Ⅳ．研究成果の刊行に関する一覧表

別紙４

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
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		2013	
Miyake N, Kosho T, Matsumoto N	Ehlers-Danlos syndrome associated with glycosaminoglycan abnormalities		Progress in heritable soft tissue disease	Springer		2013	In press
Mizumoto S, Sugahara K	Bone and skin disorders caused by a disturbance in the bioynthesis of chondroitin sulfate and dermatan sulfate.	Karamanos N	Extracellular matrix: Pathobiology and signaling	De Gruyter	Berlin	2012	97-118
Saitsu H, Kato M, **Matsumoto N**	Haploinsufficiency of *STXBP1* and Ohtahara syndrome.	Noebels J, Avoli M, Rogawski M, Olsen RW, and Delgado-Escueta AV	Jasper's basic mechanism of the epilepsies, 4th edition	Oxford University Press		2012	824-834
Ikegawa S, Nakashima M, **Matsumoto N**	TGF-β and Genetic Skeletal Diseases.	Moustakas A and Miyazawa K	TGFβ in Human Disease	Springer			Submitted
Mizumoto S, Sugahara K	Glycosaminoglycan chain analysis and characterization (Glycosylation /Epimerization) (Chapter 7)	Rédini, Françoise	Methods in Molecular Biology, "Proteoglycans: Methods and Protocols"	Humana Press, Springer	New York	2012	99-115

Mizumoto S	Reduction of Chondroitin 4-*O*-Sulfotransferase-1 Expression Causes Costello Syndrome		Trends in Glycoscience and Glycotechnology			2013	In press
Okada T	Efficient AAV vector production system: Towards gene therapy for Duchenne muscular dystrophy.	Francisco Martin	Gene Therapy - Tools and Potential Applications	InTech			In press
古庄知己	Marfan症候群, Ehlers-Danlos症候群	『小児内科』『小児外科』編集委員会	小児内科増刊号・小児疾患の診断治療基準第4版	東京医学社	東京	2012	850-853
古庄知己	エーラスダンロス症候群		別冊日本臨牀・新領域別症候群シリーズNo.20・先天異常症候群第2版（下）	日本臨牀社		2012	721-726

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Tsurusaki Y[#], ***Kosho T**[#] (# denotes equal contribution), Hatasaki K, Narumi Y, Wakui K, Fukushima Y, Doi H, Saitsu H,1 **Miyake N**, ***Matsumoto N** (*: co-correspondence)	Exome sequencing identifies an *OFD1* mutation in a family of X-linked lethal congenital malformation syndrome: delineation of male Oral-facial-digital syndrome type 1.	Clin Genet	83(2)	135-144	2012
Kondo E, Nishimura T, **Kosho T** (corresponding author), Inaba Y, Mitsuhashi S, Ishida T, Baba A, Koike K, Nishino I, Nonaka I, Furukawa T, Saito K	Recessive RYR1 mutations in a patient with severe congenital nemaline myopathy with ophthalomoplegia identified through massively parallel sequencing.	Am J Med Genet A	158A(4)	772-778	2012
Motobayashi M, Nishimura-Tadaki A, Inaba Y, **Kosho T** (corresponding author), Miyatake S, Niimi T, Nishimura T, Wakui K, **Fukushima Y**, **Matsumoto N**, Koike K	Neurodevelopmental features in 2q23.1 microdeletion syndrome: Report of a new patient with intractable seizures and review of literature.	Am J Med Genet Part A	158 (4)	861-868	2012
Kashizaki F, **Hatamochi A**, Kamiya K, Yoshizu A, Okamoto H	Patient with the vascular type of Ehlers-Danlos syndrome, with a novel point-mutation in the COL3A1 gene.	J Dermatol	40(3)	226-228	2013
Shimaoka Y, Hayashi S, Hamasaki Y, Terui K, **Hatamochi A**	Patient with the vascular type of Ehlers-Danlos syndrome, with a novel point-mutation in the COL3A1 gene.	J Dermatol	40(3)	226-228	2013

Hayashi S, Ikeda M, Kitamura Y, Hamasaki Y, **Hatamochi A**	UVA irradiation following treatment with topical 8-methoxypsoralen improves bleomycin-induced scleroderma in a mouse model, by reducing the collagen content and collagen gene expression levels in the skin.	J Dermatol Sci	67(1)	20-25	2012
Tsurusaki Y, Okamoto N, Ohashi H, **Kosho T**, Imai Y, Hibi-Ko Y, Kaname T, Naritomi K, Kawame H, Wakui K, Fukushima Y, Homma T, Kato M, Hiraki Y, Yamagata T, Yano S, Mizuno S, Sakazume S, Ishii T, Nagai T, Shiina M, Ogata K, Ohta T, Niikawa N, Miyatake S, Okada I, Mizuguchi T, Doi H, Saitsu H, ***Miyake N**, ***Matsumoto N** (*: co-corresponding).	Mutations affecting components of the SWI/SNF complex cause Coffin-Siris syndrome.	Nat Genet	44(4)	376-378	2012
***Miyake N**[#], Yano S[#] (# denotes equal contribution), Sakai C, Hatakeyama H, Shiina M, Watanabe Y, Bartley J, Abdenur JE, Wang RY, Chang R, Tsurusaki Y, Doi H, Saitsu H, Ogata K, Goto Y, ***Matsumoto N**	Mitochondrial complex III deficiency caused by a homozygous *UQCRC2* mutation presenting with neonatal-onset recurrent metabolic decompensation.	Hum Mutat			In press
***Miyake N**, Mizuno S, Okamoto N, Ohashi H, Shiina M, Ogata K, Tsurusaki Y, Nakashima M, Saitsu H, ***Matsumoto N** (*: co-corresponding).	*KDM6A* point mutations cause Kabuki syndrome.	Hum Mutat	34 (1)	108-110	2012

Miyake N[#], Elcioglu NH[#] (# denotes equal contribution), Iida A, Isguven P, Dai J, Murakami N, Takamura K, Cho T-J, Kim O-H, Nagai T, Ohashi H, Nishimura G, **Matsumoto N**, Ikegawa S	*PAPSS2* mutations cause autosomal recessive brachyolmia.	J Med Genet	49(8)	533-538	2012
Yamashita S, **Miyake N**, **Matsumoto N**, Osaka H, Iai M, Aida N, Tanaka Y	Neuropathology of Leukoencephalopathy with Brainstem and Spinal Cord Involvement and High Lactate caused by a homozygous mutation of DARS2.	Brain Dev			In press
Tsurusaki Y, Kobayashi Y, Hisano M, Ito S, Doi H, Nakashima M, Saitsu H, **Matsumoto N**, **Miyake N**	The diagnostic utility of exome sequencing in Joubert syndrome related disorders	J Hum Genet			In press
Miyatake S, **Miyake N**, Doi H, Ogata K, Kawai M, **Matsumoto N**	A novel SACS mutation in a Japanese family with atypical phenotype of autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS).	Intern Med	51	2221-2226	2012
Sakai H, Suzuki S, Mizuguchi T, Imoto K, Doi H, Kikuchi M, Tsurusaki T, Saitsu H, **Miyake N**, Masuda M, **Matsumoto N**	Rapid detection of gene mutations responsible for non-syndromic aortic aneurysm and dissection using two different methods: resequencing microarray technology and next-generation sequencing.	Hum Genet	131	591-599	2012

Miyatake S, **Miyake N**, Touho H, Nishimura-Tadaki A, Kondo Y, Okada I, Tsurusaki Y, Doi H, Sakai H, Saitsu H, Yamamoto T, Higurashi M, Kawahara N, Kawauchi H, Nagasaka K, Okamoto N, Mori T, Koyano S, Kuroiwa Y, Taguri M, Morita S, Matsubara Y, Kure S, **Matsumoto N**	Homozygous c.14576G>A Variant of *RNF213* Predicts Early-Onset and Severe Form of Moyamoya Disease.	Neurology	78	803-810	2012
Yoneda Y, Haginoya K, Arai H, Tsurusaki Y, Doi H, **Miyake N**, Osaka H, Kato M, **Matsumoto N**, Saitsu H	*De novo* and inherited mutations in the gene encoding a type IV collagen α2 chain (*COL4A2*) cause porencephaly.	Am J Hum Genet	90 (1)	86-90	2012
Kondo Y, Saitsu H, Miyamoto T, Nishiyama K, Tsurusaki T, Doi H, **Miyake N**, Ryoo N-K, Kim JH, Yu KS,***Matsumoto N**	A family of oculofaciocardiodental syndrome (OFCD) with a novel *BCOR* mutation and genomic rearrangements involving *NHS*.	J Hum Genet	57(3)	197-201	2012
Yoneda Y, Saitsu H, Touyama M, Makita Y, Miyamoto A, Hamada K, Nishiyama K, Tsurusaki Y, Doi H, **Miyake N**, Ogata K, Naritomi K, **Matsumoto N**	Missense mutations in the DNA-binding/dimerization domain of *NFIX* cause Sotos-like syndrome.	J Hum Genet	50(3)	207-211	2012
Tsurusaki Y, *Saitoh S, Tomizawa K, Sudo A, Asahina N, Shiraishi H, Ito J, Tanaka H, Doi H, Saitsu H, **Miyake N**, ***Matsumoto N** (* denotes co-correponding)	A *DYNC1H1* mutation causes a dominant spinal muscular atrophy with lower extremity predominance.	Neurogenet			In press

Saitsu H, Osaka H, Nishiyama K, Tsurusaki Y, Doi H, **Miyake N**, **Matsumoto N**	A girl with early-onset epileptic encephalopathy associated with microdeletion involving *CDKL5*.	Brain Dev	34(5)	364-367	2012
Hamdan FF[#], Saitsu H[#] (# denotes equal contribution), Masuko K, Gauthier J, Dobrzeniecka S, Spiegelman D, Lacaille JC, Décarie JC, **Matsumoto N**, Rouleau GA, Michaud JL	Mutations in *SPTAN1* in intellectual disability and pontocerebellar atrophy.	Eur J Hum Genet	20 (7)	796-800	2012
Saitsu H[#], Kato M[#] ([#] denotes equal contribution), Shimono M, Senju A, Tanabe S, Kimura T, Nishiyama K, Yoneda Y, Kondo Y, Tsurusaki Y, Doi H, **Miyake N**, Hayasaka K, **Matsumoto N**	Association of genomic deletions in the *STXBP1* gene with Ohtahara syndrome.	Clin Genet	81(4)	399-402	2012
Osaka H, Takagi A , Tsuyusaki Y, Wada T, Iai M, Yamashita S, Shimbo H, Saitsu H, Salomons GS, Jakobs C, Aida N, Shinka T, Kuhara T, **Matsumoto N**	Contiguous deletion of *SLC6A8* and *BAP31* in a patient with severe dystonia and sensorineural deafness.	Mol Genet Metab	106(1)	43-47	2012
Writzl K, Primec ZR, Stražišar BG, Osredkar D, Pečarič-Meglič N, Kranjc BS, Nishiyama K, **Matsumoto N**, Saitsu H	Early onset West syndrome with severe hypomyelination and colobo ma-like optic discs in a girl with *SPTAN1* mutation.	Epilepsia	53(6)	e106-110	2012
Saitsu H, Kato M, Koide A, Goto T, Fujita T, Nishiyama K, Tsurusaki Y, Doi H, Miyake N, Hayasaka K, **Matsumoto N**	Whole exome sequencing identifies KCNQ2 mutations in Ohtahara syndrome.	Ann Neurol	72(2)	298-300	2012

Saitsu H, Kato M, Osaka H, Moriyama N, Horita H, Nishiyama K, Yoneda Y, Kondo Y, Tsurusaki Y, Doi H, **Miyake N**, Hayasaka K, **Matsumoto N**	*CASK* aberrations in males with Ohtahara syndrome and cerebellar hypoplasia.	Epilepsia	53(8)	1441-1449	2012.
Terao Y, Saitsu H, Segawa M, Kondo Y, Sakamoto K, **Matsumoto N**, Tsuji S, Nomura Y	Diffuse central hypomyelination presenting as 4H syndrome caused by compound heterozygous mutations in POLR3A encoding the catalytic subunit of polymerase III.	J Neurol Sci	320(1-2)	102-105	2012
Nonoda Y, Saito Y, Nagai S, Sasaki M, Iwasaki T, **Matsumoto N**, Ishii M, Saitsu H	Progressive diffuse brain atrophy in West syndrome with marked hypomyelination due to SPTAN1 gene mutation.	Brain Dev			In press
Yoneda Y, Haginoya K, Kato M, Osaka H, Yokochi K, Arai H, Kakita A, Yamamoto T, Otsuki Y, Shimizu S, Wada T, Koyama N, Mino Y, Kondo N, Takahashi S, Hirabayashi S, Takanashi J, Okumura A, Kumagai T, Hirai S, Nabetani M, Saitoh S, Hattori F, Yamazaki A, Subo Y, Nishiyama K, Miyatake S, Tsurusaki Y, Doi H, **Miyake N**, **Matsumoto N**, Saitsu H	Phenotype spectrum of *COL4A1* mutations: porencephaly to schizencephaly.	Ann Neurol			In press
Miyatake S, Murakami A, Okamoto N, **Miyake N**, Saitsu H, *__Matsumoto N__	A De Novo Deletion at 16q24.3 Involving ANKRD11 in a Japanese Patient With KBG Syndrome.	Am J Med Genet Part A			In press

Miyatake S, Touho H, **Miyake N**, Ohba C, Doi H, **Matsumoto N**	Sibling cases of Moyamoya disease with different *RNF213* genotypes and varying clinical course and severity.	J Hum Genet			In press
Higashiyama Y, Doi H, Wakabayashi M, Tsurusaki Y, **Miyake N**, Saitsu H, Ohba C, Fukai R, Miyatake S, Koyano S, Suzuki Y, Kuroiwa Y, **Matsumoto N**	A novel homozygous *SCARB2* mutation causes late-onset progressive myoclonus epilepsy without renal failure.	Mov disord			In press
Kimura-Ohba S, Kagitani-Shimono K, Hashimoto N, Nabatame S, Okinaga T, Murakami A, **Miyake N**, **Matsumoto N**, Osaka H, Hojo K, Tomita R, Taniike M, *Ozono K	A case of cerebral hypomyelination with spondylo-epi-metaphyseal dysplasia.	Am J Med Genet Part A			In press
Mizumoto S, Ikegawa S, **Sugahara K**	Human genetic disorders caused by defective genes encoding biosynthetic enzymes for sulfated glycosaminoglycans.	J Biol Chem			In press
Ichikawa H, Kanoh Y, Shirasawa S, Yokoyama T, **Yue F**, Tomotsune D, **Sasaki K**	Unique kinetics of Oct3/4 microlocalization following dissociation of human embryonic stem cell colonies.	Ann Anat	195(1)	50-56	2013
Tsuchiya H, Matsunaga T, Aikawa K, Kamada N, Nakamura K, Ichikawa H, **Sasaki K**, Ohmori S	valuation of human embryonic stem cell-derived hepatocyte-like cells for detection of CYP1A inducers.	Drug Metab Pharmacokinet	27(6)	598-604	2012
Yoshie S, Ito J, Shirasawa S, Yokoyama T, Fujimura Y, Takeda K, Mizuguchi M, Matsumoto K, Tomotsune D, **Sasaki K**	Establishment of novel detection system for embryonic stem cell-derived hepatocyte-like cells based on nongenetic manipulation with indocyanine green.	Tissue Eng Part C Methods	18	12-20	2012

Ichikawa H, Nakata N, Abo Y, Shirasawa S, Yokoyama T, Yoshie S, **Yue F**, Tomotsune D, **Sasaki K**	Gene pathway analysis of the mechanism by which the Rho-associated kinase inhibitor Y-27632 inhibits apoptosis in isolated thawed human embryonic stem cells.	Cryobiology	64	12-22	2012
Nitahara-Kasahara Y, Hayashita-Kinoh H, Ohshima-Hosoyama S, Okada H, Wada-Maeda M, Nakamura A, **Okada T**, **Takeda S**	Long-term engraftment of multipotent mesenchymal stromal cells that differentiate to form myogenic cells in dogs with Duchenne muscular dystrophy.	Mol Ther	20(1)	168-177	2012
Ito M, Suzuki Y, **Okada T**, Fukudome T, Yoshimura T, Masuda A, **Takeda S**, Krejci E, Ohno K	Protein-anchoring strategy for delivering acetylcholinesterase to the neuromuscular junction.	Mol Ther	20(7)	1384-1392	2012.
Baba Y, Satoh S, Otsu M, Sasaki E, **Okada T**, Watanabe S	In vitro cell subtype-specific transduction of adeno-associated virus in mouse and marmoset retinal explant culture.	Biochimie	94(12)	2716-2722	2012
Okada H, Ishibashi H, Hayashita-Kinoh H, Chiyo T, **Nitahara-Kasahara Y**, Baba Y, Watanabe S, **Takeda S**, **Okada T**	Robust long-term transduction of common marmoset neuromuscular tissue with rAAV1 and rAAV9.	Mol Ther Nucleic Acids			In press
Tsuda Y, **Nomura Y**	Direct observation of hair components involved in formation of permanent waves.	繊維学会誌			In press
Kawada C, Hasegawa T, Watanabe M, **Nomura Y**	Dietary Glucosylceramide Enhances Tight Junction Function in Skin Epidermis via Induction of Claudin-1.	Biosci. Biotechnol. Biochem			In press

Sato Y, Arai KY, Nishiyama T, **Nomura Y**, Kishimoto Y, Aizawa S, Maruyama N, Ishigami A	Ascorbic acid deficiency leads to epidermal atrophy and UVB-induced skin pigmentation in SMP30/GNL knockout hairless mice.	J. Invest. Dermatol	132	2112-2115	2012
Ohya A, Kobayashi M, Sakai Y, Kawashima H, Kageyama S, **Nakayama J**	Lymphocyte recruitment via high endothelial venules in lymphoid stroma of Warthin's tumor.	Pathology	45(2)	150-154	2013
Maruyama M, Kobayashi M, Sakai Y, Hiraoka N, Oya A, Kageyama S, Tanaka E, **Nakayama J**, Morohoshi T	Periductal induction of high endothelial venule-like vessels in type 1 autoimmune pancreatitis.	Pancreas	42(1)	53-59	2013
Kobayashi M, Hoshino H, Suzawa K, Sakai Y, **Nakayama J**, Fukuda M	Two distinct lymphocyte homing systems involved in the pathogenesis of chronic inflammatory gastrointestinal diseases.	Semin Immunopathol	34	401-413	2012
Fujiwara M, Kobayashi M, Hoshino H, Uchimura K, Nakada T, Masumoto J, Sakai Y, Fukuda M, **Nakayama J**	Expression of long-form N-acetylglucosamine-6-O-sulfotransferase 1 in human high endothelial venules.	J Histochem Cytochem	60	397-407	2012
Karasawa F, Shiota A, Goso Y, Kobayashi M, Sato Y, Masumoto J, Fujiwara M, Yokosawa S, Muraki T, Miyagawa S, Ueda M, Fukuda MN, Fukuda M, Ishihara K, **Nakayama J**	Essential role of gastric gland mucin in preventing gastric cancer in mice.	J Clin Invest	122	923-934	2012
古庄知己	結合組織疾患–Marfan症候群とEhlers-Danlos症候群	内分泌・糖尿病・代謝内科			
古庄知己，福嶋義光	遺伝カウンセリングのノウハウ	臨牀と研究	89(5)	635-640	2012

代表的な刊行物

1. **Kosho T**. Discovery and delineation of dermatan 4-*O*-sulfotransferase-1 (D4ST1)-deficient Ehlers-Danlos syndrome. In: Current Genetics in Dermatology (Oiso N, Kawada A, eds), InTech.

2. 古庄知己. 結合組織疾患–Marfan 症候群と Ehlers-Danlos 症候群. 内分泌・糖尿病・代謝内科　34(3):210-220, 2012.

3. 古庄知己. Marfan 症候群，Ehlers-Danlos 症候群. 小児内科増刊号・小児疾患の診断治療基準第 4 版（編集:『小児内科』『小児外科』編集委員会），東京医学社（東京） 44: 850-853, 2012.

4. 古庄知己. エーラスダンロス症候群. 別冊日本臨牀・新領域別症候群シリーズ No.20・先天異常症候群第 2 版（下），日本臨牀社，721-726, 2012.

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

suggested that two brothers, aged 22 months and 7 months, from a Japanese consanguineous family reported by Sonoda and Kouno [10] would also fit the diagnosis of ATCS. The brothers had multiple distal arthrogryposis, characteristic facial features, cleft palates, short stature, hydronephrosis, cryptorchidism, and normal intelligence. Dündar et al. [9] also showed follow-up observations of the original patients: the intelligence quotient (IQ) was roughly 90 in one subject at age 7 years and 2 months and the other died of unknown cause at 5 years of age. Janecke et al. [11] from Innsbruck Medical University, Austria, reported two brothers with ATCS from a consanguineous Austrian family, one of whom died shortly after birth because of respiratory failure. The authors concluded that all these patients represented a new type of arthrogryposis with central nervous system involvement, congenital heart defects, urogenital defects, myopathy, connective tissue involvement (generalized joint laxity), and normal or subnormal mental development. In 2009, Dündar et al. reported that *CHST14* was the causal gene for ATCS through homozygosity mapping using samples from four previously published consanguineous families. The authors mentioned some follow-up clinical findings including generalized joint laxity, delayed wound healing, ecchymoses, hematomas, and osteopenia/osteoporosis; and categorized ATCS as a generalized connective tissue disorder [5].

2.2. EDS, Kosho type

We encountered the first patient with a specific type of EDS in 2000 and the second with parental consanguinity in 2003. They were Japanese girls with strikingly similar symptoms: characteristic craniofacial features; skeletal features including multiple congenital contractures, malfanoid habitus, pectus excavatum, generalized joint laxity, recurrent dislocations, and progressive talipes and spinal deformity; skin hyperextensibility, bruisability, and fragility with atrophic scars; recurrent hematomas; and hypotonia with mild motor developmental delay [12]. These symptoms overlapped those in the kyphoscoliosis type EDS (previously known as EDS type VI), which is typically associated with deficiency of lysyl hydroxylase (EDS type VIA) [13]. A rare condition with the clinical phenotype of the kyphoscoliosis type EDS but with normal lysyl hydroxylase activity were reported and named as EDS type VIB [13]. Therefore, we tentatively proposed that the two patients represented a clinically recognizable subgroup of EDS type VIB [12]. Through their long-term clinical evaluation as well as four additional unrelated Japanese patients including one with parental consanguinity and another reported by Yasui et al. [14], we concluded that they—four female patients and two male patients aged 4–32 years, represented a new clinically recognized type of EDS with distinct craniofacial characteristics, multiple congenital contractures, progressive joint and skin laxity, and multisystem fragility-related manifestations [15]. The disorder has been registered as EDS Kosho Type (EDSKT) in the London Dysmorphology Database (http://www.lmdatabases.com/index.html) and in POSSUM (http://www.possum.net.au/). In 2009, we identified *CHST14* as causal for the disorder through homozygosity mapping using samples from two consanguineous families and all the other patients were also found to have compound heterozygous *CHST14* mutations [6].

2.3. Musculocontractural EDS

Malfait et al. [7] from Ghent University, Belgium have found mutations in *CHST14* through homozygosity mapping of two Turkish sisters and an Indian girl both presenting clinically with EDS VIB and with parental consanguinity. They had distinct craniofacial features, joint contractures, and wrinkled palms in addition to common features of kyphoscoliosis type EDS including kyphoscoliosis, muscular hypotonia, hyperextensible, thin, and bruisable skin, atrophic scarring, joint hypermobility, and variable ocular involvement. Malfait et al. [7] concluded that their series and ATCS, as well as EDSKT, formed a phenotypic continuum based on their clinical observations and identification of an identical mutation in both conditions; and proposed to coin the disorder as "musculocontractural EDS" (MCEDS).

3. Pathophysiology of D4ST1-deficient EDS

3.1. Glycobiological abnormalities in D4ST1-deficient EDS

D4ST1 is a regulatory enzyme in the glycosaminoglycan (GAG) biosynthesis that transfers active sulfate to position 4 of the N-acetyl-D-galactosamine residues of dermatan sulfate (DS) (Fig. 1) [16, 17]. DS, together with chondroitin sulfate (CS) and heparan sulfate, constitutes GAG chains of proteoglycans and is implicated in cardiovascular disease, tumorigenesis, infection, wound repair, and fibrosis via DS-containing proteoglycans such as decorin and biglycan [18].

Sulfotransferase activity toward dermatan in the skin fibroblasts derived from the patients was significantly decreased to 6.7% (patient 1 with a compound heterozygous mutation: P281L/Y293C) and 14.5% (patient 3 with a homozygous mutation: P281L) of each age- and sex-matched control) (Fig. 2A). Disaccharide composition analysis of CS/DS chains isolated from the skin fibroblasts showed a negligible amount of DS and a slight excess of CS (Fig. 2B). Subsequently, we focused on a major DS proteoglycan in the skin, decorin, consisting of core protein and one GAG chain and playing an important role in assembly of collagen fibrils (Nomura, 2006). No DS disaccharides were detected in the GAG chains of decorin from the patients, whereas the GAG chains of decorin from the controls were mainly composed of DS disaccharides (approximately 95%) (Fig. 2C) [6].

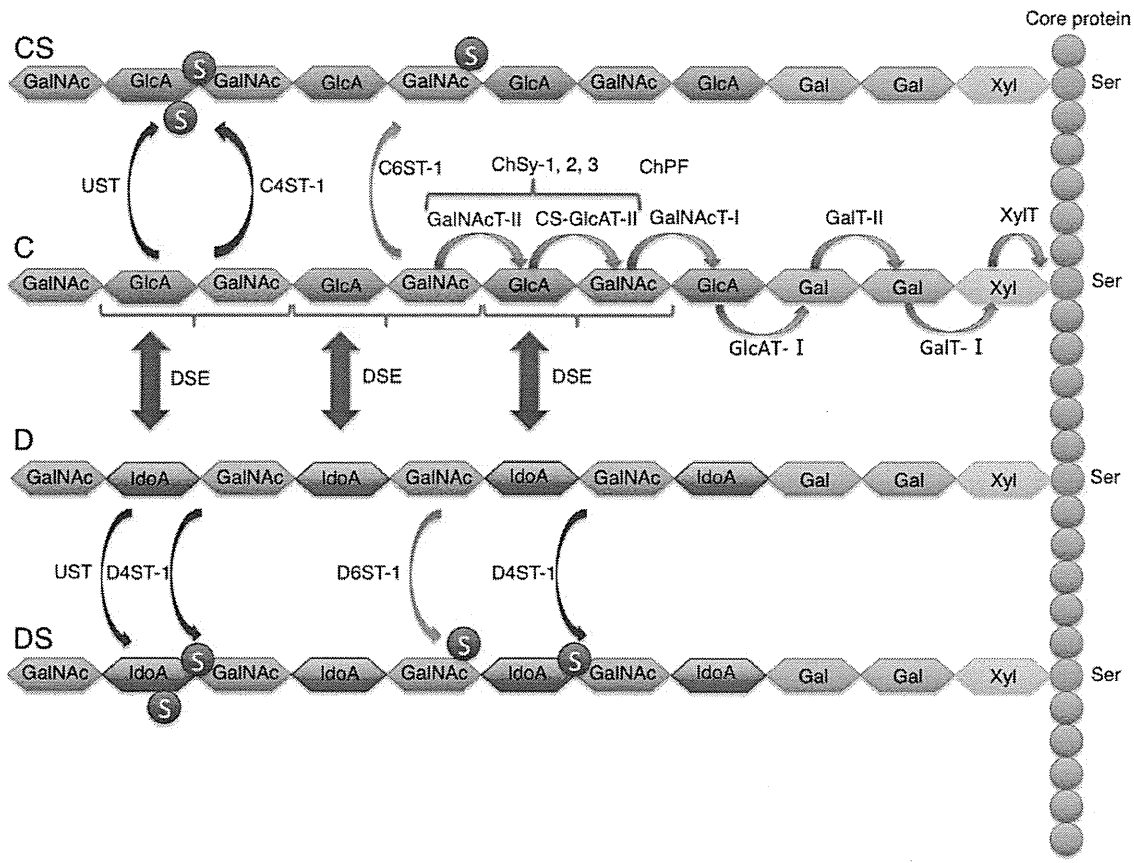
3.2. Pathological abnormalities in D4ST1-deficient EDS

Hematoxylin and eosin (H&E)-stained light microscopy on patients' skin specimens showed that fine collagen fibers were present predominantly in the reticular to papillary dermis with marked reduction of normally thick collagen bundles (Fig. 3a, b). Electron microscopy showed that collagen fibrils were dispersed in the reticular dermis, compared with the 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 (Fig. 3c, d) [6].

Patient	Family	Origin	*CHST14* mutations	Sex	Age at initial publication	References
1	1	Turkish	V49X homo	F	3.5y	[8]
2				M	1.5y	
3				F	6y	
4	2	Japanese	Y293C homo	M	4y	[10]
5				M	7m	
6	3	Austrian	R213P homo	M	0d†	[11]
7				M	12m	
8	4	Turkish	[R135G;L137Q] homo	F	1–4m†	[9]
9				M	1–4m†	
10				M	1–4m†	
11				M	3m	
12	5	Japanese	P281L/Y293C	F	11y	[12]
13	6	Japanese	P281L homo	F	14y	[12]
14	7	Japanese	P281L homo	M	32y	[15]
15	8	Japanese	K69X/P281L	M	32y	[14,15]
16	9	Japanese	P281L/C289S	F	20y	[15]
17	10	Japanese	P281L/Y293C	F	4y	[15]
18	11	Turkish	V49X homo	F	22y	[7]
19				F	21y	
20	12	Indian	E334Gfs*107 homo	F	12y	[7]
21	13	Japanese	P281L/Y293C	M	2y	[21]
22	14	Japanese	F209S/P281L	M	6y	[21]
23	15	Dutch	V48X homo	F	20y	[23]
24	16	Afghani	R274P homo	F	11y	[24]
25				F	0y	
26	17	Miccosukee	G228Lfs*13	F	16y	[25]

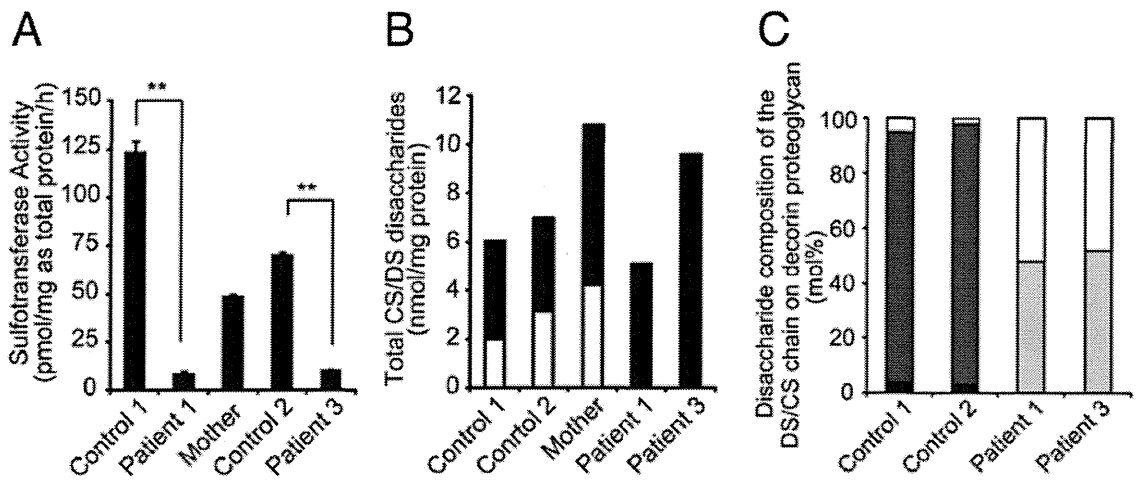
homo, homozygous mutation; /, compound heterozygous mutation; F, female; M, male; y, years old; m, months old; †, dead at the time of publication

Table 2. Reported patients with D4ST1-deficient EDS



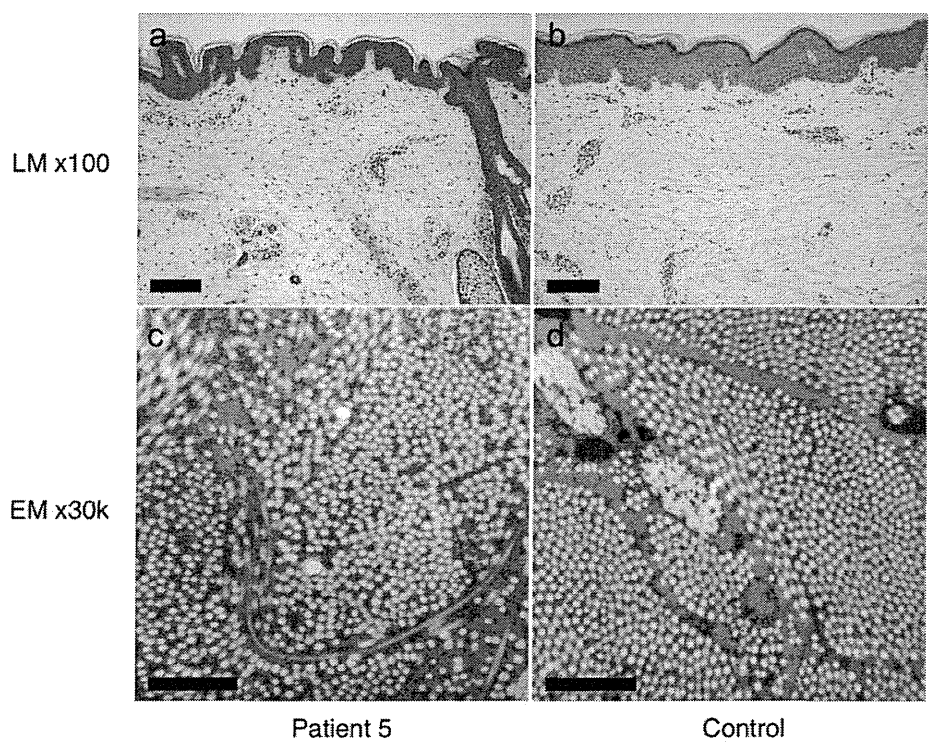
Biosynthesis of chondroitin sulfate (CS) and dermatan sulfate (DS) starts with binding a tetrasaccharide linker region, glucuronic acidβ1-3galactoseβ1-3galactoseβ1-4xyloseβ1-*O*- (GlcA-Gal-Gal-Xyl-), onto serine (Ser) residues of specific core proteins of proteoglycans, by β-xylosyltransferase (XylT), β1,4-galactosyltransferase-I (GalT-I), β1,3-galactosyltransferase-II (GalT-II), and β1,3-glucuronosyltransferase-I (GlcAT-I), respectively. Subsequently, a disaccharide chain of chondroitin (C[N-acetyl-D-galactosamine(GalNAc)-GlcA]$_n$ is synthesized by N-acetyl-D-galactosaminyltransferase-I (GalNAcT-I), N-acetyl-D-galactosaminyltransferase-II (GalNAcT-II), and CS-glucuronyltransferase-II (CS-GlcAT-II) encoded by chondroitin synthase-1, 2, 3 (ChSy-1, 2, 3); and chondroitin polymerizing factor (ChPF). CS chains are matured through sulfation by chondroitin 4-*O*-sulfotransferase-1 (C4ST-1), chondroitin 6-*O*-sulfotransferase-1 (C6ST-1), and uronyl 2-*O*- sulfotransferase (UST). A disaccharide chain of dermatan (D) is synthesized through epimerization of a carboxyl group at C5 from GlcA to L-iduronic acid (IdoA) by dermatan sulfate epimease (DSE). DS chains are matured through sulfation by dermatan 4-*O*-sulfotransferase-1 (D4ST-1), dermatan 6-*O*-sulfotransferase-1 (D6ST-1), and UST. D4ST-1 deficiency, resulting in impaired 4-*O*-sulfation lock, probably allows back epimerization from IdoA to GlcA and finally leads to loss of DS and excess of CS.

Figure 1. Biosynthesis of dermatan sulfate and chondroitin sulfate.



A. Sulfotransferase activity of skin fibroblasts: A patient (a compound heterozygous mutation, P281L/Y293C; patient 1), her heterozygous mother, and her age-matched control (control 1); another patient (a homozygous mutation, P281L; patient 3) and his age-matched control (control 2). 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.

Figure 2. Glycobiological studies [6].



H&E-stained light microscopy (LM) on skin specimens of a patient (a compound heterozygous mutation, P281L/C289S; patient 5) (a) and an age- and sex-matched control (b). Scale bars indicate 500 μm. Electron microscopy (EM) of the patient (c) and the control (d). Scale bars indicate 1 μm.

Figure 3. Pathological studies [6].