TABLE I. Comparison of Clinical Features of Patients Caused by Mutations in Each Gene

Gene	*SMARCB1*	*SMARCA4*	*SMARCE1*	*ARID1A*	*ARID1B*	*PHF6*	*SMARCB2*	*ADNP*	*TBC1D24*
Clinical diagnosis	CSS, DOORSS, KSS	CSS	CSS	CSS	CSS, ID syndrome	CSS, BFLS	NCBRS	Autism syndrome	DOORSS
Patient number	16	12	3	8	=100	12#	61	11	13
Putative mutation effects	DN or GOF	DN or GOF	DN or GOF	LOF (mosaic)	LOF	LOF	DN or GOF	DN	LOF
Growth and feeding									
Prenatal growth									
Birth weight < −2SD or 3P	27% (3/11)	27% (3/11)	67% (2/3)	17% (1/6)		0% (0/12)	33% (19/57)	0% (0/10)	0% (0/12)[a]
Birth length < −2SD or 3P	50% (3/6)	50% (3/6)	67% (2/3)	0% (0/2)		0% (0/10)	21% (8/38)		
Birth OFC < −2SD or 3P	0% (0/6)	17% (1/6)	50% (1/2)	100% (1/1)		0% (0/7)	23% (7/30)		
Postnatal growth at the last observation									
Weight < −2SD or 3P	78% (7/9)	33% (4/12)	50% (1/2)	50% (3/6)		9% (1/11)	52% (24/46)	0% (0/8)	8% (1/12)[b]
Height < −2SD or 3P	100% (11/11)	67% (8/12)	67% (2/3)	25% (2/8)		0% (0/12)	54% (30/56)	0% (0/10)	
OFC < −2SD or 3P	90% (9/10)	91% (10/11)	100% (1/1)	29% (2/7)		25% (3/12)	65% (34/52)	0% (0/10)	25% (3/12)[c]
Sucking/feeding difficulty	100% (11/11)	92% (11/12)	100% (3/3)	100% (7/7)	60% (34/57)	44% (4/9)	47% (23/49)	64% (7/11)	
Craniofacial features									
Sparse sculp hair	92% (12/13)	42% (5/12)	67% (2/3)	60% (3/5)	57% (33/58)	58% (7/12)	97% (59/61)		0% (0/12)
Hypertrichosis	73% (8/11)	100% (12/12)	100% (2/2)	100% (7/7)	93% (55/59)	27% (3/11)	44% (22/50)	0% (0/7)	
Thick eyebrows	92% (12/13)	75% (9/12)	67% (2/3)	75% (6/8)	92% (54/59)	33% (4/12)	68% (40/59)	0% (0/8)	0% (0/12)
Long eyelashes	100% (11/11)	83% (10/12)	50% (1/2)	100% (6/6)	85% (51/60)	0% (0/12)	86% (44/61)	0% (0/8)	
Ptosis	55% (6/11)	75% (9/12)	33% (1/3)	43% (3/7)		0% (0/12)	21% (12/58)	33% (3/9)	
Thin upper lip vermilion	80% (8/10)	27% (3/11)	67% (2/3)	50% (3/6)	51% (29/57)	67% (8/12)	78% (47/60)	90% (9/10)	
Thick lower lip vermilion	73% (8/11)	83% (10/12)	100% (3/3)	86% (6/7)	81% (46/57)	17% (2/12)	83% (50/60)	13% (1/8)	0% (0/12)
Cleft palate	20% (2/10)	33% (4/12)	50% (1/2)	33% (2/6)		0% (0/12)	2% (1/61)	0% (0/9)	
Skeletal-limb features									
Hypoplastic 5th fingers or toes	77% (10/13)	100% (12/12)	100% (3/3)	86% (6/7)	61% (36/59)	82% (9/11)	12% (7/57)	14% (1/7)	100% (12/12)
Hypoplastic 5th fingernails or toenails	100% (11/11)	100% (12/12)	100% (3/3)	88% (7/8)	73% (35/48)	73% (8/11)	0% (0/34) 1st 6% (2/33) All 18% (6/34)		100% (13/13)
Hypoplastic other fingernails and toenails	70% (7/10)	50% (5/10)	67% (2/3)	75% (6/8)		73% (8/11)			
Prominent interphalangeal joints	44% (4/9)	27% (3/11)	50% (1/2)	20% (1/5)	30% (15/50)	36% (4/11)	85% (50/59)	14% (1/7)	
Prominent distal phalanges	75% (6/8)	50% (5/10)	33% (1/3)	20% (1/5)	37% (19/52)	0% (0/12)	68% (40/59)	14% (1/7)	
Scoliosis	82% (9/11)	10% (1/10)	50% (1/2)	29% (2/7)		17% (2/12)	28% (17/60)	22% (2/9)	0% (0/12)
Internal complications									
Cardiovascular	42% (5/12)	42% (5/12)	67% (2/3)	38% (3/8)			10% (6/61)	27% (3/11)	
Hernia	88% (7/8)	55% (6/11)	0% (0/2)	25% (1/4)		0% (0/12)	46% (26/57)	0% (0/7)	
Hearing and vision									
Hearing impairment	73% (8/11)	33% (4/12)	50% (1/2)	33% (2/6)		30% (3/10)	7% (4/59)		100% (13/13)
Visual impairment	60% (6/10)	45% (5/11)	100% (1/1)	75% (3/4)	34% (19/56)	64% (7/11)		55% (6/11)	
Immunology									
Frequent infection	89% (8/9)	67% (8/12)	67% (2/3)	60% (3/5)	37% (21/57)	33% (4/12)	27% (13/48)	64% (7/11)	
Neurology									
Hypotonia	79% (11/14)	73% (8/11)	33% (1/3)	88% (7/8)	75% (42/56)	70% (7/10)	37% (19/51)	73% (8/11)	
Seizures	62% (8/13)	17% (2/12)	67% (2/3)	29% (2/7)		17% (2/12)		18% (2/11)	100% (13/13)
Structural CNS abnormalities	100% (12/12)	86% (6/7)	100% (2/2)	88% (7/8)	27% (13/48)			50% (5/10)	
Development and intelligence									
Developmental delay and ID									100% (13/13)
Severe	73% (8/11)	55% (6/11)	33% (1/3)	57% (4/7)	18% (8/44)	17% (2/12)	46% (28/61)	60% (6/10)	75% (3/4)
Moderate	9% (1/11)	36% (4/11)	67% (2/3)	0% (0/7)	55% (24/44)	33% (4/12)	36% (22/61)	10% (1/10)	
Mild	9% (1/11)	9% (1/11)	0% (0/3)	29% (2/7)	9% (4/44)	25% (3/12)	18% (11/61)	30% (3/10)	25% (1/4)
Speech impairment									
No words	82% (9/11)	36% (4/11)	67% (2/3)	83% (5/6)		33% (3/9)	32% (19/60)		
Bahavior									
Bahavioral abnormalities	44% (4/9)	88% (7/8)	50% (1/2)	60% (3/5)		33% (4/12)	19/?	78% (7/9)	

BFLS, Borjeson–Forssman–Lehmann syndrome; CNS, central nervous system; CSS, Coffin–Siris syndrome; DOORSS, DOORS syndrome; DN, dominant-negative; GOF, gain-of-function; ID, intellectual disability; KSS, Kleefstra syndrome; LOF, loss-of-function; NCBRS, Nicolaides–Baraitser syndrome; P, percentile; SD, standard deviation; #, excluding male patients with BFLS.

[a]intrauterine growth retardation/small for gestational age.

[b]failure to thrive.

[c]microcephaly.

and increased susceptibility to infection. They always have structural central nervous system (CNS) abnormalities, and usually have hypotonia and seizures. The "p.Lys364del" genotype, shared by nine patients, presents strikingly similar phenotypes including characteristic facial coarseness (in early childhood, round face with thick and arched eyebrows, short nose with bulbous tip and anteverted nostrils, long philtrum, small mouth, and micro-retrognathia; later, broad nasal bridge without anteverted nostrils, broad philtrum, large tongue, and protruding jaw), severe developmental delay or ID, but relatively mild internal organ complications.

SMARCA4

Heterozygous mutations in *SMARCA4* have been reported in 12 patients with CSS [Tsurusaki et al., 2012, 2014b; Kosho et al., 2013; Santen et al., 2013]. The mutations, all non-truncating (missense or in-frame deletions), are predicted to exert dominant-negative or gain-of-function effects. About half of the patients have severe developmental delay or ID, and occasionally (20–30%) speak no words. Growth impairment is mild prenatally and mild-to-moderate postnatally, and difficulty in sucking/feeding is almost always observed. Typical facial features include sparse scalp hair, thick eyebrows, long eyelashes, ptosis, flat nasal bridge, short philtrum, and thick lower lip vermilion. Hypertrichosis is always observed. Facial coarseness is not evident and a pointed chin in older ages is noted. Patients always have hypoplastic fifth fingers or toes and hypoplastic fifth fingernails or toenails, and sometimes (40–50%) have hypoplastic other fingernails or toenails. Internal organs are impaired in most. They usually have hypotonia, structural CNS abnormalities, and behavioral abnormalities.

SMARCE1

Heterozygous mutations in *SMARCE1* have been reported in three patients with CSS [Tsurusaki et al., 2012, 2014b; Kosho et al., 2013; Santen et al., 2013; Wieczorek et al., 2013]. The mutations, all non-truncating (missense), are predicted to exert dominant-negative or gain-of-function effects. Patients frequently (around 60%) have moderate developmental delay or ID and speak no words. Growth impairment is mild-to-moderate prenatally and moderate-to-severe postnatally, and difficulty in sucking/feeding is always observed. Typical facial features include sparse scalp hair, thick eyebrows, thin upper lip vermilion, and thick lower lip vermilion. Hypertrichosis is always observed, as is hypoplastic fifth fingers or toes and hypoplastic fifth fingernails or toenails. Internal organs and vision are always impaired. They always have structural CNS abnormalities and frequently have seizures.

ARID1A

Heterozygous mutations in *ARID1A* have been reported in eight patients with CSS [Tsurusaki et al., 2012, 2014b; Kosho et al., 2013; Santen et al., 2013; Wieczorek et al., 2013]. The mutations, all truncating and probably mosaic, are predicted to exert a loss-of-function effect. Patients frequently have severe developmental delay or ID and speak no words, although mild ID patients also present occasionally. Growth impairment is mild prenatally and mild-to-severe postnatally, and difficulty in sucking/feeding is always observed. Typical facial features include sparse scalp hair, thick eyebrows, long eyelashes, wide nasal bridge, and thick lower lip vermilion. Hypertrichosis is always observed. They usually have hypoplastic fifth fingers or toes, hypoplastic fifth fingernails or toenails, and hypoplastic other fingernails or toenails. Internal organs are impaired occasionally. Hepatoblastoma occurred in one patient. They usually have hypotonia and structural CNS abnormalities. Behavioral abnormalities are frequent.

ARID1B

Heterozygous mutations in *ARID1B* as well as cytogenetic abnormalities involving the gene have been reported in 67 patients with CSS [Santen et al., 2012a, 2013; Tsurusaki et al., 2012, 2014b; Kosho et al., 2013; Santen et al., 2013; Wieczorek et al., 2013] and in >30 patients with non-syndromic ID [Narahara et al., 1991; Pirola et al., 1998; Sukumar et al., 1999; Bisgaard et al., 2006; Nagamani et al., 2009; Backx et al., 2011; Nord et al., 2011; Halgren et al., 2012; Hoyer et al., 2012; Sim et al., 2014; Vengoechea et al., 2014]. *ARID1B* abnormalities are considered the leading cause of CSS (68–83%) [Santen et al., 2013; Wieczorek et al., 2013; Tsurusaki et al., 2014b] and are also represented in 0.9% of unselected ID patients [Hoyer et al., 2012]. All of the reported mutations are truncating, and are predicted to result in haploinsufficiency. The phenotypic features of those with *ARID1B* abnormalities are considered to be enormously variable. For patients with *ARID1B*-related CSS, varying severities of developmental delay or ID accompanied by speech impairment are always present. Typical facial features include coarseness, thick eyebrows, long eyelashes, broad nasal tip, thick alaenasi, large mouth, thick lower lip vermilion, and low anterior hairline. Hypertrichosis is almost always observed. They usually have hypoplastic nails of the fifth fingers/toes and frequently had small fifth fingers. About a third of those observed have callosal body underdevelopment. About half of the patients with non-syndromic ID have speech impairment and partial or complete agenesis of the corpus callosum.

PHF6

Hemizygous mutations in *PHF6* were reported to cause BFLS in males with moderate-to-severe ID, epilepsy, hypogonadism, hypometabolism, pronounced obesity, swelling of subcutaneous tissue of the face, narrow palpebral fissures, and large ears [Borjeson et al., 1962; Lower et al., 2002]. Female carriers usually show no or only mild symptoms. De novo heterozygous mutations in *PHF6* have been reported in 12 female patients [Crawford et al., 2006; Berland et al., 2011; Wieczorek

et al., 2013; Zweier et al., 2013, 2014; Di Donato et al., 2014] and are predicted to cause a loss-of-function effect. All have variable severities of developmental delay or ID. Typical facial features include bitemporal narrowing of the forehead, prominent supraorbital ridges, prominent eyebrows with high arch and synophrys, deep-set eyes, marked zygomatic arch, high nasal bridge, short nose with bulbous nasal tip, prominent columella, long shaped, slightly posteriorly rotated ears or prominent earlobes. Prenatal growth is not impaired, and postnatal growth is also normal in the majority. All have finger abnormalities including brachytelephalangy or hypoplastic nails. Other common features includedental abnormalities, linear skin hyperpigmentation, infantile sparse hair, and deep voice. Internal organs are complicated only occasionally. There is a striking overlap of sparse hair, particularly in infancy, between these female patients with *PHF6* mutations and those with CSS.

SMARCB2

Heterozygous mutations in *SMARCB2* have been reported in 61 patients with NCBRS [Tsurusaki et al., 2012; Van Houdt et al., 2012; Kosho et al., 2013; Sousa et al., 2014]. The mutations are predicted to exert dominant-negative or gain-of-function effects. All have developmental delay or ID with severe delay in about half of the patients. Prenatal growth is occasionally impaired, and postnatal growth is impaired in over half. Typical facial features include sparse hair, thick eyebrows, long eyelashes, long and/or broad philtrum, thin upper lip vermilion, and thick lower lip vermilion. Prominent interphalangeal joints and prominent distal phalanges are usually present.

ADNP

Heterozygous mutations in *ADNP* have been reported in 11 patients [Helsmoortel et al., 2014; Vandeweyer et al., 2014]. Mutations in the original 10 patients are predicted to exert a dominant-negative effect through frameshift or nonsense mutations [Helsmoortel et al., 2014], and a nonsense mutation in the eleventh patient is predicted to result in haploinsufficiency [Vandeweyer et al., 2014]. All the patients have autism together with delayed developmental milestones, mild-to-severe ID, and speech problems. Prenatal or postnatal growth is usually not impaired. Typical facial features include prominent forehead, high hairline, broad nasal bridge, and thin upper lip vermilion. They frequently have joint laxity. Internal organs could be impaired—usually gastrointestinal problems including gastroesophageal reflux and constipation, and occasionally heart defects. They frequently suffer recurrent infections. Hypotonia is usually observed in infancy, and brain abnormalities are detected by MRI in half. Behavioral problems are usual and include sleep disturbances, anxiety, and obsessive–compulsive disorder.

TBC1D24

Homozygous or compound heterozygous mutations in *TBC1D24* have been reported in 13 patients from 10 families [Campeau et al., 2014a,b]. The mutations are predicted to cause a loss of TBC1D24 function. All the patients have ID or developmental delay, seizures, deafness, short distal phalanges, and small or absent nails. The majority show increased urinary 2-oxoglutaric acid excretion. Prenatal or postnatal growth is usually not impaired. The facial features are variable with a broad nasal bridge in half. Tri-phalangeal thumbs are observed in a quarter. Internal organs are usually normal. Brain abnormalities are detected by MRI in half. Recessive mutations in *TBC1D24* were also identified in various epileptic syndromes including focal epilepsy with ID syndrome [Corbett et al., 2010], familial infantile myoclonic epilepsy [Falace et al., 2010], myoclonic epilepsy with dystonia [Guven and Tolun, 2013], and familial malignant migrating partial seizures of infancy [Milh et al., 2013]. Autosomal recessive non-syndromic deafness (DFNB86) [Rehman et al., 2014] as well as autosomal dominant non-syndromic deafness [Azaiez et al., 2014; Zhang et al., 2014] were also found to be caused by mutations in the gene.

BIOLOGICAL CHARACTERISTICS OF THE BAF COMPLEX

Originally, the BAF complex was identified in yeast (*S. cerevisiae*) [Carlson et al., 1981], and is evolutionarily highly conserved from yeast to humans. This complex works as chromatin remodeling factor, altering chromatin structure using the energy of ATP hydrolysis [Cote et al., 1994]. The BAF complex loosens chromatin structure and allows protein access to DNA or histones to activate or repress gene transcription [Martens and Winston, 2002; Wu et al., 2009]. In mammals, the BAF complex is a multisubunit com-plex composed of an ATPase subunit (either SMARCA4 or SMARCA2), common core subunits (SMARCB1, SMARCC1, and SMARCC2), and "accessory" subunits [Roberts and Biegel, 2009].

The relationship between neurological development and the BAF complex has been especially highlighted due to the identification of the numerous mutations in the genes encoding the BAF subunits in patients with syndromes displaying developmental delay, ID, or autistic features. In this current issue, Son and Crabtree [2014] describe the BAF complex functions in neuronal development in detail. For instance, switching from neuronal progenitor BAF (npBAF) to neuron specific BAF complex (nBAF) through neurological development is known [Lessard et al., 2007; Wu et al., 2007, 2009]. These two BAF complexes share most of the same components with some exceptions; BAF53a, SS18 and BAF45a/d in npBAF complex are replaced by BAF53b, CREST and BAF45b/c in nBAF complex, respectively [Lessard et al., 2007; Wu et al., 2007, 2009; Ronan et al., 2013]. Furthermore, BAF170-containing npBAF complex is also known to regulate cerebral cortical size and thickness [Tuoc et al., 2013]. BAF53b of nBAF complex plays important roles in synaptic plasticity and

memory [Vogel-Ciernia et al., 2013]. In addition, *SMARCA2* is reported to be associated with schizophrenia [Koga et al., 2009; Loe-Mie et al., 2010], and a de novo truncation mutation in *CREST* (also known as *SS18L1*) has been identified in amyotrophic lateral sclerosis, an adult onset neurodegenerative disease [Chesi et al., 2013]. This evidence might indicate that the BAF complex is also important in adult neurogenesis [Son and Crabtree, 2014]. At this moment, how the BAF complex alterations contribute to the human neurological features remains largely unknown. As the majority of patients with BAF complex diseases present with diverse neurological impairments of varying seriousness, further understanding of this field is highly desirable to elucidate the pathomechanisms of these neurological features.

BAF COMPLEX AND CANER/CANCER PREDISPOSITION SYNDROME

Before the identification of germline mutations in the BAF complex genes in CSS patients, the BAF complex was well studied in tumor development. The first link between the BAF complex and human diseases was the *SMARCB1* deletion and malignant rhabdoid tumors [Biegel et al., 1999; Versteege et al., 1998]. Heterozygous germline mutations in *SMARCB1* and *SMARCA4* were first reported to cause Rhabdoid tumor predisposition syndrome 1 [Sevenet et al., 1999] and Rhabdoid tumor predisposition syndrome 2 [Schneppenheim et al., 2010], respectively. In addition, germline mutations in *SMARCB1* have been identified in patients with familial and sporadic cases of schwannomatosis [Hulsebos et al., 2007; Boyd et al., 2008; Hadfield et al., 2008; Bacci et al., 2010]. Germline mutations in *SMARCE1* have also been detected in familial multiple spinal meningiomas [Smith et al., 2013]. Until now, many large scale studies of mutations in the BAF complex genes (including somatic mutations), in various kinds of tumors, have been published and mutations that inactivate the BAF complex were detected in almost 20% of human cancers [Kadoch et al., 2013]. This suggests that the BAF complex functions as a tumor suppressor in a variety of tissues [Hohmann and Vakoc, 2014]. Interestingly, it is reported that some BAF subunit mutations are associated with particular cancer types, suggesting that the BAF complex has multiple distinct tumor suppressor functions rather than acting via a single common pathway [Hohmann and Vakoc, 2014]. It is hoped that clarification of the mechanisms of tumorigenesis caused by mutations in each BAF complex subunits will allow the development of early diagnosis and new therapies including molecular targeting. To date, it is not known how often malignancies are observed in patients with mutations in the BAF complex genes such as CSS [Santen et al., 2012b]. Medulloblastoma, neuroblastoma, and schwannomatosis occurred in patients with molecularly-unconfirmed CSS [Schrier and Deardorff, 2014] and hepatoblastoma occurred in a patient with CSS and a mutation in *ARID1A* [Tsurusaki et al., 2012; Kosho et al., 2013]. In this current issue, Biegel et al. [2014] comprehensively review the relationship between the BAF complex and cancer/cancer predisposition syndrome.

CONCLUDING REMARKS

After decades of research, we now have robust information regarding the genetic causes of CSS and related disorders. These disorders are attributable to mutations in several genes involving the BAF complex as well as genes with probable or possible functional relation to the complex, and clinical features of each gene defect are outlined as described in the previous section. To date, CSS, NCBRS, and *ADNP*-related autism/ID syndrome, despite each constituting a distinct phenotype, would represent a group of ID syndromes that might be designated as "BAF (SWI/SNF)-related ID syndromes" [Kosho et al., 2013]. However, the full picture of clinical consequences of the BAF complex abnormalities remains to be elucidated. The current mutation detection rate in known CSS genes is less than 70% [Tsurusaki et al., 2012; Santen et al., 2013; Wieczorek et al., 2013], suggesting that other genes might also be causal for the CSS phenotype and that whole exome sequencing of larger numbers of patients, diagnosed as CSS, would uncover such genes. Furthermore, clinical consequences of each gene defect, reported to date, should be carefully interpreted because patient cohorts were biased to specific clinical diagnosis (e.g., CSS, NCBRS). It would be desirable that international collaborative studies are designed to obtain detailed clinical information and perform comprehensive genetic screening (microarray-based copy number analysis, target sequencing of a large panel of ID genes including all BAF genes reported to be causal for CSS and related disorders, and whole exome/genome sequencing) for a large number of unbiased ID patients with/without physical features just as *ARIB1B* consortium [Santen and Clayton-Smith, 2014]. Finally, it is highly expected that integration of such clinical/genetic investigation and basic research on BAF biology would contribute to future innovation of care and treatment for these patients.

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Carbohydrate (*N*-Acetylgalactosamine 4-*O*) Sulfotransferase 14 (CHST14)

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Tomoki Kosho, Shuji Mizumoto, and Kazuyuki Sugahara

Contents

Abstract

The *CHST14* gene, localized at 15q14, is a single exon gene with an open reading frame of 1131 base pairs, encoding a 43 kDa protein dermatan-4-*O*-sulfotransferase-1 (D4ST1) that catalyzes the 4-*O*-sulfation of *N*-acetyl-D-galactosamine residues in dermatan sulfate (DS). Both nearly exhaustively desulfated DS and partially desulfated DS serve as excellent substrates for the enzyme. Chst14/D4st1-deficient mice showed growth retardation as well as multiple system abnormalities including neurology such as decreased neurogenesis and diminished

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proliferation of neural stem cells. Recently, recessive loss-of-function mutations in the *CHST14* gene were found to cause a specific form of Ehlers-Danlos syndrome (EDS) designated as D4ST1-deficient EDS (DD-EDS). The disorder is characterized by progressive multisystem fragility-related manifestations (skin hyperextensibilty and fragility, progressive spinal and foot deformities, large subcutaneous hematoma) and various malformations (facial features, congenital eye/heart/gastrointestinal defects, congenital multiple contractures). Glycosaminoglycan (GAG) chains from the affected skin fibroblasts were composed of a negligible amount of DS and excess chondroitin sulfate (CS), which was suggested to result from an impaired lock by 4-*O*-sulfation due to D4ST1 deficiency followed by back epimerization from L-iduronic acid to D-glucuronic acid. GAG chains of decorin from the affected skin fibroblasts were composed exclusively of CS and no DS, the opposite features observed in normal controls. Thus, skin fragility in the disorder was supposed to be caused by impaired assembly of collagen fibrils mediated by decorin bearing a CS chain that replaced a DS chain. The disorder stresses the importance of the role of CHST14/D4ST1 and DS in human development and maintenance of extracellular matrices.

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. 101.1. It is initiated by the synthesis of a tetrasaccharide linker region, glucuronic acidβ1-3galactoseβ1-3galactoseβ1-4xyloseβ1-*O*- (GlcA-Gal-Gal-Xyl-), onto serine residues of specific core proteins of PGs, by b-xylosyltransferase, β1,4-galactosyltransferase-I, β1,3-galactosyltransferase-II, and β1,3-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

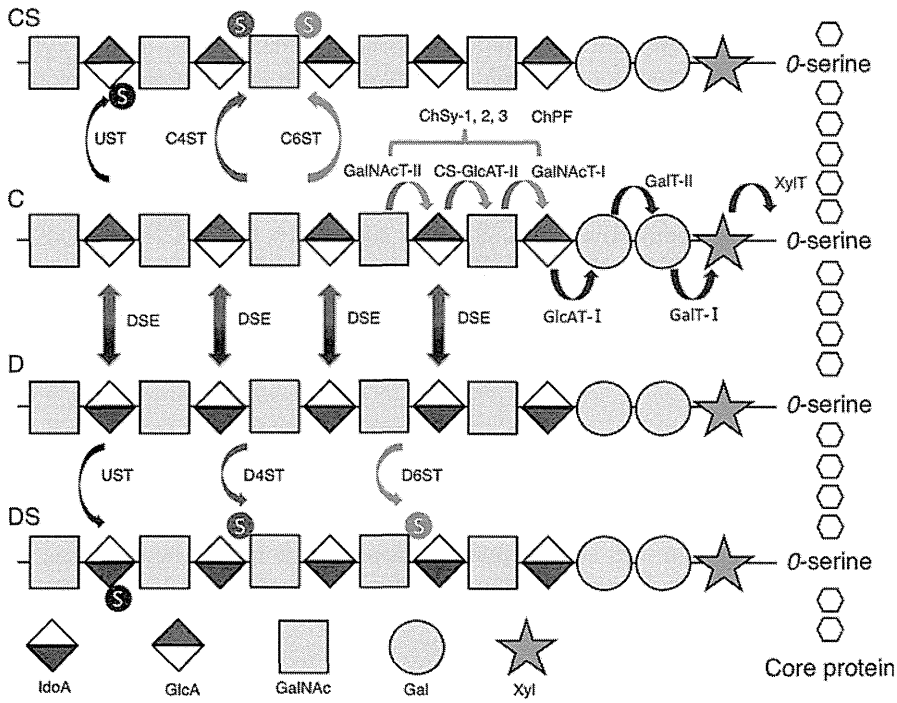

Fig. 101.1 Biosynthesis of DS and CS (Kosho 2013). *C* chondroitin, *CS* chondroitin sulfate, *D* dermatan, *DS* dermatan sulfate, *Ser* serine, *Xyl* D-xylose, *Gal* D-galactose, *GlcA* D-glucuronic acid, *GalNAc* *N*-acetyl-D-galactosamine, *IdoA* L-iduronic acid, *XylT* xylosyltransferase, *GalT-I* 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

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 FuGENE HD transfection reagent (Promega). 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 101.1) (Kosho 2013).

Table 101.1 Reported patients with DD-EDS (Kosho 2013)

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

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

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

Clinical manifestations are summarized in Table 101.2, 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).

Table 101.2 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

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

(*continued*)

Table 101.2 (continued)

Ocular	
	Strabismus
	Refractive errors (myopia, astigmatism)
	Glaucoma/elevated intraocular pressure
	Microcornea/microphthalmia
	Retinal detachment
Hearing	
	Hearing impairment
Neurological	
	Ventricular enlargement/asymmetry
Development	
	Hypotonia/gross motor delay

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. 101.2a, b). Slender and asymmetrical facial shapes with protruding jaws are noted from school age (Fig. 101.2c) (Kosho et al. 2005, 2010, 2011; Shimizu et al. 2011; Kosho 2013).

Congenital multiple contractures, such as adduction–flexion contractures of thumbs and talipes equinovarus, were cardinal features (Fig. 101.2d, g). Peculiar finger shape, described as "tapering," "slender," and "cylindrical," is also noted (Fig. 101.2e, f). Talipes deformities (planus, valgus) (Fig. 101.2h) and spinal deformities (scoliosis, kyphoscoliosis) with tall vertebral bodies and decreased physiological curvature (Fig. 101.2j, 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 2013).

Cutaneous features include hyperextensibility to redundancy, bruisability, fragility leading to atrophic scars, acrogeria-like fine palmar creases or wrinkles (Fig. 101.2e, f), hyperalgesia to pressure, and recurrent subcutaneous infections with fistula formation (Kosho et al., 2005, 2010; Shimizu et al., 2011).

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. 101.2i) (Kosho et al. 2005, 2010, 2011; Shimizu et al. 2011; Kosho 2013).

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 101.1) 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. 101.3a(a)). Disaccharide composition analysis of

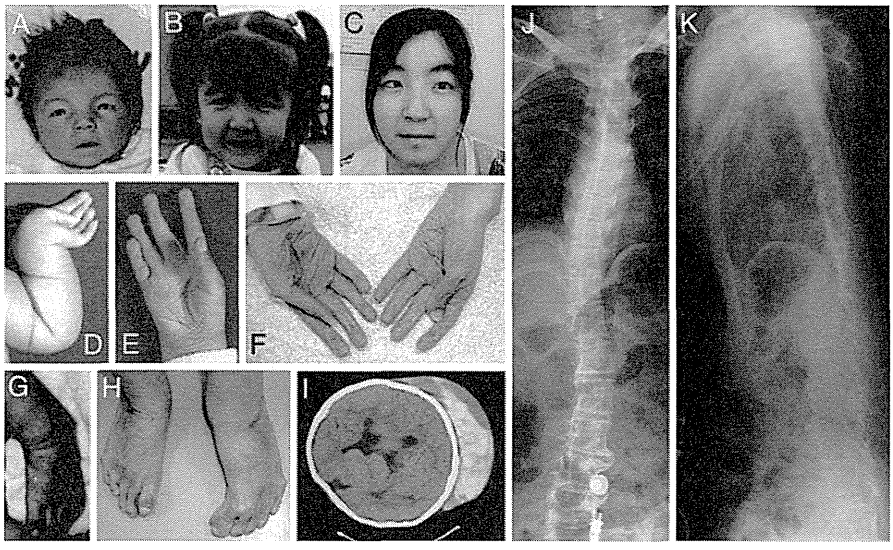

Fig. 101.2 Clinical photographs of patients with DD-EDS (Kosho et al. 2005; Kosho et al. 2010). Patient 12 at age 23 days (**a**), 3 years (**b**), 6 years (**i**), and 16 years (**c**). Patient 13 at age 3 months (**d**), 5 years (**e**), and 28 years (**f**, **j**, **k**). Patient 14 in the neonatal period (**g**) and at age 28 years (**h**). Patient number is according to Table 101.1

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. 101.3a(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. 101.3a(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 et al. 2010) (Fig. 101.3b(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. 101.3b(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);

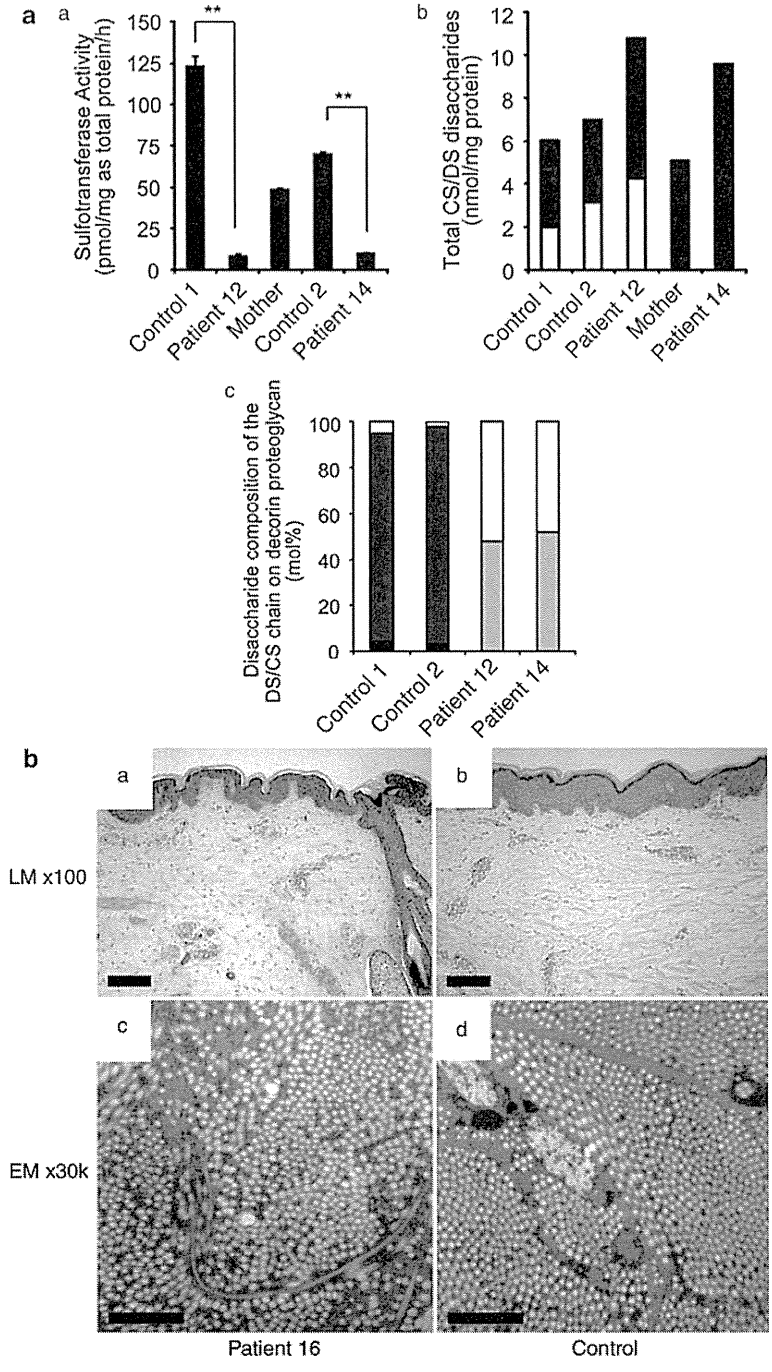

Fig. 101.3 (continued)

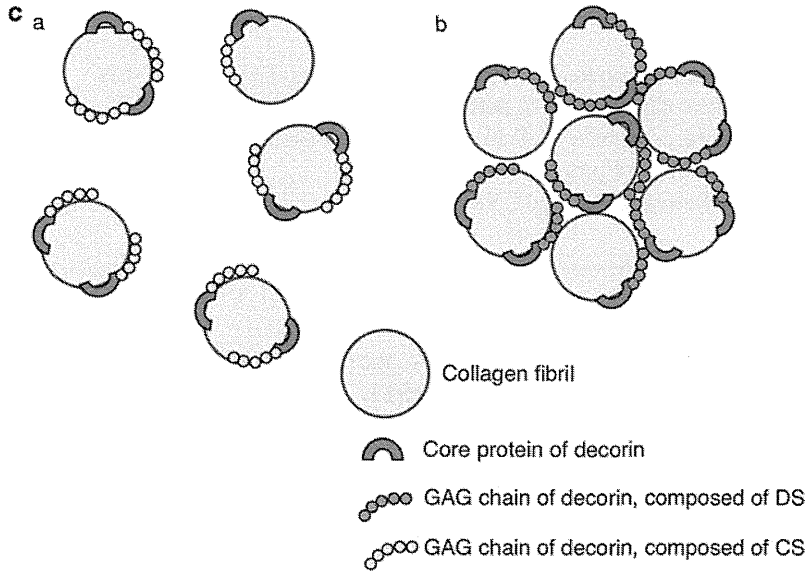

Fig. 101.3 (**a**) Glycobiological studies (Miyake et al. 2010). Control 1 is Patient 12′s age- and sex-matched control. Mother is Patient 12′s. Control 2 is Patient 14′s age- and sex-matched control. Patient number is according to Table 101.1. (*a*) Sulfotransferase activity of skin fibroblasts. (*b*) 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 GlcA-GalNAc(4S) and GlcA-GalNAc(6S), respectively, both composing CS. A *dark gray box* and a *black box* indicate IdoA-GalNAc(4S) and IdoA(2S)-GalNAc(4S), 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 101.1 (*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)

(Kosho 2011) (Fig. 101.3c(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.

Cross-References

- ▶ Carbohydrate (Chondroitin 4) Sulfotransferase 11-13 (CHST11-13)
- ▶ Carbohydrate (Chondroitin 6) Sulfotransferase 3; Carbohydrate (*N*-Acetylglucosamine 6-*O*) Sulfotransferase 7 (CHST3,7)
- ▶ Dermatan Sulfate Epimerases (DSE, DSEL)
- ▶ Uronyl-2-Sulfotransferase (UST)

Further Reading

Evers et al. (2001): Cloning of *CHST14*, the first characterization of the enzyme, and designation of the enzyme as D4ST1.

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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