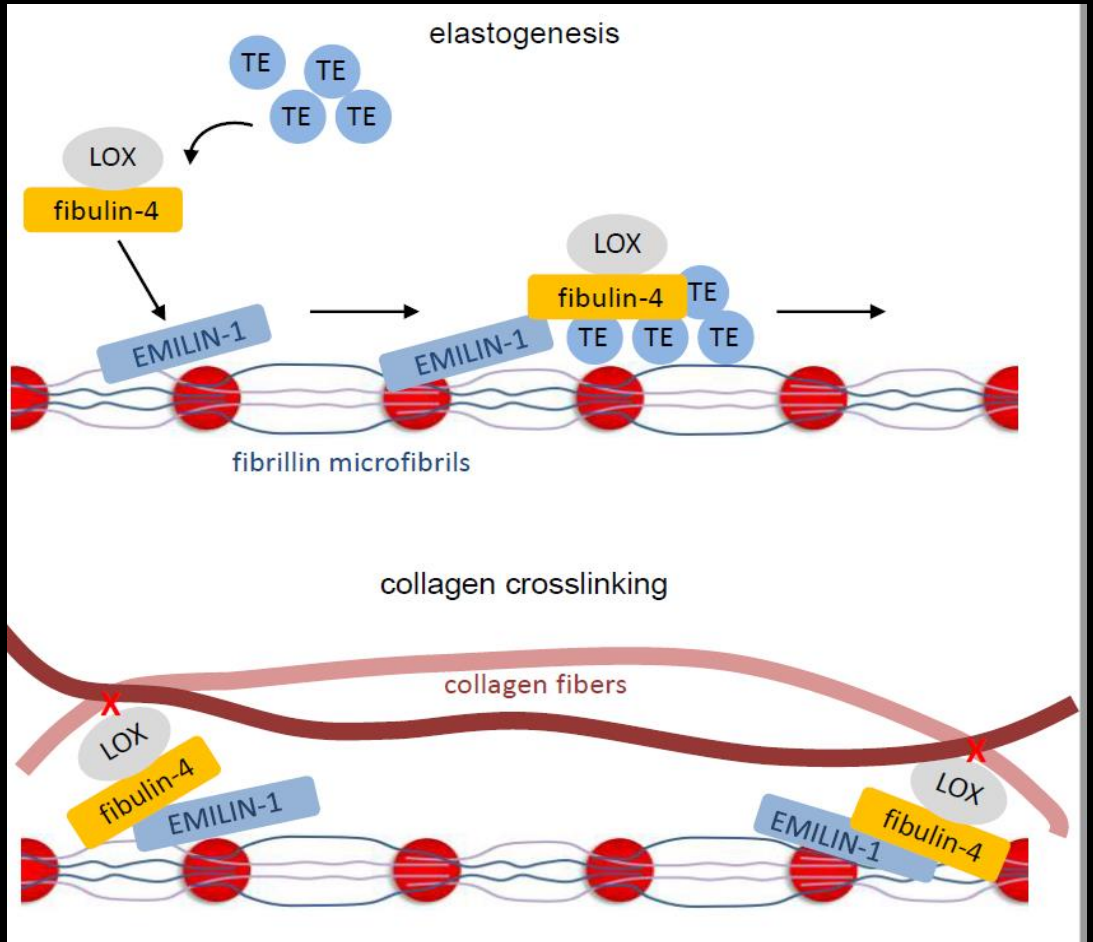
Defective EF assembly in *Emilin1* deficient human fibroblasts





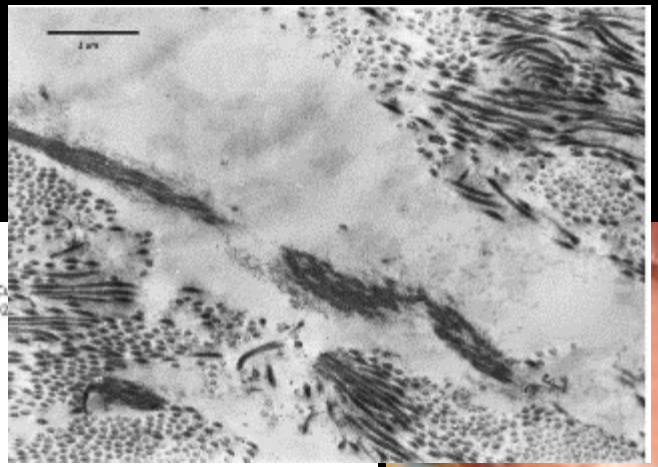


EMILIN1 function: Summary

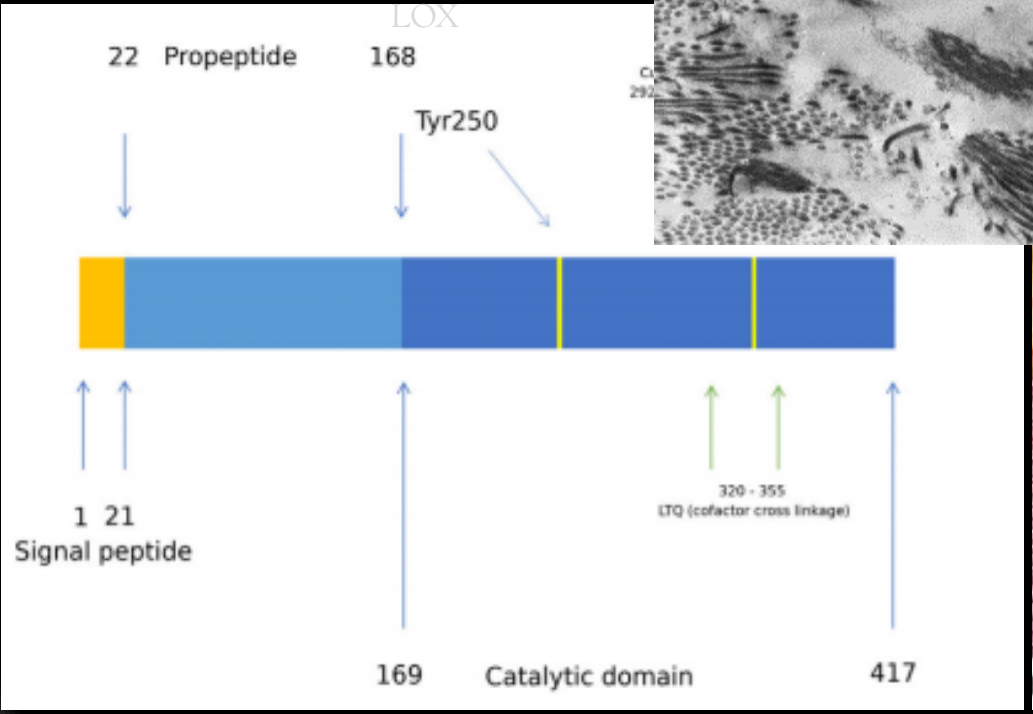


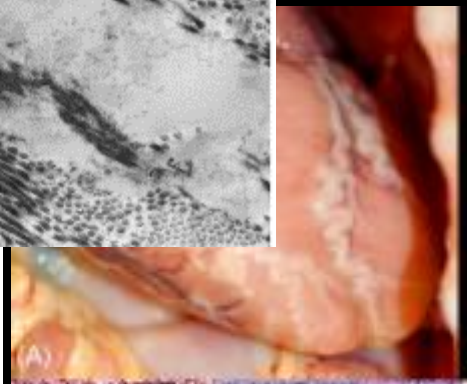
LOX is 'key' in arterial tortuosity syndromes: direct evidence

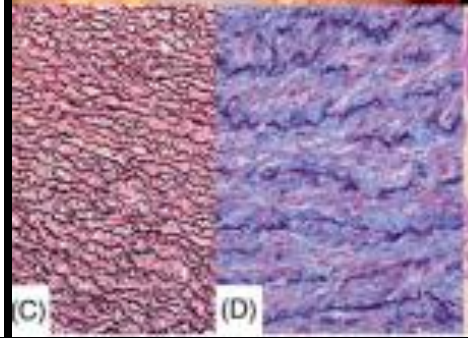
Cutis laxa
Arterial tortuosity
Osteopenia / fractures

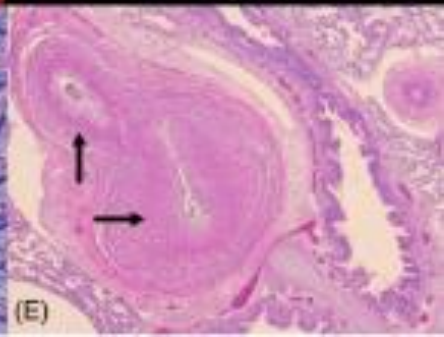


McKenzie et al, 2021

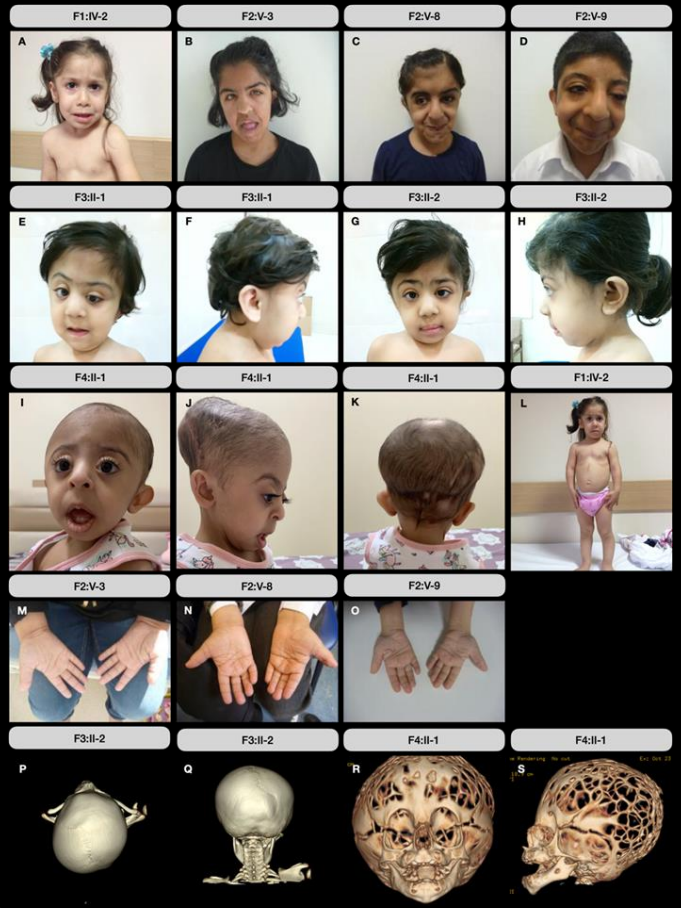








LTBP1-related Cutis laxa: short stature - craniosynostosis



Pottie et al, 2021

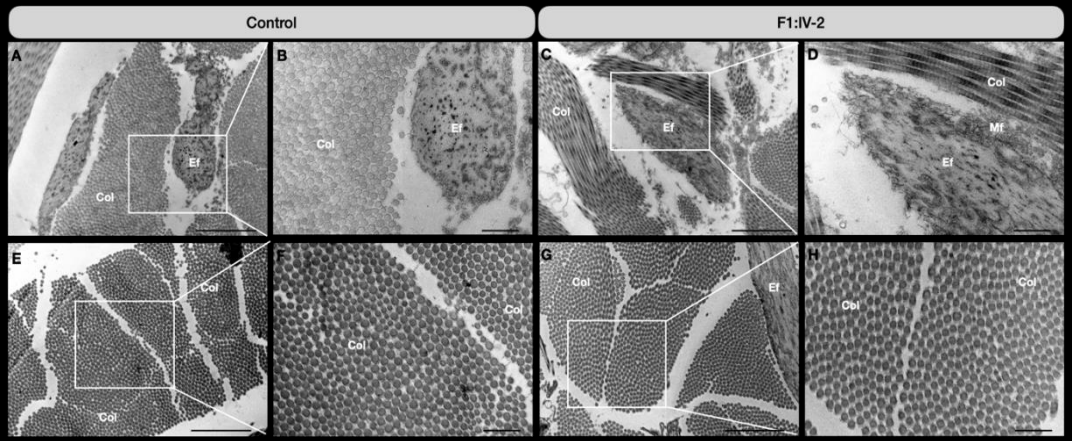
Cutis laxa

Dysmorphisms

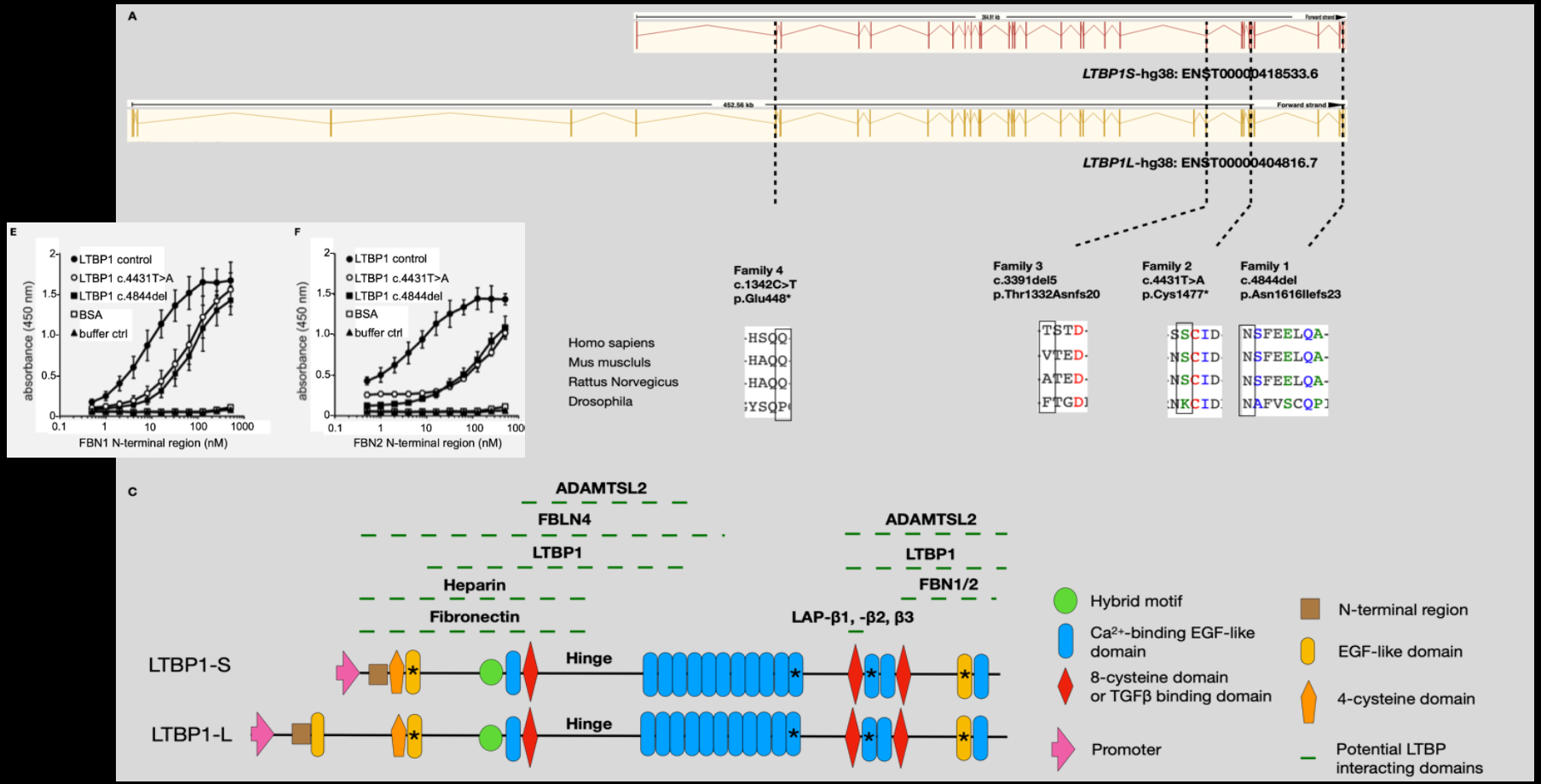
Skeletal patterning

- Craniosynostosis
- Brachydactyly
- Short stature

Variable heart defects

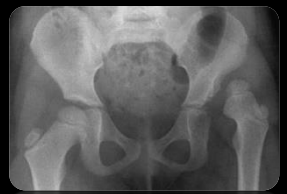
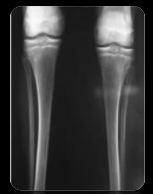
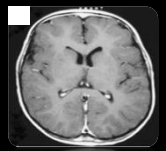


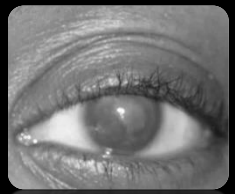
LTBP1-related Cutis laxa: short stature - craniosynostosis



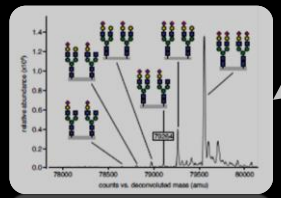
CL with skeletal/neurological involvement

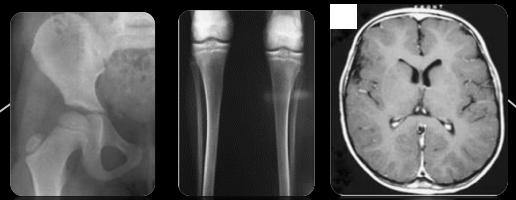
ARCL type 2a/b
ARCL type 3a/b
Wrinkly skin syndrome
Debré type cutis laxa
Neurocutaneous disorder
De Barsy syndrome

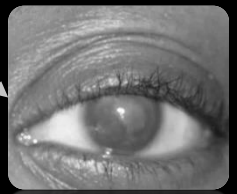






CL with skeletal/neurological involvement







No ocular involvement

No IUGR

Abnormal glycosylation

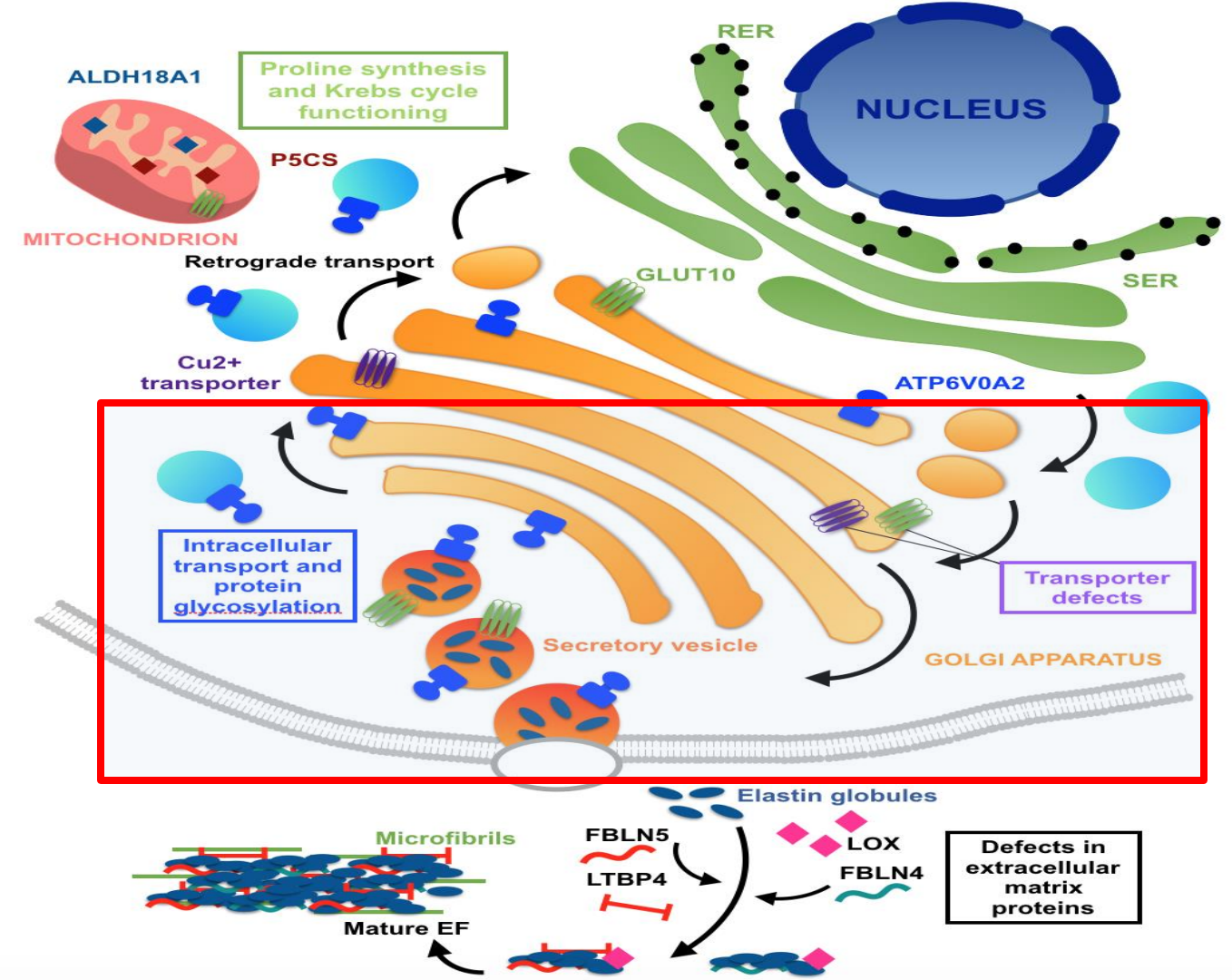
- *ATP6V0A2* (type IIa)
- *ATP6V1E1 / ATP6V1A*

Corneal clouding/Cataract

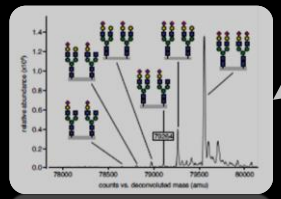
IUGR

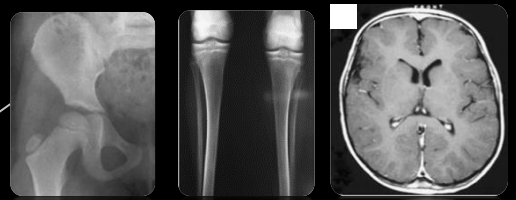
Normal glycosylation patterns

- *PYCR1* (ARCL type IIb / IIIb)
- *ALDH18A1 (Progeroid dominant, ARCL IIIa)*


ALDH18A1
Proline synthesis and Krebs cycle functioning
P5CS
MITOCHONDRION
RER
NUCLEUS
SER
Retrograde transport
GLUT10
Cu2+ transporter
ATP6V0A2
Intracellular transport and protein glycosylation
Transporter defects
Secretory vesicle
GOLGI APPARATUS
Elastin globules
Microfibrils
FBLN5
LTBP4
LOX
FBLN4
Defects in extracellular matrix proteins
Mature EF

CL with skeletal/neurological involvement





Al-Gazali 2001
Rajab 2008
Hucthagowder et al, 2009
Beyens, …, Callewaert, 2018

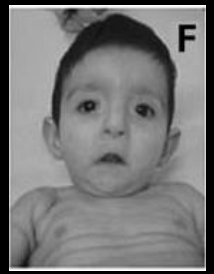
No ocular involvement, no IUGR

Abnormal glycosylation

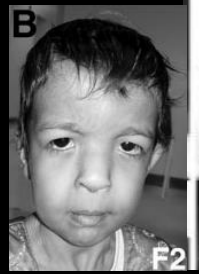
(microcephaly, Cobblestone brain, late closing fontanelles)

- *ATP6V0A2* (type IIa)
- *ATP6V1E1 / ATP6V1A*

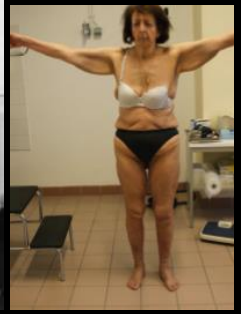
Van Damme T, … Callewaert B, Wevers R, 2017



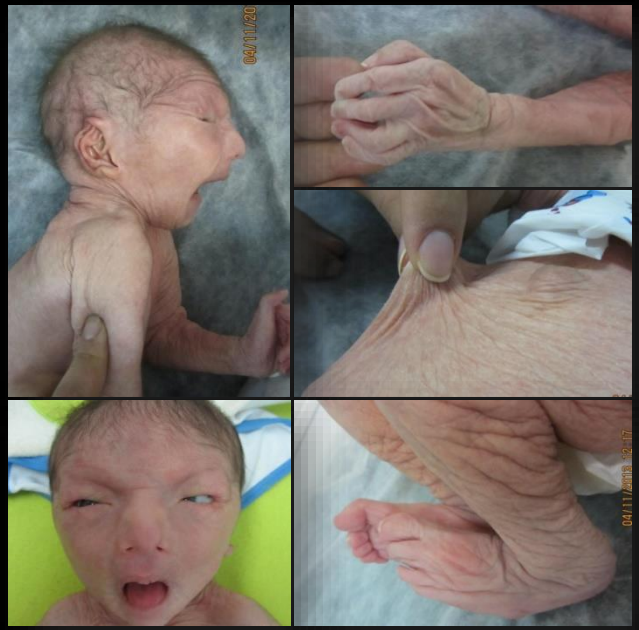
ARCL t2 (Debré)

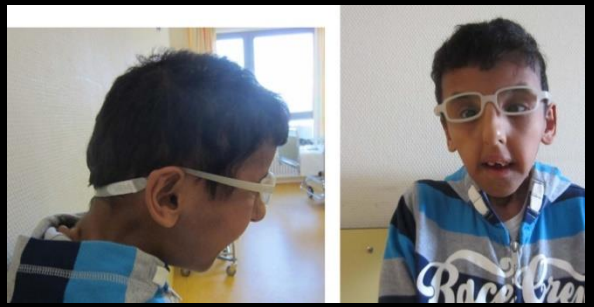


Wrinkly skin syndrome



CL with skeletal/neurological involvement: a novel ATPase defect

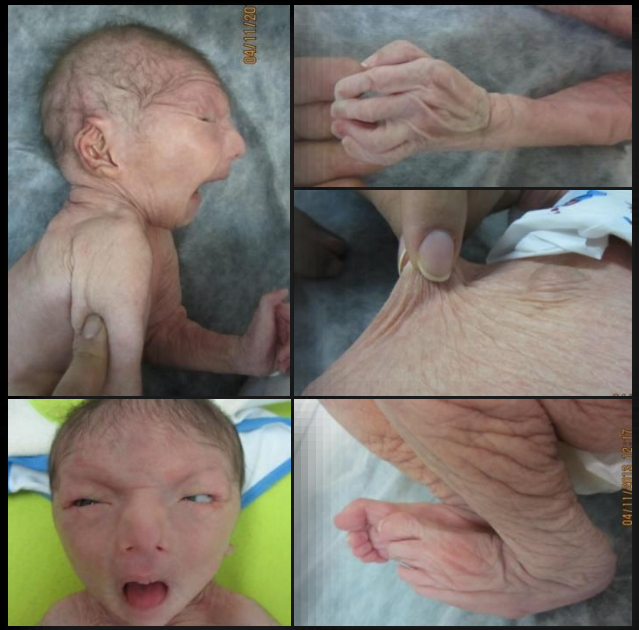


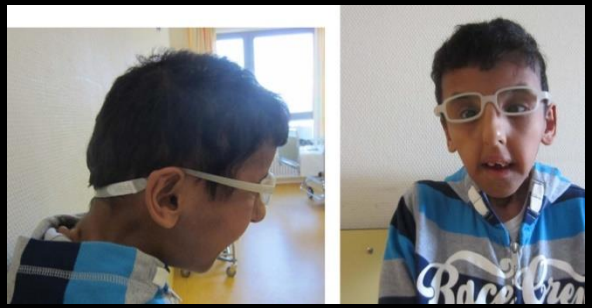


Contractures, Hip dysplasia
Marfanoid - Pneumothorax
Aortic root dilatation
Cardiac hypertrophy
Variable NMD/gyral abno

Van Damme et al, 2017

CL with skeletal/neurological involvement: a novel ATPase defect





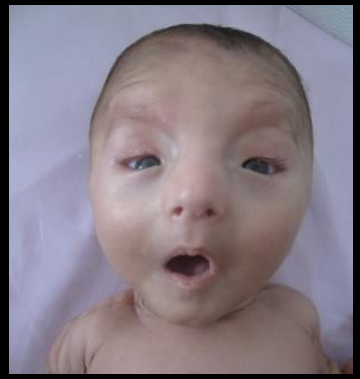
ATP6V1E1

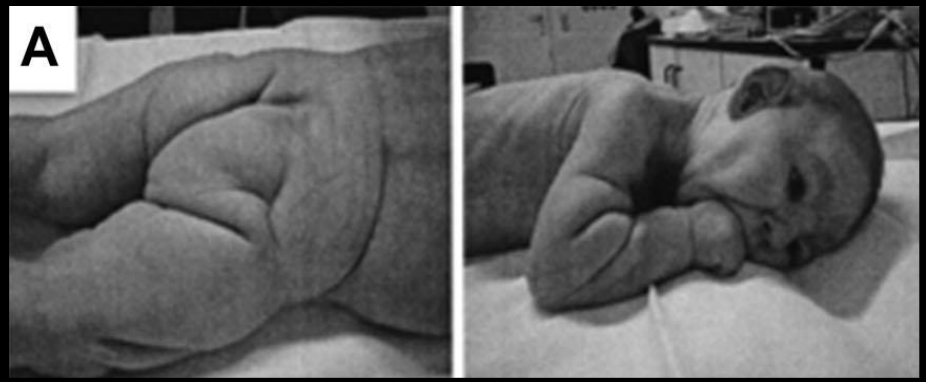
c.383T>C
p.(Leu128Pro)

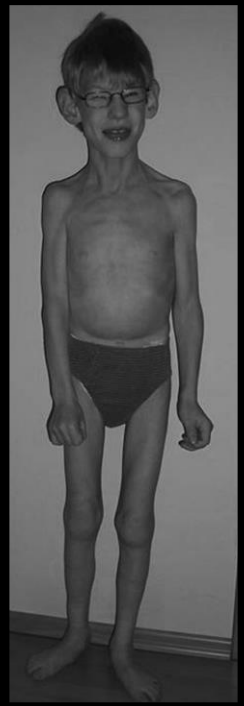
ATP6V1E1

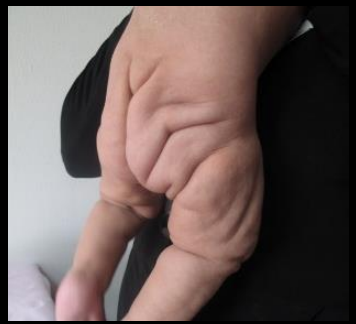
c.634C>T
p.(Arg212Trp)

CL with skeletal/neurological involvement: a novel ATPase defect



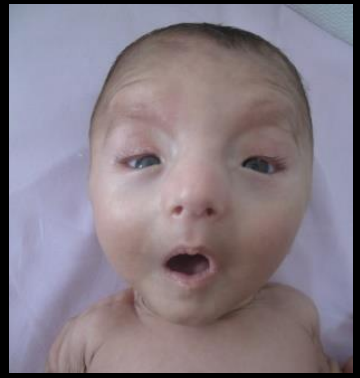


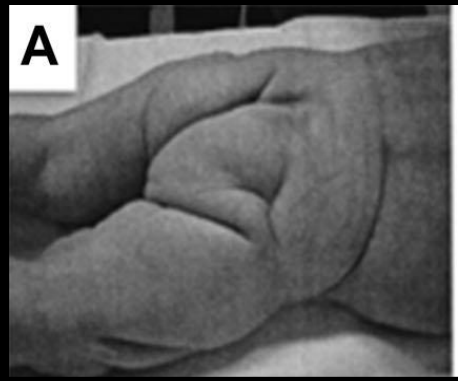


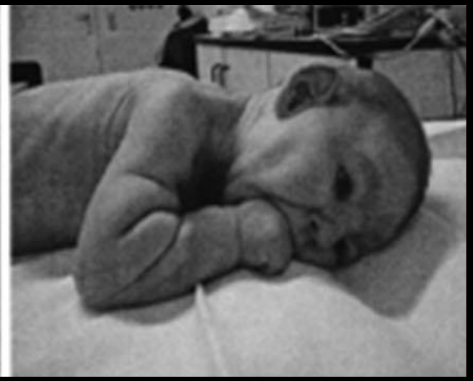


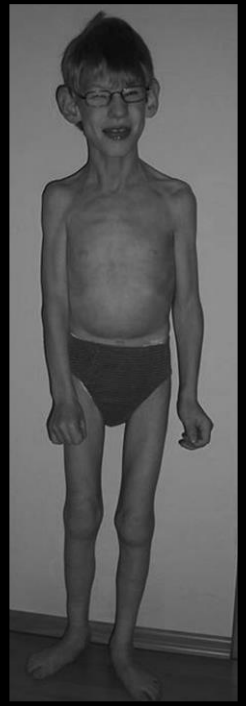
Marfanoid, ARD, tortuous aortic arch, VSD
Thin corpus callosum
Polymicrogyria, Sept. Pellucidum defect, Ventriculomegaly, White matter gliosis
Delayed NMD

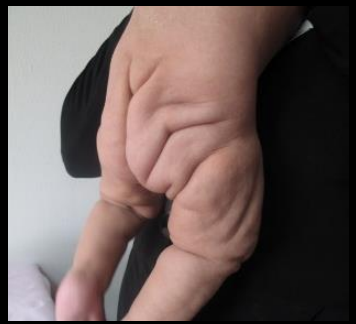
CL with skeletal/neurological involvement: a novel ATPase defect







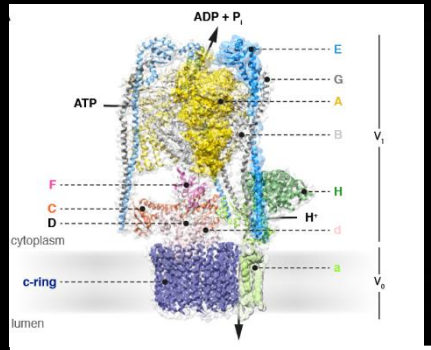


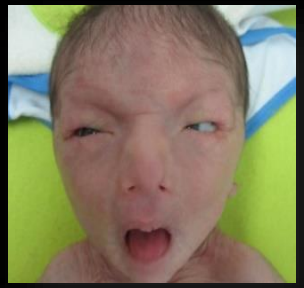


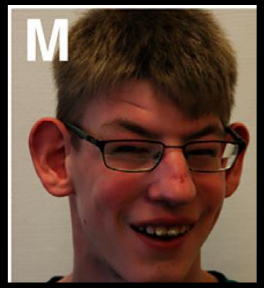
ATP6V1A
c.215G>A
p.Gly72Asp

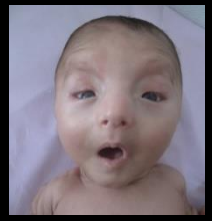
ATP6V1A
c.2012C>T
p.Gly72Asp

ATP6V1A
c.215G>A
p.Arg338Cys









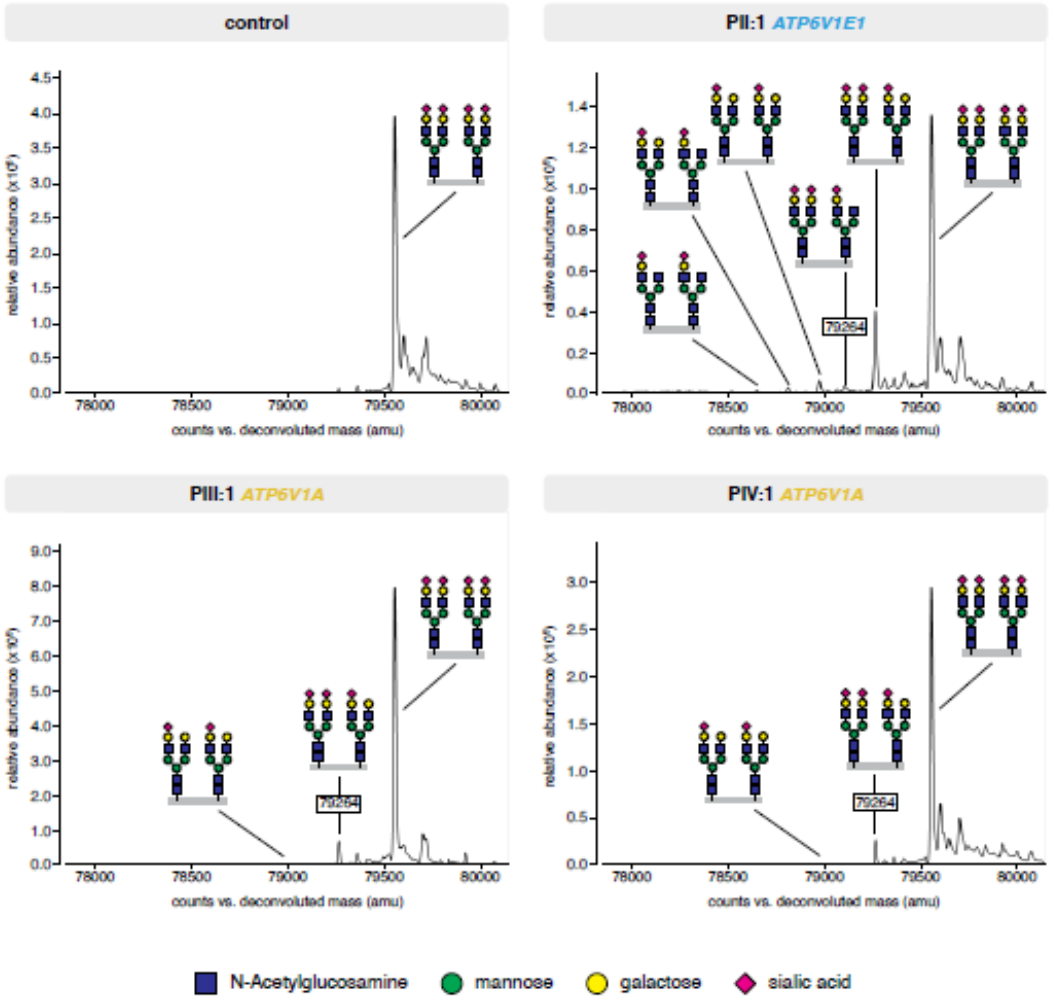
ATP6V1E1

ATP6V1A

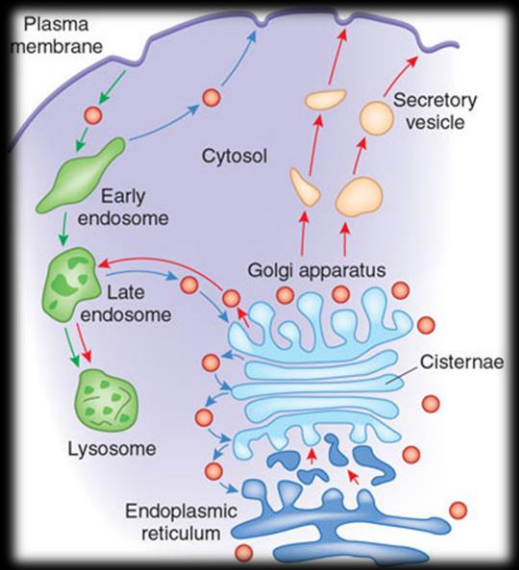
	Family I c.383T>C p.Leu128Pro	Family II c.634C>T p.Arg212Trp	Family III c.1012C>T p. Arg338Cys	Family IV & V c.215G>A p.Gly72Asp
Homo sapiens	GLVLQGLYQL **L** EPRMIVRCRK	LIAQQMMPEV **R** GALFGANANR	YTGITLSEYF **R** DMGYHVSMMA	ATIQVYEETS **G** VSVGDPVLRT
Macaca mulatta	GLVLQGLYQL **L** EPRMIVRCRK	LIAQQMMPEV **R** GALFGANANR	YTGITLSEYF **R** DMGYHVSMMA	ATIQVYEETS **G** VSVGDPVLRT
Pan troglodytes	GLVLQGLYQL **L** EPRMIVRCRK	LIAQQMMPEV **R** GALFGANANR	YTGITLSEYF **R** DMGYHVSMMA	ATIQVYEETS **G** VSVGDPVLRT
Canis familiaris	GLVLQGLYQL **L** EPRMIVRCRK	LIAQQMMPEV **R** GALFGANANR	YTGITLSEYF **R** DMGYHVSMMA	ATIQVYEETS **G** VSVGDPVLRT
Rattus norvegicus	GLVLQGLYQL **L** EPRMIVRCRK	LIAQQMMPEV **R** GALFGANANR	YTGITLSEYF **R** DMGYHVSMMA	ATIQVYEETS **G** VSVGDPVLRT
Mus musculus	GLVLQGLYQL **L** EPRMIVRCRK	LIAQQMMPEV **R** GALFGANANR	YTGITLSEYF **R** DMGYHVSMMA	ATIQVYEETS **G** VSVGDPVLRT
Xenopus tropicalis	GLILQGLFQL **L** EPRVLIRCRK	LIAQQMMPEI **R** VALFGANTNR	YTGITLSEYF **R** DMGYHVSMMA	ATIQVYEETS **G** VCVGDPVLRT
Danio rerio a	GLVLQGFYQL **L** EPRVIIRCRK	LLAQQMMPDI **R** VSLFGANPNR	YTGITLSEYF **R** DMGYNVSMMA	ATIQVYEETS **G** VCVGDPVLRT
Danio rerio b	GLVLQGFYQL **L** EPKVTIRCRK	LIAQQMMPEI **R** VALFGANQNR	YTGITLSEYF **R** DMGYNVSMMA	ATIQVYEETS **G** VSVGDPVLRT
Caenorhabditis elegans	GLVMQGLLQL **L** EKEVVLRCRE	LIANQIVPQV **R** TALFGPNPNR	YTGITLAEYF **R** DMGLNVAMMA	ATIQVYEETS **G** VTIGDPVLRT
Drosophila melanogaster 1	GLIVQGLFQL **M** EPKVILRCRE	LISQQLVPEI **R** NALFGRNVNR	YTGITLSEYF **R** DMGYNVAMMA	ATIQVYEETS **G** VTVGDPVLRT

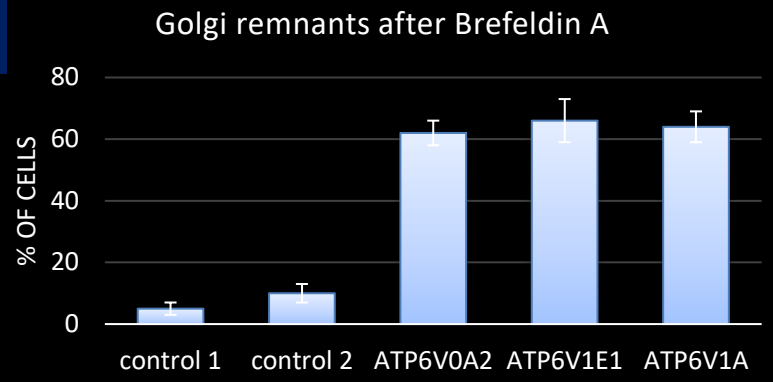
V-ATPase defects cause a CDG type 2

Transferrin isoelectrofocusing

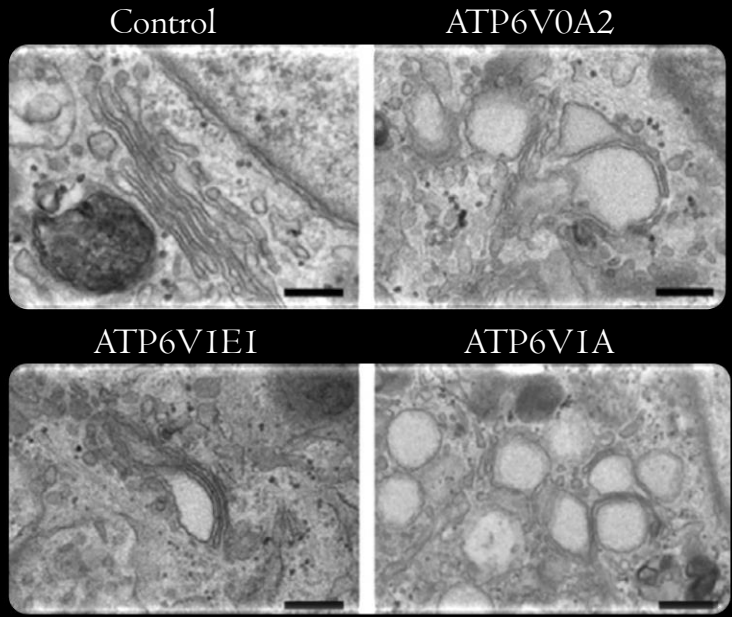


V-ATPase defects affect vesicular trafficking

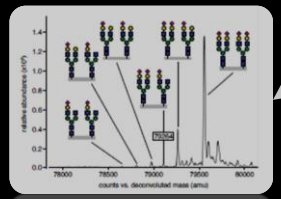


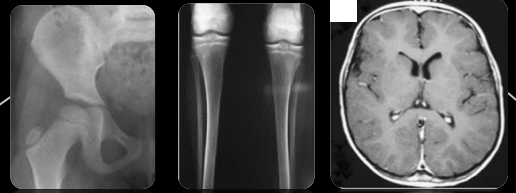


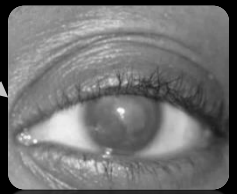
Knockout model
Pottie et al, 2022



CL with skeletal/neurological involvement







No ocular involvement

No IUGR

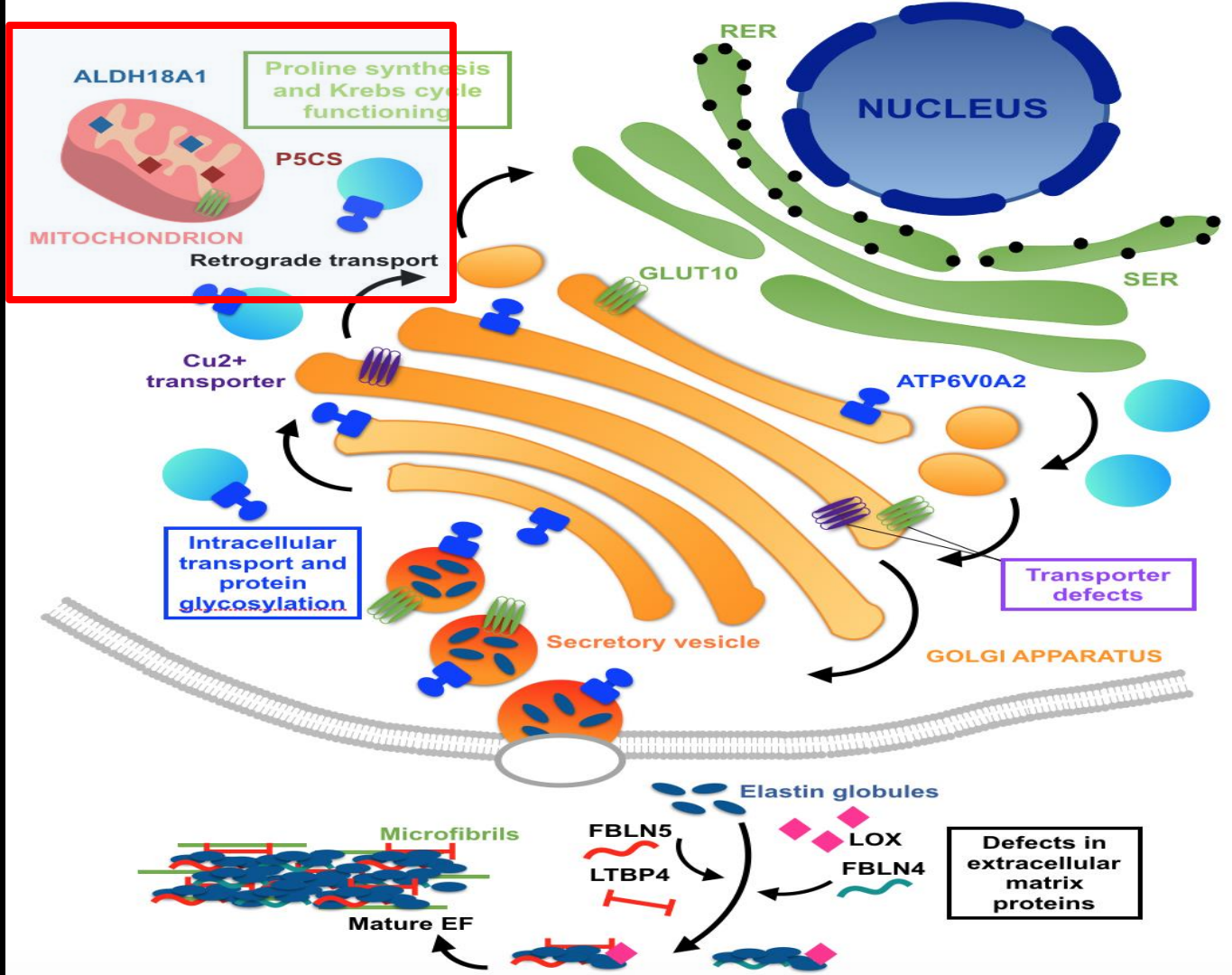
Abnormal glycosylation

- *ATP6V0A2* (type IIa)
- *ATP6V1E1 / ATP6V1A*

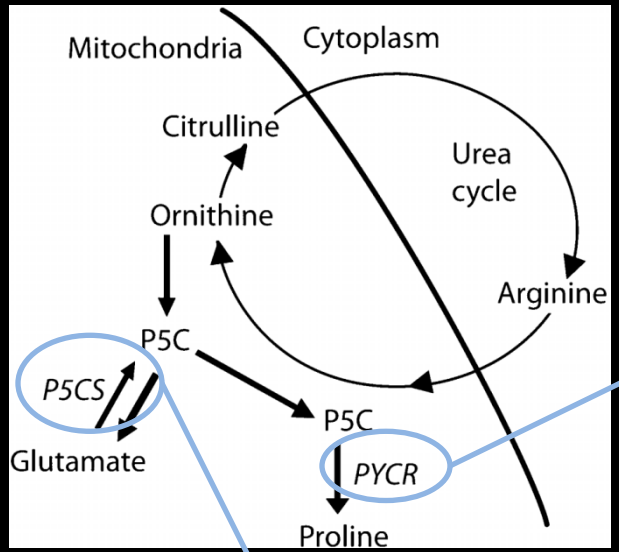
Ocular involvement / IUGR

Normal glycosylation patterns

- *PYCR1* (ARCL type IIb / IIIb)
- *ALDH18A1 (Progeroid dominant, ARCL IIIa)*


ALDH18A1
Proline synthesis and Krebs cycle functioning
P5CS
MITOCHONDRION
Retrograde transport
RER
NUCLEUS
SER
GLUT10
Cu2+ transporter
ATP6V0A2
Intracellular transport and protein glycosylation
Transporter defects
Secretory vesicle
GOLGI APPARATUS
Elastin globules
Microfibrils
FBLN5
LTBP4
LOX
FBLN4
Defects in extracellular matrix proteins
Mature EF

CL with skeletal/neurological involvement: Proline Synthesis Defects



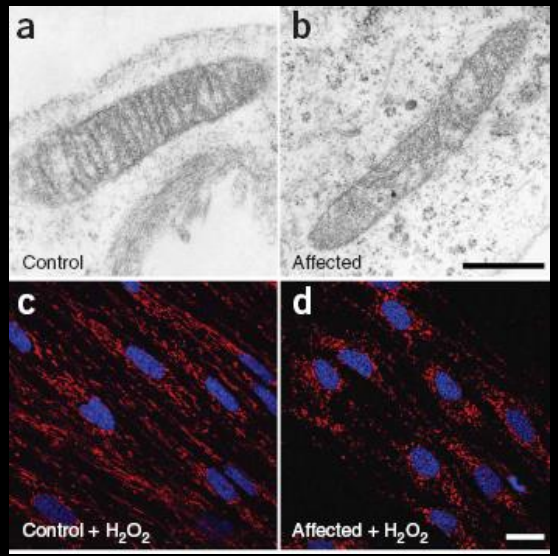
PYCR1

ALDH18A1

ΔΨ ↓

Apoptosis ↑

Control *PYCR1*

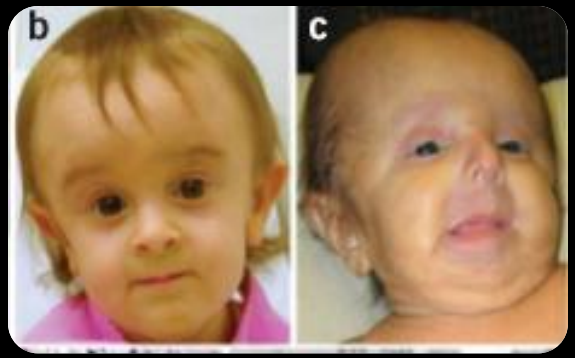


Reversade et al, 2009

Proline Synthesis Defects: spectrum encompassing de Barsy syndrome

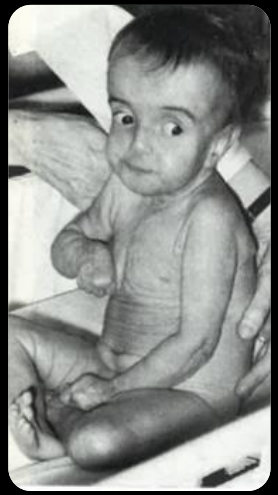
Severity

PYCR1

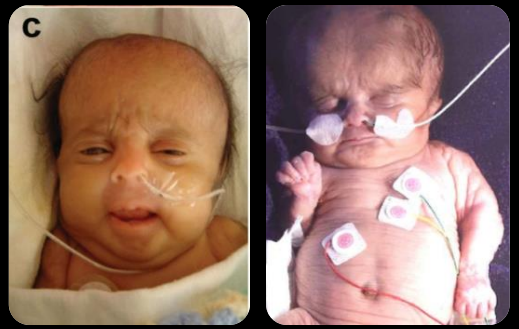


Reversade et al, 2009

de Barsy sy



ALDH18A1



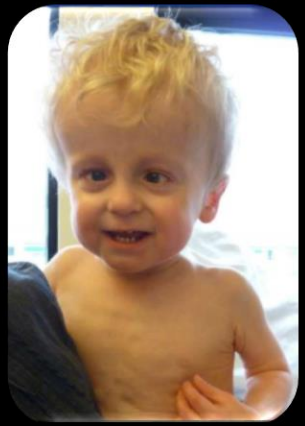
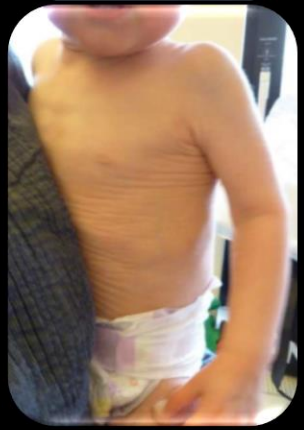
Skidmore et al, 2011
Fischer-Zirnszak, Callewaert et al, 2014

Dwarfism, oligophrenia and degeneration of the elastic tissue in skin and cornea. A new syndrome?[1]

A. M. DE BARSY, E. MOENS and L. DIERCKX

Received on March 13, 1968

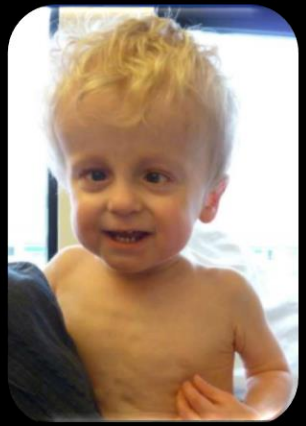
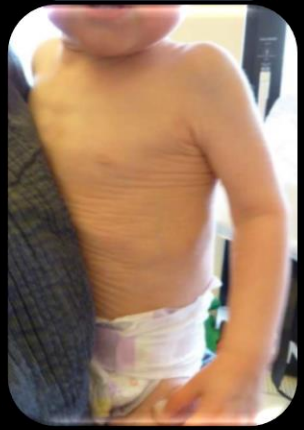


IUGR – FTT
Relative macrocephaly
Cataract
NMD, spasticity, chorea

NMR: tortuosity of the ICA



PYCR1

normal

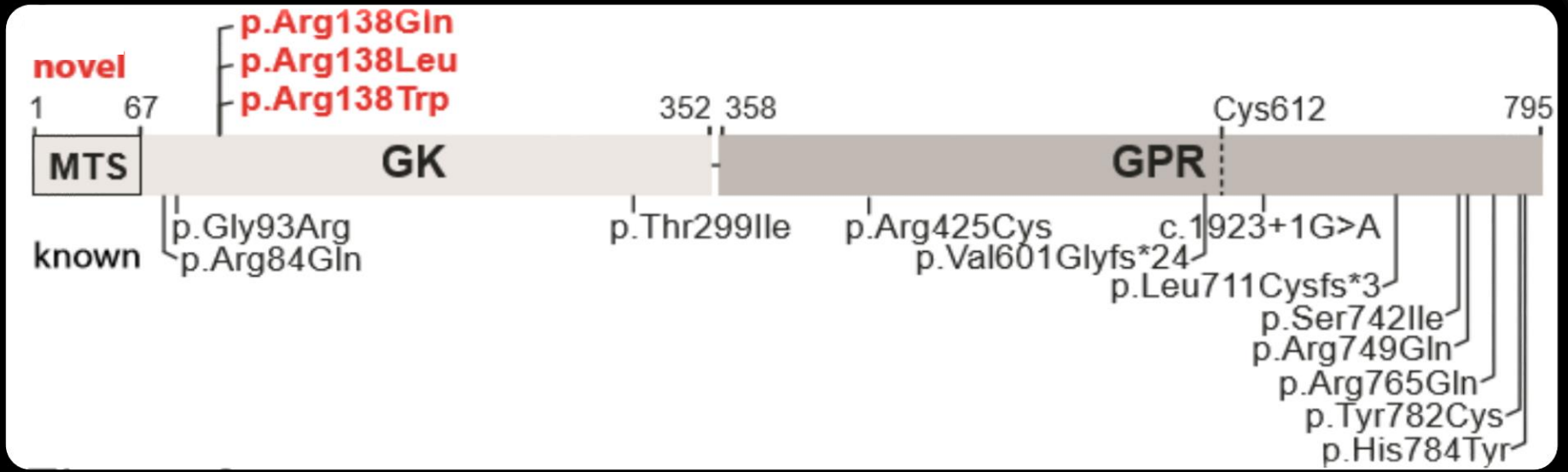
ALDH18A1

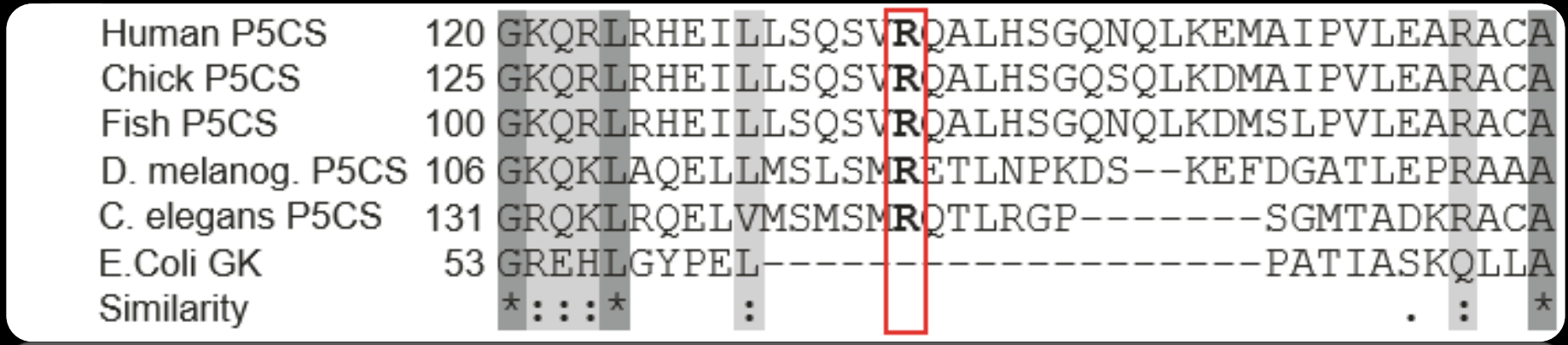
het c.412C>T

(p.Arg138Trp)

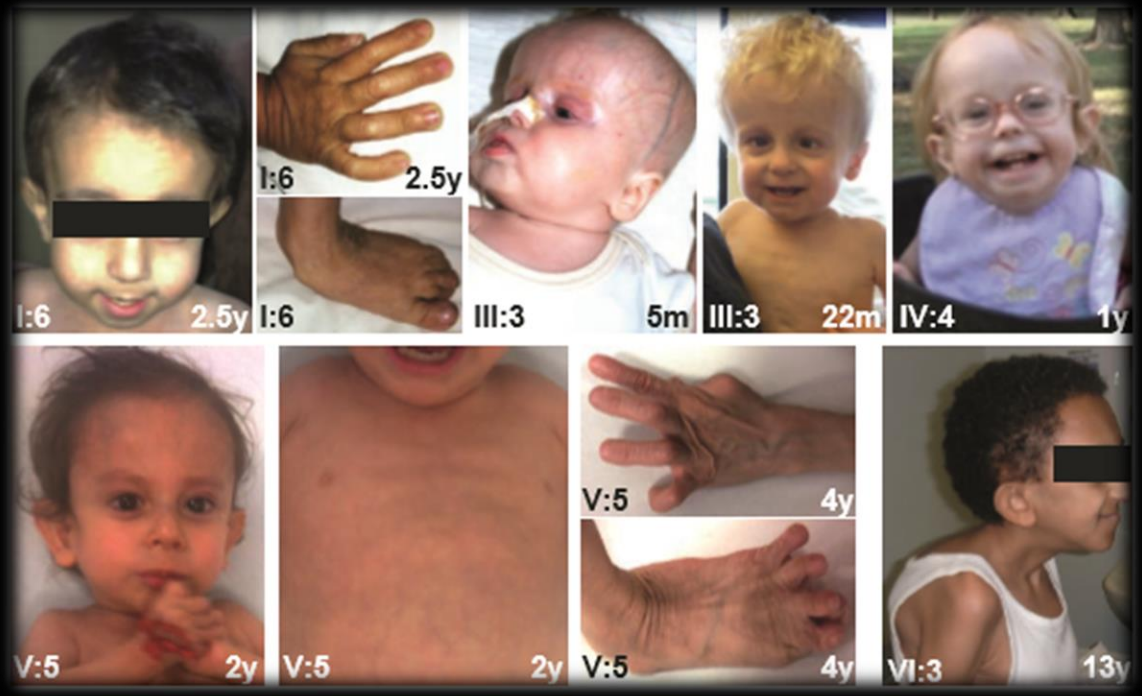
Del/dup analysis normal

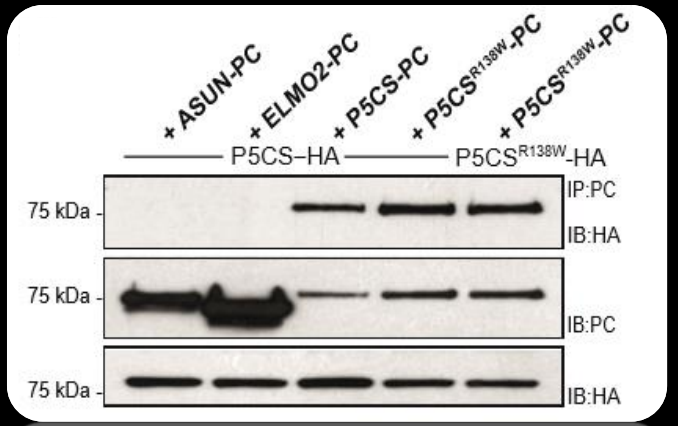
De novo





Fischer-Zirnsak, ..., Callewaert, Reversade, Kornak, 2015





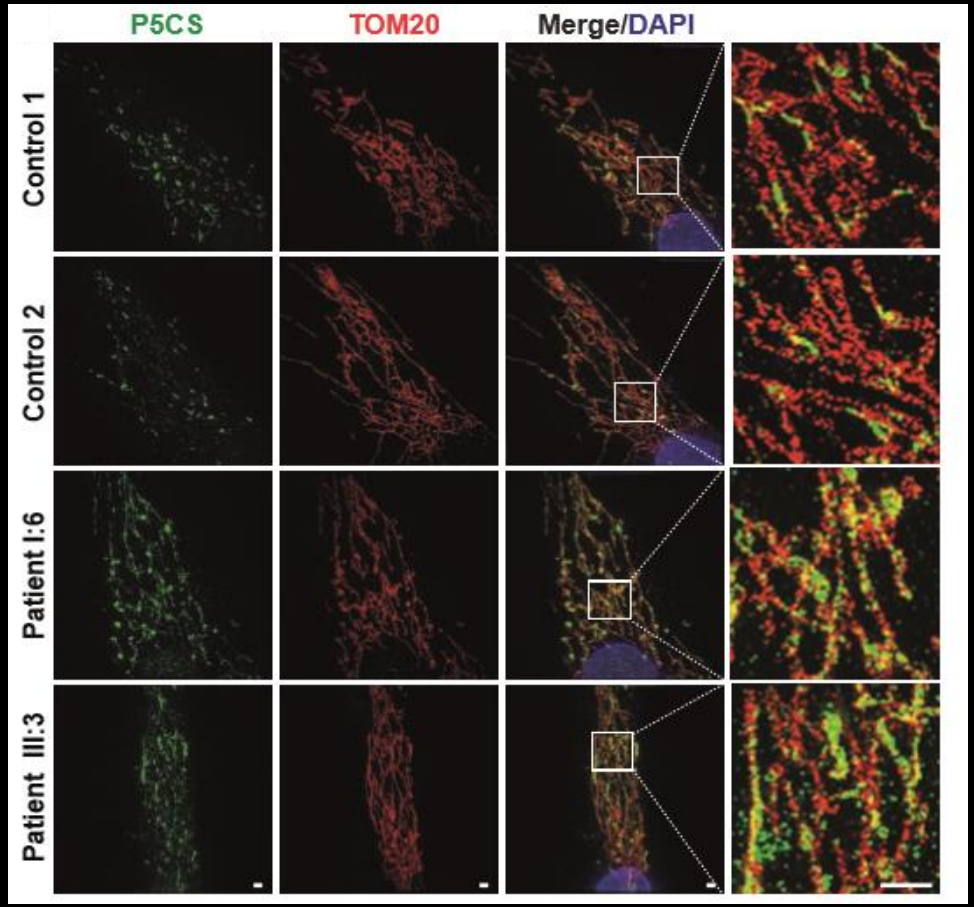
ALDH18A1

p.Arg138Trp
p.Arg138Leu
p.Arg138Gln

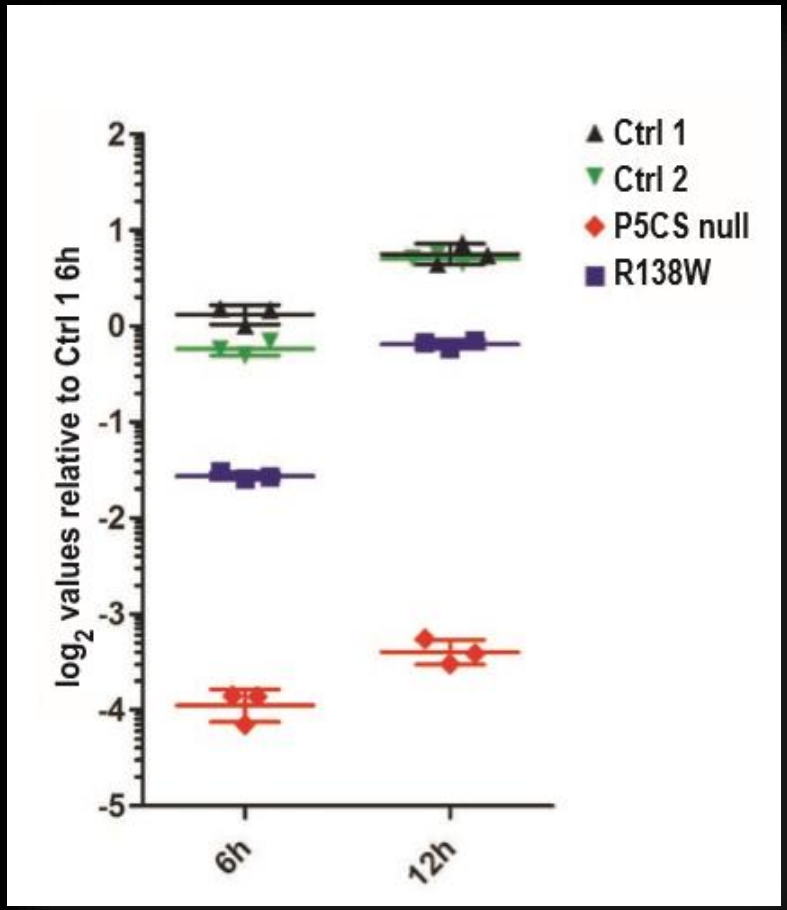
All *de novo*

Fischer-Zirnsak, ..., Callewaert, Reversade, Kornak, 2015

Superresolution microscopy

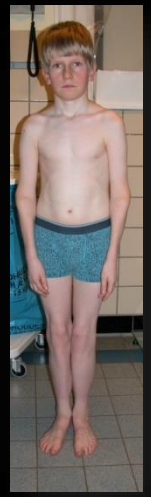
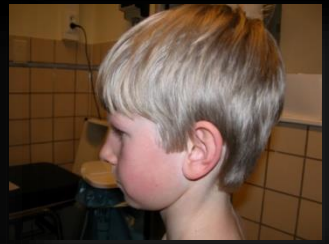
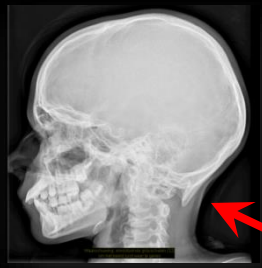


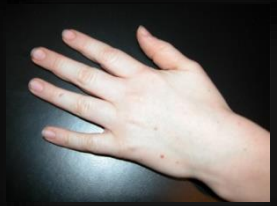
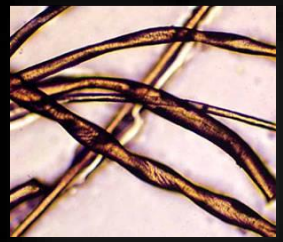
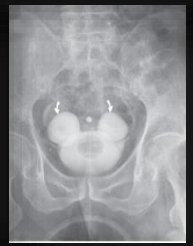
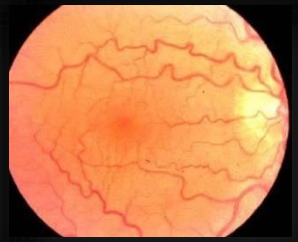
$C^{13}N^{15}$ glutamic acid labelling



Fischer-Zirnsak, ..., Callewaert, Reversade, Kornak, 2015

X-linked recessive cutis laxa

ATP7A (Cu^{2+}) transporter

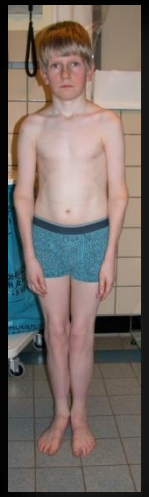
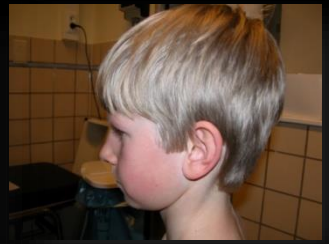
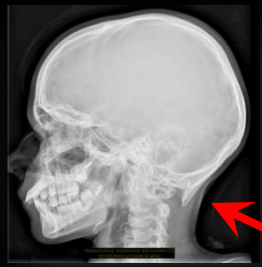
X-linked distal motor neuropathy
Occipital horn syndrome
Menkes disease

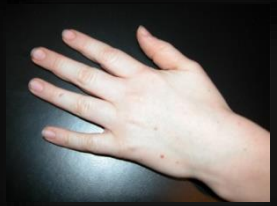
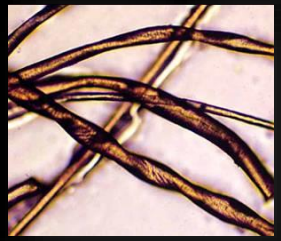
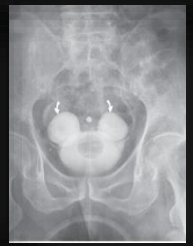
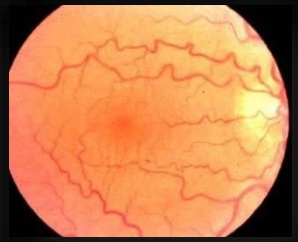
Serum Concentration	Menkes Disease [1]	Occipital Horn Syndrome	*ATP7A*-Related Distal Motor Neuropathy	Normal
Copper	0-55 µg/dL	40-80 µg/dL	80-100 µg/dL	70-150 µg/dL; (birth - 6 mos: 20-70 µg/dL)
Ceruloplasmin	10-160 mg/L	110-240 mg/L	240-310 mg/L	200-450 mg/L; (birth - 6 mos: 50-220 mg/L)

Kahler, GeneReviews

Beyens et al, 2019
De Feyter et al, 2023

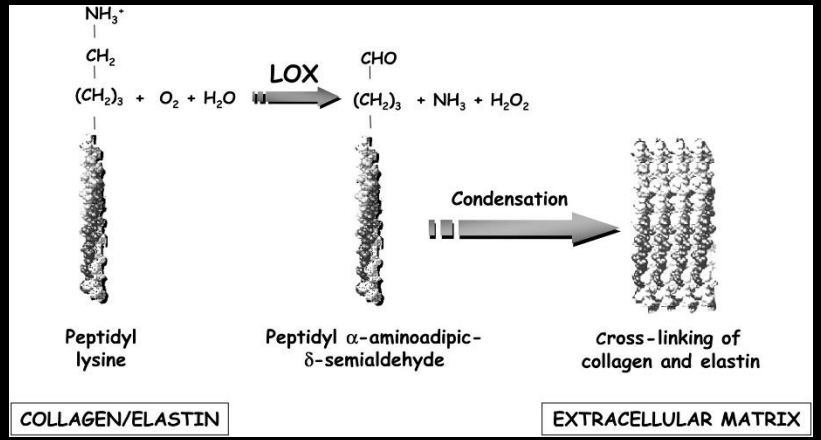
X-linked recessive cutis laxa

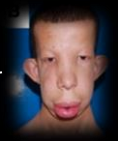
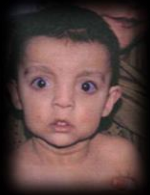
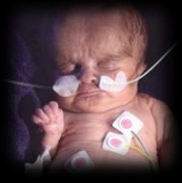
ATP7A related transporters

X-linked distal motor neuropathy
Occipital horn syndrome
Menkes disease



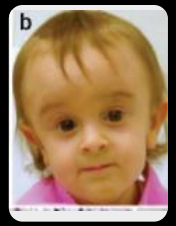
Summary (I)

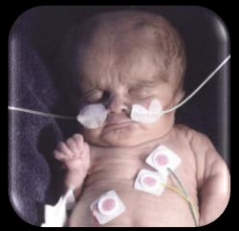
Cutis Laxa

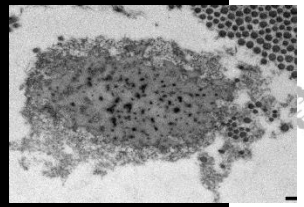
- Arterial / Lung
  - Absent / Mild
    - 
    - *ELN (FBLN5)*
    - ADCL
  - Lung
    - 
    - *LTBP4*
    - *FBLN5*
    - ARCL
  - Arteries
    - 
    - *FBLN4*
    - *SLC2A10*
    - ARCL
- Skeleton neurological
  - *GORAB*
    - 
  - RIN2
    - 
  - ATP7A
    - 
  - No IUGR/ocular
    - 
    - *ATP6V0A2*
    - CMP/Ptx
      - 
      - *ATP6V1E1*
  - Ocular/IUGR
    - Mild
      - ADCL
        - 
        - *ALDH18A1*
      - ARCL
        - 
        - *PYCR1*
    - Severe
      - 
      - *ALDH18A1 (PYCR1)*

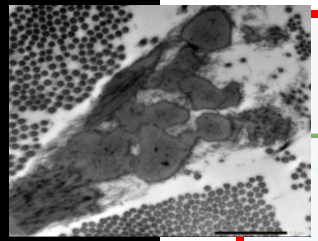
95% of patients are classified correctly

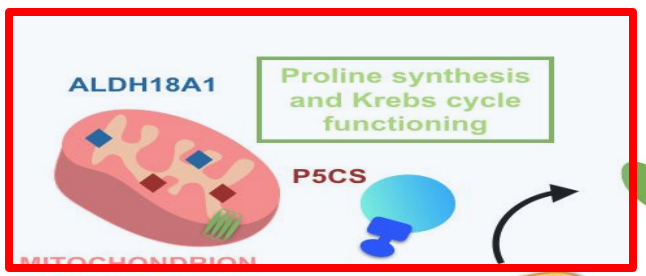
Summary (II)

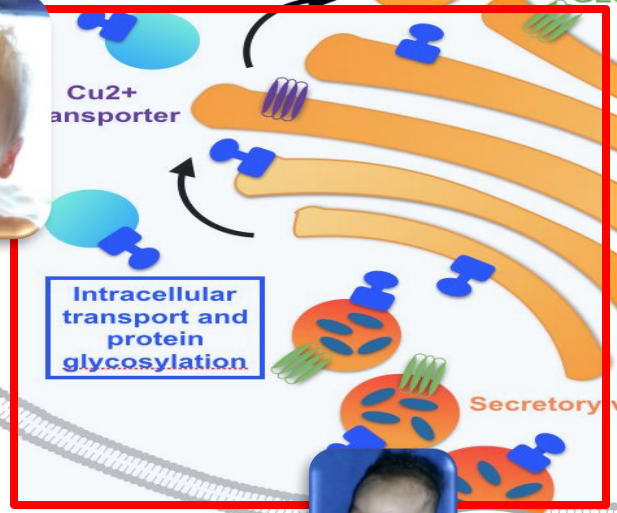


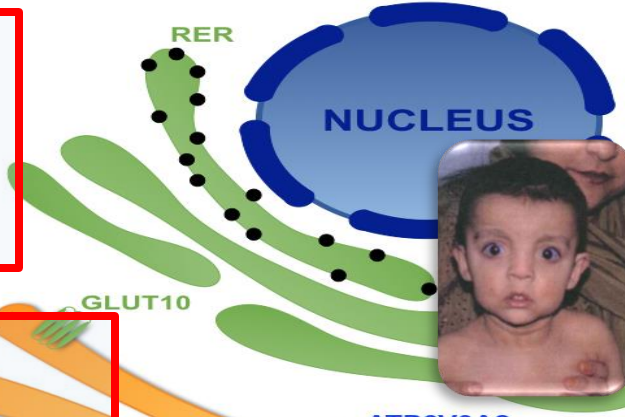


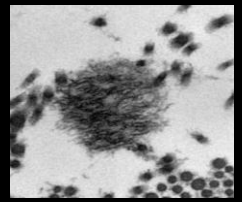


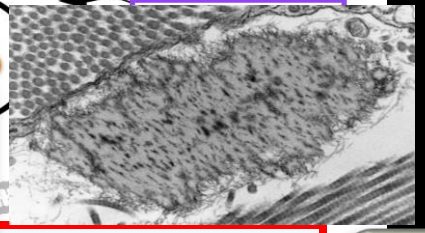


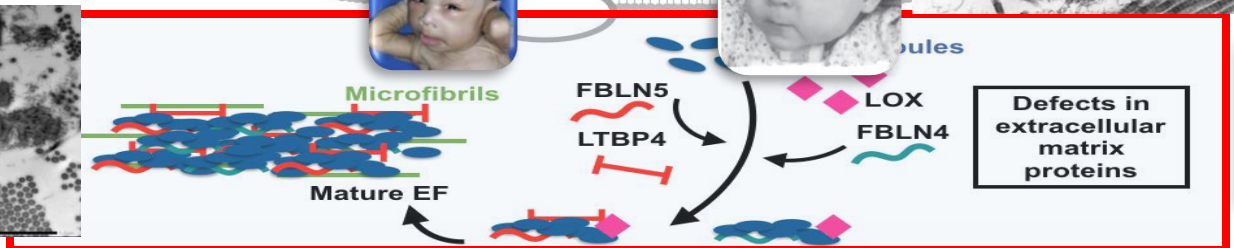

ALDH18A1
Proline synthesis and Krebs cycle functioning
P5CS
MITOCHONDRION


Retrograde transport
GLUT10
Cu2+
ansporter
Intracellular transport and protein glycosylation
Secretory


RER
NUCLEUS






Microfibrils
FBLN5
LTBP4
LOX
FBLN4
Mature EF
Defects in extracellular matrix proteins

Take Home message

Phenotype

- Classification
- Guidelines
- Patient burdens

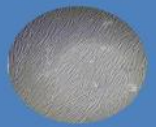
ERN-skin

Cutis laxa interna-tionale

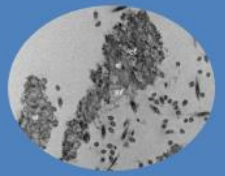
A Twist of Fate - ATS

MAC

Pathophysiology



EF Ultrastructure



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All families !!!