Clinical and molecular features of 66 patients with musculocontractural Ehles-Danlos Syndrome caused by mutations in *CHST14* (mcEDS-*CHST14*)

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SCIENTIFIC MEETING - RARER TYPES
TOKYO 2019

Musculocontractual Ehlers-Danlos syndrome caused by *CHST14* variants (mcEDS-*CHST14*)

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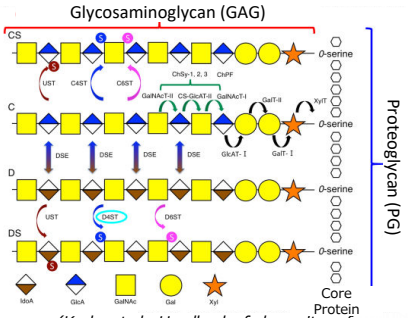
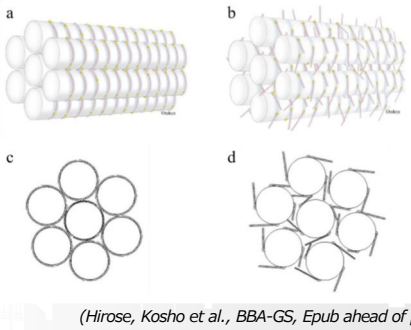
- A rare autosomal recessive syndrome caused by biallelic loss-of-function variants in *CHST14* encoding dermatan 4-*O*-sulfotransferase-1 (D4ST1).
- mcEDS-*CHST14* is clinically characterized by multiple congenital anomalies and progressive connective tissue fragility.
- D4ST1 deficiency leads to loss of dermatan sulfate (DS) in Glycosaminoglycan (GAG), which causes unassembled collagen fibrils.



(Kosho et al., Handbook of glycosyltransferase and related genes, 2013)



(Hirose, Kosho et al., BBA-GS, Epub ahead of print)

Methods

In order to delineate the detailed and comprehensive natural history of mcEDS-*CHST14*, we conducted an international collaborative study to collect clinical and molecular information of mcEDS-*CHST14* patients of diverse populations and various ages with the support of the Internaltional EDS Consortium (established in 2013).

To do this, we collected detailed clinical and molecular information of 66 patients (48 families) with mcEDS-*CHST14* including previously reported cases.

Participants

Patients : 66 patients (48 families)

Sex : 33 males　33 females

Age : From 0 month to 45 years old

Ethnicity :

Japanese　47% [31/66]

Turkish　14% [9/66]

Spanish　11% [7/66]

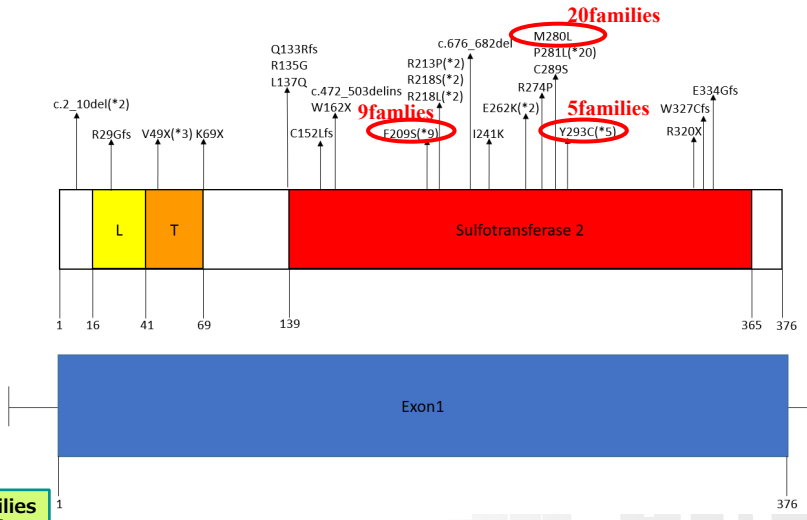
Asian other than Japanese（no details）　6% [4/66]

Pakistani, Afghan, Austrian, Dutch　each 3% [2/66]

Curacao, Indian, Bangladeshi, Moroccan　each 1.5% [1/66]

Peruvian/Mikosky, Thai/German Irish　each 1.5% [1/66]

Distribution of *CHST14* variants



missense variants	13 families
nonsense variants	4 families
frameshift variants	5 families
small del/ins	3 families

Clinical Findings

	cases	percentage (%)
[Craniofacial]		
Large fontanelle with delayed closure	40/41	98
Downslanting palpebral fissures	59/61	97
Hypertelorism	55/60	92
Small mouth/micro-retrognathia	32/37	86
High-arched palate	42/49	86
Blue sclerae	42/52	81
Ear deformity	41/51	80
Slender face/protruding jaw	27/34	79
Short nose with hypoplastic columella	38/49	78
Long philtrum	37/48	77
Crowded teeth	20/26	77
Short palpebral fissures	28/37	76
Low-set ears	35/48	73
Facial asymmetricity	21/30	70
Thin upper lip vermilion	29/47	62
Brachycephaly/flat occiput	20/40	50
Midfacial hypoplasia	20/39	51
Cleft lip/palate	4/43	9

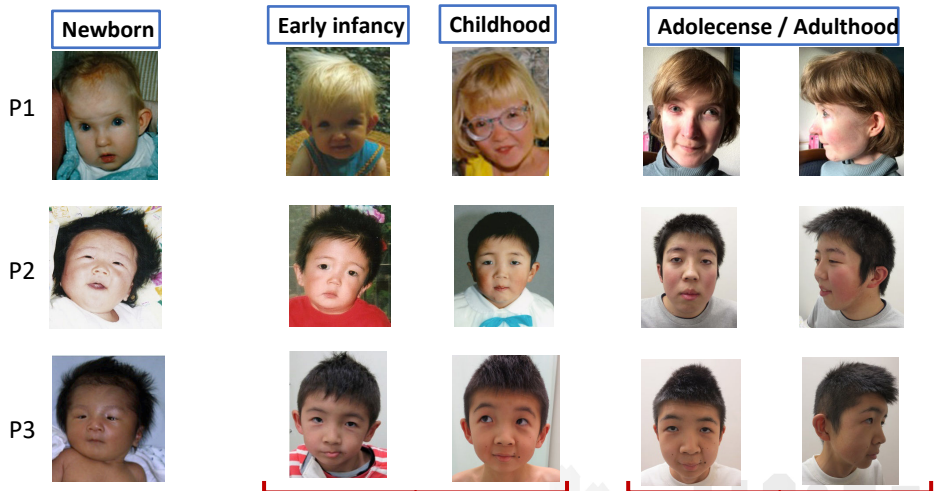
	cases	percentage (%)
[Skeletal]		
Finger shape	58/58	100
Progressive talipes deformities	48/48	100
Talipes equinovarus (clubfeet)	58/61	95
Congenital multiple contractures	56/59	95
Joint laxity	36/41	88
Spinal deformities	40/47	85
Tendon abnormalities	17/20	85
Pectus deformities	36/44	82
Adducted thumbs	44/55	80
Recurrent joint dislocations	40/51	78
Osteoporosis	14/18	78
Marfanoid habitus/slender build	28/41	68
[Skin]		
Hyperextensibility	49/49	100
Bruisability	47/47	100
Fine palmar creases	54/55	98
Fragility	43/47	91
Atrophic scars	43/48	90
Delayed wound healing	28/37	76
Hyperalgesia to pressure	25/35	71
Recurrent subcutaneous infections	13/34	38
Umbilical hernia	10/28	36
Fistula formation	11/34	32

Clinical Findings

	cases	percentage (%)
【Cardiovascular】		
Large subcutaneous hematoma	42/51	82
Valve abnormalities	15/44	34
Congenital heart defects	10/48	21
Enlargement of ascending aorta	1/42	2
【Respiratory】		
Pneumothorax	4/36	11
【Gastrointestinal】		
Constipation	32/37	86
Diverticula	8/28	29
【Urological】		
Cryptorchidism	21/24	88
Bladder dysfunction	14/29	48
hydronephrosis	18/35	51
Recurrent urinary tract infection	13/34	38
Inguinal hernia	11/37	30
Nephrolithiasis	9/32	28
【Ophthalmological/Otological】		
Refractive errors	39/42	93
Strabismus	19/35	54
Glaucoma	17/40	43
Retinal detachment	14/41	34
Hearing impairment	22/41	54

	cases	percentage (%)
【Sexual development-related】		
Poor breast development in female	15/19	79
Hypogonadism	3/19	16
【Central nervous system】		
Ventricular abnormalities	17/33	52
Tethering spinal cord	5/18	28
Hypoplasia of septum pellucidum	5/25	20
Dandy-Walker anomaly	2/25	8
【Muscular system】		
Hypotonia	35/39	90
【Development】		
Motor developmental delay	44/51	86
Intellectual disabilities	8/49	16

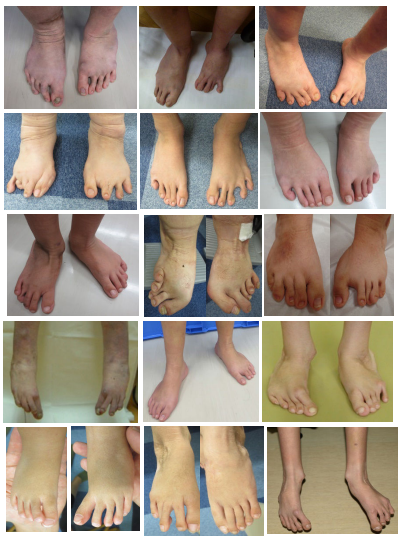
Craniofacial Features



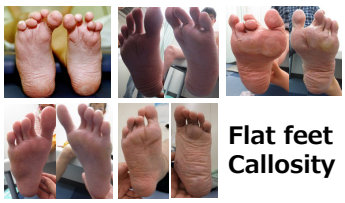
The Features of Hands and Digits

Adducted thumbs
Extension or flexion contractures of DIP, PIP, MP joints
Long and tapering digits, Cylindrical digits

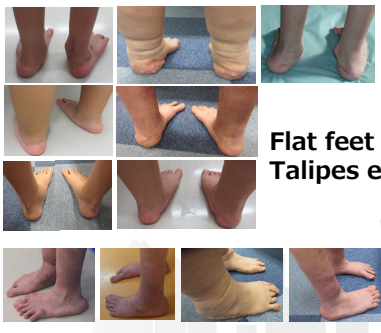
The Features of Feet and Toes



Talipes equinovarus
Toes deformities

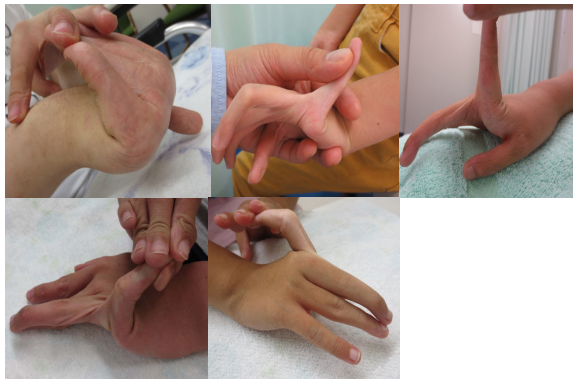


Flat feet
Callosity

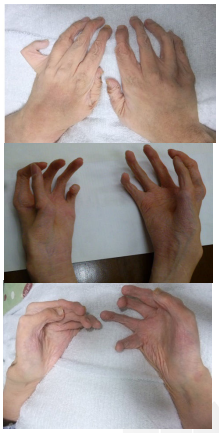


Flat feet
Talipes equinovarus

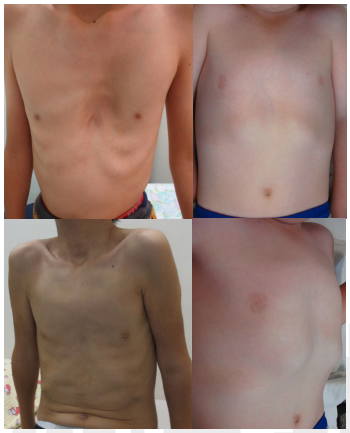
Other skeletal features



Joint laxity and hyperextension

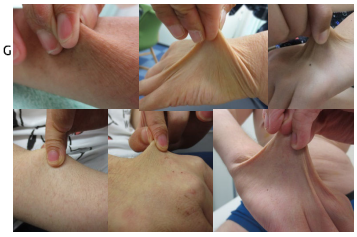


Joint contractures

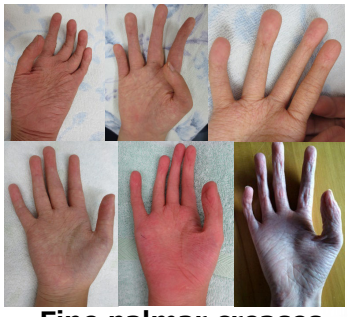


Pectus deformities

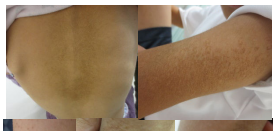
Features of the Skin

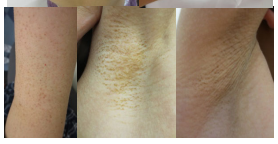


Hyperextensibility

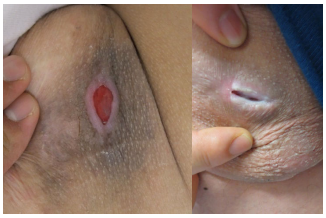


Fine palmar creases

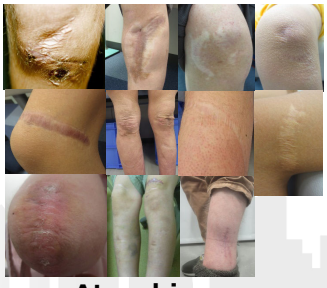




Pigmentation of the skin

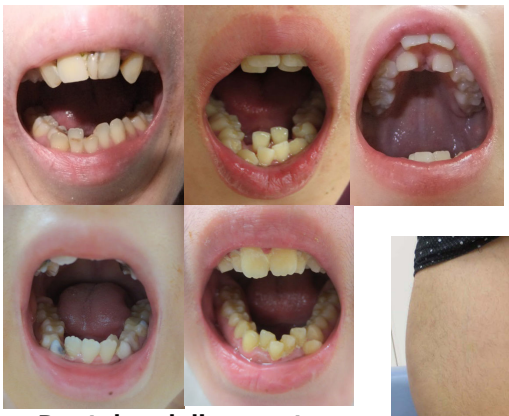


Fistula formations

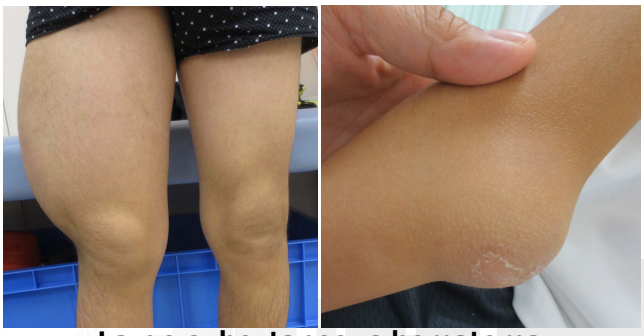


Atrophic scars

Other Findings



Dental malalignment and Dental crowding



Large subcutaneous hematoma

【Natural Course : Life Events】

Prenatal period	At birth	Neonatal period
The risk for events 44% [18/41] ・decreased fetal movement ・intrauterine growth retardation ・oligohydramnios ・single umbilical arteries ・threatened premature delivery ・fetal ultrasound abnormalities (hands and feet abnormalities, hydronephrosis, abnormalities of brain structures)	The risk for events 24% [11/45] ・cesarean section for term breech presentation ・emergency cesarean section for fetal distress ・vacuum extraction ・buccal injury	The risk for events 91% [43/47] ・found musculoskeletal complications ・feeding difficulties ・hypotonia ・respiratory failure ・hearing impairment

From infancy to childhood	adolescence	adulthood
・onset of large subcutaneous hematoma (1-10 years old) ・onset of recurrent dislocations (2-5 years old) ・cryptorchidism ・spinal deformities ・recurrent urinary tract infection ・constipation ・hearing impairment ・refractive error	・progression of musculoskeletal complications ・delayed puberty/hypogonadism ・constipation ・hearing impairment	・progression of musculoskeletal complications ・pneumothorax ・diverticulitis ・valvular disease ・constipation ・hearing impairment

【Natural Course : Fatal Cases】

	1	2	3	4	5	6	7	8	9
Age at death	0 month	1-4 month	1-4 month	1-4 month	5 years	37 years	12 years	59 years	28 years
Cause of death	Respiratory failure	-	-	-	-	Large intestinal perforation, Skin ulcer	Subcutaneous hematoma, Sepsis	Cerebral hemorrhage	Infective carditis

→ Complication-related death

Conclusions and Prospects

- This is the world's first and largest international collaborative clinical study on mcEDS-*CHST14*.
- Typical craniofacial, skeletal, and cutaneous features as well as other common multisystem features are described, and an overview of the natural history was also shown.
- mcEDS-*CHST14* is one of the serious types of EDS that can be associated with severe life-threatening symptoms.
- We are going to proceed with basic research, using KO mice and iPS cells, for the development of prevention and treatment of progressive multisystem fragility-related manifestations (e.g. skeletal deformities, large subcutaneous hematoma), which could threaten patients' lives and impair their quality of lives.

Acknowledgment

The Ehlers Danlos Society
SCIENTIFIC MEETING RARER TYPES TOKYO 2019

We would like to express our deep appreciation to the patients who cooperated with us and the collaborative researchers around the world who provided us with valuable clinical information.

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-Ms. Emiko Kise
-Ms. Tomomi Kojima

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