



## ORIGINAL ARTICLE

# Delineation of musculocontractural Ehlers–Danlos Syndrome caused by dermatan sulfate epimerase deficiency

Charlotte K. Lautrup<sup>1</sup> | Keng W. Teik<sup>2</sup> | Ai Unzaki<sup>3,4</sup> | Shuji Mizumoto<sup>5</sup> |  
Delfien Syx<sup>6</sup> | Heng H. Sin<sup>7</sup> | Irene K. Nielsen<sup>1</sup> | Sara Markholt<sup>8</sup> | Shuhei Yamada<sup>5</sup> |  
Fransiska Malfait<sup>6</sup> | Naomichi Matsumoto<sup>9</sup> | Noriko Miyake<sup>9</sup>  | Tomoki Kosho<sup>3,10</sup> 

<sup>1</sup>Department of Clinical Genetics, Aalborg University Hospital, Aalborg, Denmark

<sup>2</sup>Genetic Department, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

<sup>3</sup>Center for Medical Genetics, Shinshu University Hospital, Matsumoto, Japan

<sup>4</sup>Problem-Solving Oriented Training Program for Advanced Medical Personnel: NGSD (Next Generation Super Doctor) Project, Matsumoto, Japan

<sup>5</sup>Department of Pathobiochemistry, Faculty of Pharmacy, Meijo University, Nagoya, Japan

<sup>6</sup>Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium

<sup>7</sup>Department of Pediatrics, Sabah Women and Children's Hospital, Kota Kinabalu Sabah, Malaysia

<sup>8</sup>Department of Clinical Genetics, Aarhus University Hospital, Aarhus, Denmark

<sup>9</sup>Department of Human Genetics, Yokohama City University Graduate School of Medicine, Yokohama, Japan

<sup>10</sup>Department of Medical Genetics, Shinshu University School of Medicine, Matsumoto, Japan

## Correspondence

Noriko Miyake, Department of Human Genetics, Yokohama City University Graduate School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan.  
Email: nmiyake@yokohama-cu.ac.jp

Tomoki Kosho, Department of Medical Genetics, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan.  
Email: ktomoki@shinshu-u.ac.jp

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## Abstract

**Background:** Musculocontractural Ehlers–Danlos Syndrome (mcEDS) is a rare connective tissue disorder caused by biallelic loss-of-function variants in *CHST14* (mcEDS-*CHST14*) or *DSE* (mcEDS-*DSE*), both of which result in defective dermatan sulfate biosynthesis. Forty-one patients with mcEDS-*CHST14* and three patients with mcEDS-*DSE* have been described in the literature.

**Methods:** Clinical, molecular, and glycobiochemical findings in three additional patients with mcEDS-*DSE* were investigated.

**Results:** Three patients from two families shared craniofacial characteristics (hypertelorism, blue sclera, midfacial hypoplasia), skeletal features (pectus and spinal deformities, characteristic finger shapes, progressive talipes deformities), skin features (fine or acrogeria-like palmar creases), and ocular refractive errors. Homozygous pathogenic variants in *DSE* were found: c.960T>A/p.Tyr320\* in patient 1 and c.996dupT/p.Val333Cysfs\*4 in patients 2 and 3. No dermatan sulfate was detected in the urine sample from patient 1, suggesting a complete depletion of DS.

**Conclusion:** McEDS-*DSE* is a congenital multisystem disorder with progressive symptoms involving craniofacial, skeletal, cutaneous, and cardiovascular systems,

Charlotte K. Lautrup, Keng W. Teik and Ai Unzaki contributed equally to this work.

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similar to the symptoms of mcEDS-*CHST14*. However, the burden of symptoms seems lower in patients with mcEDS-*DSE*.

#### KEYWORDS

clinical features, delineation, dermatan sulfate, musculocontractural EDS-*DSE*

## 1 | INTRODUCTION

Musculocontractural Ehlers–Danlos Syndrome (mcEDS) is a rare connective tissue disorder, caused by biallelic loss-of-function variants in *CHST14* (mcEDS-*CHST14*) (MIM#601776) or in *DSE* (mcEDS-*DSE*) (MIM#615539), both of which result in defective dermatan sulfate (DS) biosynthesis (Brady, Demirdas, & Fournel-Gigleux, 2017; Malfait, Francomano, & Byers, 2017). Hallmarks of mcEDS include altered craniofacial features, multiple congenital contractures (e.g., adducted thumbs, talipes equinovarus), characteristic fine palmar creases, peculiar finger shapes, progressive spinal and foot deformities, large subcutaneous hematomas, and ophthalmological and urogenital involvement (Brady et al., 2017). Only five patients with mcEDS-*DSE* have been described in the literature (Müller, Mizumoto, & Suresh, 2013; Schirwani et al., 2019; Syx, Van Damme, & Symoens, 2015) in contrast to 41 patients with mcEDS-*CHST14* (Brady et al., 2017; Kono, Hasegawa-Murakami, & Sugiura, 2016; Sandal & Kaur, 2018). Here, we report detailed clinical, molecular, and glycobiological findings in three additional patients with mcEDS-*DSE*.

## 2 | CLINICAL REPORT

Patient 1, a 19-year-old man and average high school student, was born of consanguineous Turkish parents. Pregnancy was complicated by premature rupture of membranes and he was delivered by emergency cesarean section at gestational week 29. At birth, he exhibited cyanosis and bradycardia with Apgar scores of 7 at 1 min and 10 at 5 min. His birth weight was 1,215 g (−1 standard deviation [*SD*]), length was 35 cm (−3 *SDs*), and occipitofrontal circumference (OFC) was 26.7 cm (−0.5 *SD*).

In infancy to early childhood, he exhibited large anterior fontanel, brachycephaly, low hairline, wide neck, hypertelorism, blue sclera, short nose with hypoplastic columella, long philtrum, and thin upper lip vermilion. He had bilateral adducted thumbs, arachnodactyly, and rocker bottom feet, but did not exhibit talipes equinovarus. He had umbilical hernia, diastasis recti, bilateral hydronephrosis, and cryptorchidism. He experienced recurrent constipation, which was treated with laxatives. Echocardiography revealed an atrial septal defect and patent ductus arteriosus. He exhibited delayed motor development and mild hypotonia; he sat without support at

age 8 months and walked unassisted at 18 months. He underwent surgeries for strabismus and cryptorchidism at 3 and 5 years of age, respectively.

At 8 years of age, brain magnetic resonance imaging showed cortical heterotopia. He was diagnosed with myopia and strabismus, and later diagnosed with unilateral 40 dB high-frequency sensorineural hearing loss. During his school years, he experienced repeated shoulder luxation and large subcutaneous hematomas at various locations (each antebrachium and the gluteal region) after minor traumas and without the evidence of coagulation defects. He had mild scoliosis and joint hypermobility, and underwent surgery for pes cavus at 11 years of age. His skin was hyperextensible with delayed wound healing. At 15 years of age, he had a self-limiting hemoptysis with no evidence of tuberculosis.

At 18 years of age, his height was 178 cm (−0.2 *SD*), weight was 77 kg (+0.5 *SD*), and OFC was 58 cm (+2 *SDs*). He had downslanting palpebral fissures, grey sclera, but no hypertelorism. His ears were not rotated or low-set; however, his right ear showed underfolded helix, lower insertion of the lobule than on the left side, and pits on the posterior conchae. He had dental crowding, and his skin was hyperextensible, with fine palmar (Figure 1b) and solar creases, and broadened surgical scars on the right foot (Figure 1d). His fingers were long and slender with joint laxity and a swan-neck deformity, as well as the radial deviation of the bilateral second to fourth fingers (Figure 1a). He had bilateral pes cavus (Figure 1e), mild pectus excavatum (Figure 1c), and lumbar scoliosis. He had no echocardiographic abnormalities, but was diagnosed with high blood pressure and treated with an angiotensin-converting enzyme inhibitor.

Patient 2, a 14-year-old girl and average student, was born of consanguineous Indian parents. After an uncomplicated pregnancy, she had been delivered vaginally at term with a birth weight of 2.5 kg; she had normal developmental milestones. She experienced intermittent joint pain and swelling after exercise (left knee and right ankle) and exhibited scoliosis at 11 years of age. She had astigmatism, but normal hearing.

At 12.5 years of age, her height was 141 cm, weight was 27.9 kg, and OFC was 48 cm (all below the third centile). She had hypertelorism, blue sclera, and a broad tall nasal bridge; she had no skin hyperextensibility or apparent scars. Her fingers and toes were long with mild finger webbing (Figure 1f,h), and crisscrossing palmar and



**FIGURE 1** Clinical photographs of patient 1 at 18 years of age (a–e), patient 2 at 12.5 years of age (f–h), and patient 3 at 21 years of age (i–m)

solar creases (Figure 1g). Joint laxity was limited to the dorsal subluxation of the metacarpophalangeal joints, especially the thumbs. Her chest was asymmetric with pectus carinatum and she had thoracic kyphoscoliosis. Her bone mineral density, measured by dual-energy X-ray absorptiometry, was reduced to 0.659 g/cm<sup>2</sup> at the lumbar spine (normal range for 20-year-old women, 0.8–1.2 g/cm<sup>2</sup>), and 0.513 g/cm<sup>2</sup> at the femoral neck (normal range for 20-year-old women, 0.6–1.0 g/cm<sup>2</sup>). She had no echocardiographic abnormalities or muscle weakness.

Patient 3, a 22-year-old man and the older brother of patient 2, was born at term after an uncomplicated pregnancy, with a birth weight of 2.9 kg. He had bilateral talipes equinovarus, which was treated with serial casting and surgical correction at 1 year of age. His early psychomotor development was normal. He experienced right arm fracture after a fall at 4 years of age and right fifth finger fracture at 7 years of age. He developed a large subcutaneous hematoma in his left calf twice, both requiring surgical evacuation. He also had intermittent bruises over his shins. He exhibited scoliosis at 14 years of age, which progressed and required surgical correction at 20 years of age. He had myopia, but normal hearing. He attended a normal school, but did not perform well.

At 21 years of age, his height was 151 cm and weight was 40 kg (both below the third centile). He had small simple ears, mild hypertelorism, blue sclera, a broad tall nasal bridge (Figure 1i), and retained primary teeth. Atrophic surgical scars, finger webbing, and abnormal palmar (Figure 1j,k) and solar creases were present; skin hyperextensibility was absent. He had an asymmetric chest (Figure 1i), long fingers and toes (Figure 1l,m), hallux valgus, and plantar subluxation of the metatarsophalangeal joint of the halluces, as well as prominent calcaneus (Figure 1m). He developed multiple joint contractures resulting in reduced ankle dorsiflexion, hip flexion, elbow extension, and wrist dorsiflexion.

### 3 | MOLECULAR INVESTIGATION

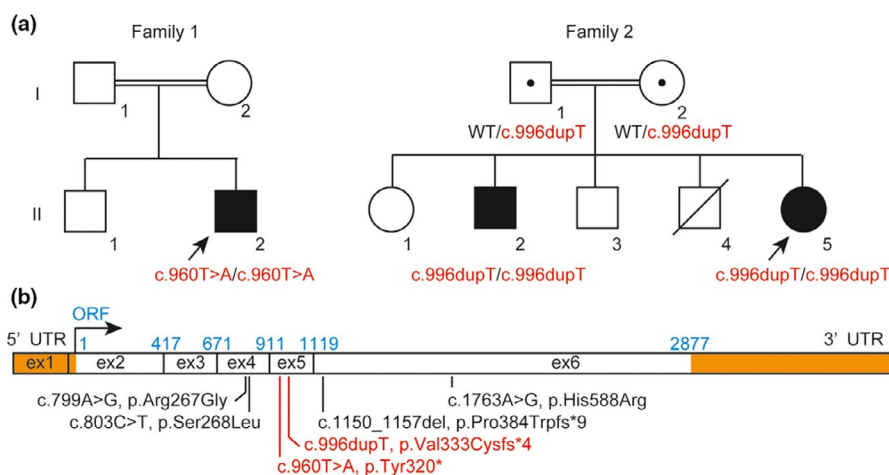
Sanger sequencing of *CHST14* and *DSE* was performed for patient 1 based on clinical suspicion of mcEDS. No pathogenic variants were detected in *CHST14*; a homozygous nonsense variant was identified in *DSE* (NM\_013352.4, c.960T>A, p.(Tyr320\*)) (Figure 2a). For patient 2, whole exome sequencing was performed (Data S1; Miyake, Tsurusaki, & Koshimizu, 2016) and a homozygous frameshift variant was identified in *DSE* (NM\_013352.4, c.996dupT, p.(Val333Cysfs\*4)); patient 3 exhibited homozygosity for this variant, whereas their parents exhibited heterozygosity (Figure 2a). None of the identified *DSE* variants were registered in ExAC, Exome Variant Server, or Human Genetic Variant Database.

### 4 | GLYCOBIOLOGICAL ANALYSIS

Disaccharide compositions of DS and chondroitin sulfate (CS) chains in urine samples from patient 1 and an age-matched healthy man were analyzed as described previously (Data S2; Mizumoto, Kosho, & Hatamochi, 2017). DS disaccharide was not detected in the urine of patient 1, whereas it was present in the urine of the age-matched healthy man (Figure S1; Table S1A). In contrast, the amount of CS disaccharides in the urine was similar between patient 1 and the age-matched healthy man (Figure S1; Table S1B).

### 5 | DISCUSSION

We presented three patients with mcEDS-*DSE* from two new families. Clinical and molecular features of the five previously reported patients (Müller et al., 2013; Schirwani et al., 2019;



**FIGURE 2** Molecular investigation. (a) Pedigree information and intrafamilial segregation of detected variants in *DSE*. (b) cDNA structure of *DSE* and pathogenic variants (mcEDS-*DSE*). Untranslated regions (UTRs) are shown as orange bars. The first base and each position of exon-exon junctions in open reading frames (ORFs) are shown in light blue. Pathogenic variants reported in this study are shown in red characters. ex: exon

TABLE 1 Clinical and molecular features of patients with mcEDS-DSE

Patient	1	2	3	4	5	6	7	8	Total (n = 8)	mcEDS- CHST14 (n = 41)
Family	1	2		3	4	5	6			
Publication	Müller et al. (2013)	Syx et al. (2015)		Schirwani et al. (2019)		This study				
Mutation (cDNA)	c.803C>T/ homo	c.799A>G/homo		Patient 1 c.1150_1157del/ homo	Patient 2 c.1763A>G/ homo	Patient 1 c.960T>A/ homo	Patient 2 c.996dupT/homo	Patient 3		
Amino acid change (amino acid)	p.Ser268Leu	p.Arg267Gly		p.Pro384Trpfs*9	p.His588Arg	p.Tyr320*	p.Val333Cysfs*4			
Age at the publication (years)	2	48	39	33	2	19	14	22		
Sex	M	F	F	M	M	M	F	M	M 5, F 3	M 22, F 19
Origin	Indian	Spanish		Portuguese	Pakistani	Turkish	Indian			
Craniofacial	Yes	NR	NR	NR	Yes	Yes	NR	NR	3/3 (100%)	23
Large fontanel with delayed closure (early childhood)	NR	Yes	Yes	Yes	NR	NR	NR	NR	3/3 (100%)	
Small mouth/micro- retrognathia (infancy)	NR	NR	NR	Yes <sup>a</sup>	NR	No	No	Yes	2/4 (50%)	11
Slender face/protruding jaw (from adolescence)	NR	NR	NR	No <sup>a</sup>	NR	Yes	No	No	1/4 (25%)	10
Facial asymmetry (from adolescence)	Yes	Yes	Yes	NR	NR	Yes	Yes	Yes	6/6 (100%)	35
Hypertelorism	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	7/8 (88%)	34
Downslanting palpebral fissures	NR	Yes	Yes	No <sup>a</sup>	Yes	Yes	No	No	4/7 (57%)	25
Short palpebral fissures	Yes	Yes	Yes	NR	NR	Yes	Yes	Yes	6/6 (100%)	
Blue sclera	NR	Yes	Yes	NR	NR	Yes	Yes	Yes	5/6 (83%)	
Midfacial hypoplasia	NR	Yes	Yes	No <sup>a</sup>	NR	Yes	Yes	No	2/7 (29%)	16
Short nose with hypoplastic columella	NR	Yes	Yes	No <sup>a</sup>	No <sup>a</sup>	No	No	No		

(Continues)

TABLE 1 (Continued)

Patient	1	2	3	4	5	6	7	8	Total (n = 8)	mEDS- CHST14 (n = 41)
Ear deformity (e.g. low-set, posterior rotation, prominent)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	7/8 (88%)	33
Palatal abnormalities (e.g. high, cleft)	Yes	NR	NR	Yes	No	No	Yes	NR	3/5 (60%)	25
Long philtrum and/or thin upper lip vermillion	NR	Yes (thin upper lip vermillion)	Yes (both)	No <sup>a</sup>	Yes (thin upper lip vermillion) <sup>a</sup>	No	No	No	3/7 (43%)	24
Crowded teeth	Yes	NR	NR	Yes	NR	Yes	NR	NR	3/3 (100%)	
Brachycephaly/flat occiput	Yes	NR	NR	No <sup>a</sup>	Yes	Yes	No	No	3/6 (50%)	
Others		Hypotonic face with wrinkled eyelids, cheeks, and neck		Prominent forehead						
<b>Skeletal</b>										
Congenital multiple contractures <sup>a</sup>	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	7/8 (88%)	41
Adducted thumbs	Yes (bil)	No	No	Yes (bil)	Yes (bil)	Yes (bil)	No	No	4/8 (50%)	33
Talipes equinovarus	Yes (bil)	Yes (bil)	Yes (bil)	Yes (bil)	Yes (bil)	No	No	Yes (bil)	6/8 (75%)	41
Recurrent/chronic joint dislocations	NR	No	NR	No	No	Yes (shoulder)	No	No	1/6 (17%)	20
Pectus deformities	NR	NR	NR	NR	No	Yes (mild excavatum)	Yes (excavatum, asymmetric)	Yes (excavatum, asymmetric)	3/4 (75%)	18
Spinal deformities	NR	No	Yes (mild to moderate scoliosis)	No	No	Yes (mild lumbar scoliosis)	Yes (scoliosis, thoracic kyphoscoliosis)	Yes (scoliosis)	4/7 (57%)	22
Finger shape characteristics	Yes (long, tapering)	Yes (long, slender, tapering)	Yes (long, slender, tapering)	Yes (cylindrical)	Yes (long, slender)	Yes (long, slender)	Yes (long, slender)	Yes (long, slender)	8/8 (100%)	35

(Continues)

TABLE 1 (Continued)

Patient	1	2	3	4	5	6	7	8	Total (n = 8)	mEDS- CHST14 (n = 41)
Progressive foot deformities	NR	Yes (short, broad feet with short toes)	NR	Yes (wide feet with clawed toes)	Yes	Yes (cavus)	Yes (uni. planus)	Yes (hallux valgus, planus, cavus)	6/6 (100%)	26
Marfanoid habitus/slender build	NR	NR	NR	No	NR	No	Yes	Yes	2/4 (50%)	13
Joint hypermobility	Yes	Yes <sup>b</sup>	Yes <sup>b</sup>	No	NR	Yes	No	No	4/7 (57%)	
Osteoporosis	NR	NR	NR	NR	NR	NR	Yes	NR	1/1 (100%)	
Others		Joint pain		Chronic pain, brachydactyly, Madelung deformity	Torticollis		Joint pain	Fractures		
Skin										
Hyperextensibility	NR	Yes	Yes	No <sup>c</sup>	No	Yes	No	No	3/7 (43%)	24
Bruisability	NR	Yes	Yes	NR	Yes	No	No	Yes	4/6 (67%)	21
Fragility	NR	Yes	Yes	No	No	No	No	No	2/7 (29%)	21
Atrophic scars	Yes	NR	NR	NR	No	No	No	Yes	2/5 (40%)	
Hyperalgesia to pressure	NR	NR	NR	NR	NR	NR	NR	NR	0/0 (0%)	8
Fine or acrogeria-like palmar creases	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7/8 (88%)	28
Recurrent subcutaneous infections	NR	NR	NR	NR	NR	No	No	No	0/3 (0%)	8
Fistula formation	NR	NR	NR	NR	NR	No	No	No	0/3 (0%)	
Delayed wound healing	Yes	NR	NR	NR	NR	Yes	No	No	2/4 (50%)	
Umbilical hernia	NR	NR	NR	NR	NR	Yes	No	No	1/3 (33%)	
Others		Transparent, thin	Transparent, thin	Piezogenic pedal papules						
Cardiovascular										
Congenital heart defects	Yes (PFO)	NR	No	No	Yes (ASD)	Yes (ASD, PDA)	No	NR	3/6 (50%)	6

(Continues)

TABLE 1 (Continued)

Patient	1	2	3	4	5	6	7	8	Total (n = 8)	mcEDS- CHST14 (n = 41)
Valve abnormalities	No	Yes (MVP, myxomatous valve with ruptured chordae, severe MR)	No	No	NR	No	No	NR	1/6 (17%)	7
Enlargement of ascending aorta	No	No	No	No	NR	No	No	NR	0/6 (0%)	2
Large subcutaneous hematoma	NR	Yes	Yes	NR	No	Yes (elbow, arm, forehead, knee, gluteal region)	NR	Yes (calf)	4/5 (80%)	20
Respiratory	NR	NR	NR	No	No	No	No	No	0/5 (0%)	3
Pneumothorax/ Hemopneumothorax	NR	NR	NR	No	No	No	No	No	0/5 (0%)	3
Gastrointestinal	NR	NR	NR	No	No	Yes	No	No	1/5 (20%)	9
Constipation	NR	NR	NR	No	No	No	No	No	0/5 (0%)	4
Diverticula (e.g. perforation, infection)	NR	NR	NR	No	No	No	No	No	0/5 (0%)	4
Others			Eventration after gallbladder surgery							
Urological	NR	NR	NR	NR	NR	No	NR	NR	0/1 (0%)	7
Nephrolithiasis or cystolithiasis	NR	NR	NR	No	NR	Yes (bil)	NR	NR	1/2 (50%)	10
Hydronephrosis	NR	Yes (prolapse after two deliveries)	NR	NR	NR	No	NR	NR	1/2 (50%)	2
Bladder dysfunction	NR	NR	NR	NR	NR	No	NR	NR	0/1 (0%)	3
Recurrent urinary tract infection	NR	NR	NR	NR	NR	No	NR	NR	0/1 (0%)	3

(Continues)



TABLE 1 (Continued)

Patient	1	2	3	4	5	6	7	8	Total (n = 8)	mcEDS- CHST14 (n = 41)
Inguinal hernia	Yes (lt)	NR	Yes	Yes (bil)	NR	Yes (lt)	No	No	4/6 (67%)	2
Cryptorchidism in male	NR	NR	NR	Yes	No	Yes (bil)	NR	No	2/4 (50%)	17
Ophthalmological										
Strabismus	NR	No	No	No	Yes	Yes (esotropia)	No	No	2/7 (29%)	14
Glaucoma or elevated intraocular pressure	NR	No	No	No	No	No	No	No	0/7 (0%)	8
Refractive error	NR	No	No	Yes (my)	No	Yes (my)	Yes (as)	Yes (my)	4/7 (57%)	16 (hy 4, my 12, as 5)
Retinal detachment	NR	No	No	NR	NR	No	No	No	0/5 (0%)	6
Otolological										
Hearing impairment	NR	NR	NR	NR	NR	Yes (mild, uni, SNHL for high- pitched sound)	No	No	1/3 (33%)	10
Sexual development-related										
Hypogonadism	NR	NR	NR	NR	NR	No	NR	No	0/2 (0%)	
Others		Uterine prolapse after two deliveries								
Central nervous system										
Ventricular abnormalities (enlargement, asymmetry)	No	NR	NR	NR	No	No	NR	NR	0/3 (0%)	8
Hypoplasia of septum pellucidum	No	NR	NR	NR	No	No	NR	NR	0/3 (0%)	
Dandy-Walker variant	No	NR	NR	NR	No	No	NR	NR	0/3 (0%)	
Muscular system										
Hypotonia	NR	Yes	Yes	NR	NR	Yes	NR	NR	3/3 (100%)	14
Muscle weakness	Yes	Yes	NR	NR	NR	Yes	No	No	3/5 (60%)	
Development										

(Continues)

TABLE 1 (Continued)

Patient	1	2	3	4	5	6	7	8	Total (n = 8)	mcEDS- <i>CHST14</i> (n = 41)
Motor developmental delay	Yes	NR	NR	NR	Yes	Yes	No	NR	3/4 (75%)	23
Intellectual disabilities	No	NR	NR	No	NR	No	No	Yes	1/5 (20%)	4

Abbreviations: as, astigmatism; ASD, atrial septal defect; bil, bilateral; F, female; hy, hyperopia; lt, left; M, male; MR, mitral valve regurgitation; MVP, mitral valve prolapse; my, myopia; No, absent; NR, not recorded; PDA, patent ductus arteriosus; PFO, persistent foramen ovale; SNHL, sensorineural hearing loss; uni, unilateral; Yes, present.

<sup>a</sup>Judged from images in the relevant report.

<sup>b</sup>In younger ages but not in adulthood.

<sup>c</sup>Only at the elbows.

Syx et al., 2015), including additional information of the sisters reported by Syx et al. (2015) and the three patients in this series are reviewed in Table 1. Truncating variants in *DSE* were identified in the three current patients, whereas previously detected variants were missense in three families and a frameshift variant in one family. Significant reduction or loss of epimerase activity and a marked reduction in DS disaccharides were demonstrated in the patient with p.(Ser268Leu) (Müller et al., 2013). A minor fraction of DS was detected as the glycosaminoglycan component of decorin in the patient with p.(Arg267Gly) (Syx et al., 2015). The preservation of DS moieties in mcEDS-*DSE*, in contrast to the complete loss of DS in mcEDS-*CHST14* (Dündar, Müller, & Zhang, 2009; Miyake, Kosho, & Mizumoto, 2010), suggested the residual activity of mutant DSE or partially compensating activity of dermatan sulfate epimerase-like protein (encoded by *DSEL*) (Syx et al., 2015). The measurement of the disaccharide compositions of DS and CS chains in a urine sample is a recently established non-invasive method to screen for mcEDS-*CHST14* through the assessment of DS biosynthesis (Mizumoto et al., 2017). The lack of DS in the urine sample from patient 1 in this study suggests that this test may also be useful for screening of mcEDS-*DSE*.

Frequent (affecting at least three patients) craniofacial and skeletal features in mcEDS-*DSE* are shown in Table 1. Two reported patients (Schirwani et al., 2019; Syx et al., 2015) and patient 2 in the present report had joint pain. Frequent skin, vascular, ocular, nervous, and muscle features are also shown in Table 1. Even though the number of patients with mcEDS-*DSE* is small and an accurate frequency of each feature in patients with mcEDS-*CHST14* is unavailable, the general patterns of symptoms seem to be similar between the two subtypes. However, several patients with mcEDS-*CHST14* had life-threatening complications (e.g., infectious endocarditis, Kono et al., 2016; Kosho, Miyake, & Hatamochi, 2010, fulminant gastric ulcer, Kosho et al., 2010; diverticular perforation, Kosho et al., 2010; Mochida, Amano, & Miyake, 2016), and five patients died (Dündar, Kurtoglu, & Elmas, 2001; Janecke, Li, & Boehm, 2016). No such serious complication has yet been observed in patients with mcEDS-*DSE*. Syx et al. (2015) hypothesized that the residual availability of some DS structures, including iduronic acid-containing disaccharide units, might contribute to an attenuated phenotype.

In conclusion, mcEDS-*DSE* constitutes a multisystem disorder with congenital and progressive features, as well as the depletion of DS, similar to mcEDS-*CHST14*. However, symptoms tend to be milder in patients with mcEDS-*DSE*.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

The data are not available for public access because of patient privacy concerns, but are available from the corresponding author on reasonable request.

## ORCID

Noriko Miyake  <https://orcid.org/0000-0003-0987-310X>

Tomoki Kosho  <https://orcid.org/0000-0002-8344-7507>

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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