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Kosho T	Discovery and delineation of dermatan 4-*O*-sulfotransferase-1 (D4ST1)-deficient Ehlers-Danlos syndrome	Oiso N, Kawada A	Current Genetics in Dermatology	InTech	Croatia	2013	73-86

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古庄知己	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.	日本遺伝カウンセリング学会誌	34(1)	2013	21-29

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(1) 日本工業規格Ａ列４番の用紙を用いること。
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Abstract

Glycosaminoglycans (GAGs) such as dermatan sulfate (DS), chondroitin sulfate (CS), and heparan sulfate are side chains composed of repeating disaccharides bound to core proteins to form proteoglycans (PGs). Biosynthesis of CS and DS is shown in Fig. 156.1. It is initiated by the synthesis of a tetrasaccharide linker region, glucuronic acidb1-3galactoseb1-3galactoseb1-4xyloseb1-*O*- (GlcA-Gal-Gal-Xyl-), onto serine residues of specific core proteins of PGs, by b-xylosyltransferase, b1,4-galactosyltransferase-I, b1,3-galactosyltransferase-II, and b1,3-glucuronosyltransferase-I, respectively. Subsequently, a repeating disaccharide region [*N*-acetyl-D-galactosamine(GalNAc)-GlcA]$_n$ of chondroitin is elongated by the actions of *N*-acetyl-D-galactosaminyltransferase-I, *N*-acetyl-D-galactosaminyltransferase-II, and CS-glucuronyltransferase-II encoded by chondroitin synthase -1, -2, and -3 and chondroitin polymerizing factor. CS chains are matured by modifications by chondroitin 4-*O*-sulfotransferase, chondroitin 6-*O*-sulfotransferase, and uronyl 2-*O*- sulfotransferase (UST). A disaccharide repeating region of dermatan is synthesized through epimerization of a carboxyl group at C5 from GlcA to L-iduronic acid (IdoA) by dermatan sulfate epimerase (DSE). A mature DS chain is synthesized through sulfation by dermatan 4-*O*-sulfotransferase (D4ST), dermatan 6-*O*-sulfotransferase (D6ST), and UST.

156 Carbohydrate (*N*-Acetylgalactosamine 4-0) Sulfotransferase 14 (CHST14)

Tomoki Kosho, Shuji Mizumoto, and Kazuyuki Sugahara

Contents

Introduction

Glycosaminoglycans (GAGs) such as dermatan sulfate (DS), chondroitin sulfate (CS), and heparan sulfate are side chains composed of repeating disaccharides bound to core proteins to form proteoglycans (PGs). Biosynthesis of CS and DS is shown in Fig. 156.1. It is initiated by the synthesis of a tetrasaccharide linker region, glucuronic acidb1-3galactoseb1-3galactoseb1-4xyloseb1-*O*- (GlcA-Gal-Gal-Xyl-), onto serine residues of specific core proteins of PGs, by b-xylosyltransferase,

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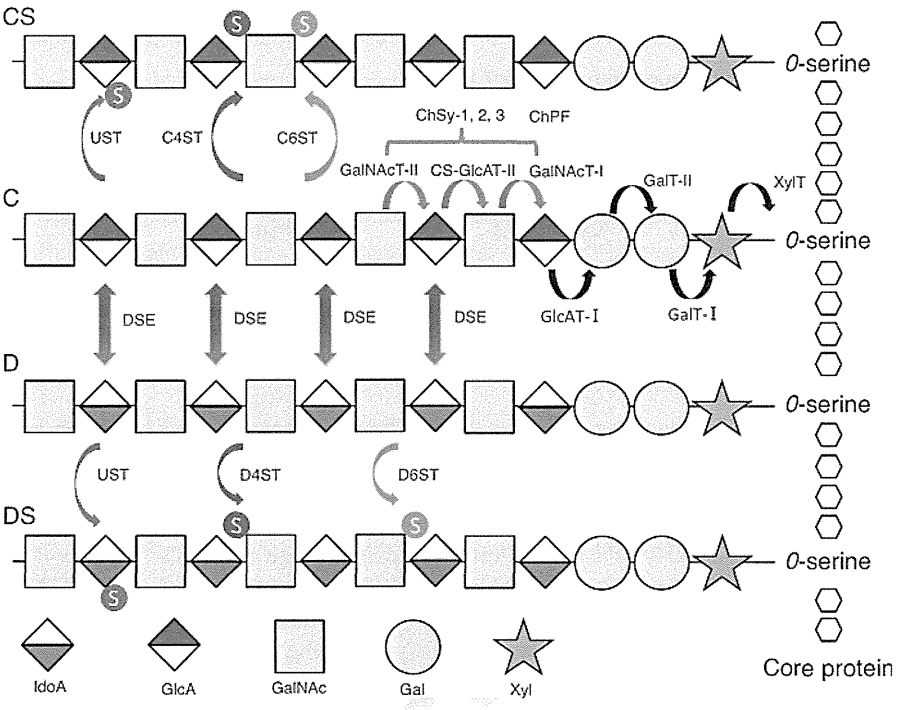

Fig. 156.1 Biosynthesis of DS and CS (Kosho in press). *C* chondroitin, *CS* chondroitin sulfate, *D* dermatan, *DS* dermatan sulfate, *Ser* serine, *Xyl* D-xylose, *Gal* D-galactose, *GlcA* D-glucuronic acid, *GalNAc* *N*-acetyl-D-galactosamine, *IdoA* L-iduronic acid, *XylT* xylosyltransferase, *GalT-I* galactosyltransferase-I, *GalT-II* galactosyltransferase-II, *GlcAT-I* glucuronyltransferase-I, *GalNAcT-I* *N*-acetyl-D-galactosaminyltransferase-I, *CS-GlcAT-II* CS-glucuronyltransferase-II, *GalNAcT-II* *N*-acetyl-D-galactosaminyltransferase-II, *ChSy* chondroitin synthase, *ChPF* chondroitin polymerizing factor, *C4ST* chondroitin 4-*O*-sulfotransferase, *C6ST* chondroitin 6-*O*-sulfotransferase, *UST* uronyl 2-*O*-sulfotransferase, *DSE* dermatan sulfate epimerase, *D4ST* dermatan 4-*O*-sulfotransferase, and *D6ST* dermatan 6-*O*-sulfotransferase

b1,4-galactosyltransferase-I, b1,3-galactosyltransferase-II, and b1,3-glucuronosyltransferase-I, respectively. Subsequently, a repeating disaccharide region [*N*-acetyl-D-galactosamine(GalNAc)-GlcA]$_n$ of chondroitin is elongated by the actions of *N*-acetyl-D-galactosaminyltransferase-I, *N*-acetyl-D-galactosaminyltransferase-II, and CS-glucuronyltransferase-II encoded by chondroitin synthase −1, −2, and −3 and chondroitin polymerizing factor. CS chains are matured by modifications by chondroitin 4-*O*-sulfotransferase, chondroitin 6-*O*-sulfotransferase, and uronyl 2-*O*- sulfotransferase (UST). A disaccharide repeating region of dermatan is synthesized through epimerization of a carboxyl group at C5 from GlcA to L-iduronic acid (IdoA) by dermatan sulfate epimerase (DSE). A mature DS chain is synthesized through sulfation by dermatan 4-*O*-sulfotransferase (D4ST), dermatan 6-*O*-sulfotransferase (D6ST), and UST.

Databanks

IUBMB enzyme nomenclature: E.C.2.8.2.35

Carbohydrate (*N*-acetylgalactosamine 4-0) sulfotransferase 14 (CHST14)

Species	Gene symbol	GenBank accession number	UniProt ID	PDB accession number
Mus musculus	*Chst14*	NM_028117.3	Q80V53	N/A
Homo sapiens	*CHST14*	NM_130468	Q8NCH0	N/A

Name and History

The *CHST14* gene encodes dermatan 4-*O*-sulfotransferase-1 (D4ST1), which catalyzes the 4-*O*-sulfation of GalNAc residues in DS. Evers et al. (2001) cloned cDNA of *CHST14*, based on its homology to *CHST10* coding for human natural killer-1 sulfotransferase. Evers et al. (2001) showed mRNA of *CHST14* to be expressed ubiquitously and the protein to transfer sulfate to the C-4 hydroxyl of GalNAc in the sequence IdoA-GalNAc immediately after epimerization of GlcA to IdoA and designated the enzyme as D4ST1. Mikami et al. (2003), who had identified CHST14/D4ST1 independently by public database search, reported further characterization of the enzyme specificities that partially desulfated DS also served as an excellent acceptor, while nearly exhaustively desulfated DS had been shown to be an acceptor (Evers et al. 2001). In 2009–2010, human CHST14/D4ST1 deficiency was identified as a clinically recognizable syndrome and designated as "D4ST1-deficient Ehlers–Danlos syndrome (DD-EDS)."

Structure

The *CHST14* gene, localized at 15q14, is a single exon gene with an open reading frame (ORF) of 1,131 base pairs (Evers et al. 2001). Human CHST14/D4ST1, consisting of 376 amino acids with an estimated molecular mass of 43 kDa, is a type II membrane protein with an N-terminal transmembrane region, binding sites for 3′-phosphoadenosine-5′-phosphosulfate (PAPS), and two potential *N*-glycosylation sites (Evers et al. 2001).

Enzyme Activity Assay and Substrate Specificity

This enzyme catalyzes transfer of sulfate to C4 position of GalNAc residues of dermatan. The standard reaction mixture (60 μl) includes 10 μl of the enzyme sources, 50 mM imidazole-HCl, pH 6.8, 2 mM dithiothreitol, 10 μM [^{35}S]PAPS (~1 or 3 × 10^5 dpm), and desulfated DS as an acceptor (10 nmol as disaccharide) (Mikami et al. 2003). The reaction mixtures are incubated at 37 °C for 1 h and

subjected to gel filtration using a syringe column packed with Sephadex G-25 (superfine) (Mikami et al. 2003). [^{35}S]Sulfate incorporation into polysaccharides is quantified by determination of the radioactivity in the flow-through fractions by liquid scintillation counting (Mikami et al. 2003).

Both nearly exhaustively desulfated DS and partially desulfated DS serve as excellent substrates for the enzyme (Evers et al. 2001; Mikami et al. 2003).

Preparation

Cell lysates are prepared with 200 μl of the M-PER® mammalian protein extraction reagent (Thermo Fisher Scientific Inc., Waltham, MA). A DNA fragment, which encodes the human CHST14/D4ST1 protein lacking the first N-terminal 62 amino acids including the predicted transmembrane region, was subcloned into the BamHI site of the expression vector p3XFLAG-CMV-8 (Sigma), resulting in the fusion of *CHST14* to the preprotrypsin leader sequence and the 3XFLAG tag sequence at the N-terminus present in the vector. The expression plasmid was transfected into COS-7 cells using FuGENE6 transfection reagent (Roche Diagnostics, Basel, Switzerland). After 3 days the culture medium was incubated with the anti-FLAG affinity resin (Sigma or Wako, Osaka, Japan), which was washed with 25 mM Tris, pH 7.4/150 mM NaCl/0.05 % Tween-20, and then analyzed by SDS–PAGE followed by western analysis using anti-FLAG monoclonal antibody conjugated with horseradish peroxidase (Sigma or Wako) (Mikami et al. 2003; van Roij et al. 2008).

Biological Aspects

Clinical features of human CHST14/D4ST1 deficiency suggest that CHST14/D4ST1 and DS would play a crucial role in fetal development and maintenance of connective tissues in multiple organs/tissues. Pathophysiological evidence revealed in human CHST14/D4ST1 deficiency indicates the substantial role of CHST14/D4ST1 to regulate CS/DS disaccharide composition of a GAG chain of decorin (and probably other DS-PGs), the GAG chains of which would exhibit various biological effects such as appropriate assembly of collagen fibrils mediated by decorin. Ubiquitous expression of *CHST14* would also suggest multisystem effects of the enzyme.

Knockout and Transgenic Mice

Knockout mice were generated by homologous recombination and targeting of the only coding exon (exon 1) of the *Chst14* gene (Tang et al. 2010; Bian et al. 2011). Phenotypic analysis of the F2 mice showed that the mutation affected bone metabolism, cardiology, neurology, ophthalmology, metabolism, and growth

(Tang et al. 2010). Chst14/D4st1-deficient mice had decreased neurogenesis and diminished proliferation of neural stem cells (NSCs) accompanied by increased expression of glutamate–aspartate transporter (GLAST) and epidermal growth factor (EGF) in comparison with wild-type controls as well as Chst11/C4st1-deficient mice (Bian et al. 2011). There is no report regarding *Chst14* transgenic mice.

Human Disease

Recessive loss-of-function mutations in the *CHST14* gene were identified in patients with three independently reported conditions: a rare type arthrogryposis syndrome, "adducted thumb–clubfoot syndrome (ATCS)" (Dündar et al. 2009); a specific type of Ehlers–Danlos syndrome (EDS), "EDS, Kosho type" (Kosho et al. 2010; Miyake et al. 2010); and a subset of kyphoscoliosis-type EDS without lysyl hydroxylase deficiency, "musculocontractural EDS") (Malfait et al. 2010). These conditions were concluded to represent a single clinical entity, a new form of EDS coined as "D4ST1-deficient EDS (DD-EDS)" (Kosho et al. 2011; Shimizu et al. 2011). To date, 26 patients with DD-EDS have been reported (Table 156.1) (Kosho in press). Au2 Au3

Clinical manifestations are summarized in Table 156.2, characterized by progressive multisystem fragility-related manifestations (skin hyperextensibility and fragility, progressive spinal and foot deformities, large subcutaneous hematoma) and various malformations (facial features, congenital eye/heart/gastrointestinal defects, congenital multiple contractures) (Kosho et al. 2011; Shimizu et al. 2011).

Characteristic craniofacial features including large fontanelle, hypertelorism, short and downslanting palpebral fissures, blue sclerae, short nose with hypoplastic columella, low-set and rotated ears, high palate, long philtrum, thin upper lip vermilion, small mouth, and micro-retrognathia are noted at birth to early childhood (Fig. 156.2a, b). Slender and asymmetrical facial shapes with protruding jaws are noted from school age (Fig. 156.2c) (Kosho et al. 2005, 2010, 2011; Shimizu et al. 2011; Kosho in press).

Congenital multiple contractures, such as adduction–flexion contractures of thumbs and talipes equinovarus, were cardinal features (Fig. 156.2d, g). Peculiar finger shape, described as "tapering," "slender," and "cylindrical," is also noted (Fig. 156.2e, f). Talipes deformities (planus, valgus) (Fig. 156.2h) and spinal deformities (scoliosis, kyphoscoliosis) with tall vertebral bodies and decreased physiological curvature (Fig. 156.2j, k) develop. Marfanoid habitus, recurrent joint dislocations, and pectus deformities (flat and thin, excavatum, carinatum) are also evident (Kosho et al. 2005, 2010, 2011; Shimizu et al. 2011; Kosho in press).

Cutaneous features include hyperextensibility to redundancy, bruisability, fragility leading to atrophic scars, acrogeria-like fine palmar creases or wrinkles (Fig. 156.2e, f), hyperalgesia to pressure, and recurrent subcutaneous infections with fistula formation (Kosho et al., 2005, 2010; Shimizu et al., 2011).

t2.1 **Table 156.1** Reported patients with DD-EDS (Kosho in press)

t2.2 Patient	Family	Origin	*CHST14* mutations	Sex	Age at initial publication	References
t2.3 1	1	Turkish	V49X homo	F	3.5 y	Dündar et al. 1997
t2.4 2	1	Turkish	V49X homo	M	1.5 y	Dündar et al. 1997
t2.5 3	1	Turkish	V49X homo	F	6 y	Dündar et al. 1997
t2.6 4	2	Japanese	Y293C homo	M	4 y	Sonoda and Kouno 2000
t2.7 5	2	Japanese	Y293C homo	M	7 m	Sonoda and Kouno 2000
t2.8 6	3	Austrian	R213P homo	M	0 d[a]	Janecke et al. 2001
t2.9 7	3	Austrian	R213P homo	M	12 m	Janecke et al. 2001
t2.10 8	4	Turkish	[R135G;L137Q] homo	F	1–4 m[a]	Dündar et al. 2001
t2.11 9	4	Turkish	[R135G;L137Q] homo	M	1–4 m[a]	Dündar et al. 2001
t2.12 10	4	Turkish	[R135G;L137Q] homo	M	1–4 m[a]	Dündar et al. 2001
t2.13 11	4	Turkish	[R135G;L137Q] homo	M	3 m	Dündar et al. 2001
t2.14 12	5	Japanese	P281L/Y293C	F	11 y	Kosho et al. 2005
t2.15 13	6	Japanese	P281L homo	F	14 y	Kosho et al. 2005
t2.16 14	7	Japanese	P281L homo	M	32 y	Kosho et al. 2010
t2.17 15	8	Japanese	K69X/P281L	M	32 y	Kosho et al. 2010
t2.18 16	9	Japanese	P281L/C289S	F	20 y	Kosho et al. 2010
t2.19 17	10	Japanese	P281L/Y293C	F	4 y	Kosho et al. 2010
t2.20 18	11	Turkish	V49X homo	F	22 y	Malfait et al. 2010
t2.21 19	11	Turkish	V49X homo	F	21 y	Malfait et al. 2010
t2.22 20	12	Indian	E334Gfs*107 homo	F	12 y	Malfait et al. 2010
t2.23 21	13	Japanese	P281L/Y293C	M	2 y	Shimizu et al. 2011
t2.24 22	14	Japanese	F209S/P281L	M	6 y	Shimizu et al. 2011
t2.25 23	15	Dutch	V48X homo	F	20 y	Voermans et al. 2012
t2.26 24	16	Afghani	R274P homo	F	11 y	Mendoza-Londono et al. 2012
t2.27 25	16	Afghani	R274P homo	F	0 y	Mendoza-Londono et al. 2012
t2.28 26	17	Miccosukee	G228Lfs*13	F	16 y	Winters et al. 2012

t2.29 *Homo* homozygous mutation, / compound heterozygous mutation, *F* female, *M* male, *y* years old, *m* months old, *d* day

[a]Dead at the time of publication

Au4 [b]Also reported in a paper by Yasui et al. (2003)

Au5 t3.1 **Table 156.2** Clinical manifestations in DD-EDS (Kosho et al. 2011). *ASD* atrial septal defect, *MVP* mitral valve prolapse, *MR* mitral valve regurgitation, *AR* aortic valve regurgitation, *ARD* aortic root dilation

t3.2	*Craniofacial*	
t3.3		Large fontanelle (early childhood)
t3.4		Hypertelorism
t3.5		Short and downslanting palpebral fissures
t3.6		Blue sclerae
t3.7		Short nose with hypoplastic columella
t3.8		Ear deformities (prominent, posteriorly rotated, low set)
t3.9		Palatal abnormalities (high, cleft)
t3.10		Long philtrum and thin upper lip
t3.11		Small mouth/micro-retrognathia (infancy)
t3.12		Slender face with protruding jaw (from school age)
t3.13		Asymmetric face (from school age)
t3.14	*Skeletal*	
t3.15		Marfanoid habitus/slender build
t3.16		Congenital multiple contractures (fingers, wrists, hips, feet)
t3.17		Recurrent/chronic joint dislocations
t3.18		Pectus deformities (flat, excavated)
t3.19		Spinal deformities (scoliosis, kyphoscoliosis)
t3.20		Peculiar fingers (tapering, slender, cylindrical)
t3.21		Progressive talipes deformities (valgus, planus, cavum)
t3.22	*Cutaneous*	
t3.23		Hyperextensibility/redundancy
t3.24		Bruisability
t3.25		Fragility/atrophic scars
t3.26		Fine/acrogeria-like palmar creases
t3.27		Hyperalgesia to pressure
t3.28		Recurrent subcutaneous infections/fistula
t3.29	*Cardiovascular*	
t3.30		Congenital heart defects (ASD)
t3.31		Valve abnormalities (MVP, MR, AR, ARD)
t3.32		Large subcutaneous hematomas
t3.33	*Gastrointestinal*	
t3.34		Constipation
t3.35		Diverticula perforation
t3.36	*Respiratory*	
t3.37		(Hemo)pneumothorax

(*continued*)

t3.38 **Table 156.2** (continued)

t3.39	*Urogenital*	
t3.40		Nephrolithiasis/cystolithiasis
t3.41		Hydronephrosis
t3.42		Dilated/atonic bladder
t3.43		Inguinal hernia
t3.44		Cryptorchidism
t3.45		Poor breast development
t3.46	*Ocular*	
t3.47		Strabismus
t3.48		Refractive errors (myopia, astigmatism)
t3.49		Glaucoma/elevated intraocular pressure
t3.50		Microcornea/microphthalmia
t3.51		Retinal detachment
t3.52	*Hearing*	
t3.53		Hearing impairment
t3.54	*Neurological*	
t3.55		Ventricular enlargement/asymmetry
t3.56	*Development*	
t3.57		Hypotonia/gross motor delay

The most serious complication is recurrent large subcutaneous hematoma, which sometimes progresses acutely and massively to be treated intensively (admission, blood transfusion, surgical drainage) and is supposed to be caused by the rupture of subcutaneous arteries or veins (Fig. 156.2i) (Kosho et al. 2005, 2010, 2011; Shimizu et al. 2011; Kosho in press).

Sulfotransferase activity toward dermatan in the affected skin fibroblasts was significantly decreased to 6.7 % in a patient with a compound heterozygous mutation "P281L/Y293C" (Patient 12, in Table 156.1) and to 14.5 % in a patient with a homozygous mutation "P281L" (Patient 14), compared with each age- and sex-matched control (Miyake et al. 2010) (Fig. 156.3a(a)). Disaccharide composition analysis of CS/DS chains isolated from the affected skin fibroblasts (Patient 12, 14) showed a negligible amount of DS and excess CS, which was suggested to result from impaired 4-*O*-sulfation lock due to D4ST1 deficiency followed by back epimerization from IdoA to GlcA (Dündar et al. 2009; Miyake et al. 2010) (Fig. 156.3a(b)). A major DS-PG in the skin, decorin, was also investigated, which consists of a core protein and a single GAG chain that plays an important role in assembly of collagen fibrils possibly through electrostatic interaction between decorin DS chains and adjacent collagen fibrils (Nomura 2006). GAG chains of decorin from the affected skin fibroblasts contained exclusively CS and no DS disaccharides, while those from the controls contained mainly DS disaccharides (approximately 95 %) (Miyake et al. 2010) (Fig. 156.3a(c)).

Light microscopy of hematoxylin- and eosin-stained affected skin specimens showed that fine collagen fibers were present predominantly in the reticular to papillary dermis with marked reduction of normally thick collagen bundles (Miyake

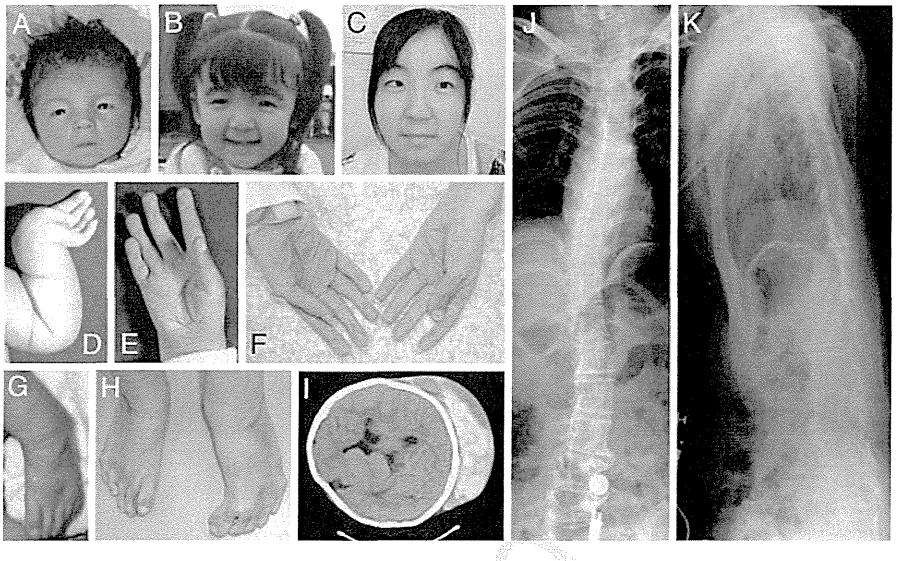

Fig. 156.2 Clinical photographs of patients with DD-EDS (Kosho et al. 2005; Kosho et al. 2010). Patient 12 at age 23 days (**a**), 3 years (**b**), 6 years (**i**), and 16 years (**c**). Patient 13 at age 3 months (**d**), 5 years (**e**), and 28 years (**f**, **j**, **k**). Patient 14 in the neonatal period (**g**) and at age 28 years (**h**). Patient number is according to Table 156.1

et al. 2010) (Fig. 156.3b(a, b)). Electron microscopy showed that collagen fibrils in affected skin specimens were dispersed in the reticular dermis, compared with the regularly and tightly assembled ones observed in the control's, whereas each collagen fibril in affected skin specimens was smooth and round, not varying in size and shape, similar to each collagen fibril of the control's (Miyake et al. 2010) (Fig. 156.3b(c, d)).

These glycobiological and pathological findings suggested skin fragility in this disorder to be caused by impaired assembly of collagen fibrils resulting from the replacement of a DS with a CS chain of decorin (Miyake et al. 2010); (Kosho 2011) (Fig. 156.3c(a, b)). The disorder represents the first human disorder that emphasizes the role of CHST14/D4ST1 and DS to play in human development and the maintenance of the extracellular matrices (Zhang et al. 2010).

Future Perspectives

Detailed evaluation of knockout mice and patients with DD-EDS would contribute to delineate multisystem roles of CHST14/D4ST1 and DS. Pathological investigation of various organs/tissues would address the question whether involvement of other organs/tissues might result from impaired assembly of collagen fibrils mediated by decorin. Glycobiological investigation focusing on various DS-PGs would uncover the contribution of DS-PGs in addition to decorin.

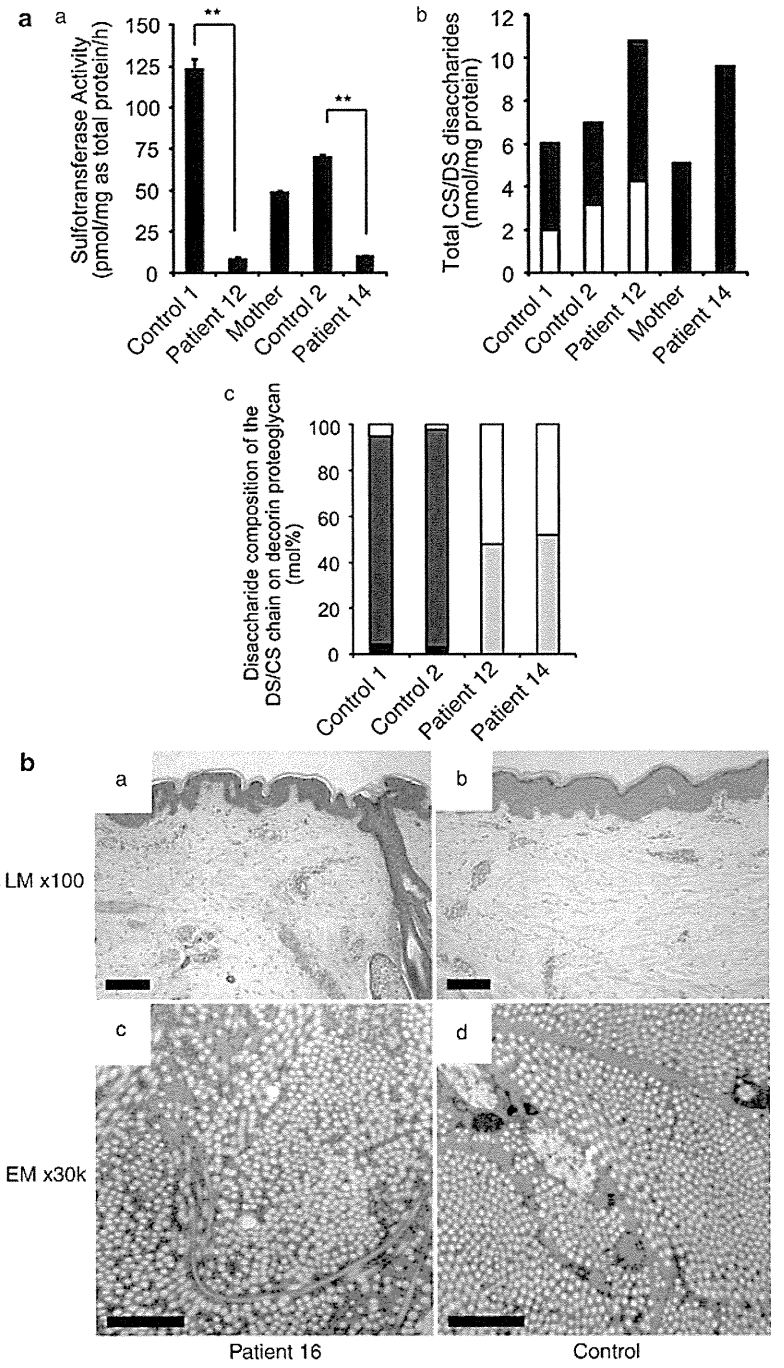

Fig. 156.3 (continued)

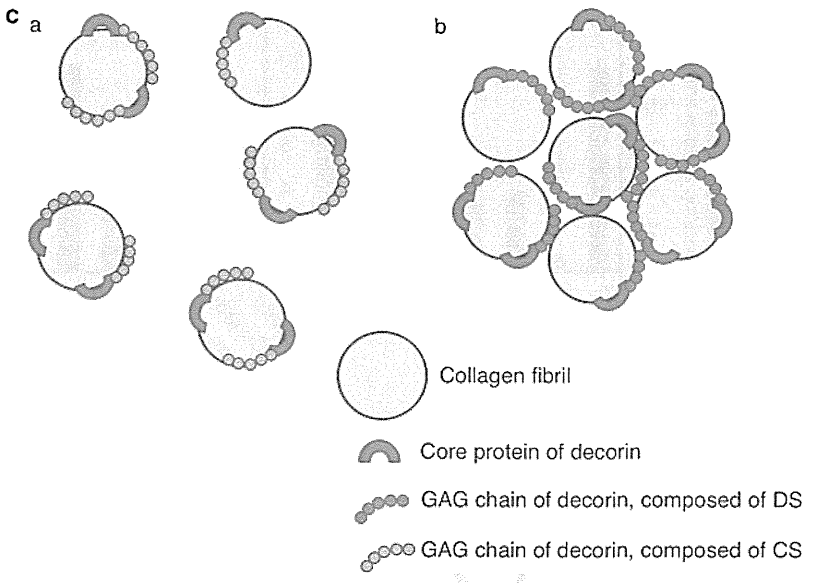

Fig. 156.3 (**a**) Glycobiological studies (Miyake et al. 2010). Control 1 is Patient 12′s age- and sex-matched control. Mother is Patient 12′s. Control 2 is Patient 14′s age- and sex-matched control. Patient number is according to Table 156.1. (*a*) Sulfotransferase activity of skin fibroblasts. (*b*) The total amounts of CS and DS derived from skin fibroblasts. The total disaccharide contents of CS and DS are shown in a *black box* and a *white box*, respectively. (*c*) Proportion of the disaccharide units in the CS/DS hybrid chains in decorin secreted by the fibroblasts. A *white box* and a *light gray box* indicate GlcUA-GalNAc (4S) and GlcUA-GalNAc (6S), respectively, both composing CS. A *dark gray box* and a *black box* indicate IdoUA-GalNAc(4S) and IdoUA-GalNAc (6S), respectively, both composing DS. (**b**). Pathological studies (Miyake et al. 2010). Light microscopy (LM) of a hematoxylin- and eosin-stained skin specimen of Patient 16 in Table 156.1 (*a*) and that of her age- and sex-matched control. (*b*) *Scale bars* indicate 500 μm. Electron microscopy (EM) of a skin specimen of Patient 16 (*c*) and that of the control (*d*). *Scale bars* indicate 1 μm. (**c**) Schema of binding model of decorin to collagen fibrils (Nomura 2006). Putative spatial relationship between collagen fibrils and decorin in skin specimens of patients with DD-EDS (*a*) and normal control subjects (*b*) (Kosho 2011)

Cross-References

- ▶ Carbohydrate Sulfotransferase 11 (CHST11), Chondroitin 4-*O*-Sulfotransferase-1 (C4ST1)
- ▶ Carbohydrate Sulfotransferase 3 (CHST3), Chondroitin 6-*O*-Sulfotransferase (C6ST1)
- ▶ Dermatan Sulfate Epimerase (DSE)
- ▶ Uronyl 2-*O*-Sulfotransferase (UST)

Further Reading

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Mikami et al. (2003): Further characterization of enzyme specificities.
Dündar et al. (2009): Identification of the first human disease associated with CHST14/D4ST1 deficiency as an arthrogryposis syndrome.
Kosho et al. (2010): Detailed clinical information of D4ST1-deficient EDS.
Miyake et al. (2010): Further characterization of pathophysiology of CHST14/D4ST1 deficiency especially showing impaired assembly of collagen fibrils resulting from loss of DS in the GAG chain of decorin.
Shimizu et al. (2011): Clinical delineation of D4ST1 deficiency.
Kosho et al. (2011): Designation of D4ST1 deficiency as "D4ST1-deficient EDS (DD-EDS)."

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Chapter 6

Discovery and Delineation of Dermatan 4-*O*-Sulfotransferase-1 (D4ST1)-Deficient Ehlers-Danlos Syndrome

Tomoki Kosho

Additional information is available at the end of the chapter

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1. Introduction

The Ehlers-Danlos syndrome (EDS) is a heterogeneous group of heritable connective tissue disorders affecting as many as 1 in 5000 individuals, characterized by joint and skin laxity, and tissue fragility [1]. The fundamental mechanisms of EDS are known to consist of dominant-negative effects or haploinsufficiency of mutant procollagen α-chains and deficiency of collagen-processing-enzymes [2]. In a revised nosology established in the nomenclature conference held in June 1997 at Villefranche-sur-Mer, France, Beighton et al. [3] classified EDS into six major types (Table 1): classical type (OMIM#130000), hypermobility type (OMIM#130020), vascular type (OMIM#130050), kyphoscoliosis type (OMIM#225400), arthrochalasia type (OMIM#130060), and dermatosparaxis type (OMIM#225410). Additional minor variants of EDS have been identified with molecular and biochemical abnormalities: dermatan 4-*O*-sulfotransferase-1 (D4ST1)-deficient type/musculocontractural type (OMIM#601776), Brittle cornea syndrome (OMIM#229200), EDS-like syndrome due to tenascin-XB deficiency (OMIM#606408), EDS with progressive kyphoscoliosis, myopathy, and hearing loss (OMIM#614557); the spondylocheiro dysplastic form (OMIM#612350), cardiac valvular form (OMIM#225320), and progeroid form (OMIM#130070) [4] (Table 1). This chapter focuses on a recent breakthrough in EDS: discovery and delineation of D4ST1-deficient EDS (DD-EDS).

2. History of D4ST1-deficient EDS

DD-EDS, caused by loss-of-function mutations in the carbohydrate sulfotransferase 14 (*CHST14*) gene coding D4ST1, has been identified independently as a rare type of arthrogryposis syndrome, "adducted thumb–clubfoot syndrome (ATCS)" [5]; as a specific

form of EDS, "EDS, Kosho Type" (EDSKT) [6]; and as a subset of kyphoscoliosis type EDS without evidence of lysyl hydroxylase deficiency, "Musculocontractural EDS" (MCEDS) [7].

	Prevalence [§]	Inheritance	Causative gene(s)
Major types			
Classical type	1/20,000	AD	*COL5A1*, *COL5A2*
Hypermobility type	1/5,000-20,000	AD	*TNXB*[#]
Vascular type	1/50,000-250,000	AD	*COL3A1*
Kyphoscoliosis type	1/100,000	AR	*PLOD*
Arthrochalacia type	30	AD	*COL1A1**, *COL1A2**
Dermatosparaxis type	8	AR	*ADAMTS-2*
Other variants			
D4ST1-deficient type	26	AR	*CHST14*
Brittle cornea syndrome	11	AR	*ZNF469*
EDS-like syndrome due to tenascin-XB deficiency	10	AR	*TNXB*
EDS with progressive kyphoscoliosis myopathy, and hearing loss	7	AR	*FKBP14*
Spondylocheiro dysplastic form	8	AR	SLC39A13
Cardiac valvular form	4	AR	*COL1A2*
Progeroid form	3	AR	*B4GALT7*

[§], a fraction number represents the prevalence such as "one affected person in 20,000 individuals" for "1/20,000" and an integral number represents the sum of previously reported patients; AD, autosomal dominant; AR, autosomal recessive; *COL5A1* or *COL5A2*, α1(V) or α2(V) procollagen; *TNXB*, tenascin-X; [#], in a small subset of cases; *COL3A1*, α1(III) procollagen; *PLOD*; lysyl hydroxylase; *COL1A1* or *COL1A2*, α1(I) or α2(I) procollagen; *, splice-site mutations of the genes; *ADAMTS2*; procollagen I N-proteinase; *CHST14*, carbohydrate sulfotransferase 14; *ZNF469*, zinc finger protein 469; *FKBP14*, FK506-binding protein 14; *SLC39A13*, a membrane-bound zinc transporter; *B4GALT7*; xylosylprotein 4-beta-galactosyltransferase

Table 1. Classification of Ehlers-Danlos Syndromes

2.1. Adducted thumb–Clubfoot syndrome

The original report of ATCS was written by Dündar et al. [8] from Erciyes University, Turkey, presenting two cousins, a boy aged 3.5 years and a girl aged 1.5 years, from a consanguineous Turkish family. In common, they had moderate to severe psychomotor developmental delay, ocular anterior chamber abnormality, facial characteristics, generalized joint laxity, arachnodactyly, camptodactyly, and distal arthrogryposis with adducted thumbs and clubfeet. They reported another patient with ATCS, a boy aged 3 months, from a consanguineous Turkish family including three affected siblings who died of unknown etiology between the ages of 1 and 4 months [9]. The patient also had bilateral nephrolithiasis, a unilateral inguinal hernia, and bilateral cryptorchidism. The authors