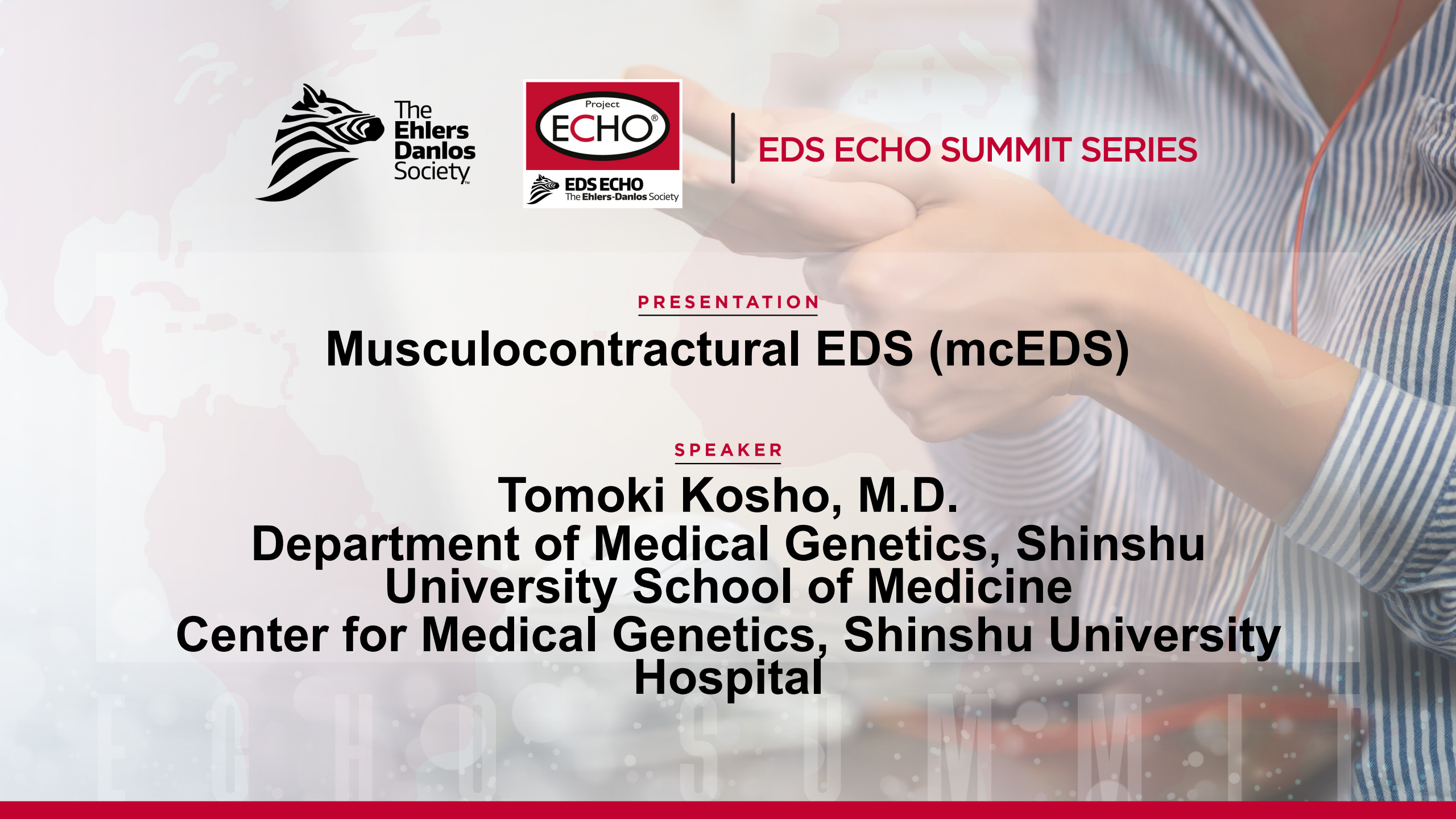

EDS ECHO SUMMIT SERIES

PRESENTATION

Musculocontractural EDS (mcEDS)

SPEAKER

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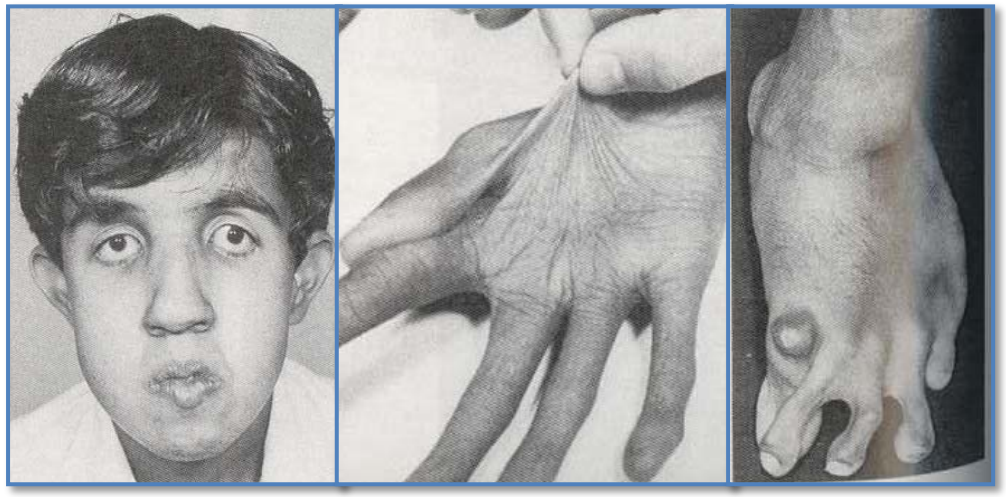
musculocontractural EDS

caused by mutations in *CHST14* (mcEDS-*CHST14*; MIM#601776) or *DSE* (mcEDS-*DSE*; MIM#615539)

- A recently delineated form of EDS
- Autosomal recessive inheritance
- Caused by systemic depletion of dermatan sulfate resulting from loss-of-function mutations in
  - *CHST14*, encoding carbohydrate sulfotransferase 14 (CHST14) or dermatan 4-*O*-sulfotransferase 1 (D4ST1)
  - *DSE*, encoding dermatan sulfate epimerase (DSE)
- Might not be extremely rare
  - mcEDS-*CHST14*: 48 patients from 33 families reported
  - mcEDS-*DSE*: 8 patients from 6 families reported

History of mcEDS-*CHST14*

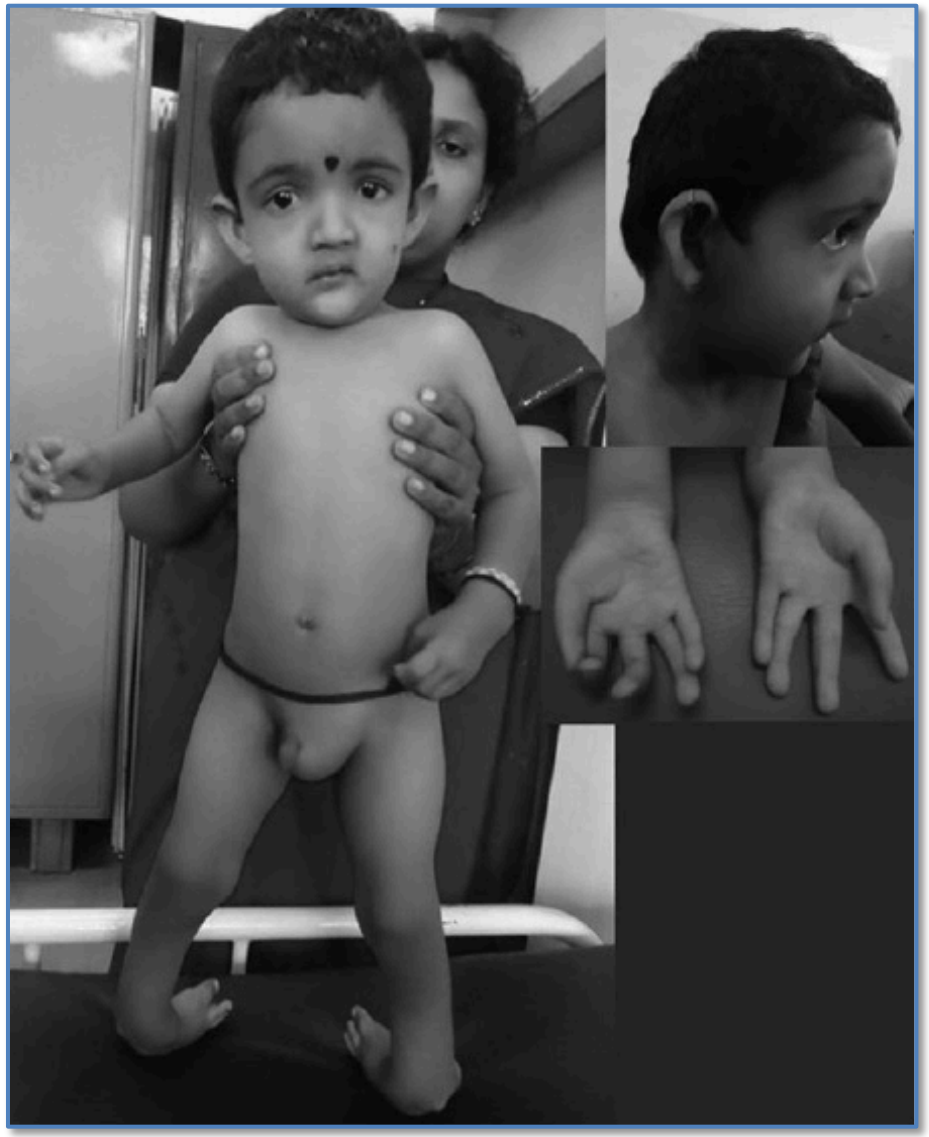
- The “original” patients were Pakistani siblings reported by Prof. Steinmann et al. in 1975!
- The causal gene “*CHST14*” was independently identified as
  - Adducted thumb-clubfoot syndrome, a rare arthrogryposis syndrome [Dündar et al., 1997; Sonoda and Kouno, 2000; Dündar et al., 2001; Janecke et al., 2001; Dündar et al., 2009]
  - EDS, Kosho type, a specific form of EDS [Kosho et al., 2005; Kosho et al., 2010; Miyake et al., 2010]
  - EDS musculocontractural type, a subset of kyphoscoliosis type EDS without lysyl hydroxylase deficiency [Malfait et al., 2010]



The “historic” case [Steinmann et al., Helv Paediatr Acta 30: 255-274, 1975], molecularly proved and republished in 2016 [Janecke et al., Am J Med Genet A 170: 103-115, 2016]

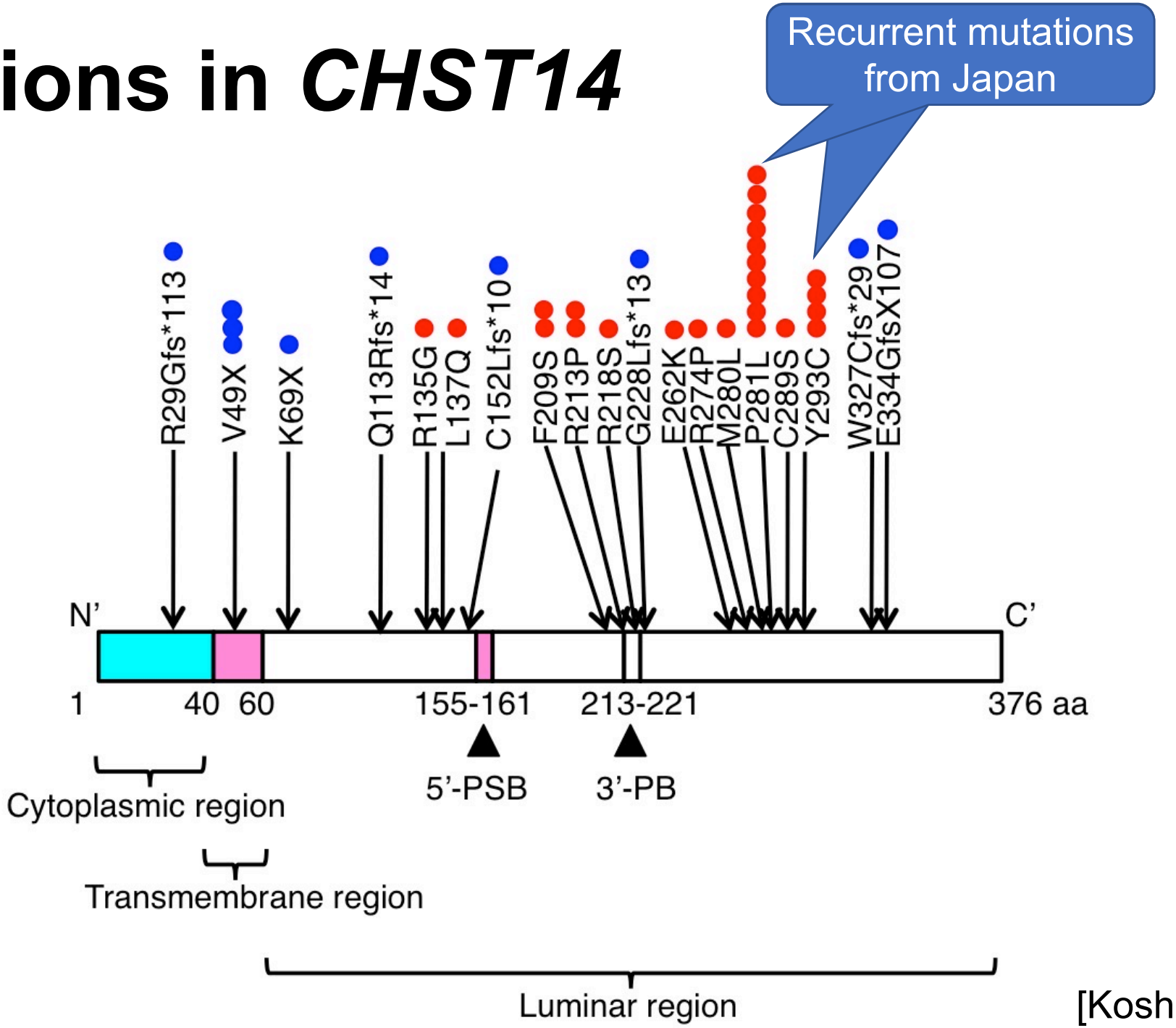
History of mcEDS-*DSE*

- The original case, an Indian boy, was reported by Prof. Janecke and colleagues with molecular and glycobiological evidences [Müller et al., 2013]



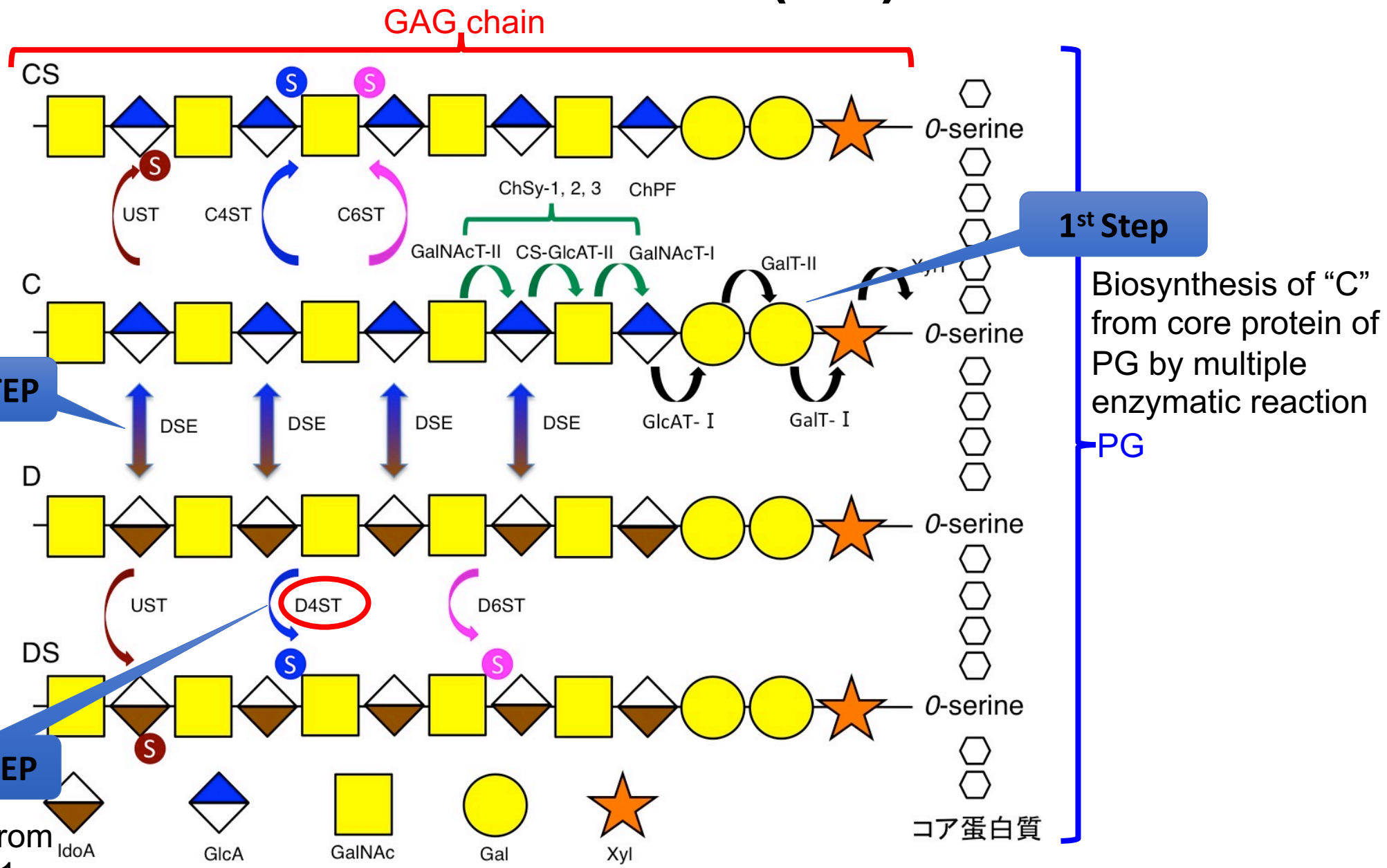
[Müller et al., 2013]

Mutations in *CHST14*



[Kosho, 2016; modified]

Biosynthesis of dermatan sulfate (DS)



1st Step

Biosynthesis of "C" from core protein of PG by multiple enzymatic reaction

PG

2nd STEP

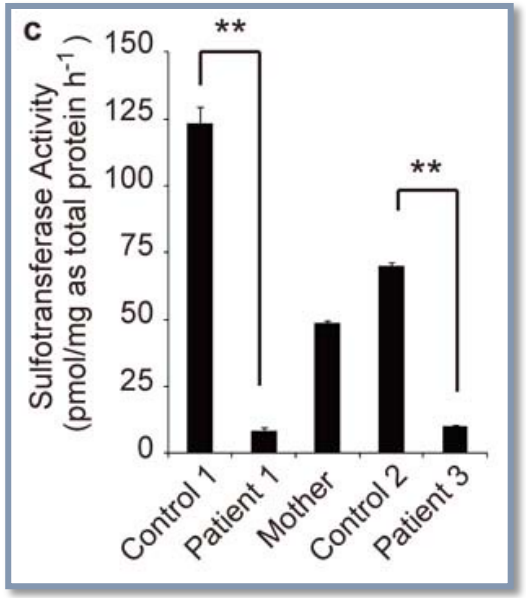
Biosynthesis of "D" from "C" by DSE

3rd STEP

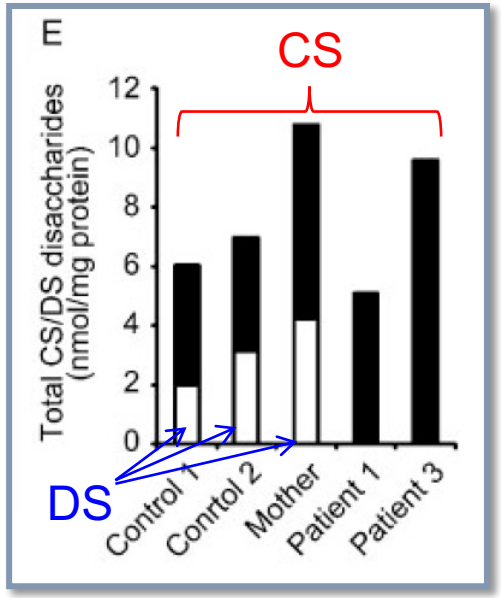
Biosynthesis of "DS" from "D" by CHST14/D4ST1

[Kosho et al., 2013; Kosho, 2016]

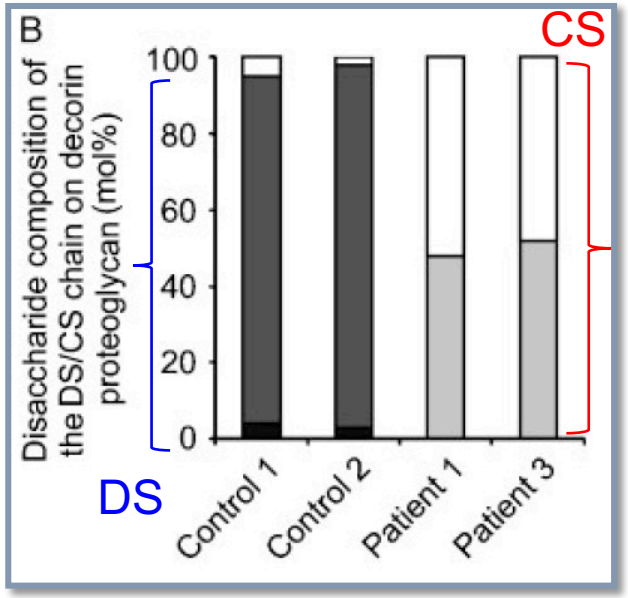
Glycobiological abnormalities



Loss of sulfotransferase activity in the patients' skin fibroblasts



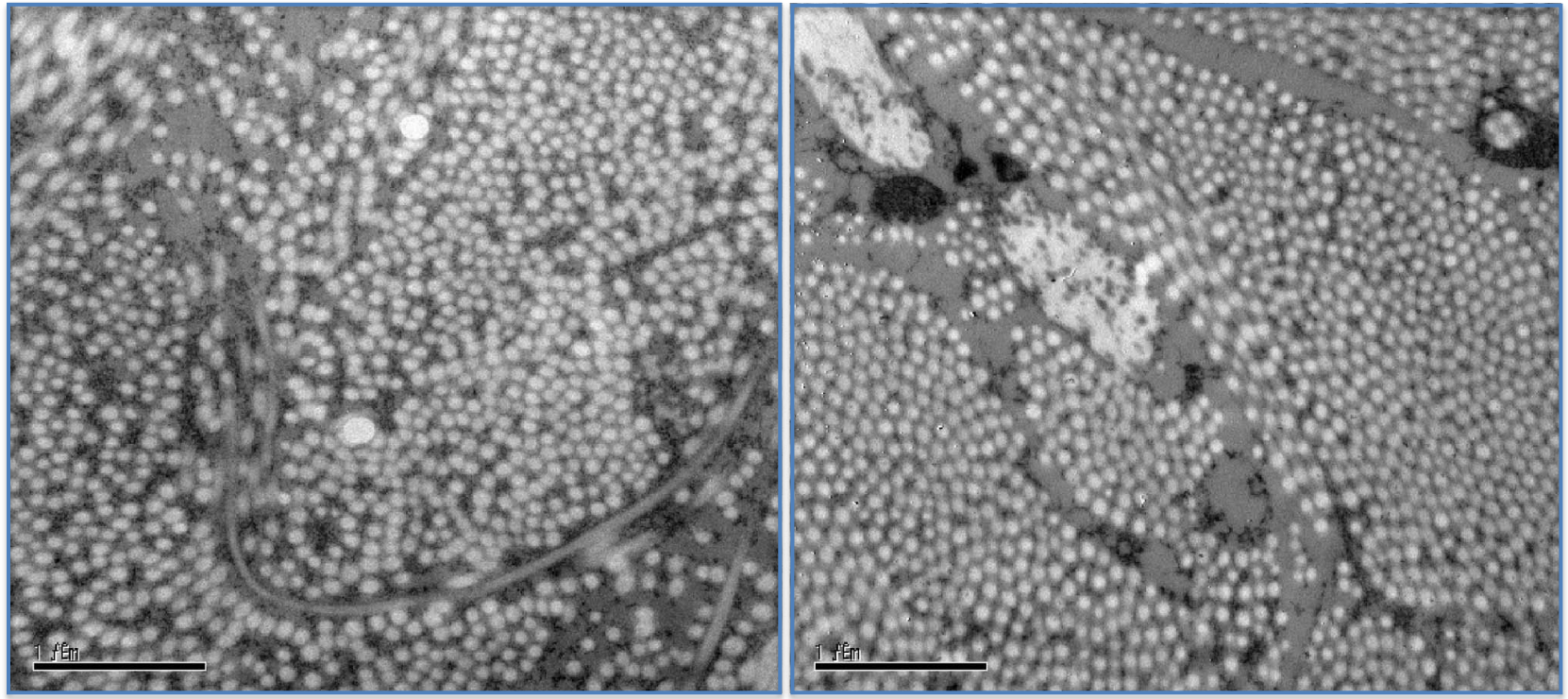
Loss of DS, replaced by CS, in the patients' skin fibroblasts



Only CS in the decorin GAG chains of the patients' fibroblasts; mostly DS in the control

[Miyake et al., 2010]

Ultrastructural abnormalities (skin)

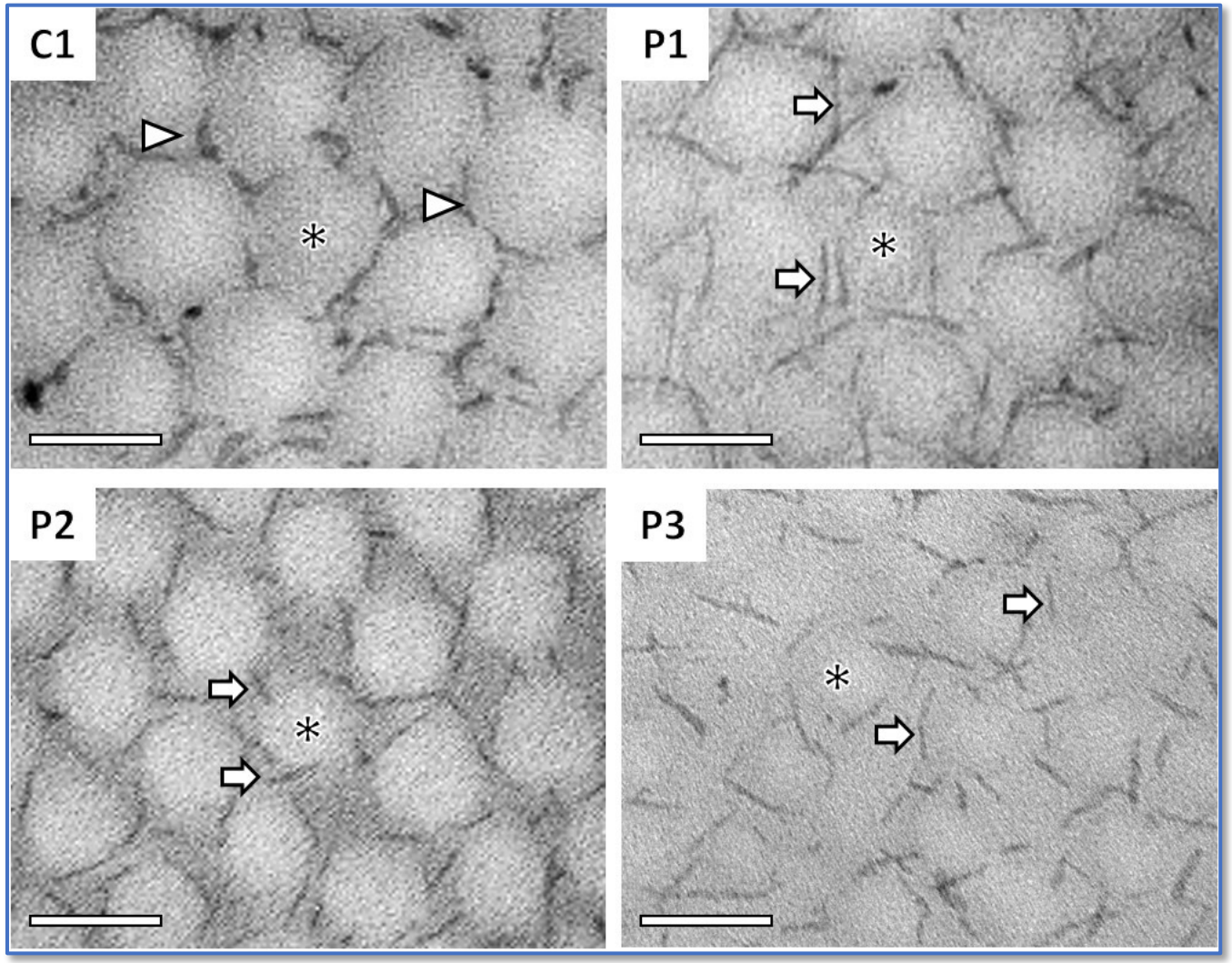


EM x30k Patient 5 Control

Impaired assembly of collagen fibrils was observed

[Miyake et al., 2010]

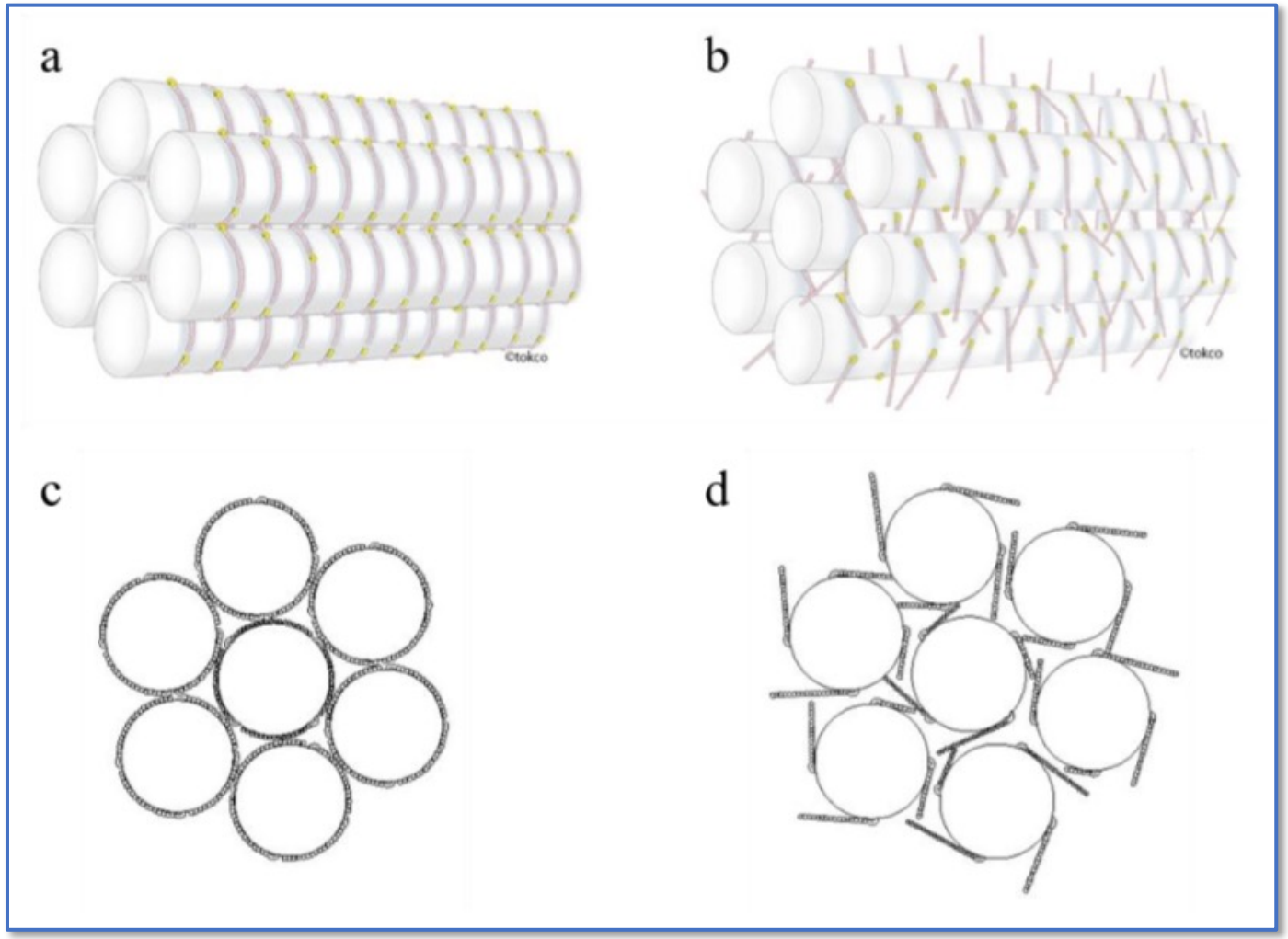
Searching pathophysiology (skin)



- Using cupromeronic blue staining that can visualize GAG chains
- In affected skin samples, linear CS GAG chains were stretching from the outer surface of collagen fibrils to adjacent fibrils
- In healthy control samples, DS GAG chains were round and wrapping collagen fibrils

[Hirose et al., 2019]

Proposed pathophysiology (skin)



“Ring-mesh” structure of GAG side chains surrounding collagen fibrils [Watanabe et al., 2016]

- The key proteoglycan would be decorin, having a role in assembling collagen fibrils with its GAG chains
- Conformational change of decorin GAG chains (DS to CS) causes disruption of the ring-mesh structure of GAG side chains surrounding collagen fibrils, resulting in marked skin hyperextensibility and fragility

[Hirose et al., 2019]

Natural history/features & complications

- mcEDS-*CHST14*: 48 patients from 33 families have been published [Dündar et al. 1997; Sonoda and Kouno 2000; Dündar et al. 2001; Janecke et al. 2001; Yasui et al., 2003; Kosho et al. 2005; Kosho et al., 2010; Malfait et al. 2010; Shimizu et al. 2011; Mendoza-Lodondo et al. 2012; Voermans et al. 2012; Winters et al. 2012; Syx et al. 2015; Janecke et al., 2016; Mochida et al., 2016; Kono et al. 2016; Sandal et al., 2018; Uehara et al., 2018].
- mcEDS-*DSE*: 8 patients from 6 families have been published [Müller et al., 2013; Syx et al., 2015; Schirwani et al., 2020; Lautrup et al., 2020].

Craniofacial features

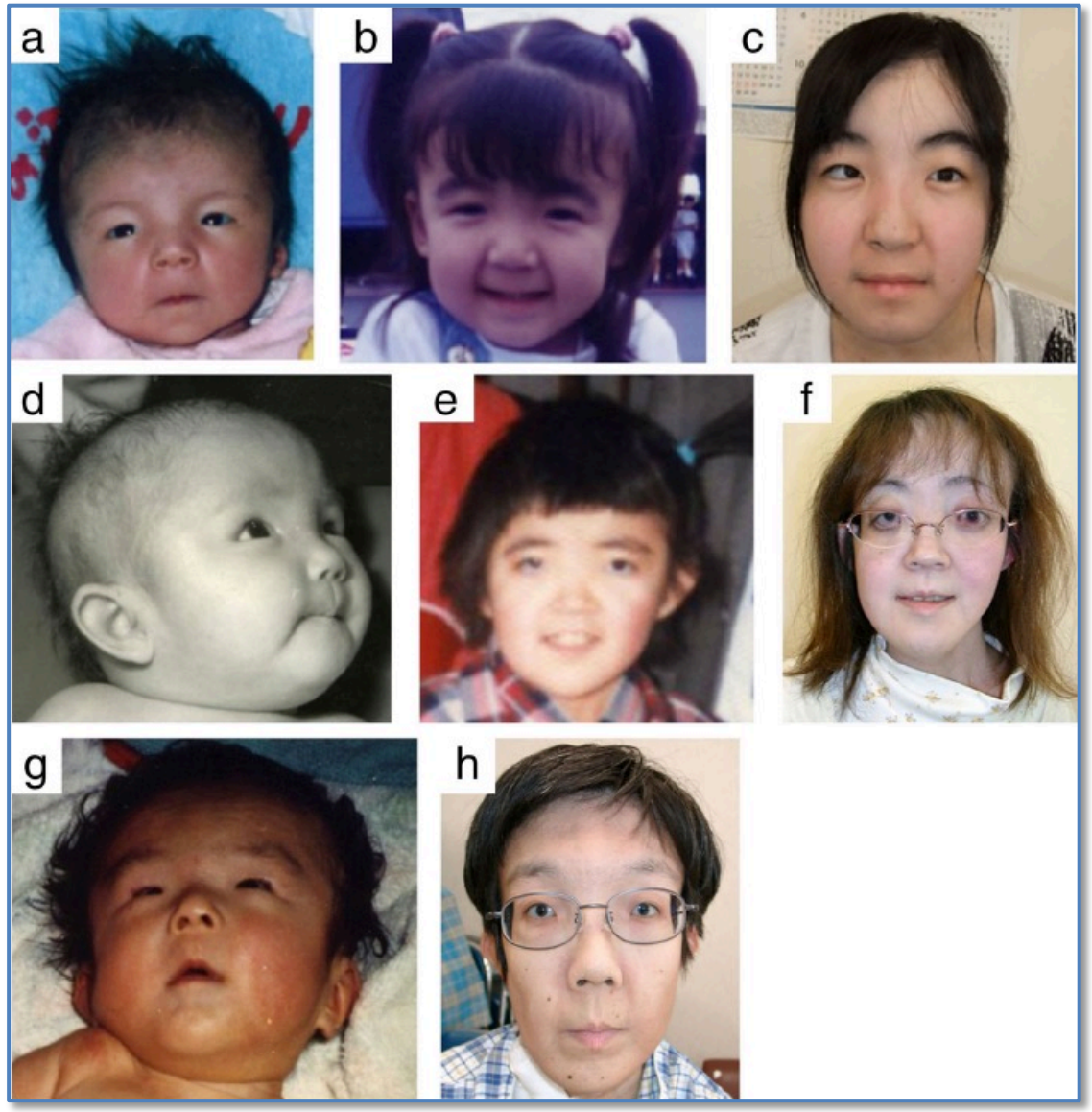
From infancy to childhood

- Large fontanelle
- Hypertelorism
- Downslanting palpebral fissures
- Blue sclerae
- Short nose with hypoplastic columella
- Ear deformities
- High palate
- Long philtrum and/or thin upper lip vermilion
- Small mouth and/or micro-retrognathia
- These features become less evident in childhood

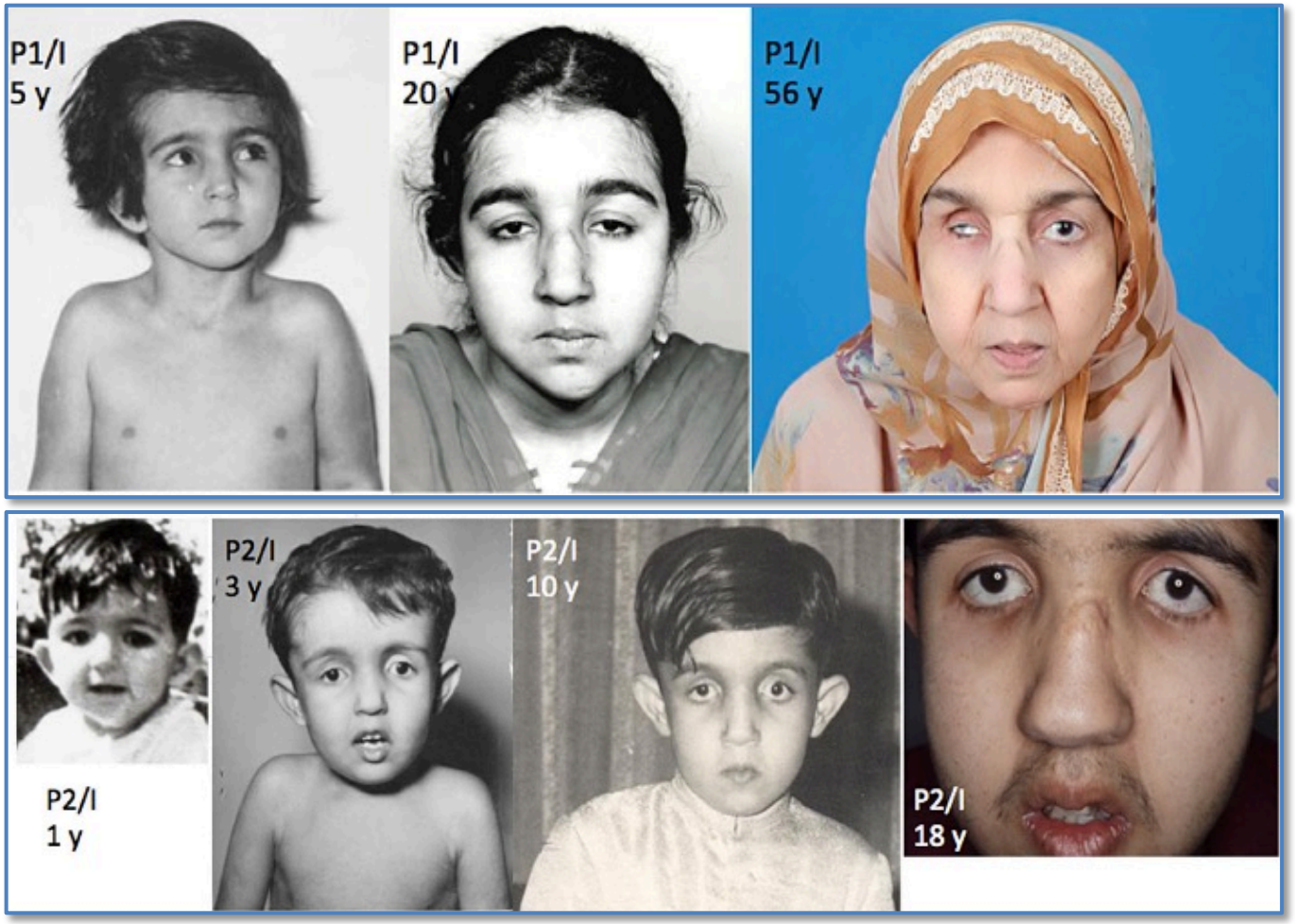
From adolescence to adulthood

- Slender facial shapes with protruding jaw
- Facial asymmetry

Craniofacial features



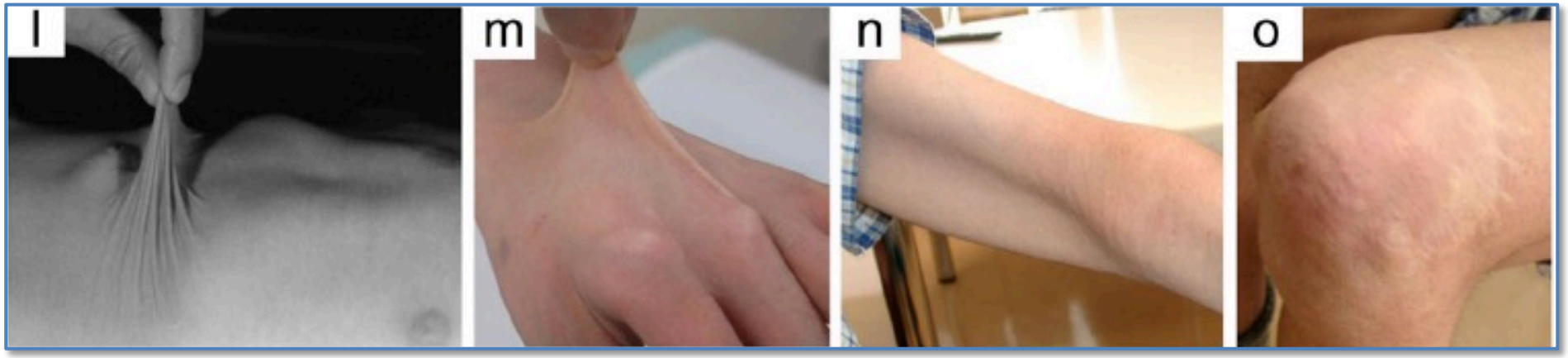
[Kosho et al., 2010; Kosho, 2016]

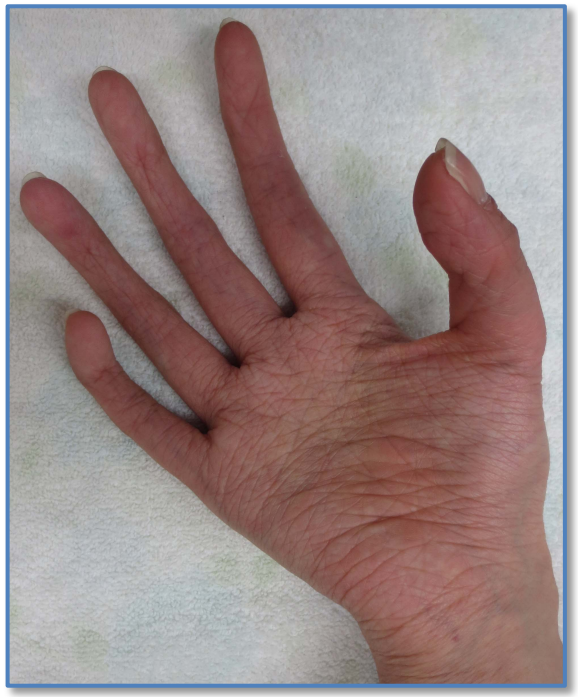


[Janecke et al., 2016]

Cutaneous features

- Hyperextensibility (from childhood) and redundancy (from adolescence)
- Bruisability
- Fragility with atrophic scars
- Acrogeria-like fine palmar creases/wrinkles
- Hyperalgesia to pressure
- Recurrent subcutaneous infection with fistula formation

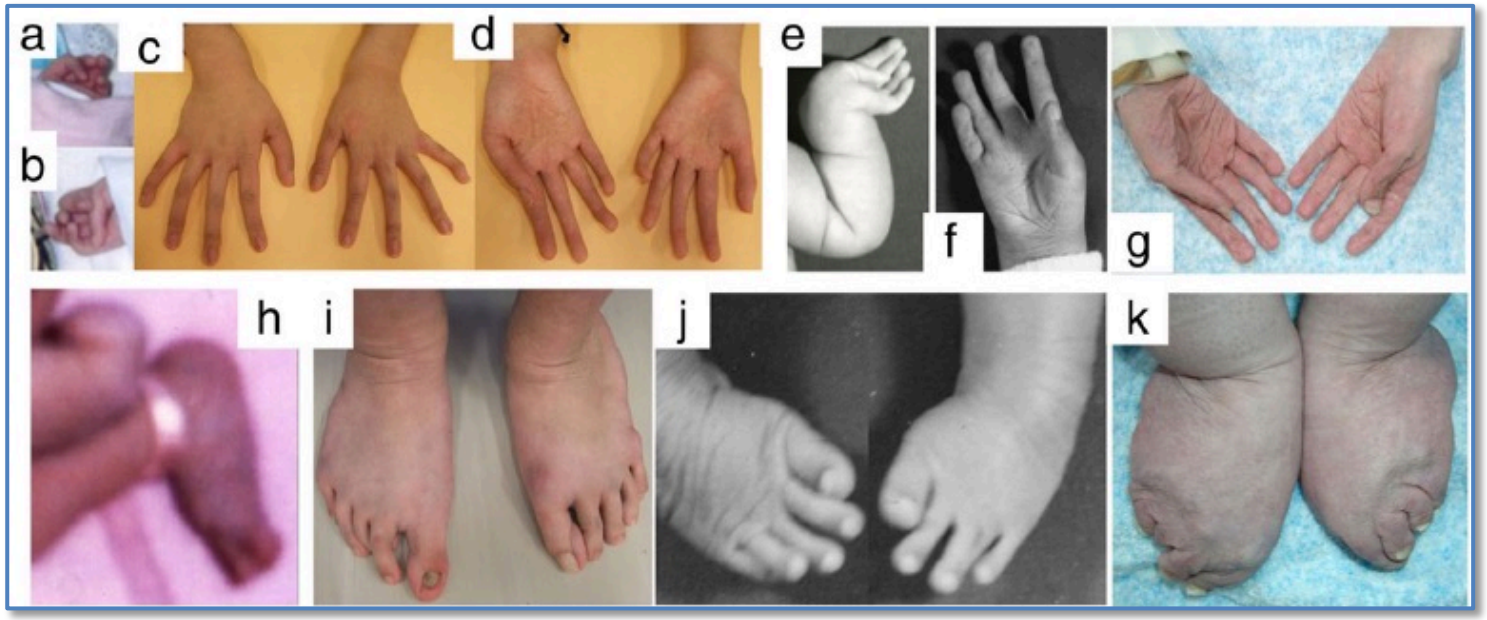


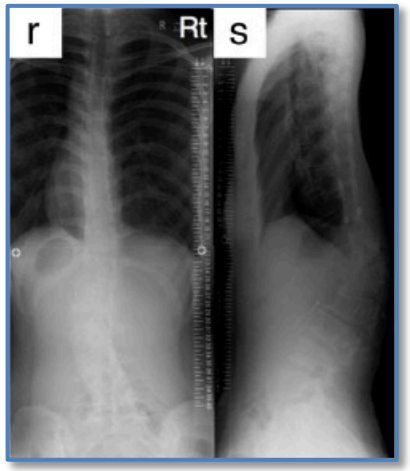


[Kosho et al., 2015; Kosho et al., 2010; Kosho, 2016]

Skeletal features

- Multiple congenital contractures, cardinal features
  - Adduction-flexion contractures of thumbs
  - Talipes equinovarus
- Characteristic finger shapes (arachnodactyly, tapering, slender, cylindrical)
- Spinal deformities (decreased physiological curvature, scoliosis, kyphoscoliosis)
- Progressive talipes deformities (planus, valgus, severer)
- Recurrent, chronic or easy joint dislocations
- Pectus deformities (flat and thin, excavatum, carinatum)
- Marfanoid habitus

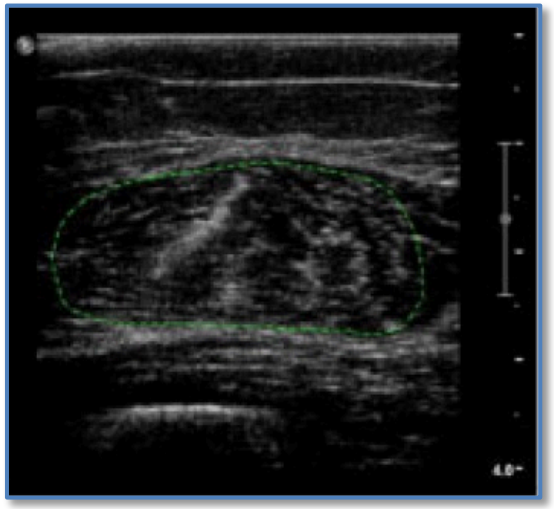




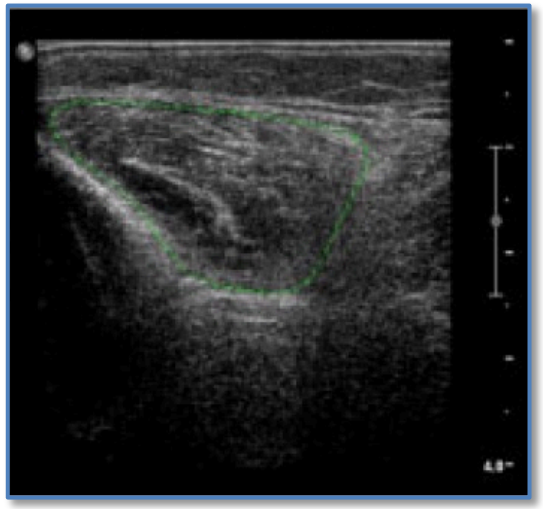
[Kosho et al., 2015; Kosho et al., 2010; Kosho, 2016]

Muscular features

- Muscle hypotonia or weakness
- Elevation of serum CK (n=4; 277, 698, 1838, 3000 IU/L) [Janecke et al.,2016]
- Myopathic changes suggested, similar to other EDS types [Dündar et al., 1997; Voermans et al., 2012]

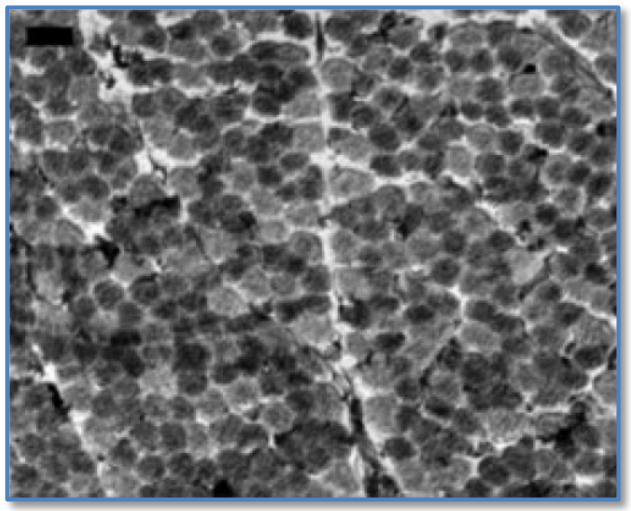


Normal at the rt. rectus femoris muscle

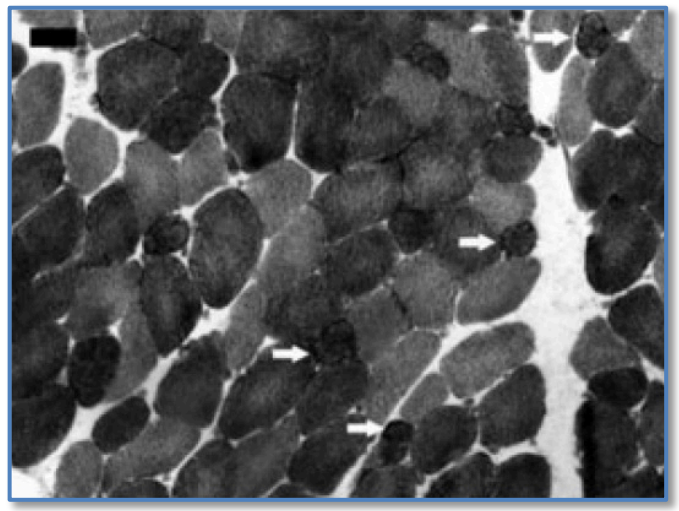


Increased at the rt. anterior tibial muscle

Echo intensity on quantitative muscle US



Normal at age 1 year (gracilis muscle)



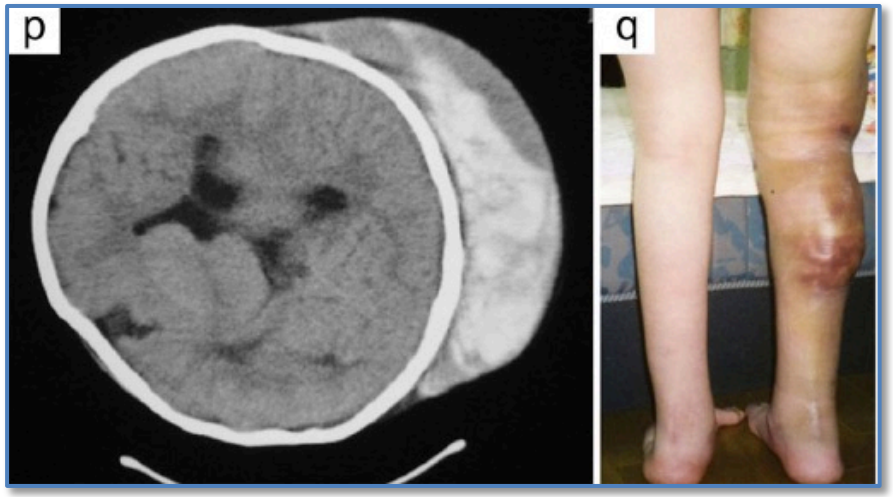
Myopathic changes at age 20 years (vastus lateralis), with increased variation of muscle fiber diameters, type 1 predominance, and type 1 fibers with incipient lobulation

Muscle biopsy

[Voermans et al., 2012]

Cardiovascular complications

- Congenital heart defects
  - Atrial septal defect
- Valve abnormalities and/or artic root dilatation
- Infectious endocarditis
- Recurrent large subcutaneous hematomas
  - Skull, extremities, hips, …
  - Occur even after minor trauma
  - Can spread acutely and massively with severe pain to hemorrhagic shock requiring intensive treatment
  - Intranasal DDAVP after trauma could effectively prevent serious large subcutaneous hematomas



[Kosho et al., 2015; Kosho et al., 2010; Kosho, 2016]

Gastrointestinal/urogenital complications

Gastrointestinal

- Constipation
- Diverticula perforation
- Others
  - Severe progressive gastric ulcer
  - Common mesentery
  - Spontaneous volvulus of the small intestine associated with absent gastrocolic omentum
  - Duodenal obstruction due to malrotation

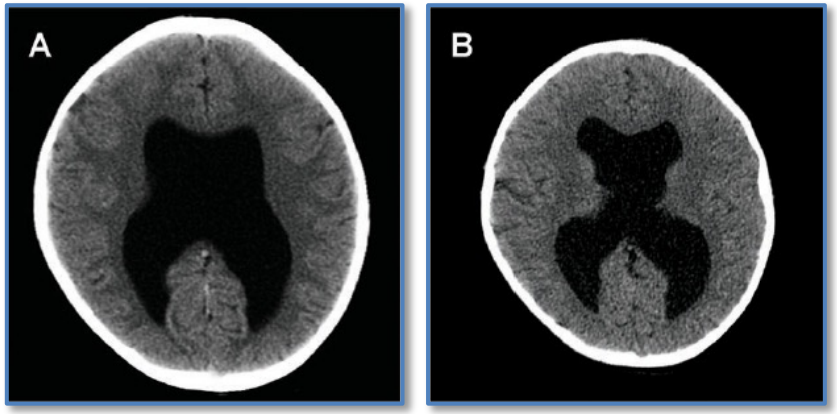
Urogenital

- Hydronephrosis
- Nephrolithiasis/cystolithiasis
- Recurrent urinary tract infection
- Cryptorchidism in most male patients

Neurological abnormalities/development

Neurological abnormalities

- Ventricular abnormalities
  - Enlargement
  - Asymmetry
- Spinal cord tethering
- Others
  - Dandy-Walker variant
  - Hypoplastic corpus callosum



[Winters et al., 2012]

Development

- Gross motor developmental delay
  - Mainly because of muscle hypotonia
  - Median age of unassisted walking: 2 years and 6 months (1 year and 5 months - 5 years)
- Normal intelligence in most

Vision/hearing and others

Vision/hearing

- Ocular complications
  - Refractive errors
    - Myopia, astigmatism, hyperopia
  - Strabismus
  - Microcornea
  - Glaucoma/elevated intraocular pressure
  - Retinal detachment
- Hearing
  - Hearing impairment
    - High-pitched sound

Others

- Poor breast development in female (beyond adolescence)
- Pneumothorax/pneumohemothorax (adult)

Diagnostic criteria (International Classification 2017)

Major criteria

- Congenital multiple contractures, characteristically adduction-flexion contractures and/or talipes equinovarus (clubfoot)
- Characteristic craniofacial features, which are evident at birth or in early infancy
- Characteristic cutaneous features including skin hyperextensibility, easy bruisability, skin fragility with atrophic scars, increased palmar wrinkling

Minimal criteria suggestive for mcEDS
At birth or in early childhood:
Major criterion (1): Congenital multiple contractures AND (2) characteristic craniofacial features
In adolescence and in adulthood:
Major criterion (1): Congenital multiple contractures AND (3) characteristic cutaneous features
➡Confirmatory molecular testing is obligatory to reach a final diagnosis.

Minor criteria

- Recurrent/chronic dislocations
- Pectus deformities (flat, excavated)
- Spinal deformities (scoliosis, kyphoscoliosis)
- Peculiar fingers (tapering, slender, cylindrical)
- Progressive talipes deformities (valgus, planus, cavum)
- Large subcutaneous hematomas
- Chronic constipation
- Colonic diverticula
- Pneumothorax/pneumohemothorax
- Nephrolithiasis/cystolithiasis
- Hydronephrosis
- Cryptorchidism in males
- Strabismus
- Refractive errors (myopia, astigmatism)
- Glaucoma/elevated intraocular pressure

[Malfait et al., 2017]

Healthcare guideline

- ***Initial screening after diagnosis***
  - Congenital cardiac, ocular, and renal abnormalities and hearing loss
- ***From Infancy to childhood***
  - Orthopedic intervention for clubfoot
  - Physical therapy for motor developmental delay
  - Laxatives and/or enemas for constipation
  - Surgical fixation for cryptorchidism in males
  - Regular checkups for ophthalmological, otological, urological, and cardiovascular problems
  - After walking independently, prevention of skin lacerations, joint dislocations, or large subcutaneous hematomas resulting from progressive foot deformities and falling
  - Intranasal DDAVP after trauma is considered to prevent large subcutaneous hematomas.
  - Wrist sphygmomanometer for hyperalgesia to pressure
- ***From adolescence to adulthood***
  - Assessment/treatment of spinal deformities
  - Possible emergency complications: large subcutaneous hematomas, diverticular perforation
  - Psychosocial support

[Shimizu et al., 2012; Kosho, 2016]

Ongoing research projects

- Clinical
  - International collaborative study for natural history by the International Consortium for EDS (the EDS Society)
  - Effectiveness of DDAVP for large subcutaneous hematoma
  - Skeletal features, hearing, ophthalmological complications, …
- Basic
  - Comprehensive pathophysiological investigation
    - KO mice (Nippon Medical University, Shinshu University)
    - iPS cells (Shinshu University)
  - Therapeutic approach (AAV-mediated gene therapy)

Thank you for your attention !