TABLE I. Clinical Characteristics of Reported Patients With D4ST1 Deficiency (Continued)

Family	Patient	Origin	*CHST14* Mutations	Age at initial publicaion (d, days; m, months; y, years)	Sex	Craniofacial													Skeletal									Cutaneous						Cardiovascular				Gastrointestinal		
						Large fontanelle (early childhood)	Hypertelorism	Down-slanting palpebral fissures	Blue sclerae	Short nose with hypoplastic columella	Ear deformities	Palatal abnormalities	Long philtrum and thin upper lip	Small mouth/micro-retrognathia in infancy	Short neck	Slender face/protruding jaw from school age	Facial asymmetricity from school age	Malfanoid habitus/slender build	Congenial multiple contractions	Recurrent/chronic joint dislocations	Pectus deformities	Spinal deformities	Peculiar fingers (tapering – slender and cylindrical)	Progressive talipes deformities	Hyperextensibility/ redundancy	Bruisability	Fragility/atophic scars	Fine/Acrogeria-like palmar creases	Hyperalgesia to pressure	Recurrent subcutaneous infections/fistula	Congenital heart defects	Valve abnormalities	Large subcutaneous hematomas	(Hemo) pneumathorax	Constipation	Others
ATCS																																							
1	1	Turkish	V49X homo	3.5y	F	+	+	+	+		P, PR	H	+		+				+			Exa	KSa	+	Planus, valgus#				+a			–						
	2			1.5y	M	+	+	+	+	+	P, PR		+		+	+a		+a	+	+a		Exa	KSa	+	Planus, valgus#				+a			–						
	3			6y	F		+	+		+	P		+			+	+	+	+			F–T	S	+	Varus				+									
2	4	Japanese	Y293C homo	4y	M	+	+	+		+	LS	CL/CP	+						+	+		Ca		+	Planus, valgus													
	5			7m	M	+	+	+		+	LS	CSP	+						+	+				+								ASD						
3	6	Austrian	R213P homo	0d†	M	+	+	+			PR, LS				+				+				S	+								ASD, CoA					Common mesentery
	7			12m	M	+	+	+	+		D, PR				+	+a		+a	+			F–Ta		+	Planus, valgus#				+a			–						Absence of gastrocolic omentum, spontaneous volvulus of small intestine
4	8	Turkish	R135G / L137Q	1–4m†	F														+																			
	9			1–4m†	M														+																			
	10			1–4m†	M														+																			
	11			3m	M	+	+	+	+		D, LS	H	+		+				+					+								–						
MCEDS																																							
1	1	Turkish	V49X homo	22y	F	+		+		+	PR, LS	H	+			+	+	+	+			F–T	KS	+	Planus, valgus	+	+	+	+		+	–	–					Hiatal hernia, gastroesphageal reflux, abdominal pain
	2			21y	F	+		+	+			H	+						+	+		F–T	S	+	Small, broad	+	+	+	+									
2	3	Indian	E334GfsX107 homo	12y	F				+		LS		–					+	+	+			KS	+	Planus, valgus	+	+	+	+		+							Duodenum obstruction due to malrotation
EDSKT																																							
1	1	Japanese	P281L / Y293C	11y	F	+	+	+	+	+	LS	H	+	+		+	+	+	+	+		Ex	KS	+	Planus, valgus	+	+	+	+	+	+	ASD	TR, TVP, MVP	+	–	+	Gastric ulcer§
2	2	Japanese	P281L homo	14y	F	+	+	+	+	+	LS	H	+	+		+	+	+	+	+		F–T	S	+	Cavus, valgus	+	+	+	+	+	+	–		+	+§	+	Diverticular perforation§
3	3	Japanese	P281L homo	32y	M	+	+	+	+	+	LS	H	+	+		+	+	+	+	+		F–T	KS	+	Planus, valgus	+	+	+	+	+	+		AR, ARD, MR	+	+	+	Diverticular perforation
4	4	Japanese	K69X / P281L	32y	M		+		+			H				+	+	+	+	+		Ex	KS	+	Planus, valgus	+	+	–	+	–	–			+	+	–	
5	5	Japanese	P281L / C289S	20y	F	+	+	+	+	+	LS	H	+	+		+	+	+	+	+		Ex	S	+	Planus, valgus	+	+	+	+	+	+		AR, MR, IE	+	–	+	
6	6	Japanese	P281L / Y293C	4y	F	+	+	+	+	+	LS	H	+						+	+		Ex	S	+	Planus	+	+	+	+	+	+			+	–	+	
Present report (EDSKT)																																							
7	7	Japanese	P281L / Y293C	2y	M	+	+	+	+	+	PR, LS	H	+	+					+	+		F–T	S	+	Planus, valgus	+	+	+	+	–	+	–	ARD	–	–	+	
8	8	Japanese	F209S / P281L	6y	M	+	+	+	+	+	PR, LS	H	+	+					+	+	+	Ex		+	Planus	+	+	–	+	+	–	PDA	MVP	+	–	+	Abdominal pain

ATCS, adducted thumb-clubfoot syndrome; EDSKT, Ehlers–Danlos Syndrome, Kosho Type; MCEDS, Musculocontractural Ehlers–Danlos Syndrome
+, present; Blank, information not available; †, died; F, female; M, male; P, prominent; PR, posteriorly rotated; LS, low set; D, dysplastic; H, high; CL, cleft lip; CP, cleft palate; CSP, cleft soft palate;
Ex, excavatum; F–T, flat and thin; Ca, carinatum; KS, kyphoscoliosis; S, scoliosis; ASD, atrial septal defect; CoA, coarctation of aorta; PDA, patent ductus arteriosus;
TR, tricuspid valve regurgitation; TVP, tricuspid valve prolapse; MVP, mitral valve prolapse; AR, aortic valve regurgitation; ARD, aortic root dilation; MR, mitral valve regurgitation; IE, infectious endocarditis
ATCS Patient 1 died at age 6 years [Dündar et al., 2009].
a, Information from reassessment by Dündar et al. [2009], describing ATCS P2 at age 15 years and ATCS P7 at age 8 years
b, Information from reassessment by Kosho et al. [2010], describing EDSKT1 at age 16 years and EDSKT2 at age 32 years.

TABLE II. Clinical Characteristics of Reported Patients With D4ST1 Deficiency

		Urogenital				Ophthalmological						Development			Growth (prenatal)				Growth (postnatal)				
Family	Patient	Nephro (Cysto) lithiasis	Cryptorchidism	Others	Breast development	Strabismus	Refractive errors	Glaucoma/elevated intraocular pressure	Others	Hearing impairment	Ventricular abnormalities (brain)	Gross motor delay	Age of unassisted walk (y, years; m, months)	Mental delay	Gestational weeks	Birth length (centile or SD)	Birth weight (centile or SD)	Birth OFC (centile or SD)	Age (y, years; m, months)	Height (centile or SD)	Weight (centile or SD)	OFC (centile or SD)	References
ATCS																							
1	1					+					Enl	+	No	+	Term				3.5y	25-50th	50th	50th	Dündar et al., 1997
	2					+		+			Asym	+		+c	Term				1.5y	50th	10th	10–25th	Dündar et al., 1997
																			15ya	25–50th	<3rd		Dündar et al., 2009
	3					+													6y	10–25th	<3rd		Dündar et al., 2009
2	4		+	Hydronephrosis										–	39wk	–0.6	–0.9	–0.8	4y2m	–3.9	–1.8	–0.9	Sonoda and Kouno, 2000
	5		+	Hydronephrosis, inguinal hernia								–		–	38wk	–1.6	–1.3	–0.5	7m	–2.1	–1.4	–1.1	Sonoda and Kouno, 2000
3	6		+	Horseshoe kidney							Enl				32wk	25th	10th	25th					Janecke et al., 2001
	7		+			+					Asym	–		–	38wk	50th	25th	50th	8ya	10-25th	<3rd		Janecke et al., 2001
																							Dündar et al., 2009
4	8																						Dündar et al., 2001
	9																						Dündar et al., 2001
	10																						Dündar et al., 2001
	11	+	+	Inguinal hernia							Enl, Asym								3m	<3rd	3–10th	10th	Dündar et al., 2001
MCEDS																							
1	1	+			–		My	+	Retinal detachment, pthysis bulbi	+		+	4y		42wk	±0	–0.67		22y	–2.0		±0	Malfait et al., 2010
	2	+		Hydronephrosis, renal ptosis, ureteral stenosis	–		My	+	Retinal detachment	+		+	2y		42wk				14y	+0.68		>2.0	
2	3						My		Microcornea			+			Term		–0.88						Malfait et al., 2010
EDSKT																							
1	1			Bladder dilation, recurrent UTI, involuntary contractionb	–b	+	Hy	–	Microcornea	+	Enl	+	2y	+d	42wk	–0.1	–1.3	–1.0	7y	+0.8	–1.0	±0	Kosho et al., 2005
																			11y	+0.2	–2	+0.2	Kosho et al., 2010
																			16y	+0.3	–0.4	+0.2	
2	2	+		Atonic bladder, recurrent UTI	–b	+	My, As	+b		+		+	No	–	Term		–2.0		15y	–3.2			Kosho et al., 2005
																							Kosho et al., 2010
3	3		+	Hypogonadism		+	My, As	–	Microphthalmia	+		+		–	40wk	+1.3	+0.5	+0.8	30y	+1.2	–1.7		Kosho et al., 2010
4	4					–	–	–	Retinal detachment	–				–					23y	–0.4	–2.4		Yasui et al., 2003
																							Kosho et al., 2010
5	5	+		Delayed menarche, irregular menstruation	–	+	My, As	+		–		+	2y2m	–	39wk	–1.1	–0.4	+1.0	19y	–0.1	–0.8		Kosho et al., 2010
6	6					+	My, As	+		+		+	1y5m	–	41wk	–1.2	–0.5	–0.6	4y	–1.2	–1.3	–0.9	Kosho et al., 2010
Present report																							
7	7		+			+	Hy, As, Am	–				+	No	+	38wk3d	–1.3	+0.2	+0.4	2y	–2.2	–2.4	–1.2	Patient 1
8	8		+			+				–	Enl	+	2y6m	–	38wk	+0.3	+0.3	–0.5	6y	–0.7	–1.4	+0.1	Patient 2

ATCS, adducted thumb-clubfoot syndrome; EDSKT, Ehlers-Danlos Syndrome, Kosho Type; MCEDS, Musculocontractural Ehlers-Danlos Syndome

+, present; Blank, information not available; UTI, urinary tract infection; Hy, hyperopia; My, myopia; As, astigmatism; Am, amblyopia; Enl, enlargement; Asym, asymmetry; No, not ambulant

a, Information from reassessment by Dündar et al. [2009], describing ATCS P2 at age 15 years and ATCS P7 at age 8 years.

b, Information from reassessment by Kosho et al. [2010], describing EDSKT1 at age 16 years and EDSKT at age 32 years.

c, IQ was 91 at Porteus test and 86 at Goodenough test at age 7 years and 2 months [Janecke et al., 2001];

d, mild learning dissability

were cardinal features in patients with ATCS, EDSKT, and MCEDS. Peculiar fingers described as "tapering," "slender," and "cylindrical" were also common features. Aberrant finger movement was described in EDSKT1 [Kosho et al., 2010], EDSKT7, and EDSKT8. EDSKT1, EDSKT2, EDSKT3, and EDSKT5 were found to have tendon abnormalities such as anomalous insertions of flexor muscles, which might result in contractures [Kosho et al., 2005, 2010]. In childhood, spinal deformities (scoliosis, kyphoscoliosis) and talipes deformities (planus, valgus) occurred and progressed. Malfanoid habitus, recurrent joint dislocations, and pectus deformities (flat and thin, excavatum, carinatum) were also evident. Talipes equinovarus in seven EDSKT patients and MCEDS3 was surgically repaired [Kosho et al., 2005, 2010; Malfait et al., 2010]. EDSKT3 received tendon transplantations for defects of tendons to bilateral thumbs, and EDSKT4 received surgical fixation of bilateral ankle joints as well as surgery for carpal tunnel syndrome [Kosho et al., 2010]. MCEDS1 underwent surgery for rapidly worsened kyphoscoliosis at age 14 years [Malfait et al., 2010].

Bone mineral density (BMD) was decreased in ATCS2 at age 15 years (Z score −1.6), ATCS3 at age 6 years (Z score −4.6) [Dündar et al., 2009], EDSKT2 at age 29 years (Z score −2.4 for the lumbar spine 1–4, −2.3 for the 33% radius), and EDSKT3 at age 31 years (Z score −3.7 for the lumbar spine 1–4, −3.6 for the femoral neck) [unpublished data], whereas BMD was normal in ATCS7 at age 8 years [Dündar et al., 2009] and EDSKT1 at age 15 years (Z score +1.6 for the lumbar spine 1–4, −0.9 for the femoral neck) [unpublished data]. Urine N-telopeptide of collagen type I (NTX), an osteoclast marker, was increased at 92.8 nmol BCE/mmol Cr in EDSKT1 at age 16 years, 70.3 nmol BCE/mmol Cr in EDSKT2 at age 28 years, and 238.4 nmol BCE/mmol Cr in EDSKT3 at age 31 years [unpublished data] (normal values for premenopausal females, 9.3–54.3; males, 13.0–66.2), whereas serum bone specific alkaline phosphatase (BAP), an osteoblast marker, was normal at 12.5 U/L in EDSKT1 at age 16 years, 25.6 U/L in EDSKT2 at age 28 years, and 15.1 U/L in EDSKT3 at age 31 years (normal values, 9.6–35.4) [unpublished data]. These results in biochemical markers of bone turnover suggested an increase in osteoclast activity with normal osteoblast activity, which could cause oeteopenia or osteoporosis.

Radiologically, diaphysial narrowing of phalanges and metacarpals was noted in EDSKT1 at age 11 and 16 years, EDSKT2 at age 10 and 28 years, EDSKT3 at age 31 years, EDSKT5 at age 19 years [Kosho et al., 2005, 2010], and EDSKT7 at age 2 years and 6 months. Talipes valgus and planus or cavum, with diaphysial narrowing of phalanges and metatarsals, were noted in ATCS7 at age 8 years [Dündar et al., 2009], EDSKT1 at age 11 and 16 years, EDSKT2 at age 14 and 28 years, EDSKT6 at age 4 years [Kosho et al., 2005, 2010], and EDSKT7 at age 2 years and 6 months. Tall vertebral bodies were noted in EDSKT1 at age 11 and 16 years, EDSKT2 at age 14 and 28 years, EDSKT3 at age 31 years, EDSKT4 at age 31 years, EDSKT5 at age 19 years [Kosho et al., 2005, 2010], and MCEDS2 at age 21 years [Malfait et al., 2010], whereas they were not noted in EDSKT6 at age 2 years [Kosho et al., 2010] and EDSKT7 at age 2 years and 6 months.

Cutaneous features were common in most patients with EDSKT and MCEDS, including hyperextensibility to redundancy, bruisability, fragility leading to atrophic scars, acrogeria-like fine palmar creases or wrinkles, hyperalgesia to pressure, and recurrent subcutaneous infections with fistula formation, which lead to skin defects including decubitus necessitating plastic surgery in EDSKT2 [Kosho et al., 2005, 2010]. Excessive palmar creases were observed in ATCS2, ATCS3, and ATCS7, and delayed wound healing and ecchymoses were also recorded ATCS patients [Dündar et al., 2009]. Palmar creases increased and became deeper according to the ages, as compared among photographs of EDSKT1 at age 11 and 16 years, EDSKT2 at age 5 years and 32 years, EDSKT3 at age 32 years, EDSKT5 at age 19years, and EDSKT6 at age 4 years [Kosho et al., 2005, 2010].

Seven patients with EDSKT suffered from large subcutaneous hematomas, which sometimes progressed acutely and massively to be treated intensively (admission, blood transfusion, surgical drainage). These lesions were supposed to be caused by rupture of subcutaneous arteries or veins. Hematoma formation was mentioned in a follow-up observation of ATCS patients [Dündar et al., 2009]. Bleeding time was prolonged in ATCS7 (9 min) [Dündar et al., 2009] and EDSKT4 (11 min) [Yasui et al., 2003; Kosho et al., 2010], whereas it was normal in EDSKT1 (3 min) [Kosho et al., 2005], EDSKT3 (1 min) [unpublished data], and EDSKT7 (1.3 min). EDSKT1 had, to prevent large subcutaneous hematomas, intranasal administration of 1-desamino-8-D-arginine vasopressin (DDAVP) after injuries [Kosho et al., 2005, 2010]. A large hematoma over the buttocks in EDSKT4 was treated with intranasal DDAVP and intramuscular conjugated estrogen [Yasui et al., 2003; Kosho et al., 2010].

Two ATCS and two EDSKT patients had congenital heart defects (atrial septal defect was the most common, observed in three), and five EDSKT patients had cardiac valve abnormalities. EDSKT5 suffered from infectious endocarditis probably resulting from aortic valve or mitral valve regurgitation, and underwent surgery. Three adult patients with EDSKT developed pneumothorax or hemopneumothorax, treated with chest tube drainage; and two of them suffered from diverticular perforation, treated surgically. Various gastrointestinal abnormalities were observed: Constipation in seven EDSKT patients and abdominal pain in one EDSKT and one MCEDS patients, as well as common mesentery in ATCS6, absent gastrocolic omentum and spontaneous volvulus of small intestine in ATCS7, gastric ulcer necessitating partial gastrectomy in EDSKT1, and duodenum obstruction due to malrotation treated surgically in MCEDS3 [Janecke et al., 2001; Dündar et al., 2009; Kosho et al., 2010; Malfait et al., 2010].

Urological complications included nephrolithiasis or cystolithiasis in one ATCS, two EDSKT, and two MCEDS patients; hydronephrosis in two ATCS and one MCEDS patients, dilated or atonic bladder with recurrent urinary tract infection in two EDSKT patients, and horseshoe kidney in one ATCS patient. Hydronephrosis in MCEDS2 was caused by renal ptosis and ureteral stenosis, for which a ureteral stent was placed with a laparoscopic procedure, complicated by severe hemorrhage due to excessive tissue fragility [Malfait et al., 2010].

Cryptorchidism was observed in five ATCS and three EDSKT male patients. EDSKT3, who received orchiopexy, showed hypogonadism in adulthood. In female patients older than adolescence, poor breast development was noted in three EDSKT (EDSKT1 and

EDSKT2 showed normal menstruation cycles; EDSKT5 showed delayed menarche and irregular menstruation cycles) and two MCEDS patients. No female patients have been reported to be pregnant.

Various ophthalmological complications were observed: Strabismus in four ATCS and seven EDSKT patients, refractive errors in six EDSKT and three MCEDS patients, glaucoma or elevated intraocular pressure in one ATCS, three EDSKT, and two MCEDS patients; microcornea or microphthalmia in two EDSKT and one MCEDS patients, and retinal detachment in one EDSKT and two MCEDS. Retinal detachment in EDSKT4 [Kosho et al., 2010] and glaucoma in MCEDS1 [Malfait et al., 2010] required surgery. Hearing impairment was noted in four EDSKT patients (predominantly for high-pitched sound in EDSKT1, EDSKT2, and EDSKT6) and two MCEDS.

Gross motor developmental delay was observed in two ATCS, seven EDSKT, and three MCEDS patients; and ages of unassisted walk in patients who accomplished it ranged from 1 year and 5 months to 4 years (median, 2 years and 1 month). EDSKT2, at age 32 years, could not walk unassisted because of severe foot deformities and muscle weakness of the legs [Kosho et al., 2010]. An underlying myopathic process was suggested in ATCS2 because of reduced amplitude muscle action potentials with normal distal latency time and nerve conduction velocity, whereas muscle biopsy did not reveal any histological abnormality [Dündar et al., 1997]. Mild mental delay was suggested in two ATCS and two EDSKT patients. ATCS2 was reported to have global psychomotor delay at the initial publication [Dündar et al., 1997], whereas his IQ was around 90 at age 7 years and 2 months [Janecke et al., 2001]. Five ATCS and two EDSKT patients showed ventricular enlargement and/or asymmetry on brain ultrasonography, CT or MRI. ATCS7 also showed absence of the left septum pellucidum [Janecke et al., 2001]. EDSKT6 had tethering of a spinal cord, and underwent duraplasty [Kosho et al., 2010].

Growth assessment was performed using data described with SD scores, excluding data described with centile scores. Patients with *CHST14* mutations showed mild prenatal growth retardation: The mean birth length −0.5 SD and the median −0.6 SD (n = 9; range, −1.6 SD to +1.3 SD); the mean birth weight −0.6 SD and the median −0.67 SD (n = 11; range, −2.0 SD to +0.5 SD); and the mean birth OFC −0.2 SD and the median −0.5 SD (n = 8; range, −1.0 SD to +1.0 SD). Postnatal growth was also mildly impaired with slenderness and relative macrocephaly: The mean height −0.9 SD and the median −0.6 SD (14 data from 12 patients; range, −3.9 SD to +1.2 SD); the mean weight −1.5 SD and the median −1.4 SD (11 data from 9 patients; range, −2.4 SD to −0.4 SD); the mean OFC −0.2 SD and the median ±0 SD (10 data from 8 patients; range, −1.2 SD to >2.0 SD).

Light microscopic investigations on skin specimens from EDSKT5 and EDSKT6 showed that fine collagen fibers were predominant in the reticular to papillary dermis and normally thick collagen bundles were markedly reduced [Miyake et al., 2010]. Electron microscopic investigations of the specimens showed that collagen fibrils were dispersed in the reticular dermis, compared with regularly and tightly assembled ones observed in the control, whereas each collagen fibril was smooth and round, not varying in size and shape, similar to each fibril of the control [Miyake et al., 2010]. These findings suggested that the main pathological basis of this disorder would be insufficient assembly of collagen fibrils, compatible with the evidence that dermatan sulfate of decorin proteoglycan, a key regulator of collagen fibril assembly that contains both chondroitin sulfate and dermatan sulfate in its glycosaminoglycan chains and controls the distance between collagen fibrils, was found to be completely lost and replaced by chondroitin sulfate in patients' fibroblasts [Miyake et al., 2010]. However, both light microscopic and electron microscopic findings of skin were assessed as normal in ATCS7 [Dündar et al., 2009]. In MCEDS2, most collagen bundles were small-sized, some of which were composed of variable diameter collagen fibrils separated by irregular interfibrillar spaces [Malfait et al., 2010].

This comprehensive review of the patients with loss-of-function mutations in *CHST14* (D4ST1 deficiency) supports the notion that ATCS, EDSKT, and MCEDS would be a single clinical entity with variable inter- and intra-familial expressions and with different presentations depending on the patients' ages at diagnosis or at publication. The disorder, we preferably would like to coin simply as EDS due to D4ST1 deficiency or D4ST1 deficient EDS (DD-EDS), is a clinically recognizable syndrome, characterized by progressive multisystem fragility-related manifestations including joint dislocations and deformities, skin hyperextensibility, bruisability, and fragility; recurrent large subcutaneous hematomas, and other cardiac valvular, respiratory, gastrointestinal, and ocular complications, which are considered to result from connective tissue weakness and be consequences of insufficient decorin-mediated assembly of collagen fibrils caused by D4ST1 deficiency. The disorder also shows various malformations including distinct craniofacial features, multiple congenital contractures, and congenital defects in cardiovascular, gastrointestinal, renal, ocular, and central nervous systems, which might not simply be accountable for connective tissue weakness but could be considered as inborn errors of development. In a recent review focusing on ATCS, Zhang et al. [2010] state that D4ST1 deficiency is the only recognized condition resulting from a defect specific to DS biosynthesis, and that the disorder emphasizes the roles D4ST1 play in human development and extracellular matrix maintenance.

DD-EDS could be detected at birth from characteristic craniofacial and skeletal features and molecular genetic testing gives definitive diagnosis. Initial screening for congenital cardiac, ocular, and renal abnormalities and hearing loss would be necessary. In infancy, orthopedic intervention for talipes equinovarus (serial plaster casts, surgery) as well as physical therapy for motor developmental delay would be the center of management. Laxatives and/or enema are considered in patients with constipation. Surgical fixation is considered for cryptorchidism in males. Regular follow-up for ophthalmological (strabismus, refractive errors, glaucoma), otological (otitis media with effusion, hearing loss), urological (urination, bladder enlargement), and cardiovascular (valve abnormalities, aortic root dilation) problems should be continued. After walking independently, attention should be paid to progressive foot deformities and trauma that could cause skin lacerations, joint dislocations, and massive subcutaneous hematomas. Intranasal DDAVP after injuries is considered to prevent large subcutaneous hematomas. From adolescence, assessment of spinal deformities (scoliosis, kyphoscoliosis) and secondary sex

characteristics (breast development in females and gonadal function in males) would be necessary. In adulthood, appropriate treatments should be performed on occasional emergency complications ([hemo]peumothorax, diverticular perforation). Wrist-type sphygmomanometer would be suitable for patients with hyperalgesia to pressure [unpublished observation].

Very recently, Janecke et al. [2011] have claimed that it would lead to confusion for clinicians and researchers to categorize the D4ST1 deficiency into a type of EDS and that an appropriate term should be "Dermatan sulfate-deficient adducted thumb-clubfoot syndrome." The reasons were described as follows: Clinically, "adducted thumb" and "clubfoot" would be the most distinguishable features at birth; etiologically, the molecular basis would differ substantially from EDS. In reply to the article, we have presented sufficient evidences for categorizing the disorder into a type of EDS: Clinically, the disorder would satisfy all the hallmarks of EDS (skin hyperextensibility, joint hypermobility, and tissue fragility affecting the skin, ligaments, joints, blood vessels, and internal organs), and the patients should be treated as having generalized connective tissue fragility in the lifelong management; etiologically, multisystem fragility in the disorder was found to be caused by impaired assembly of collagen fibrils caused by dermatan sulfate loss in the decorin glycosaminoglycan chain [Kosho et al., submitted].

In conclusion, ATCS, EDSKT, and MCEDS; which were found independently to be caused by D4ST1 deficiency, would be a single clinical entity with variable expressions and with different presentations depending on the patients' ages. The syndrome is characterized by a unique set of clinical features including progressive multisystem fragility-related manifestations (joint dislocations and deformities, skin hyperextensibility, bruisability, and fragility; recurrent large subcutaneo us hematomas, and other cardiac valvular, respiratory, gastrointestinal, and ocular complications) resulting from impaired assembly of collagen fibrils, as well as various malformations (craniofacial features, multiple congenital contractures, and congenital defects in cardiovascular, gastrointestinal, renal, ocular, and central nervous systems) resulting from inborn errors of development.

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A Response to: Loss of Dermatan-4-sulfotransferase 1 (D4ST1/CHST14) Function Represents the First Dermatan Sulfate Biosynthesis Defect, "Dermatan Sulfate-Deficient Adducted Thumb–Clubfoot Syndrome". Which Name is Appropriate, "Adducted Thumb–Clubfoot Syndrome" or "Ehlers–Danlos Syndrome"?

We thank Janecke et al. [2011] for their letter about a recently recognized dermatan 4-O-sulfotransferase 1 (D4ST1) deficiency caused by loss-of-function *CHST14* (MIM# 608429) mutations, independently found in an arthrogryposis syndrome "Adducted Thumb–Clubfoot Syndrome" (ATCS) [Dündar et al., 2009], a specific form of Ehlers-Danlos syndrome (EDS) as we have proposed (EDS, Kosho Type; EDSKT) [Miyake et al., 2010], and a subset of kyphoscoliosis type EDS without evidence of lysyl hydroxylase deficiency (EDS type VIB) coined as "Musculocontractural EDS" (MCEDS) [Malfait et al., 2010]. Janecke et al. [2011] proposed that these three conditions constitute a clinically recognizable and genetically identical type of connective tissue disorder and that the disorders should not be categorized into a form of EDS, but be termed collectively "Dermatan Sulfate-Deficient Adducted Thumb–Clubfoot Syndrome" to avoid possible confusion for both clinicians and researchers. The proposal is based on their clinical and molecular recognition of the disorder. First, the presence of multiple congenital malformations such as facial dysmorphism, cleft lip/palate, intestinal abnormalities, renal abnormalities, and features such as nephrolithiasis and muscle hypotonia in these patients are not typical in EDS, though features such as joint laxity, skin hyperextensibility/fragility, and bleeding diathesis are typical in EDS. Second, the molecular basis in the disorder is different from that in EDS.

EDS comprises a heterogeneous group of heritable connective tissue disorders, with the hallmarks being skin hyperextensibility, joint hypermobility, and tissue fragility affecting the skin, ligaments, joints, blood vessels, and internal organs [Steinmann et al., 2002]. Dominant-negative effects or haploinsufficiency of mutant procollagen α-chain genes or deficiency of collagen-processing enzymes have been found to cause EDS [Mao and Bristow, 2001]. In a revised nosology, EDS was classified into six major types [Beighton et al., 1998] and several other forms have also been identified based on the molecular and biochemical abnormalities [Abu et al., 2008; Giunta et al., 2008; Kresse et al., 1987; Schalkwijk et al., 2001; Schwarze et al., 2004].

Homozygous or compound heterozygous *CHST14* mutations have been found in 11 patients aged 0 day to 6 years at the initial publication (from four families) with ATCS [Dündar et al., 1997, 2001, 2009; Janecke et al., 2001; Sonoda and Kouno, 2000], in six patients aged 2–32 years (from six families) with EDSKT [Kosho et al., 2005, 2010; Miyake et al., 2010; Yasui et al., 2003], and in three patients aged 12–22 years (from two families) with MCEDS [Malfait et al., 2010]. Lack of detailed clinical information from later childhood to adulthood in ATCS and lack of detailed clinical information from birth to early childhood in EDSKT and MCEDS have made it difficult to determine whether the three conditions would be distinct clinical entities or a single clinical entity with variable expressions and with different presentations depending on the patients' ages at diagnosis [Miyake et al., 2010], though the latter notion was suspected to be appropriate [Janecke et al., 2011; Malfait et al., 2010]. We, therefore, have just published an article in *American Journal of Medical Genetics Part A*, describing detailed clinical findings and courses of two additional unrelated EDSKT patients, aged 2 and 6 years, which could definitely unite the three conditions [Shimizu et al., 2011]. Furthermore, we have presented a comprehensive review of all reported patients with D4ST1 deficiency, which concludes that the three conditions constitute a clinically recognizable disorder, characterized by progressive multisystem fragility-related manifestations and various malformations and allows us to term the disorder "D4ST1-deficient EDS" [Shimizu et al., 2011]. The clinical manifestations are summarized in Table 1.

We have categorized D4ST1 deficiency into a form of EDS for substantial reasons. Clinically, the disorder satisfies all the hallmarks of EDS [Steinmann et al., 2002]. All patients we have encountered were diagnosed with EDS and have been managed as having generalized connective tissue fragility, such as preventing skin wounds, hematomas, joint dislocations, and progressive talipes and spinal deformities. Careful surgical suturing of torn skin and regular evaluations of internal organs (e.g., cardiac valve abnormalities, aortic root dilation, and bladder enlargement) and ocular abnormalities are also conducted. ATCS is surely a helpful term to detect and diagnose patients at birth, but it is indeed questionable whether the term would be appropriate for the lifelong management of patients with the disorder. Furthermore, clinical manifestations extending beyond the core features of EDS are considered not as excluding information from EDS as Janecke et al. [2011] have claimed, but as wide clinical variability in EDS such as muscle hypotonia and chronic pain in most of the types, talipes equinovarus and facial characteristics in vascular type, and congenital hip dislocation in arthrochalasia type [Beighton et al., 1998; Voermans et al., 2009].

Etiologically, multisystem fragility in D4ST1 deficiency was illustrated to be caused by impaired assembly of collagen fibrils resulting from loss of dermatan sulfate (DS) in the decorin glycosaminoglycan side chain [Miyake et al., 2010], which justifies terming the

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Table 1. Clinical Manifestations in D4ST1 Deficiency

Craniofacial	*Cardiovascular*
Large fontanelle (early childhood)	Congenital heart defects (ASD)
Hypertelorism	Valve abnormalities (MVP, MR, AR, ARD)
Short and downslanting palpebral fissures	Large subcutaneous hematomas
Blue sclerae	*Gastrointestinal*
Short nose with hypoplastic columella	Constipation
Ear deformities (prominent, posteriorly rotated, low set)	Diverticula perforation
Palatal abnormalities (high, cleft)	*Respiratory*
Long philtrum and thin upper lip	(Hemo) pneumothorax
Small mouth/microretrognathia (infancy)	*Urogenital*
Slender face with protruding jaw (from school age)	Nephrolithiasis/cystolithiasis
Asymmetric face (from school age)	Hydronephrosis
Skeletal	Dilated/atonic bladder
Marfanoid habitus/slender build	Inguinal hernia
Congenital multiple contractures (fingers, wrists, hips, feet)	Cryptorchidism
Recurrent/chronic joint dislocations	Poor breast development
Pectus deformities (flat, excavated)	*Ocular*
Spinal deformities (scoliosis, kyphoscoliosis)	Strabismus
Peculiar fingers (tapering, slender, cylindrical)	Refractive errors (myopia, astigmatism)
Progressive talipes deformilies (valgus, planus, cavum)	Glaucoma/elevated intraocular pressure
Cutaneous	Microcornea/microphthalmia
Hyperextensibility/redundancy	Retinal detachment
Bruisability	*Hearing*
Fragility/atrophic scars	Hearing impairment
Fine/acrogeria-like palmar creases	*Neurological*
Hyperalgesia to pressure	Ventricular enlargement/asymmetry
Recurrent subcutaneous infections/fistula	*Development*
	Hypotonia/gross motor delay

ASD: atrial septal defect; MVP: mitral valve prolapse; MR: mitral valve regurgitation; AR: aortic valve regurgitation; ARD: aortic rot dilation.

disorder a form of EDS. However, ultrastructural findings in the skin from patients with ATCS and MCEDS were not consistent with those in patients with EDSKT, characterized by intact collagen fibrils not assembled regularly or tightly [Miyake et al., 2010]. For patients with ATCS, the skin was assessed as normal [Dündar et al., 2009]. For those with MCEDS, most collagen bundles were found to be small sized, some of which were composed of variable diameter collagen fibrils separated by irregular interfibrillar spaces [Malfait et al., 2010]. Ultrastructural and glycobiological studies on the skin from other patients as well as those on other affected tissues such as bone, muscle, and intestine would be necessary to delineate the wide spectrum of pathophysiology. Involvement of other DS-containing proteoglycans such as biglycan should also be investigated. Various malformations observed in the disorder might not simply be explained by connective tissue fragility, as they are considered to be inborn errors of development [Dündar et al., 2009; Zhang et al., 2010].

Based on the clinical, molecular, ultrastructural, and glycobiological data to date, D4ST1 deficiency is characterized by a unique set of clinical features consisting of progressive multisystem fragility-related manifestations and various malformations (Table 1). Further clinical and etiological evidences would solve the problem regarding which name should be the most appropriate: "Dermatan Sulfate-Deficient Adducted Thumb-Clubfoot Syndrome" or "D4ST1-Deficient EDS." Until then, we propose that the name "D4ST1-Deficient EDS (Adducted Thumb-Clubfoot Syndrome)" would be preferable.

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Title	デルマタン4-O-硫酸基転移酵素-1欠損に基づく新型エーラスダンロス症候群の発見と疾患概念の確立
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綜　説

デルマタン4-O-硫酸基転移酵素-1欠損に基づく新型エーラスダンロス症候群の発見と疾患概念の確立

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Discovery and Delineation of a New Type of Ehlers-Danlos Syndrome Caused by Dermatan 4-O-sulfotransferase Deficiency

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Key words: Ehlers-Danlos syndrome (Kosho Type), dermatan 4-O-sulfotransferase deficiency, decorin, arthrogryposis, connective tissue fragility

エーラスダンロス症候群（古庄型），デルマタン硫酸4-O-硫酸基転移酵素欠損症，デコリン，先天性多発関節拘縮，結合組織脆弱性

I　エーラスダンロス症候群とは

エーラスダンロス症候群（Ehlers-Danlos症候群；EDS）は，皮膚・関節の過伸展性，各種組織の脆弱性を特徴とする先天性疾患の総称であり[1]，古典型（Classical type），関節型（Hypermobility type），血管型（Vascular type），後側彎型（Kyphoscoliosis type），多発関節弛緩型（Arthrochalasia type），皮膚脆弱型（Dermatosparaxis type）の6つの主病型に分類されている。いずれもコラーゲン分子そのもの，または修飾酵素の遺伝子変異により生じる[2)3)]。近年，主病型に属さない新たな病型が，その生化学的，遺伝学的基盤とともに相次いで発見されている（表1）[4)-12)]。最近我々は，顔貌上の特徴，先天性多発関節拘縮，進行性の結合組織脆弱性（皮膚弛緩，関節弛緩・変形，巨大皮下血腫など）を呈する全く新しいタイプのEDS（EDS, Kosho Type；EDSKT）を見出した。本稿では，患者さんとの出会い，原因遺伝子単離，病態解明，そして疾患概念確立に至る経緯を紹介する。

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II　患者さんとの出会いと原因遺伝子探索の道のり

1人目の患者さん（表2，3におけるEDSKT1）に出会ったのは，筆者が埼玉県立小児医療センター遺伝科に勤務していた2000年である。それまでに，同センターで古典型患者さんを診察する機会があり，皮膚が容易に裂け，関節脱臼を繰り返す，といった症状に悩まされているにも関わらず，医療者を含めた周囲の理解が得られず，また日本においてはほとんど専門家がいない「日の当たらない」疾患であることを感じていた。当時7歳の女児は，顔貌上の特徴，内反足を含む先天性多発関節拘縮，くも状指を有し，年齢とともに皮膚関節の過伸展性・脆弱性が目立ってきていた（図1）。初診時の担当医は，多発関節弛緩型との診断をしていた。筆者が再診で偶然担当し，詳しく経過を聞くと，転倒など軽微な外力で巨大な皮下血腫を生じる重症例であることが明らかになった。診察上も，独特な手足の変形や手掌の皺といったきわだった特徴を呈していた。以後1年弱の外来診療のなかで，原因検索として，典型的ではないが出血症状から血管脆弱性の可能性を考え，まずは血管型EDSの可能性を考えた。皮膚生検を行い，培養皮膚線維芽細胞を用いたIII型コラーゲン蛋白分析を千葉大学皮膚科簇持　淳助教授（現獨協医科大学皮膚科教授）に依頼した。結果，

表1　Ehlers-Danlos 症候群の分類

	頻度/患者数	遺伝形式	原因遺伝子
大病型			
古典型（Classical type）	1/20,000	AD	*COL5A1*, *COL5A2*
関節型（Hypermobility type）	1/5,000～20,000	AD	大多数は不明 少数例で TNXB
血管型（Vascular type）	1/50,000～250,000	AD	*COL3A1*
後側彎型（Kyphoscoliosis type）	1/100,000	AR	*PLOD*
多発関節弛緩型（Arthrochalasia type）	約30人	AD	*COL1A1**, *COL1A2**
皮膚脆弱型（Dermatosparaxis type）	8人	AR	*ADAMTS-2*
その他の病型			
Brittle cornea syndrome	11人	AR	*ZNF469*
EDS-like syndrome due to tenascin-XB deficiency	10人	AR	*TNXB*
Progeroid form	3人	AR	*B4GALT7*
Cardiac valvular form	4人	AR	*COL1A2*
EDS-like spondylocheirodysplasia	8人	AR	*SLC39A13*
D4ST-1-deficient EDS	22人	AR	*CHST14*

AD：常染色体優性遺伝，AR：常染色体劣性遺伝
COL5A1：V型プロコラーゲン α1鎖遺伝子，*COL5A2*：V型プロコラーゲン α2鎖遺伝子，*TNXB*：テナシンX遺伝子
PLOD：リジルヒドロキシラーゼ遺伝子，＊：スプライス異常によるエクソン6のスキップ
ADAMTS-2：プロコラーゲンⅠ N-プロテイナーゼ遺伝子
ZNF469：コラーゲン生合成・組織化に関わる転写因子の遺伝子
B4GALT7：β4ガラクトース転移酵素-7（GalT-Ⅰ）遺伝子
SLC39A13：亜鉛トランスポーター機能を持つタンパクの遺伝子
CHST14：デルマタン4-O-硫酸基転移酵素（D4ST-1）遺伝子

III型コラーゲンの産生は正常であり，血管型EDSは否定され，病型を確定することはできなかった。

2人目の患者さん（EDSKT2）とは，筆者が2003年に当院勤務となってからの出会いである。取り組むべきテーマを見つけられずにいたある日，福嶋義光部長（医学部遺伝医学・予防医学講座教授）に興味のある疾患について聞かれた。「EDSです」と答えると，「外勤先の療育センターに1人いる」とのことであった。26歳になっているはずの女性は，同センターへの通院を終了していた。カルテを見ると，出生直後から当院整形外科で入院・通院加療をしていることがわかった。古いカルテ庫から当院のカルテを取り出すと，EDSKT1と全く同様に出生時には内反足，手指関節拘縮，顔貌上の特徴を認め，その後，皮膚裂傷，関節脱臼，巨大皮下血腫など進行性の結合組織脆弱性を呈していた（図1）。

2人は，これまでの分類には当てはまらない新しい型のEDSであると直感し，論文を作成することにした。文献検索をすると，後側彎型（旧分類ではVI型）に類似した脊椎変形，皮膚や動脈の脆弱性を呈しているものの，後側彎型の病因であるlysyl hydroxylaseの欠損を認めないEDSVIB型（lysyl hydroxylaseの欠損を伴う通常の後側彎型をEDS VI Aと分類する場合）に分類されていたPakistan姉弟例[1)13)]に酷似した臨床像であることを見出した（図2）。Lysyl hydroxylaseの欠損の有無をスクリーニング（尿デオキシピリジノリン／ピリジノリン比）したが，予想どおり正常パターンであり欠損はなかった。そこで，暫定分類をEDS VI B型としてAmerican Journal of Medical Genetics誌に報告した[14)]。EDSKT2およびPakistan姉弟例の両親が血族結婚であったことから，常染色体劣性遺伝の可能性が推測された。病態解明へ向け，2005年度信州医学振興会医学研究助成および2007年度信州若手研究者萌芽研究支援事業の支援を得て，関連遺伝子解析を行ったが，原因遺伝子を同定することはできなかった。

新規疾患として確立するためにも，また，原因遺伝子を同定するためにも，新たな患者さんの収集が必要であった。そんな折，遠方に在住のEDS患者さんから「自分の病状は他の病型のだれとも違うと思うので，相談にのってほしい」と話を持ちかけられた。この患者さんがEDSKT3であり，自身の病型診断のために

表2　D4ST-1欠損症患者の臨床的特徴

家系	患者	出身	CHST14変異	論文発表時年齢	性別	頭蓋顔面							骨格										皮膚									心臓血管		呼吸	胃腸	
						大きい泉門（乳幼児期）	眼間開離	眼瞼裂斜下	青色強膜	（鼻柱の低形成を伴う）短い鼻	耳介変形	口蓋の異常	長い人中と薄い上口唇	小さい口と小さく後退した下顎（乳幼児期）	短頸	下顎突出（学童期以降）を伴った面長な顔貌	顔面左右差（学童期以降）	マルファン症候群様体型	先天性多発関節拘縮	反復性／慢性脱臼	胸郭異常	脊椎異常	くも状／円筒状の手指	進行性の足部変形	過伸展性／弛緩	易出血性	脆弱性／萎縮性瘢痕	細かい早老症様の手掌の皺	圧迫への痛覚過敏	反復性皮下感染／ろう孔	先天性心疾患	弁の異常	巨大皮下血腫（血）気胸	便秘	その他
ATCS																																				
1	1	トルコ	V49X ホモ	3.5歳	女	｜	｜	｜	｜		大きい，後傾	高口蓋	＋		｜				＋				｜									－				
	2			1.5歳	男	＋	＋	＋	＋	｜	大きい，後傾		＋		＋	＋#		＋#	＋	＋#	漏斗胸#	後側彎#	＋	外反扁平#				＋#		外反扁平#		－				
	3			6歳	女		＋	｜		＋	大きい		＋			＋	＋	＋	＋		平坦/薄い	側彎	＋	内反				＋								
2	4	日本	Y293C ホモ	4歳2月	男	｜	｜	＋		＋	低位	口唇口蓋裂	｜						＋	｜	鳩胸		＋	外反扁平												
	5			7月	男	＋	＋	＋		｜	低位	軟口蓋裂	＋						｜	＋			＋								ASD				
3	6	オーストリア	R213P ホモ	0日†	男	｜	＋	＋			後傾，低位				＋				＋			側彎	＋								ASD, CoA				共通腸管膜
	7			12月	男	｜	｜	｜	｜		異形成，後傾				｜	＋#		＋#	＋		平坦/薄い#		＋	外反扁平				｜#			－				胃結腸ひだの欠損 特発性の小腸捻転
｜	8	トルコ	R135G/L137Q	1-4月†	女														＋																
	9			1-4月†	男														＋																
	10			1-4月†	男														＋																
	11			3月	男	｜	｜	｜	＋		異形成，低位	高口蓋	｜		｜				＋				＋								－				
EDSKT																																				
1	1	日本	P281L/Y293C	16歳	女	｜	＋	｜	＋	＋	低位	高口蓋	＋	＋		＋	＋	＋	＋	＋	漏斗胸	後側彎	＋	外反扁平	＋	＋	＋	＋	＋	＋	ASD	TR, TVP, MVP	＋	－	＋	胃潰瘍
2	2	日本	P281L ホモ	32歳	女	｜	｜	｜	｜	｜	低位	高口蓋	＋	＋		＋	＋	＋	＋	＋	平坦/薄い	側彎	｜	外反凹	＋	＋	＋	＋	＋	＋	－		＋	＋	＋	大腸憩室炎，穿孔
3	3	日本	P281L ホモ	32歳	男	｜	＋	＋	＋	＋	低位	高口蓋	＋	＋		＋	＋	＋	＋	＋	平坦/薄い	後側彎	＋	外反扁平	＋	＋	＋	＋	＋	＋		AR, ARD, MR	＋	＋	＋	大腸憩室炎，穿孔
4	4	日本	K69X/P281L	32歳	男		｜		＋			高口蓋				＋	＋	＋	＋		漏斗胸	後側彎	＋	外反扁平	＋	＋	－	＋	－	－			＋	＋	－	
5	5	日本	P281/C289S	20歳	女	｜	＋	｜	＋	｜	低位	高口蓋	｜	＋		＋	＋	｜	＋	｜	漏斗胸	側彎	＋	外反扁平	｜	＋	＋	｜	｜	＋		AR, MR, IE	＋	－	＋	
6	6	日本	P281L/Y293C	4歳	女	｜	＋	＋	＋	＋	低位	高口蓋	｜						＋		漏斗胸	側彎	＋	扁平	＋	＋	＋	＋	＋	＋			＋	－	＋	
7	7	日本	P281L/Y293C	2歳	男	｜	｜	＋	｜	｜	後傾，低位	高口蓋	＋	＋					｜		平坦/薄い	後彎	＋	外反扁平	＋	＋	｜	＋	－	＋	－	ARD	－	－	＋	
8	8	日本	F209S/P281L	6歳	男	｜	｜	＋	＋	｜	後傾，低位	高口蓋	＋	＋					＋	＋	漏斗胸		｜	扁平	｜	｜	－	＋	＋	－	PDA	MVP	＋	－	＋	腹痛
MCEDS																																				
1	1	トルコ	V49X ホモ	22歳	女	｜		｜		｜	後傾，低位	高口蓋	｜			＋	｜	｜	＋		平坦/薄い	後側彎	＋	外反扁平	＋	＋	＋	｜		｜	－	－				腹痛
	2			21歳	女	｜		｜	｜			高口蓋	＋						｜	｜	平坦/薄い	側彎	＋	小さく広い	＋	＋	＋	＋								
2	3	インド	E334GfsX107ホモ	12歳	女				＋		低位		－					＋	＋	＋		後側彎	＋	外反扁平	＋	＋	＋	＋	＋		＋						軸捻転に伴う 十二指腸閉塞

ATCS，adducted thumb-clubfoot syndrome；EDSKT，Ehlers-Danlos Syndrome，Kosho Type；MCEDS，Musculocontractural Ehlers-Danlos Syndome；†，死亡；空欄，情報なし；

ASD，心房中隔欠損；CoA，大動脈縮窄；PDA，動脈管開存；TR，三尖弁閉鎖不全；TVP，三尖弁逸脱；MVP，僧帽弁逸脱；AR，大動脈弁閉鎖不全；ARD，大動脈根部拡張；MR，僧帽弁閉鎖不全；IE，感染性心内膜炎；

ATCS1は6歳時死亡［Dundar et al., 2009］.

#，Dundarらが再評価した時の情報（ATCS2は15歳，ATCS7は8歳）。

表3　D4ST-1欠損症患者の臨床的特徴

家系	患者	Urogenital 腎(膀胱)結石	Urogenital 停留精巣	Urogenital その他	眼科 乳房発育	眼科 斜視	眼科 屈折異常	眼科 緑内障/眼圧上昇	眼科 その他	聴覚異常	脳室形態異常	発達 粗大運動	発達 独歩年齢	発達 精神遅滞	成長 在胎週数	出生時身長 (centile or SD)	出生時体重 (centile or SD)	出生時頭囲 (centile or SD)	出生後計測年齢1	身長 (centile or SD)	体重 (centile or SD)	頭囲 (centile or SD)	出生後計測年齢2	身長 (centile or SD)	体重 (centile or SD)	頭囲 (centile or SD)	引用文献
ATCS																											
1	1					+					拡大	+	不可	+	満期				3.5y	25-50th	50th	50th					Dundar et al., 1997
	2					+		+			左右差	+		+‡	満期				1.5y	50th	10th	10-25th	15y	25-50th	<3rd		
	3					+													6y	10-25th	<3rd						Dundar et al., 2010
2	4		+	水腎症										−	39週	−0.6	−0.9	−0.8	4y2m	−3.9	−1.8	−0.9					Sonoda and Kouno, 2000
	5		+	水腎症，そけいヘルニア								−		−	38週	−1.6	−1.3	−0.5	7m	−2.1	−1.4	−1.1					
3	6		+	馬蹄腎							拡大				32週	25th	10th	25th									Janecke et al., 2001
	7		+			+					左右差	−		−	38週	50th	25th	50th	8y	10-25th	<3rd						
4	8																										Dundar et al., 2001
	9																										
	10																										
	11	+	+	そけいヘルニア							拡大，左右差								3m	<3rd	3-10th	10th					
EDSKT																											
1	1			膀胱拡張，不随意収縮，反復性尿路感染症	−	+	遠視	−	小角膜	+		+	2歳	+¶	42週	−0.1	−1.3	−1.0	7y	+0.8	−1.0	±0	16y	+0.3	−0.4	+0.2	Kosho et al., 2010
2	2	+		弛緩性膀胱，反復性尿路感染症	−	+	近視，乱視	+		+		+	不可	−	満期		−2.0		15y	−3.2							Kosho et al., 2010
3	3		+	性腺機能低下症		+	近視，乱視	−	小眼球	+		+		−	40週	+1.3	+0.5	+0.8	30y	+1.2	−1.7						Kosho et al., 2010
4	4					−	−	−	網膜剝離	−				−					23y	−0.4	−2.4						Kosho et al., 2010
5	5	+		初潮遅延，生理不順	−	+	近視，乱視	+		−		+	2歳2月	−	39週	−1.1	−0.4	+1.0	19y	−0.1	−0.8						Kosho et al., 2010
6	6					+	近視，乱視	+		+		+	1歳5月	−	41週	−1.2	−0.5	−0.6	4y	−1.2	−1.3	−0.9					Kosho et al., 2010
7	7		+			+	遠視	−				+	2歳	+	38週3日	−1.3	+0.2	+0.4	2y	−2.2	−2.4	−1.2					Shimizu et al., 2011
8	8		+			+				−	拡大	+	2歳6月	−	38週	+0.3	+0.3	−0.5	6y	−0.7	−1.4	+0.1					Shimizu et al., 2011
MCEDS																											
1	1	+			−		近視	+	網膜剝離，眼球癆	+		+	4歳		42週	±0	−0.67		22y	−2.0		±0					Malfait et al., 2010
	2	+		腎下降と尿道狭窄に伴う水腎症	−		近視	+	網膜剝離	+		+	2歳		42週				14y	+0.68		>2.0					
2	3						近視		小眼球			+			満期		−0.88										Malfait et al., 2010

ATCS, adducted thumb-clubfoot syndrome；EDSKT, Ehlers-Danlos Syndrome, Kosho Type；MCEDS, Musculocontractural Ehlers-Danlos Syndome；
Hy, 遠視；My, 近視；As, 乱視；Enl, 脳室拡大；Asym, 脳室左右差；No, 歩行不可
‡, IQは7歳2カ月時，Porteus testで91，Goodenough testで86であった［Janecke et al., 2001］。¶, 学習障害

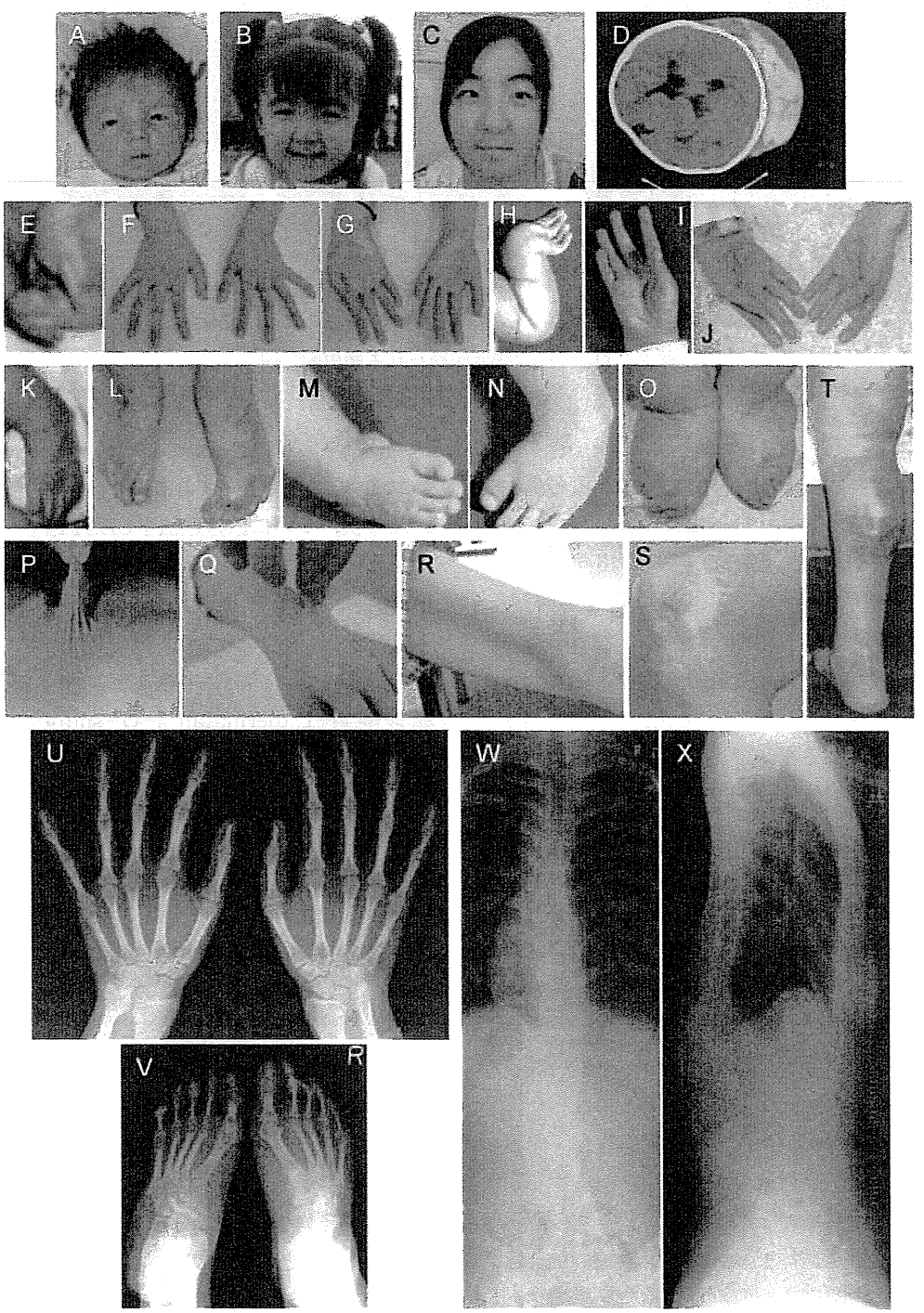

図1　外表写真およびレントゲン写真[14)28)]

EDSKT1：日齢23（A，E），3歳（B），6歳（D），16歳（C，F，G，U，V，W，X）。
EDSKT2：2カ月（M，N），3カ月（H），1歳2カ月（P），5歳（I），28歳（J，O）。
EDSKT3：新生児（K），31歳（L，R，S）。
EDSKT5：16歳（T），19歳（Q）。

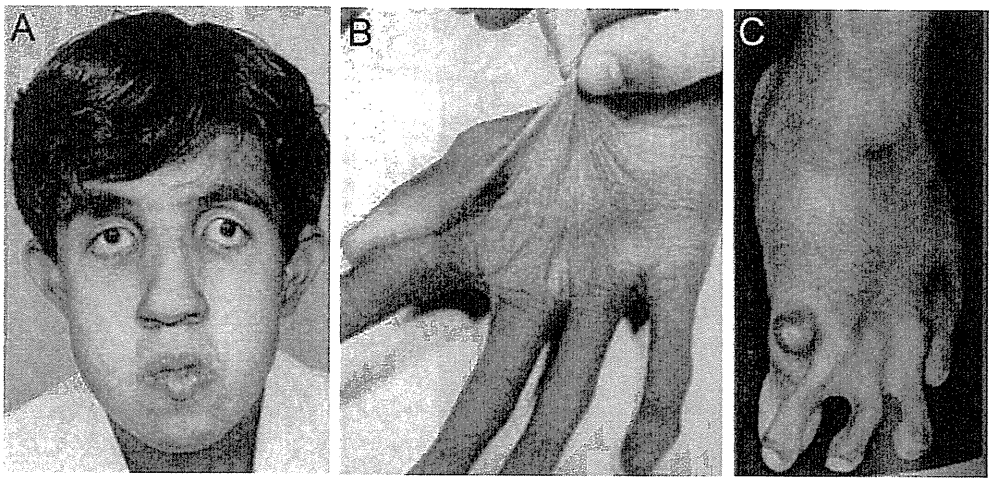

図2　D4ST-1欠損症が疑われる歴史的症例
A，B，C：EDS VI B と分類されてきた Steinmann らが報告した Pakistan 人姉弟例（写真は弟）[1)13)]。

獨協医科大学皮膚科簇持教授の外来に受診，皮膚生検を受けたところであった。その後出会う機会があり，新型 EDS であると確信，入院先の病院に出向き，主治医と情報交換を行うとともに，本人より研究協力の承諾をいただいた。この患者さんの両親も血族結婚であったことが，きわめて重要な意味を持つことになった。

福嶋部長と相談をするなかで，両親が血族結婚の2家系があれば，連鎖解析で遺伝子を単離できるのではないか，ということになった。そこで，先天異常症候群の解析に関して長く共同研究をしてきた横浜市立大学大学院医学研究科遺伝学の松本直通教授に話を持ちかけた。松本研では，高密度 SNP アレイの登場により，旧来のマイクロサテライトマーカーなどを用いた多型解析では原因遺伝子同定が困難とされていた少数の小家系でも遺伝子単離が可能になりつつあるところであり，快く解析を引き受けて下さることになった。米国で Duane 症候群の遺伝子単離に成功[15)]し，帰国したばかりの三宅紀子助教（現准教授）が担当することになり，両親血族結婚の2家系を利用した連鎖解析による原因遺伝子単離プロジェクトが動き始めた。あらためて上記3人の患者さんの家族に協力を依頼し，両親，同胞から検体をいただくことができた。

Affymetrix 社の SNP 10K アレイを用いたホモ接合体マッピングにより責任領域を15q15の8.1 Mb に限局（Lod score 2.885），さらに，その近傍のマイクロサテライトマーカー解析を用いたハプロタイプ解析により責任領域を7.3 Mb にまで狭小化した。同領域に局在する109遺伝子のなかから機能的に関連性の疑われる7つの遺伝子を選択し，変異解析を行った。2008年秋，ついに原因遺伝子*CHST14*を突き止めることに成功した。予想どおり，EDSKT2およびEDSKT3はミスセンス変異をホモ接合体で，EDSKT1はミスセンス変異を複合ヘテロ接合体で有していることがわかった[16)]。*CHST14*は，デルマタン4-O-硫酸基転移酵素-1（dermatan 4-O-sulfotransferase-1；D4ST-1）をコードする遺伝子である（図3）[17)]。D4ST-1は，プロテオグリカン（proteoglycan；PG）の側鎖であるグリコサミノグリカン（glycosaminoglycan；GAG）を構成するデルマタン硫酸（dermatan sulfate；DS）のNアセチルガラクトサミン残基の4位に硫酸基を付加する酵素である（図4）[17)-19)]。しかしながら，糖鎖修飾酵素である D4ST-1の異常がどのような機序で全身結合組織の顕著な脆弱性を惹起するのかは，不明のままであった。新規疾患として世界に発信していくには，機能解析が必須であり，解決には時間がかかることが予想された。

その後も新たな患者さんとの出会いが続いた。EDSKT4は，当科の website に相談を持ちかけていただいた札幌医科大学第一内科の石田禎夫准教授，安井 寛助教より紹介された。すでに巨大皮下血腫を反復し，特異な骨格症状を有する EDS として論文発表されていた32歳男性患者さんであった[20)]。後に，本患者さんただ1人がナンセンス変異を持つことがわかり，きわめて重要なケースとなった。EDSKT5は，本症候群の皮膚病理に関する相談に，獨協医科大学皮膚科簇持教授を訪ねたときに出会った患者さんである。当時19歳の彼女は，この土曜日，偶然簇持教授の外来に

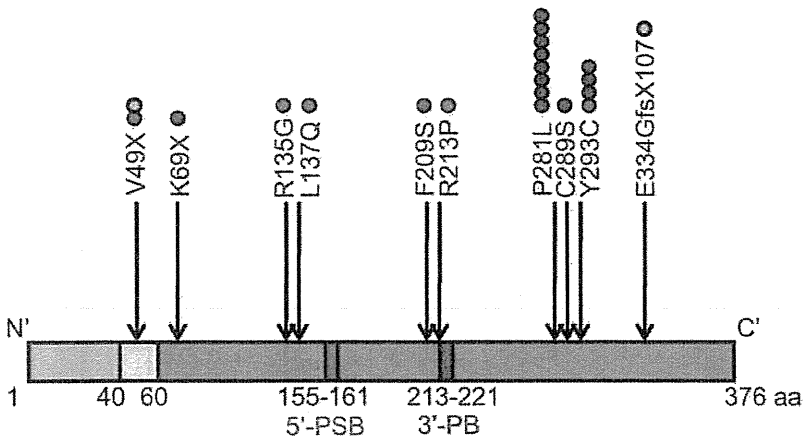

図3　*CHST14* 遺伝子の構造と変異が検出された部位[16)23)29)]

赤は5'-phosphosulfate binding site（5'-PSB）を，青は3'-phosphate binding site（3'-PB）を示す。水色部分は細胞質部，黄色部分は膜貫通部，桃色部分は管腔部である。矢印はこれまでに報告された変異を示す。赤丸はATCSにおいて，青丸はEDSKTにおいて，水色丸はMCEDSにおいて検出された変異を示す。

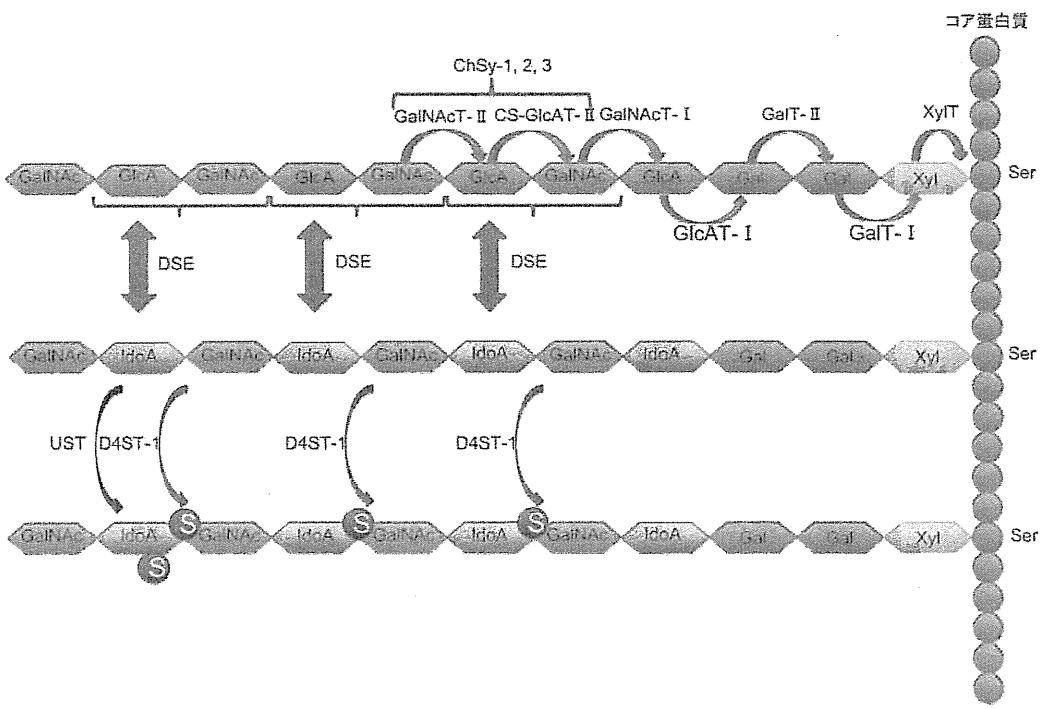

図4　デルマタン硫酸（DS）の生合成[19)]

DSの生合成は，コンドロイチン硫酸（CS），ヘパラン硫酸，ヘパリンと同様，プロテオグリカンのコア蛋白質上にある特定のセリン残基（Ser）にキシロース（Xyl）―ガラクトース（Gal）―ガラクトース（Gal）―グルクロン酸（GlcA）の4糖が結合するところから始まる。これらの反応は，それぞれキシロース転移酵素（XylT），ガラクトース転移酵素-Ⅰ（GalT-Ⅰ），ガラクトース転移酵素-Ⅱ（GalT-Ⅱ），グルクロン酸転移酵素-Ⅰ（GlcAT-Ⅰ）によって行われる。N-アセチルガラクトサミン（GalNAc）が，GalNAc転移酵素-Ⅰ（GalNAcT-Ⅰ）によってGlcAに転移されると，次いでCS-グルクロン酸転移酵素-Ⅱ（CS-GlcAT-Ⅱ）とGalNAc転移酵素-Ⅱ（GalNAcT-Ⅱ）により，GlcAとGalNAcが順次転移し，CS特有の［GlcA-GalNAc］の2糖繰り返し領域が合成される。コンドロイチン合成酵素（ChSy-1，2，3）は，CS-GlcAT-ⅡとGalNAcT-Ⅱ両方の活性を持つ。ChSyファミリーによって［GlcA-GalNAc］$_n$の糖鎖骨格が形成された後，または，その反応の途中で，DSエピメラーゼ（DSE）により，GlcA残基のC5位のカルボキシル基が異性化し，イズロン酸（IdoA）となる。これにより，DSの2糖配列［IdoA-GalNAc］$_n$が形成される。その後，主としてデルマタン4-O-硫酸基転移酵素-1（D4ST-1）によるGalNAc残基の4位硫酸化（一部はウロノシル2-O-硫酸基転移酵素（UST）によるIdoAの2位硫酸化も）による修飾を受けて，成熟したDS鎖が合成される。

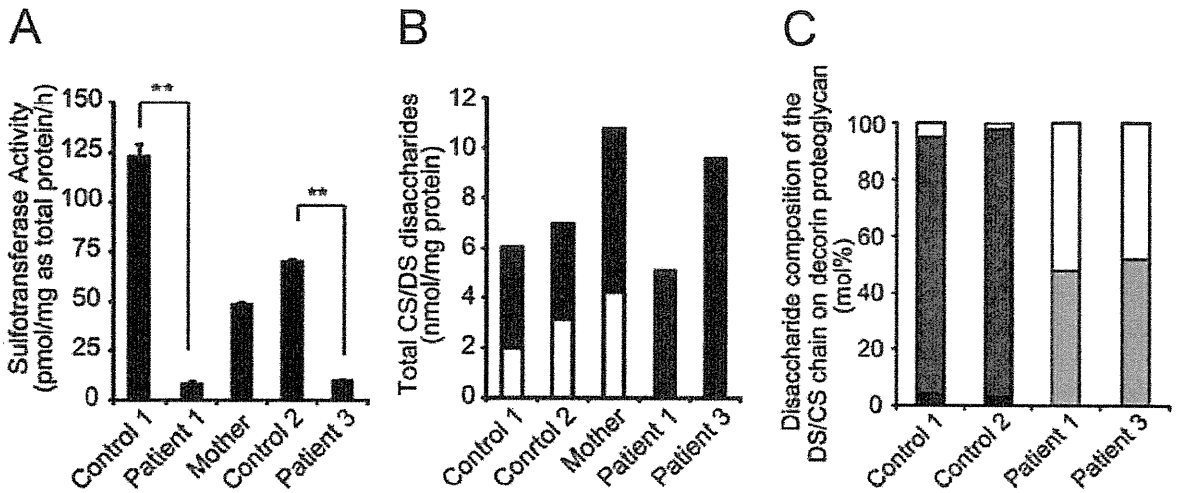

図5　糖鎖分析[16]

Patient 1はEDSKT1を，Motherはその母親を，Patient 3はEDSKT3を示す。A：培養皮膚線維芽細胞におけるデルマタンに対する硫酸基転移酵素活性。EDSKT1，EDSKT3の酵素活性は著明に減少し，EDSKT1の母親では半分程度に減少している。B：培養皮膚線維芽細胞中に含まれる全CS/DS量。コンドロイチン硫酸（CS）を黒で，デルマタン硫酸（DS）を白で示す。EDSKT1およびEDSKT3では全てCSになっている。C：デコリン（DCN）のグリコサミノグリカン（GAG）鎖に含まれるCS/DS組成。CS分画の［GlcA-GalNAc（4S)］を白で，［GlcA-GalNac（6S)］を明るい灰色で示す。DS分画の［IdoA-GalNAc（4S)］を暗い灰色で，［IdoA（2S)-GalNAc（4S)］を黒で示す。正常コントロールではほぼDSであるが，EDSKT1およびEDSKT3では全てCSとなっている。

受診していた。待合室にたたずむ彼女の様子から，新型EDSと直感し，簇持教授に聞いたところ，「実はちょうど相談したいと思っていた患者さんが今日来ている」とのことであった。急遽診察をさせていただき，研究協力の同意を得て，検体をいただくことができた。EDSKT6は当時4歳の女児である。2009年のEDS患者会に際し，簇持教授から，「今度の会に新型EDS疑いのお子さんが行くから，相談にのってあげてほしい」と伝達えられていた。参加したところ，前を通り過ぎた女児の様子を見て新型EDSと確信，その後かかりつけの病院にうかがい，診察をさせていただき，研究協力の同意を得て，検体をいただくことができた。そして，これら3人すべてに*CHST14*の変異が検出された。

D4ST-1のクローニングは米国Washington大学病理学のBaenziger博士らの研究チームによって行われたが[17]，熾烈なデッドヒートを演じていた[18]のが北海道大学大学院先端生命科学研究院プロテオグリカンシグナリング医療応用研究室の菅原一幸教授（当時は神戸薬科大学）らの研究チームであった。菅原教授に，新型EDS患者細胞の機能解析を依頼したところ，快く引き受けて下さり，菅原教授，山田修平准教授，そして水本秀二博士研究員による精緻な糖鎖分析が始まった。D4ST-1酵素活性を調べると，患者由来培養皮膚線維芽細胞ではコントロールに比べて著明に低下していること，保因者であるEDSKT1の母では半分程度に低下していることが明らかになった（図5A)[16]。次に，培養皮膚線維芽細胞中に含まれるDSとコンドロイチン硫酸（chondroitin sulfate；CS）の含有量を比較すると，コントロールではDS，CSともに存在したが，患者由来細胞ではDSが消失し，CSのみとなっていた（図5B)[16]。さらに，DSを含有する代表的なPGであるデコリン（decorin；DCN）に着目した。DCNはDSからなる1本のGAG鎖を有するが，患者細胞においてはDSが消失し，全てCSになっていた（図5C)[16]。DCNは，GAG鎖がコラーゲン細線維（collagen fibrils）間の距離を調節することによって，これを密に束ね（assembly），細胞外マトリックスを形成するのに重要な役割を果たす[21)22)]。DCNが，糖鎖修飾酵素異常とコラーゲン・ネットワークの構築とをつなぐリンクになっている可能性が高まったのである。これを裏付けるには，病理組織所見の解釈が必須と考えられた。簇持教授，三宅准教授と検討を重ね，患者皮膚の電子顕微鏡像において，コラーゲン細線維が正常人のように密に束ねられず，ばらけて存在することを突き止めた（図6)[16]。以上から，少なくとも

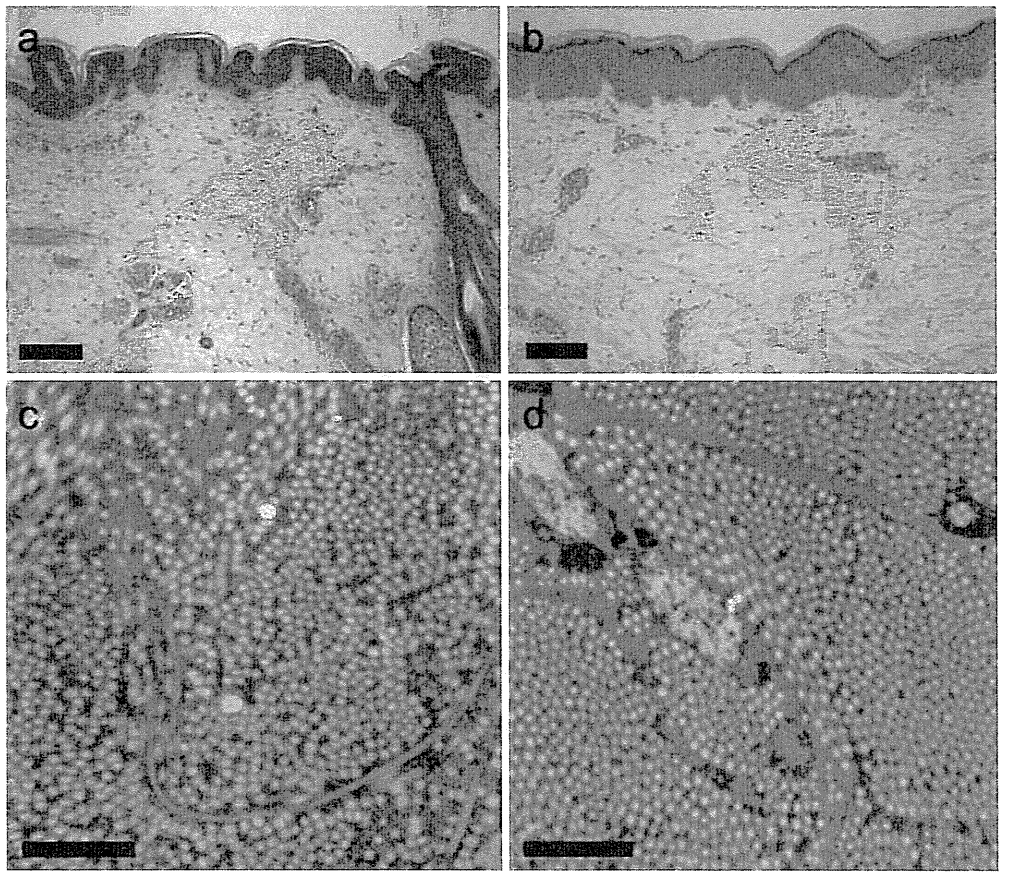

図6　病理解析の結果[16]

a，b：H&E染色による光顕所見（×100）。EDSKT5（a）では，コントロール（b）に比べ，コラーゲン線維束が繊細に見える。スケールバーは500 μm を示す。

c，d：電顕所見（×30,000）。EDSKT5（c）では，コントロール（d）に比べ，コラーゲン細線維の径は同等であるが，ばらけて存在していることがわかる。スケールバーは1 μm を示す。

本症候群における進行性結合組織脆弱性の主たる発症機構は「D4ST-1欠損→DCNに付加するGAGの組成変化（DSが消失しCSに置換）→DCNが媒介するコラーゲン細線維のassembly不全」（図7）という病態である可能性が高いと考えた[16]。

インパクトの高い研究成果であることを確信し，松本研と協力して投稿の準備をしていた2009年12月11日の朝のことであった。いつものようにアメリカ人類遺伝学会会員に毎月電子配信されてくるAmerican Journal of Human Genetics誌の目次にD4ST-1の文字を見つけた。*CHST14* の変異に基づくD4ST1の欠損が，内転母指および内反足を特徴とする新しい先天性多発関節拘縮症（arthrogryposis）“adducted thumb-clubfoot syndrome（ATCS）”を引き起こすとの報告であった[23]。両親血族結婚の3家系を用いたホモ接合体マッピングは全く同じ手法であった。筆頭著者は世界に先駆けて2家系を報告した[24][25]トルコErciyes大学遺伝学のDündar教授，遺伝子解析を行ったのは責任著者で1家系の報告をしていた[26]オーストリアInnsbruck医科大学小児科のJanecke教授らのチーム，そして糖鎖解析を行ったのはまたもやBaenziger教授らのチームであった。新しいarthrogryposisとして報告されていた日本人兄弟例も含まれていた[27]。我々は，幼児から成人にかけての患者さんを見てきたが，診療においてEDSとの認識がゆらぐことはなかった。出生時には確かに特徴的な手指の内転と内反足を含む多発関節拘縮を呈しており，一時的にarthrogryposisと診断された患者さん，arthrogryposisの1つFreeman-Sheldon症候群と診断された患者さんはいたが，ATCSは全くノーマークであった。我々の発見した新型EDSとATCSが同一疾患か否か，これにより，我々の知見の価値が決まると

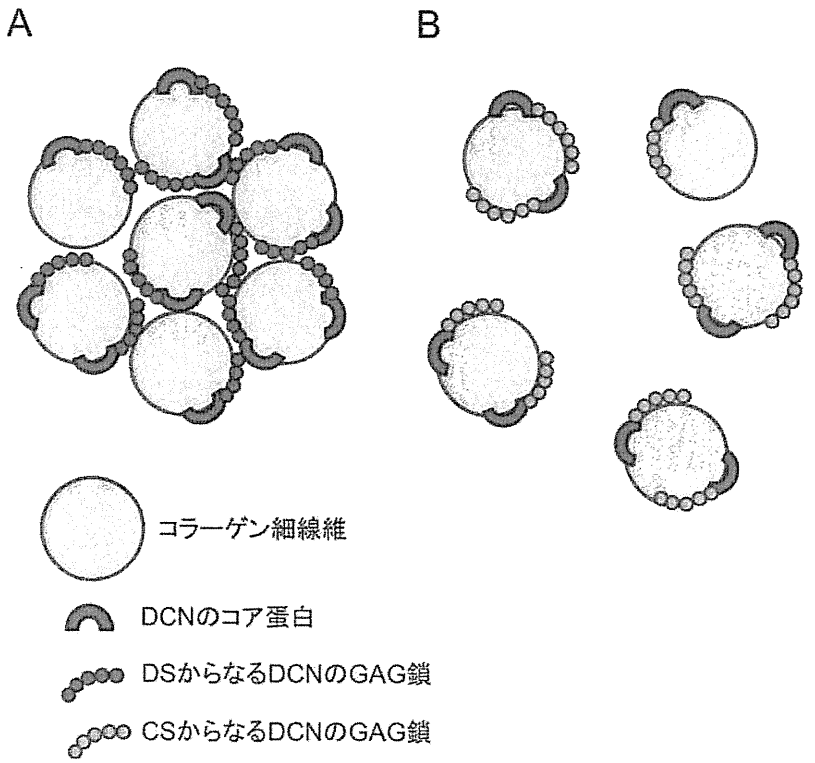

図7　推定される進行性結合組織脆弱性の発症機構
A：正常。B：D4ST-1欠損症。D4ST-1欠損に基づきデコリン（DCN）に付加するグリコサミノグリカン（GAG）鎖の組成変化，すなわちデルマタン硫酸（DS）が消失しコンドロイチン硫酸（CS）に置換，が生じ，DCNが媒介するコラーゲン細線維のassembly不全を来すと考えられる。なお，DCNが媒介するコラーゲン細線維のassemblyモデルは，Nomuraらが提唱するもの[22]を示す。

考えられた。Dündar教授らの論文を精読したところ，加齢に伴い結合組織脆弱性が明らかになると言及されていおり，また全く同一の遺伝子変異もあり，同一疾患といずれは分類される予感はあったが，縦断的な臨床情報が乏しいこと，皮膚病理組織を正常と解釈したことなどから，現時点で同一疾患とは結論できないと位置付け，投稿を急ぐことにした。しかしながら，新型EDSが臨床的にどのようなものかをアピールしきれないこと，そしてやはり先行論文があることが影響したのであろう，high impact journalsに受理されることはなかった。松本教授，三宅准教授と話し合いを重ね，詳細な臨床像を古庄が，遺伝子単離および機能解析を三宅准教授が別々に投稿し，同一疾患であるかもしれないがまずは新型EDSと位置付け，その原因遺伝子を独立して単離したと位置付けた。そしてようやく2010年4月14日に臨床像がAmerican Journal of Medical Genetics誌[28]に，5月25日に病態がHuman Mutation誌[16]に受理された。まもなく奇形症候群の世界的データベースであるLondon Dysmorphology Database（http://www.lmdatabases.com/index.html）およびPOSSUM（http://www.possum.net.au/）から，掲載許可を求める問い合わせがあり，我々の報告した6例は，暫定的にEDSKTと称されることになった。

III　疾患概念の確立へ向けて

筆者らの報告にわずかに遅れる形で，EDSを含めた結合組織疾患の研究を長年引っ張ってきたベルギーGhent大学病院遺伝学De Paepe教授とMalfait先生らのチームから，D4ST-1の欠損が，EDS VI Bに分類されていた2家系（トルコ人，インド人）3症例の原因であると報告された。ATCS，EDSKTを含めて同一疾患と位置付けられ，Musculocontractural EDS（MCEDS）との名称が提案された[29]。

ATCS，EDSKT，MCEDSは同一遺伝子変異に基づくが臨床的には異なるallelic diseasesなのか，同一疾患の家族間または年齢によるvariabilityといえるのかを結論付けるためには，ATCS患者において情報の乏しい学童以降の状況，またEDSKT患者において情報の乏しい乳幼児期の状況を把握することが