Glycosaminoglycans and diseases

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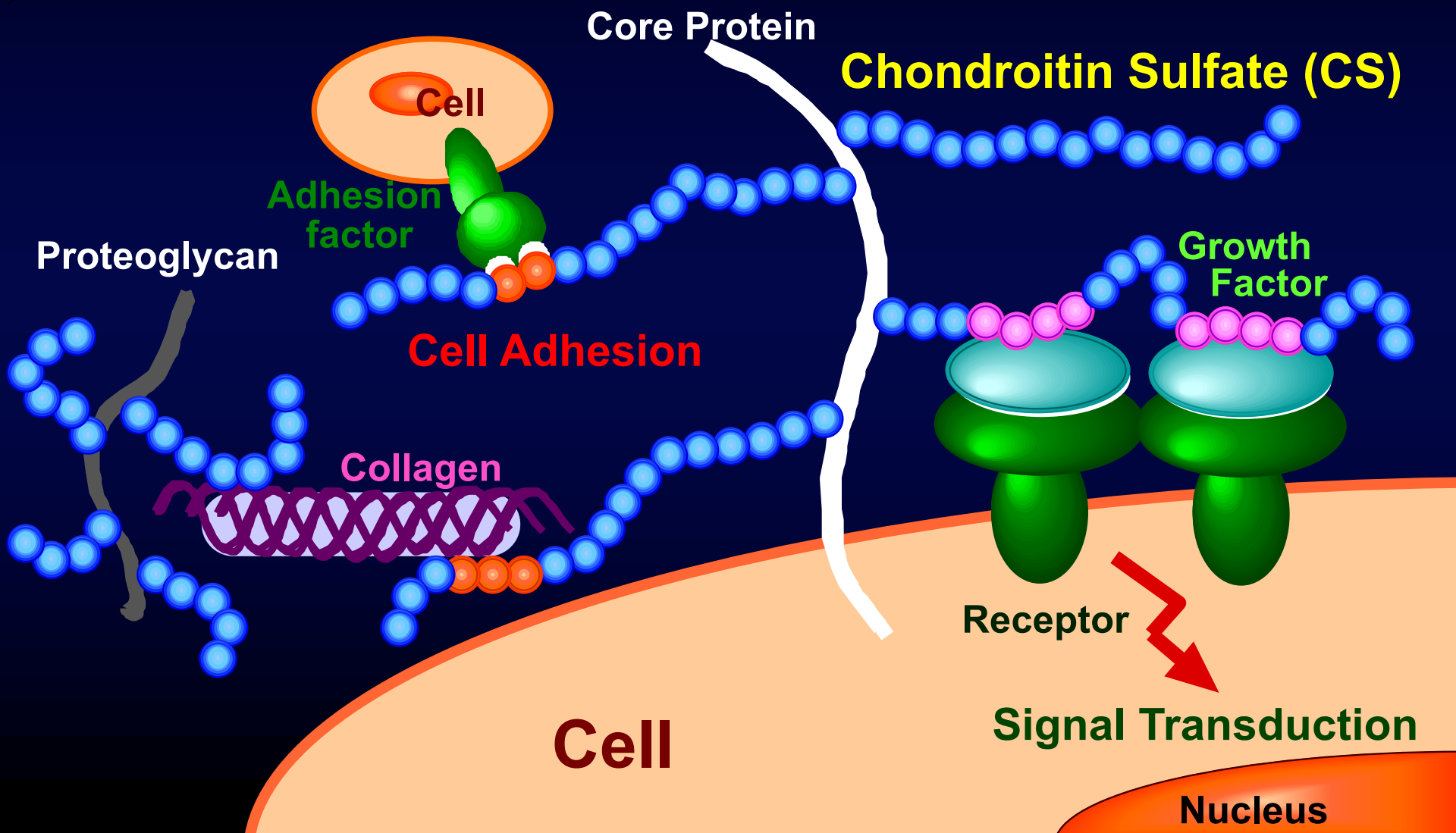
Contents

- Introduction
- Cancer and GAGs
- Spinal Cord Injury
- Infection of Pathogens via GAGs
- Mucopolysaccharidoses
- Congenital Disorders Caused by Defects in Biosynthetic Enzymes of GAGs

Functions of Cell Surface and Extracellular Matrix Proteoglycans



Glycosaminoglycans

- Chondroitin sulfate
- Dermatan sulfate
- Heparin
- Heparan sulfate
- Keratan sulfate
- Hyaluronan

Glycosaminoglycans

Polysaccharides composed of repeating disaccharide units containing an amino sugar and modified with sulfate groups.

Chondroitin Sulfate…Cartilage
Dermatan Sulfate…Skin, Aorta
Heparan Sulfate…Basement membrane
Heparin…Anticoagulant drug
Keratan Sulfate…Cornea

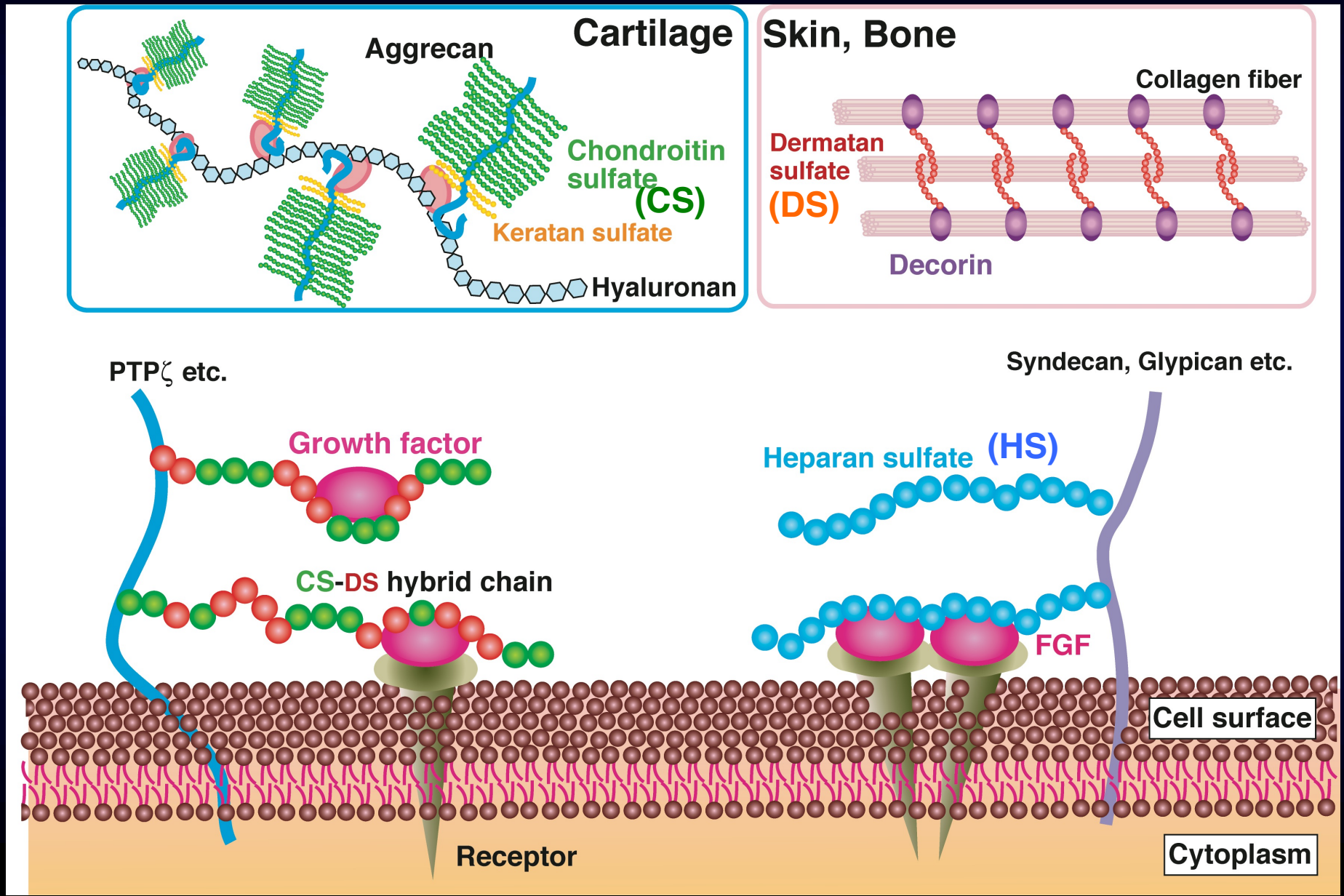
Functions of Proteoglycans

Interact with various bioactive proteins including cell growth factors, morphogens, cytokines, extracellular matrix components, nerve growth factors, coagulation factors, etc.

↓

Exhibit various functions including cell growth, cell adhesion, cell migration, anticoagulation, morphogenesis, tissue regeneration etc.

Various functions of CS, DS, and HS-proteoglycans at cell surfaces and in extracellular matrix



Protein Factors interacting with GAGs

Cell Adhesion Molecules
CD44
L-Selectin
P-Selectin
RANTES
von Willebrand factor
MAC-1
N-CAM

Growth Factors/Morphogens
Fibroblast growth factors
Hepatocyte growth factor
Midkine/Pleiotrophin
Platelet derived growth factor
Vascular endothelial growth factor
Transforming growth factor-β
Glial-derived neurotrophic factor
Brain-derived neurotrophic factor
HB-EGF
Amphiregulin
Neuregulin
Insulin-like growth factor
Bone morphogenetic proteins
Sonic hedgehog
Wints

Virus protein
Glycoprotein C

Coagulation
Heparin cofactor II
Antithrombin III
Factor Xa
Leuserpin
Thrombin

ECM Components
Tenascin-X
Opticin
Fibronectin
Collagens
Laminins
Tenascin
Thrombospondin
Vitronectin

Proteinases
Elastases
Cathepsin G

Chemokines
Interferon-γ
Interleukin-2, -3, -4, -5, -7, -8, -12
Macrophage inflammatory peptides 1
Monocyte chemoattractant protein-1
Secondary lymphoid tissue chemokin
Stromal cell-derived factor-1β
Platelet factor 4
GM-CSF
TNF-alpha

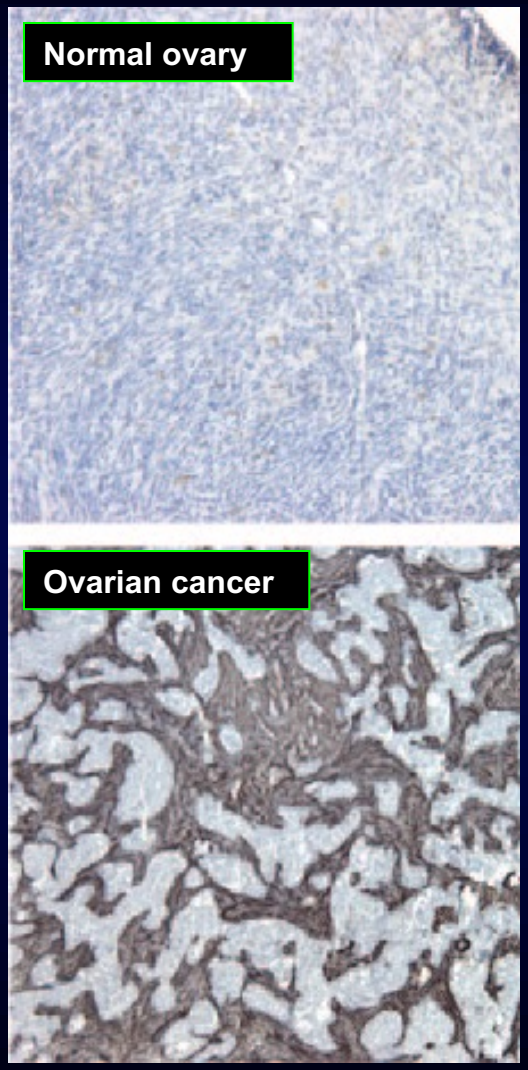
Others
β-Amyloid peptide
Cardiotoxins from spitting cobra ven
α-Defensin
EGF-TM7 receptors CD97 and EMR2
Extracellular superoxide dismutase
Lipoprotein lipase
Thyroglobulin
Tissue plasminogen activator
Plasminogen activator inhibitor
Follistatin
Angiostatin
Endostatin
ApoB, ApoE

(Partially Shown)

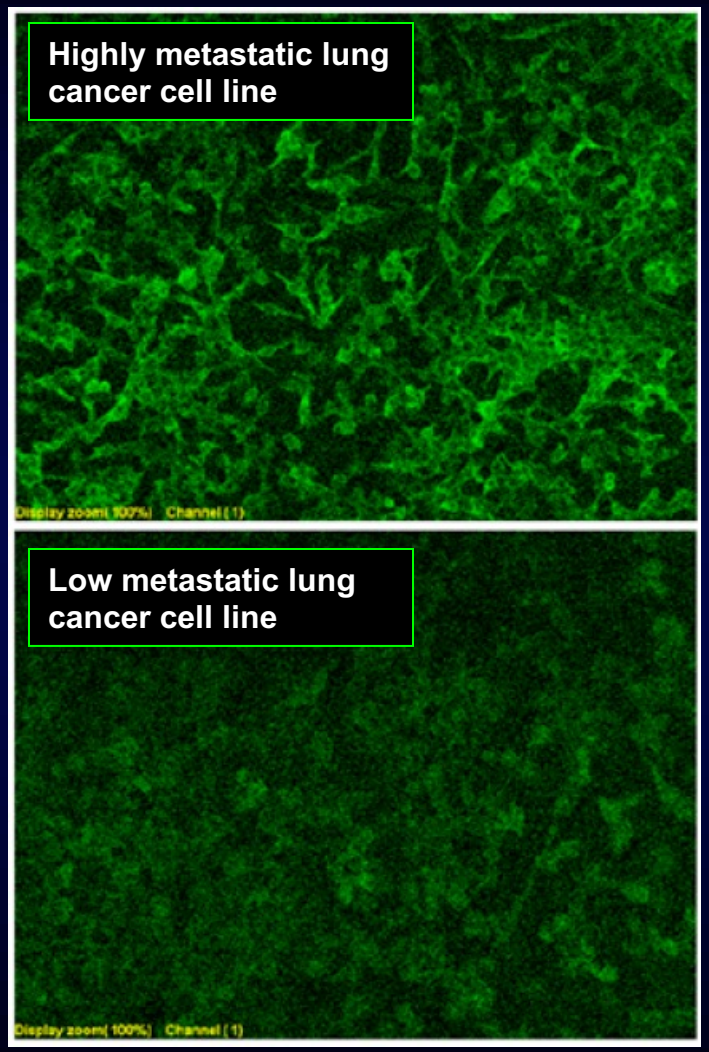
Diseases Related to Proteoglycans and Glycosaminoglycans

Cancer and Glycosaminoglycans

Immunostaining with an antibody against highly sulfated chondroitin sulfate

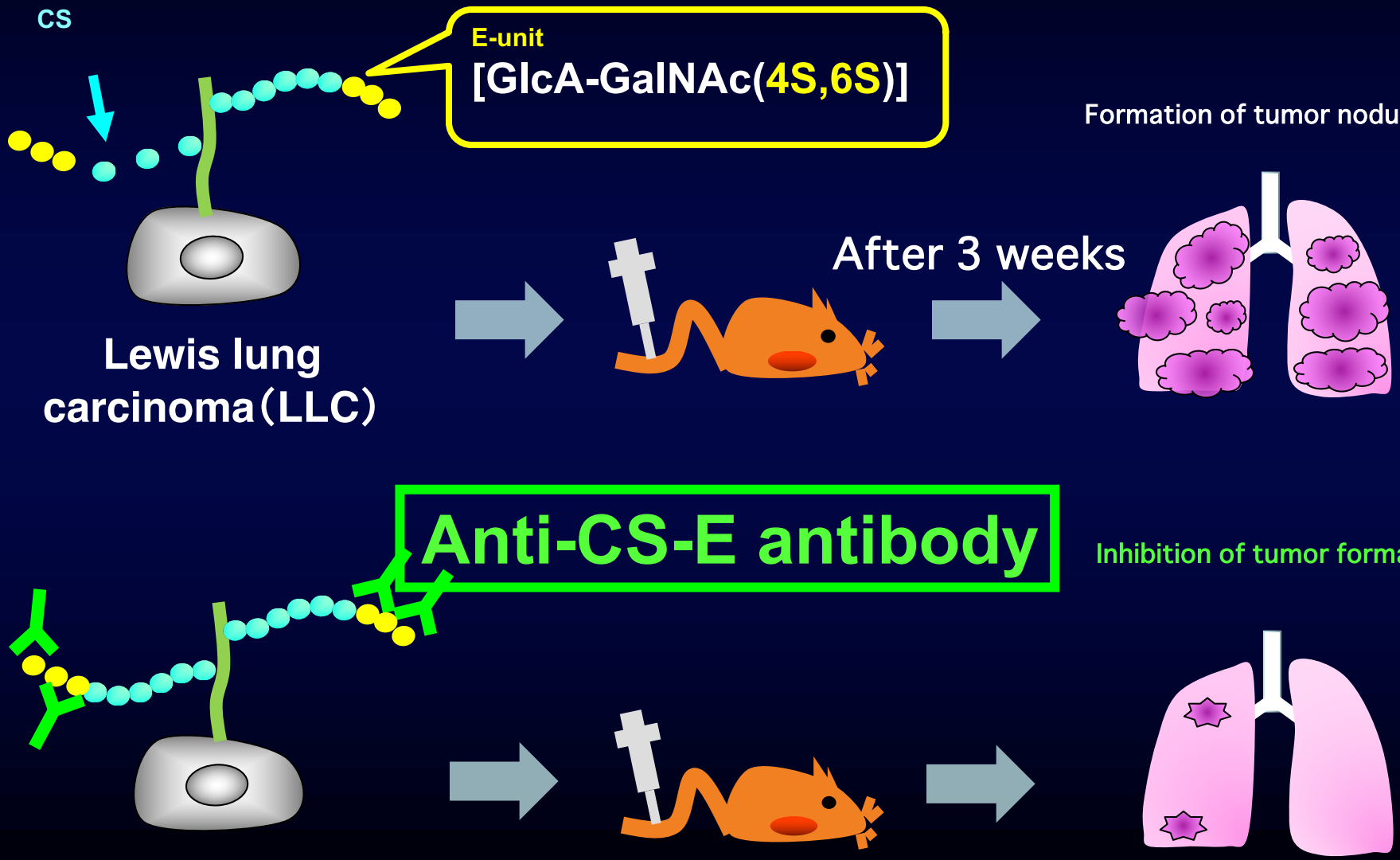


ten Dam *et al.*, Am. J. Pathol. (2007).

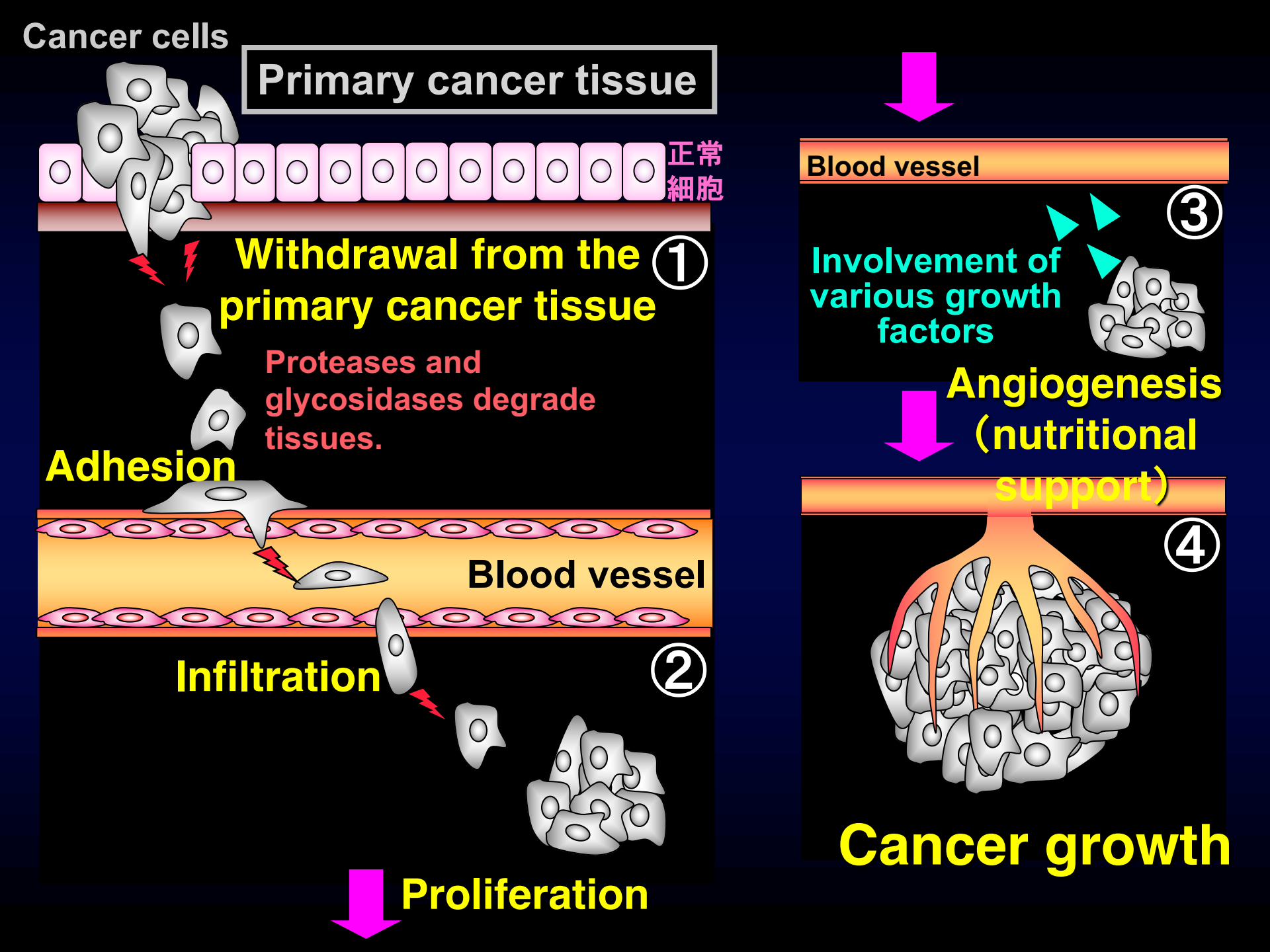


Strongly expressed in the highly metastatic cell line. Li, *et al.*, J. Biol. Chem. (2008).

Inhibition of tumor formation by an antibody against highly sulfated chondroitin sulfate



Li *et al.*, J. Biol. Chem. (2008)


Cancer cells
Primary cancer tissue
正常細胞
Withdrawal from the primary cancer tissue
①
Proteases and glycosidases degrade tissues.
Adhesion
Blood vessel
Infiltration
②
Proliferation
Blood vessel
Involvement of various growth factors
③
Angiogenesis (nutritional support)
④
Cancer growth

MMPs: Matrix metalloproteinases

MMP1: Collagenase-1

MMP2: Gelatinase A

MMP3: Stromelysin-1

MMP7: Matrilysin-1

MMP8: Collagenase-2

MMP9: Gelatinase B

MMP10: Stromelysin-2

MMP11: Stromelysin-3

MMP12: Macrophage metalloelastase

MMP13: Collagenase-3

MMP14: MT1-MMP

MMP15: MT2-MMP

MMP16: MT3-MMP

MMP17: MT4-MMP

MMP18: Collagenase-4

MMP19: Stromelysin-4

MMP20: Enamelysin

MMP21: X-MMP

MMP23: CA-MMP

MMP24: MT5-MMP

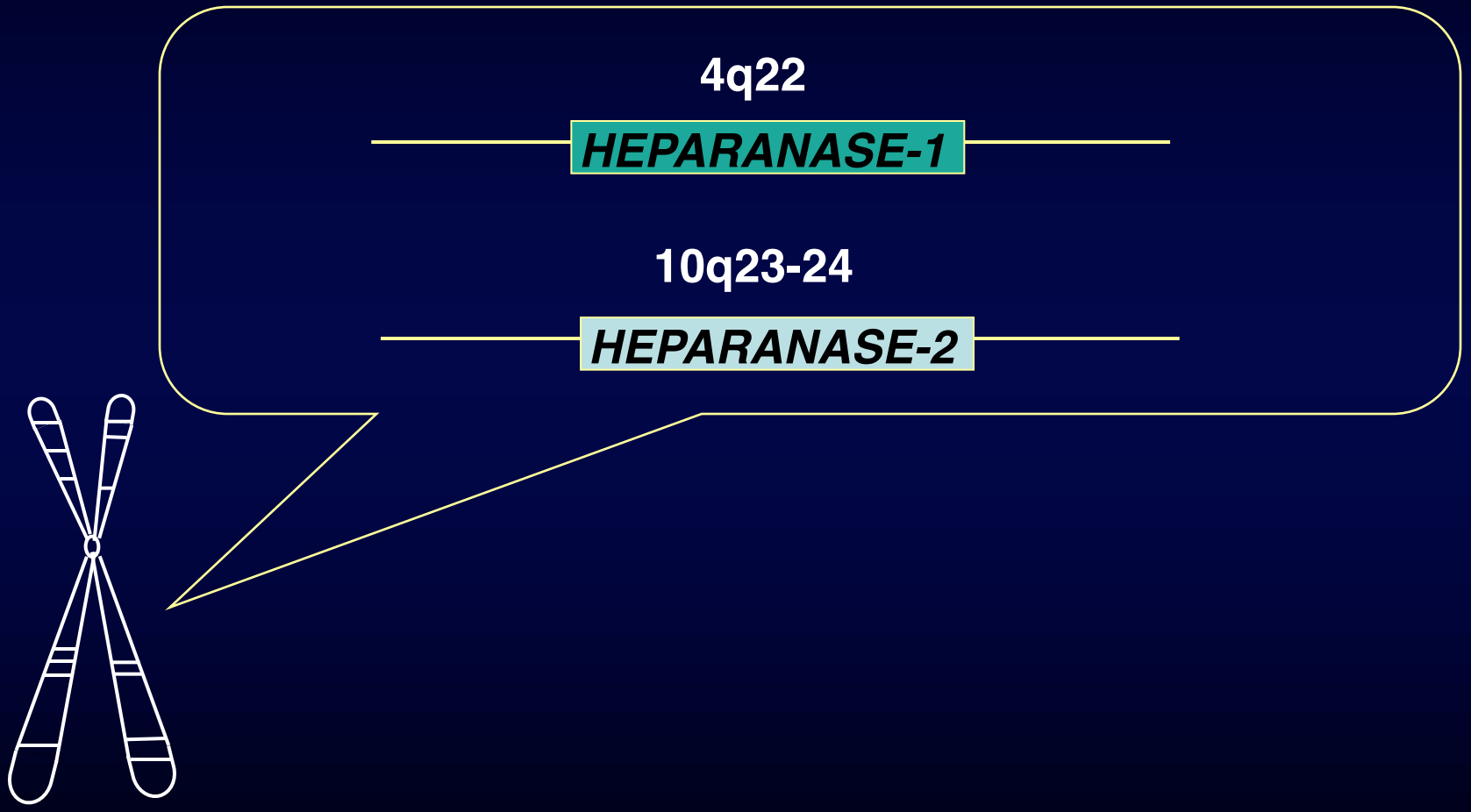
MMP25: MT6-MMP

MMP26: Matrilysin-2

MMP27: C-MMP

MMP28: Epilysin

Human heparanases



Spinal Cord Injury

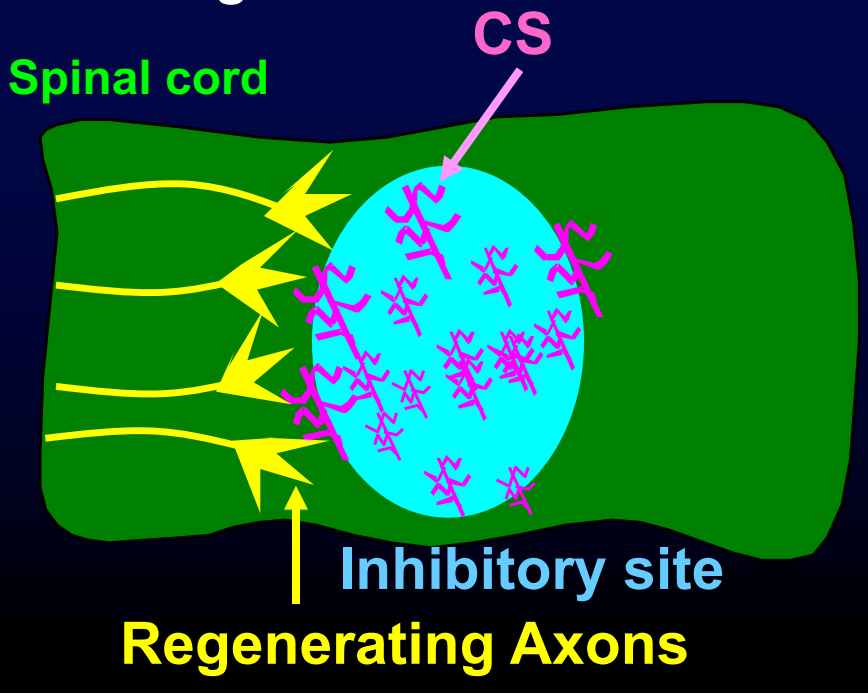
- **Number of annual occurrences in Japan**
  - **More than 5,000 (40/1,000,000)**
- **Number of patients : More than100,000**
- **Causes**
  - **Traffic accidents**
  - **Sports injuries**

In the adult centers the nerve paths are something fixed, ended and immutable. Everything must die, nothing may be regenerated. **— Cajal, 1928**

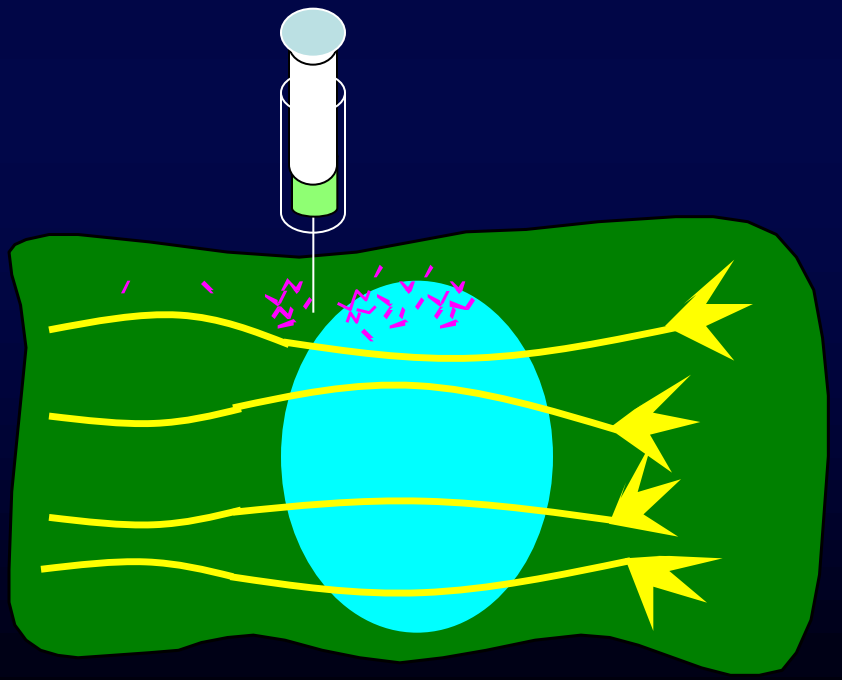
Removal of chondroitin sulfate (CS) promotes functional recovery after spinal cord injury

Bradbury et al., *Nature* 416, 636-640 (2002)
Alilain *et al.*, *Nature* 475, 196-200 (2011)

CS in a glial scar is inhibitory to axon growth.



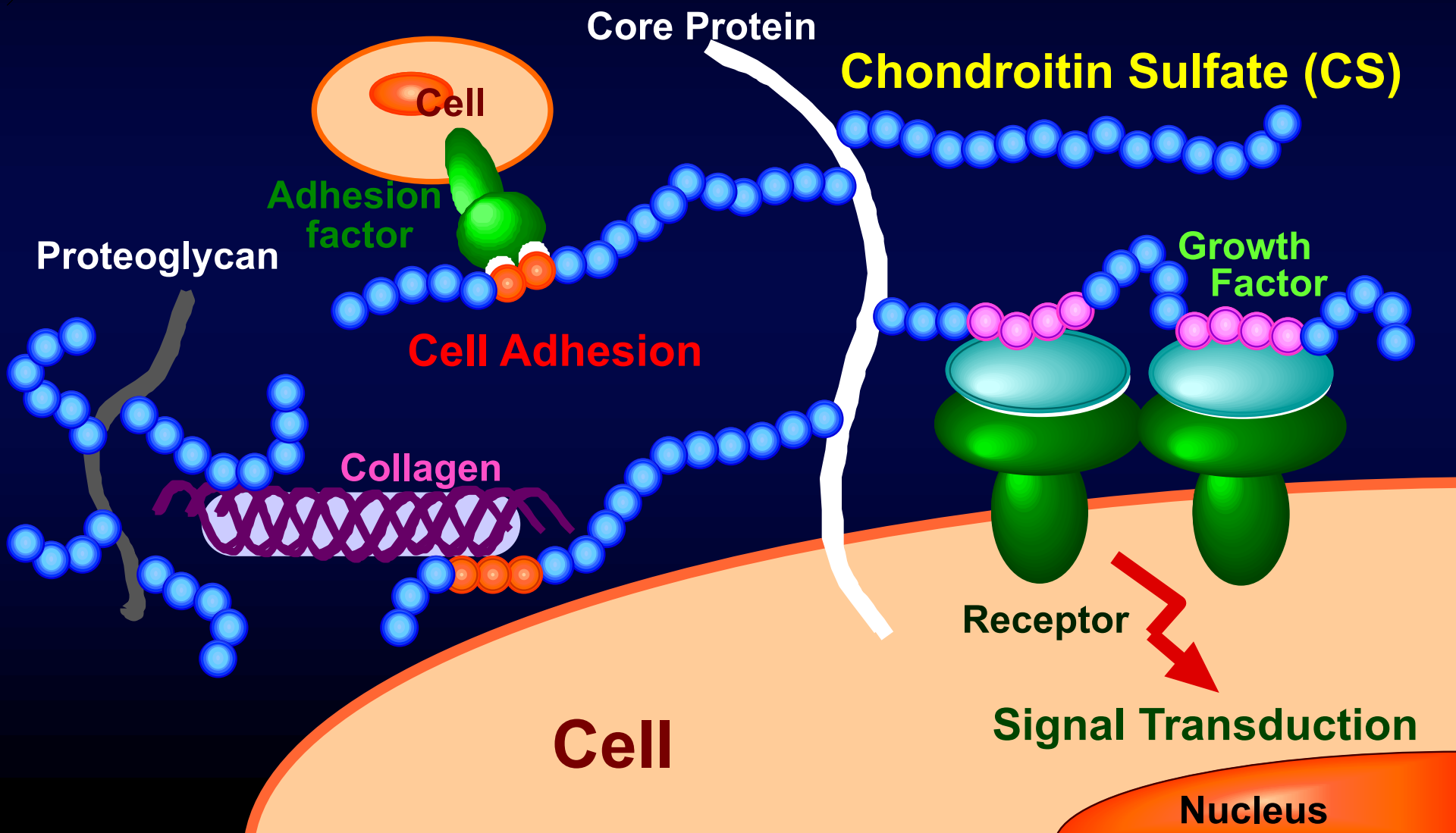
Removal of CS by a bacterial degrading enzyme.



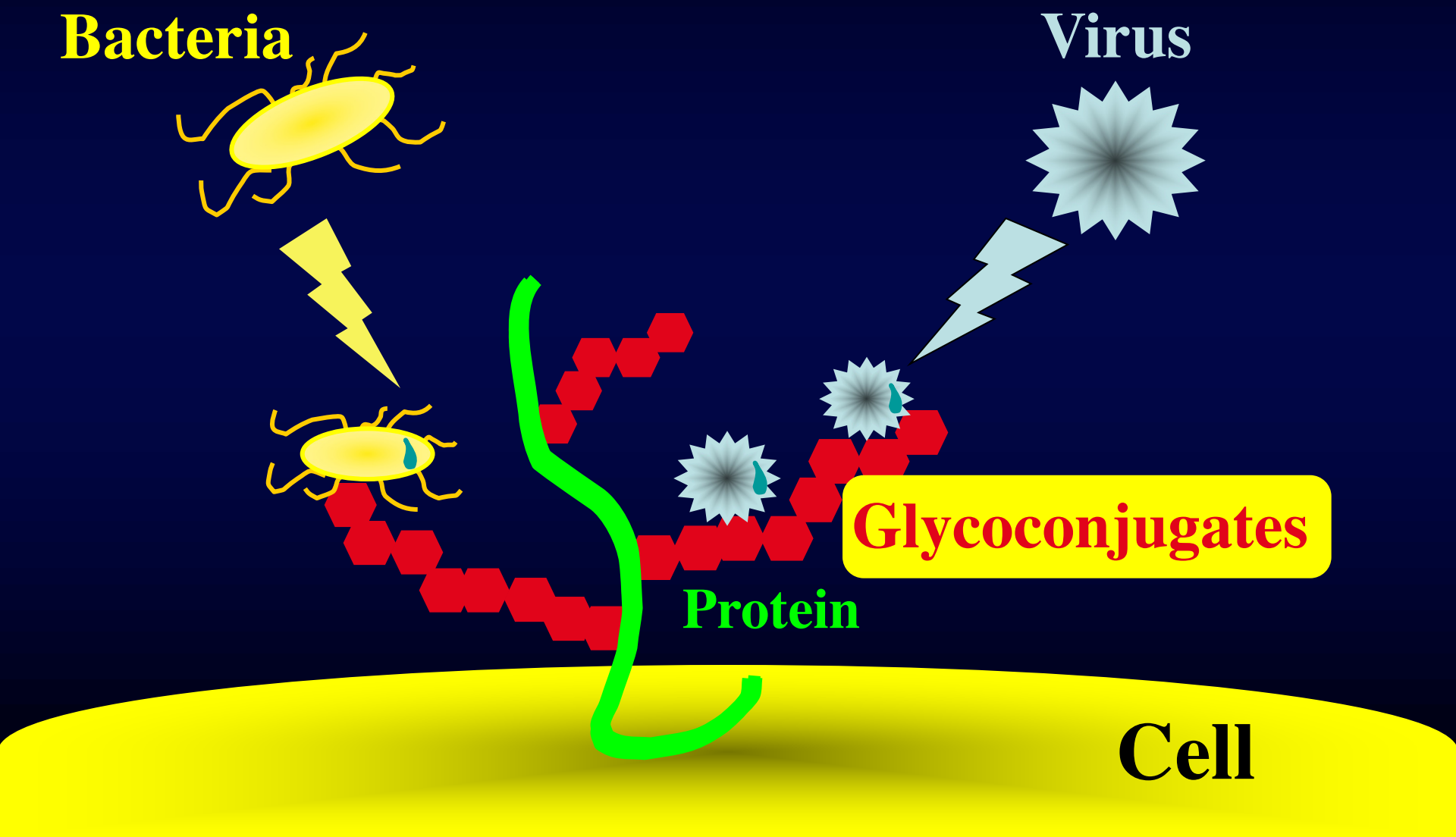
Infections of Pathogens via Glycosaminoglycans

Herpes Simplex Virus (HSV)
Human Immunodeficiency Virus (HIV)
Hepatitis C Virus
Dengue Virus
Japanese Encephalitis Virus
Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2)
Malaria Parasite
And more…

Functions of Cell Surface and Extracellular Matrix Proteoglycans



Glycoconjagates and infection by bacteria and viruses



Lysosome Diseases

Lysosome diseases, lysosomal storage diseases are a group of rare inherited metabolic disorders that result from defects in enzymes required for the metabolism in lysosome, leading to accumulation of the large molecules within the cell.

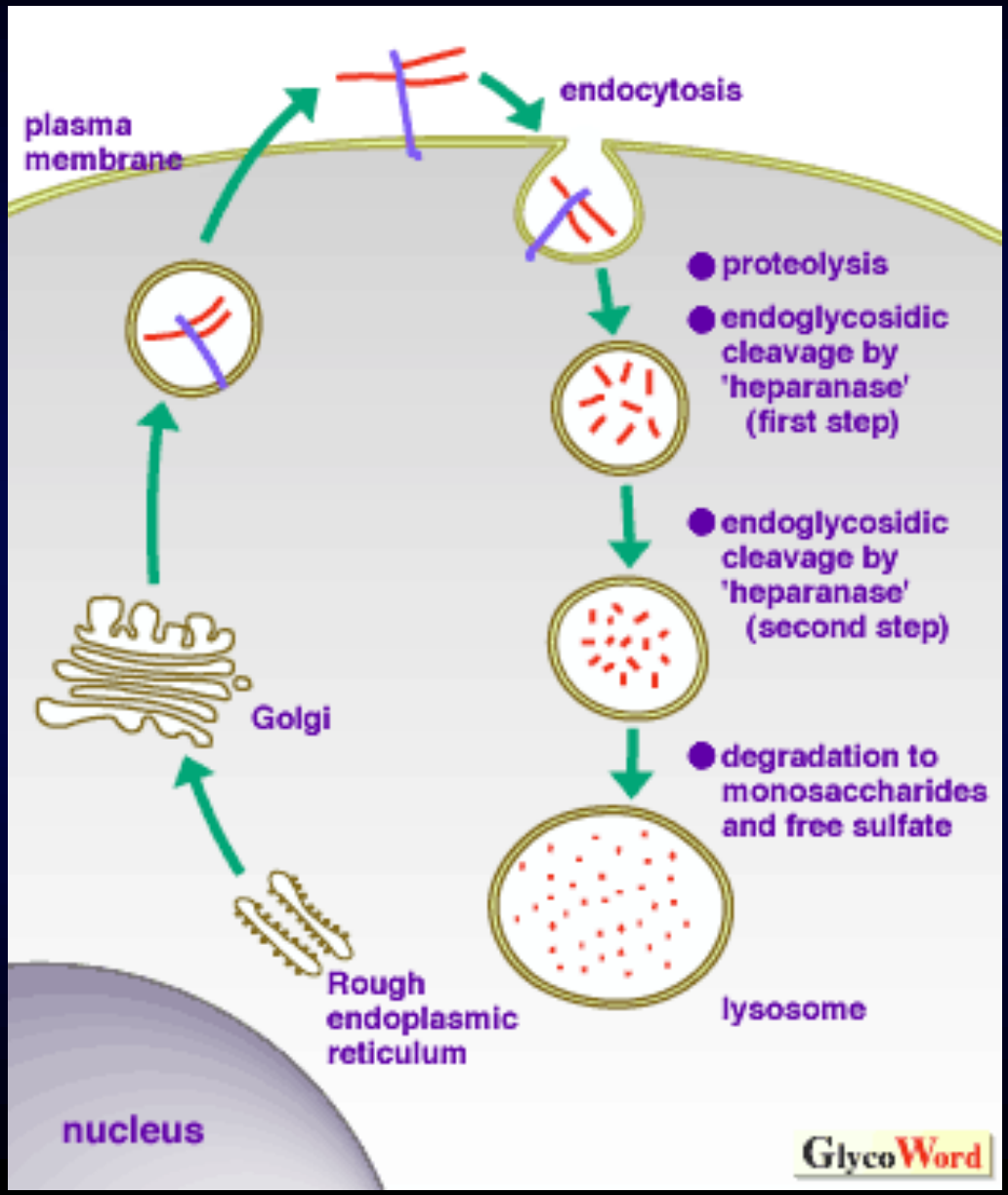
Various types of lysosome Diseases

Pompe disease
GM1 gangliosidosis
GM2 gangliosidosis
（Tay–Sachs disease,
Sandhoff disease）
Fabry disease
Farber disease
Gaucher disease
Niemann–Pick disease
Krabbe disease

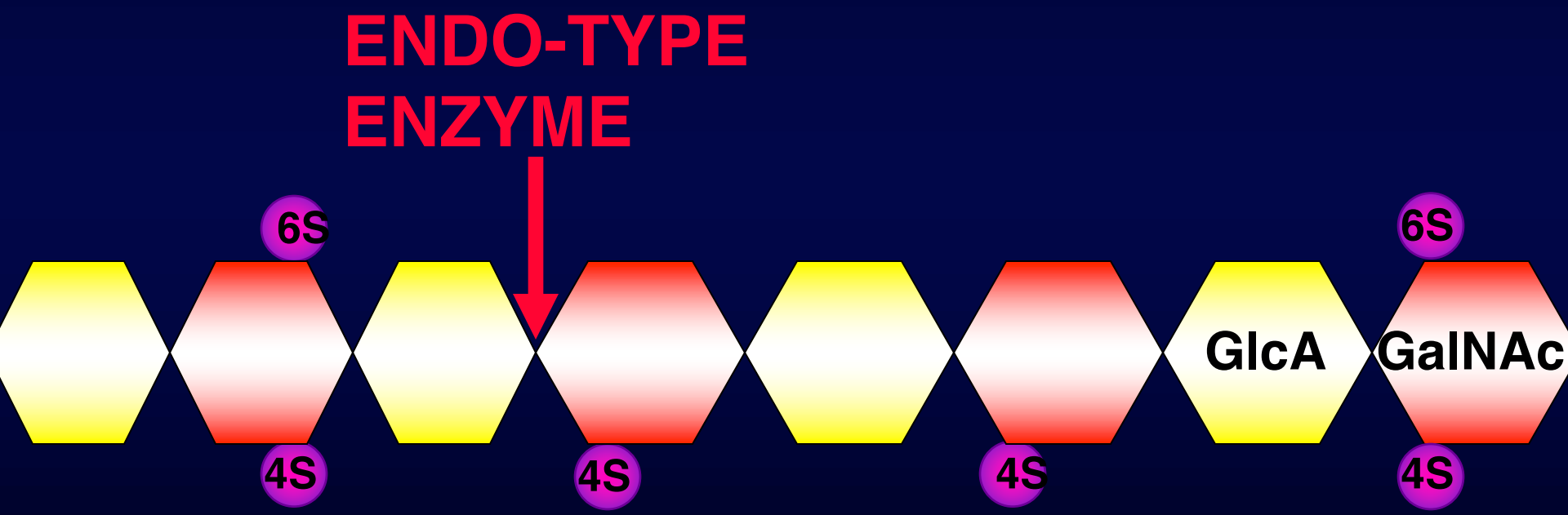
Mucopolysaccharidoses

Multiple sulfatase deficiency
Sialidosis
Galactosialidosis
I-cell disease
Alpha-mannosidosis
Beta-mannosidosis
Fucosidosis
Aspartylglucosaminuria
Schindler disease/Kanzaki disease
Wolman disease
Danon disease
Sialic acid storage disease
Neuronal ceroid lipofuscinoses
etc

Cellular catabolism of glycoproteins



DEGRADATION OF CS/DS



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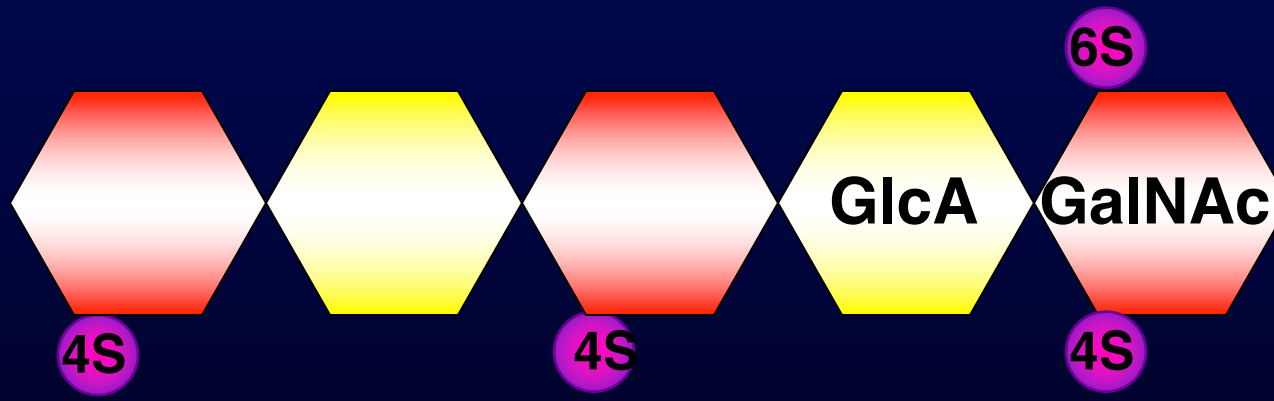
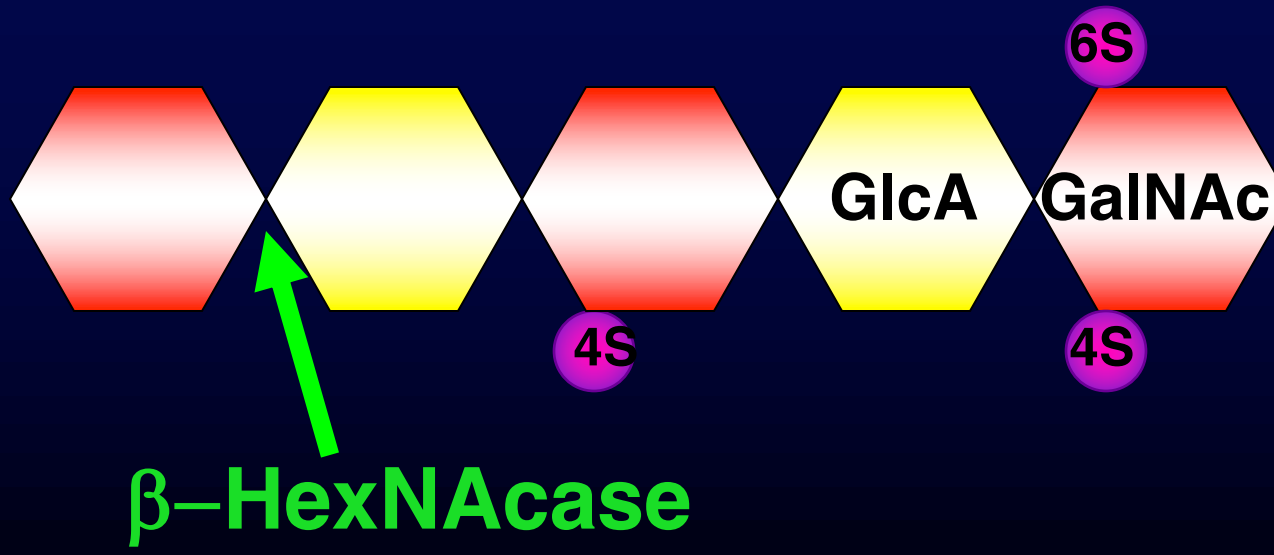


4-Sulfatase

DEGRADATION OF CS/DS



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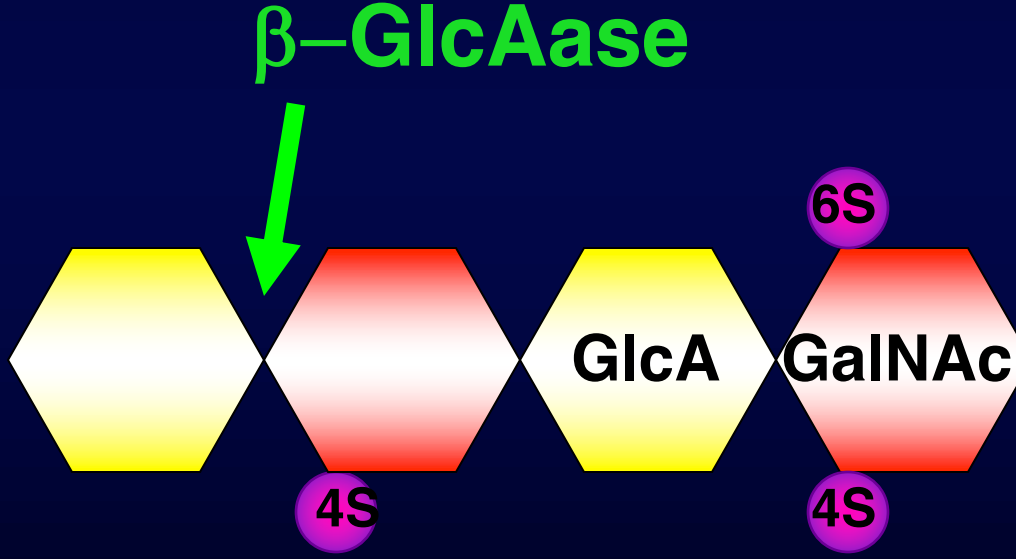

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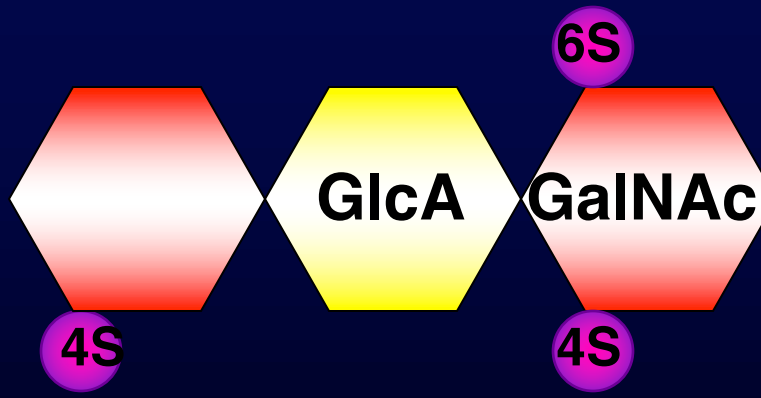
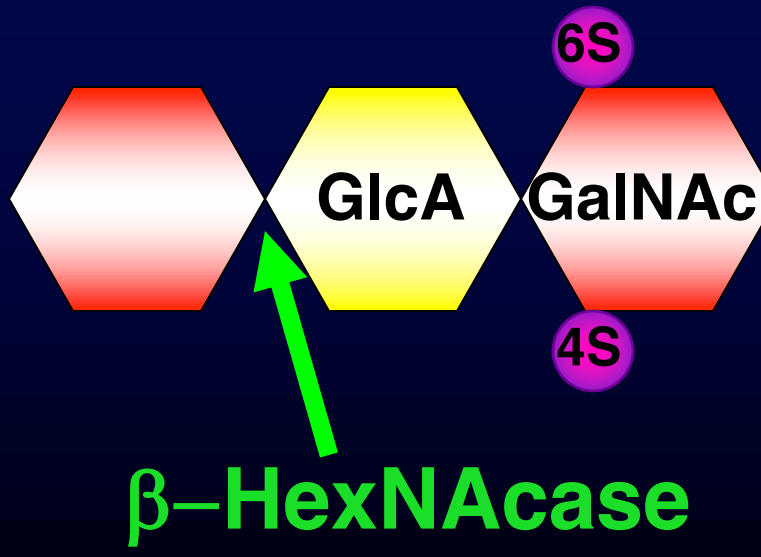


4-Sulfatase

DEGRADATION OF CS/DS



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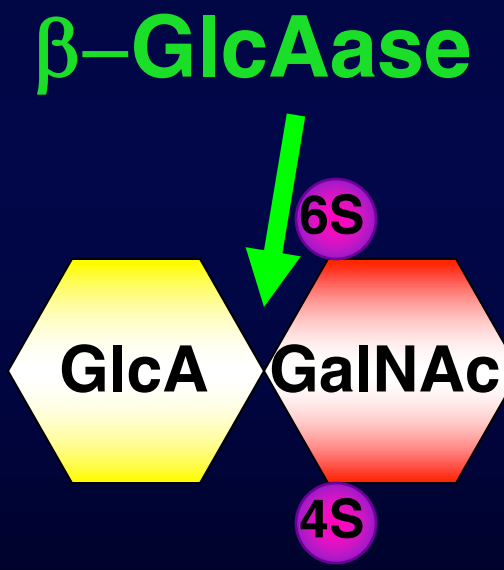

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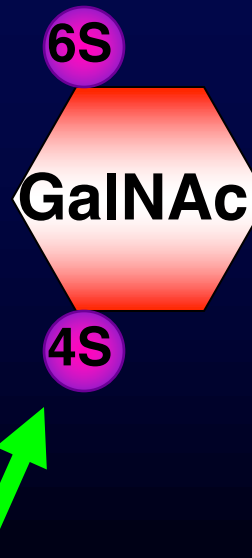
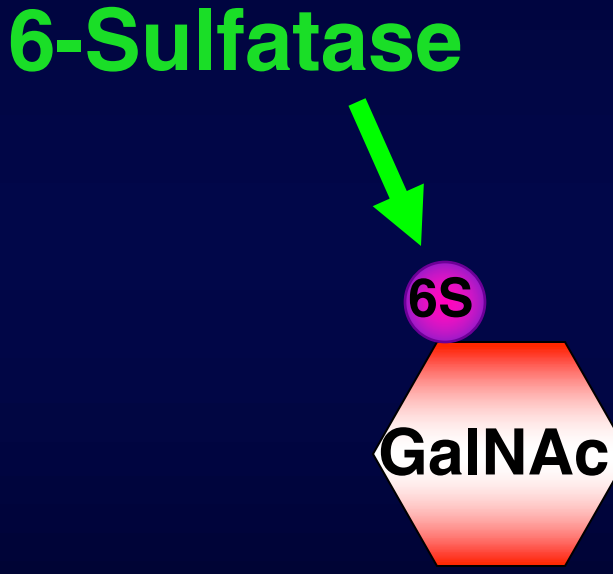


4-Sulfatase

DEGRADATION OF CS/DS



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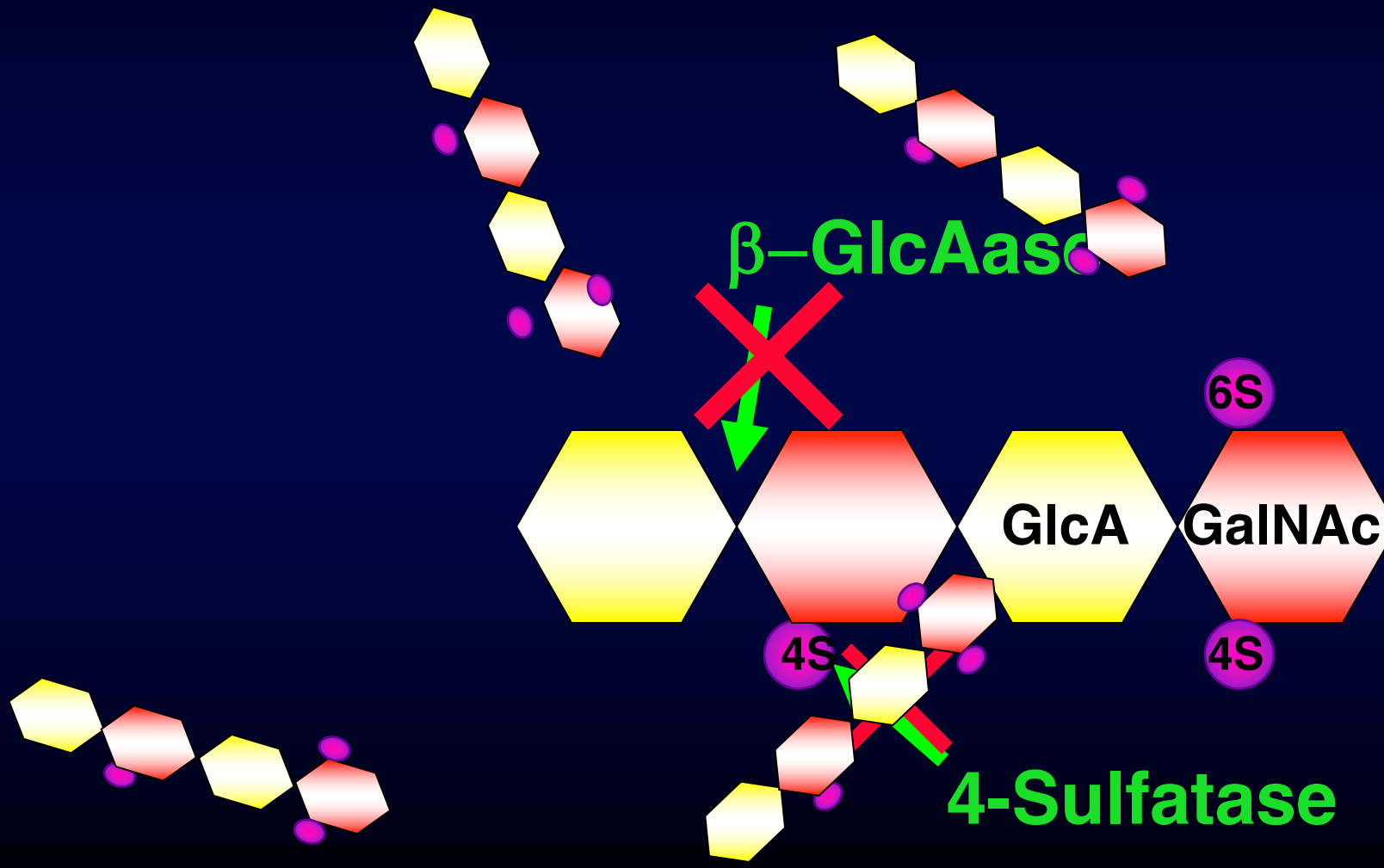

ムコ多糖症(MPS)

Type	Eponym	Enzyme deficiency	Stored substrates
MPS I	Hurlur Scheie	α-Iduronidase	DS, HS
MPS II	Hunter	Iduronate 2-sulfatase	DS, HS
MPS III	Sanfilippo	Heparan sulfate degrading enzymes	HS
MPS IV	Morquio	Galactose-6-sulfatase	CS, DS, KS
MPS VI	Maroteaux-Lamy	*N*-Acetyl-*D*-galactosamine-4-sulphatase	DS
MPS VII	Sly	β-*D*-Glucuronidase	DS, HS

※ HS :Heparan sulfate

Type	Eponym	Enzyme Deficiency	Stored GAG	Pathological Conditions
MPS I	Hurler	α-L-iduronidase	HS, DS	Mental retardation, skeletal deformities, cloudy corneas, hepatosplenomegaly, joint contracture, hearing loss, short statue
	Scheie			Joint contracture, cloudy corneas, aortic closure
MPS II	Hunter（X-linked recessive inheritance）	iduronate-2-sulfatase	HS, DS	（Severe type）Mental retardation, hepatosplenomegaly （Mild type）Joint contracture
MPSIII	Sanfiloppo (type A) (type B) (type C) (type D)	HS-*N*-sulfatase α-*N*-acetylglucosaminidase acetyl-CoA: α–glucosaminide *N*-acetyltransferase α–*N*-acetylglucosamine-6-sulfatase	HS	Mild skeletal changes, mental retardation
MPS IV	Morqio (type A) (type B)	galactose-6-sulfatase (*N*-acetylgalactosamine-6-sulfatase) β-galactosidase	KS, C6S KS	Skeletal deformities（anterior thoracic protrusion, vertebral posterolateral）, cloudy corneas、aortic regurgitation
MPS VI	Maroteaux - Lamy	*N*-acetylgalactosamine 4-sulfatase	DS	Skeletal deformities, cloudy corneas, hepatosplenomegaly, heart disorder
MPS VII	Sly	β-D-glucuronidase	HS, DS	Skeletal deformities, cloudy corneas, mental retardation

Type	Eponym	Enzyme Deficiency	Stored GAG	Pathological Conditions
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MPS VI	Maroteaux - Lamy	*N*-acetylgalactosamine 4-sulfatase	DS	Skeletal deformities, cloudy corneas, hepatosplenomegaly, heart disorder
MPS VII	Sly	β-D-glucuronidase	HS, DS	Skeletal deformities, cloudy corneas, mental retardation

MPS IX

Deficiency：Hyaluronidase 1
Storage：HA in plasma
Symptoms：Mild phenotype
（Periarticular masses and mild short stature）

Tratment of lysosome disease

1. Symptomatic treatment
2. Enzyme replacement therapy (ERT)
3. Bone marrow transplantation
4. Gene therapy

Enzyme Replacement Therapy, ERT

ERT is a medical treatment which replaces an enzyme that is deficient or absent in the body. Increasing the concentration of the missing enzyme within the body improves the body's normal cellular metabolic processes and reduces substrate concentration in the body.

Problems on ERT

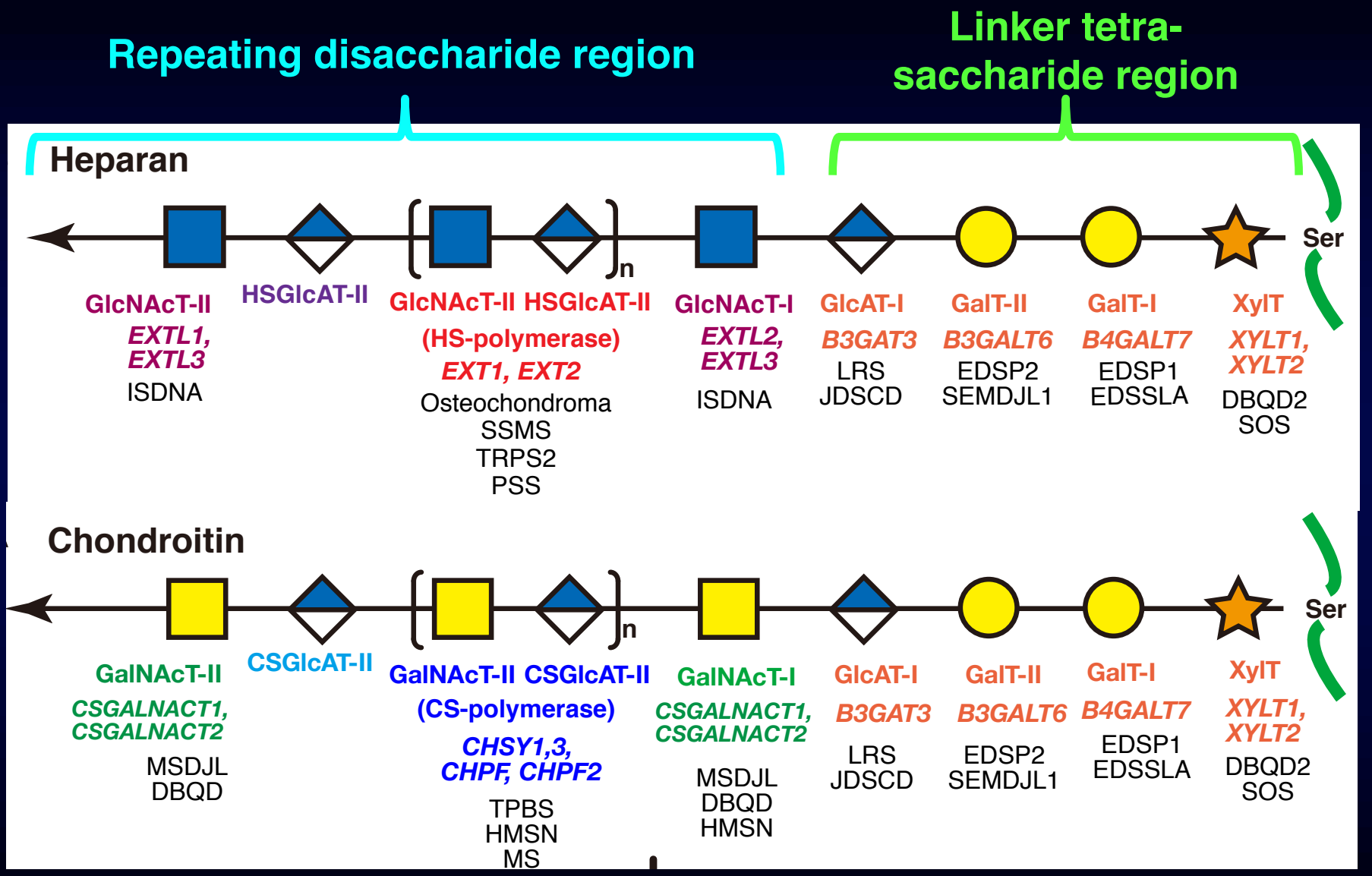
1. Less available to certain areas in the body (brain, bone, and heart)
2. Less efficient to be incorporated into cells
3. Less half life in the body
4. Need to be treated earlier in life time
5. Unwanted immune response against the enzyme
6. Expensive costs

Congenital disorder of glycosylation (CDG)

It is caused by a deficiency of glycosyltransferase, which is involved in the biosynthesis of sugar chains on glycoproteins.

Common symptoms of this disease include hypotonia in infancy, poor weight gain, severe psychomotor developmental delay, characteristic facial features, epilepsy, ophthalmologic abnormalities such as esotropia, skin symptoms such as fatty deposits in the buttocks and nipple retraction, pericardial effusion, cardiomyopathy, liver dysfunction, and abnormalities in blood clotting factors.

Biosynthesis of HS and CS backbones

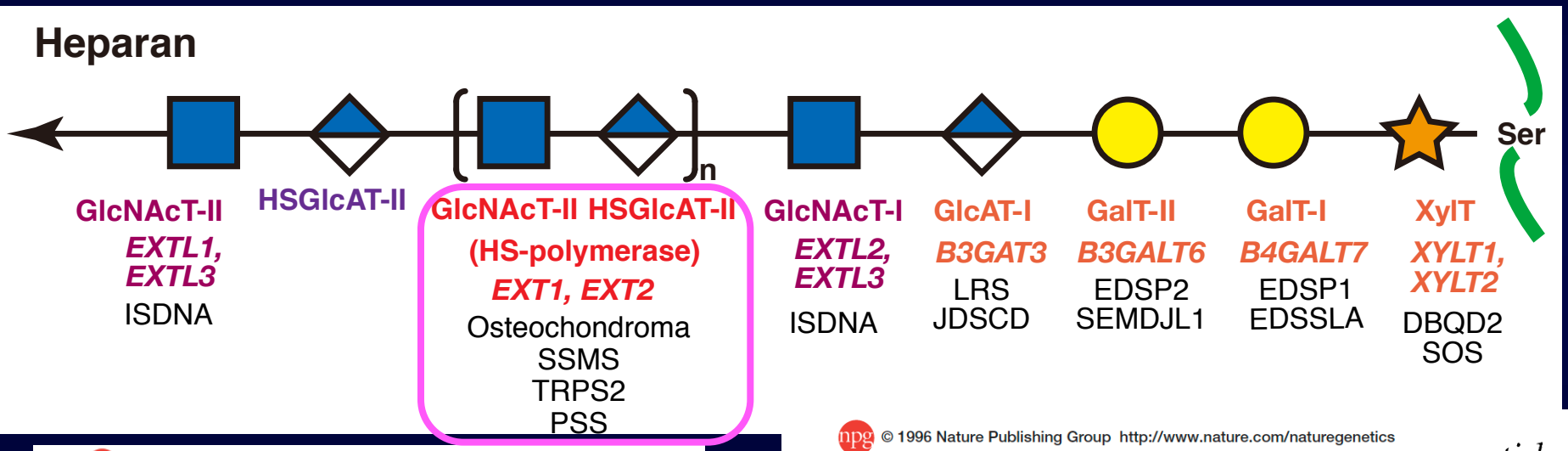


Shuji Mizumoto, Shuhei Yamada
Trends in Glycoscience and Glycotechnology, 2020, 32, E45-E51

Human genetic disorders caused by mutations in EXT1 or EXT2

Repeating disaccharide region of HS

Linker tetra-saccharide region



article

Cloning of the putative tumour suppressor gene for hereditary multiple exostoses (*EXT1*)

Jung Ahn*[1], Hermann-Josef Lüdecke*[2], Steffi Lindow[2], William A. Horton[3], Brendan Lee[3], Michael J. Wagner[1], Bernhard Horsthemke[2] & Dan E. Wells[1]

article

The *EXT2* multiple exostoses gene defines a family of putative tumour suppressor genes

Dominique Stickens[1]*, Gregory Clines[1]*, David Burbee[1,3], Purita Ramos[1], Sylvia Thomas[1], Deborah Hogue[4], Jacqueline T. Hecht[4], Michael Lovett[1,3] & Glen A. Evans[1,2,3]

Hereditary multiple exostosis is caused by mutations in HS biosynthetic enzymes EXT1/EXT2

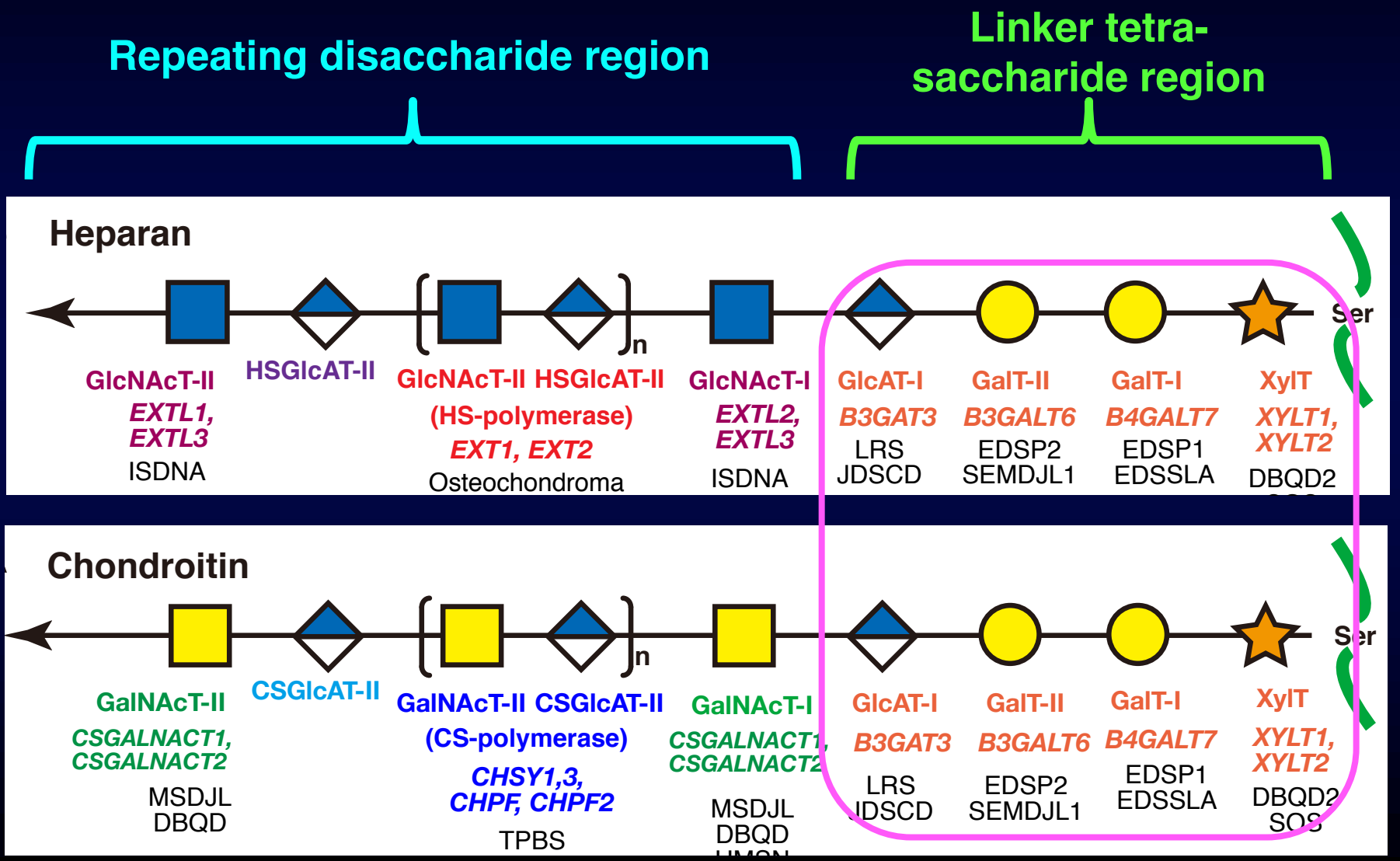
Hereditary multiple exostosis is an autosomal dominant skeletal disorder characterized by the presence of cartilage capped bony outgrowths mainly located at the juxtaepiphyseal region of the long bones.

It is caused by mutations in EXT1 and EXT2.

The heterooligomeric complex of EXT1 and EXT2 represents the biologically relevant form of the HS polymer modification

Solomon L, Am J Hum Genet, 16, 351, 1964

Proteoglycan Linkeropathy caused by the mutations in the biosynthetic enzymes of the linker region



Proteogycan Linkeropathy

•Proteogycan Linkeropathy is a collective term for diverse connective tissue disorders caused by mutations in the glycosyltransferases responsible for the biosynthesis of the linker region tetrasaccharide, which is characterized by bone, skin, connective tissue, and heart defects.

Genetic disorders	Affected genes
Desbuquois dysplasia type 2	*XYLT1*
Spondyloocular syndrome	*XYLT2*
Spondylodysplastic Ehlers-Danlos syndrome	*B4GALT7, B3GALT6*
Larsen-like syndrome	*GlcAT-I*

Human genetic disorders caused by mutations in enzymes responsible for biosynthesis of CS, DS, and HS

Genetic disorders	Affected genes	Refs.
Spondyloepiphyseal dysplasia, Omani type	*C6ST-1*	Am. J. Med. Genet. 2008
Severe osteopenia and fractures	*GlcAT-I*	BMC Med. Genet. 2016; J. Med. Genet. 2020
A mild skeletal dysplasia and joint laxity	*GalNAcT1*	Hum. Mutat. 2017; 2020
Musculocontractural Ehlers-Danlos syndrome	*D4ST-1* *DSE*	Hum. Mutat. 2010; Clin. Biochem. 2017; BBA 2019 Mol. Genet. Genomic Med. 2020; Hum. Mutat. 2022
A novel type of spondylo-epi-metaphyseal dysplasia	*EXTL3*	J. Hum. Genet. 2017
Pseudodiastrophic dysplasia	*CANT1*	J. Med. Genet. 2020
Desbuquois dysplasia type 2 Pseudotorsion dysplasia	*XYLT1* *XYLT2*	In preparation

① Ehlers-Danlos syndrome caused by mutations in D4ST-1

② A novel type of spondylo-epi-metaphyseal dysplasia caused by mutations in EXTL3

① Ehlers-Danlos syndrome caused by mutations in D4ST-1

② A novel type of spondylo-epi-metaphyseal dysplasia caused by mutations in EXTL3

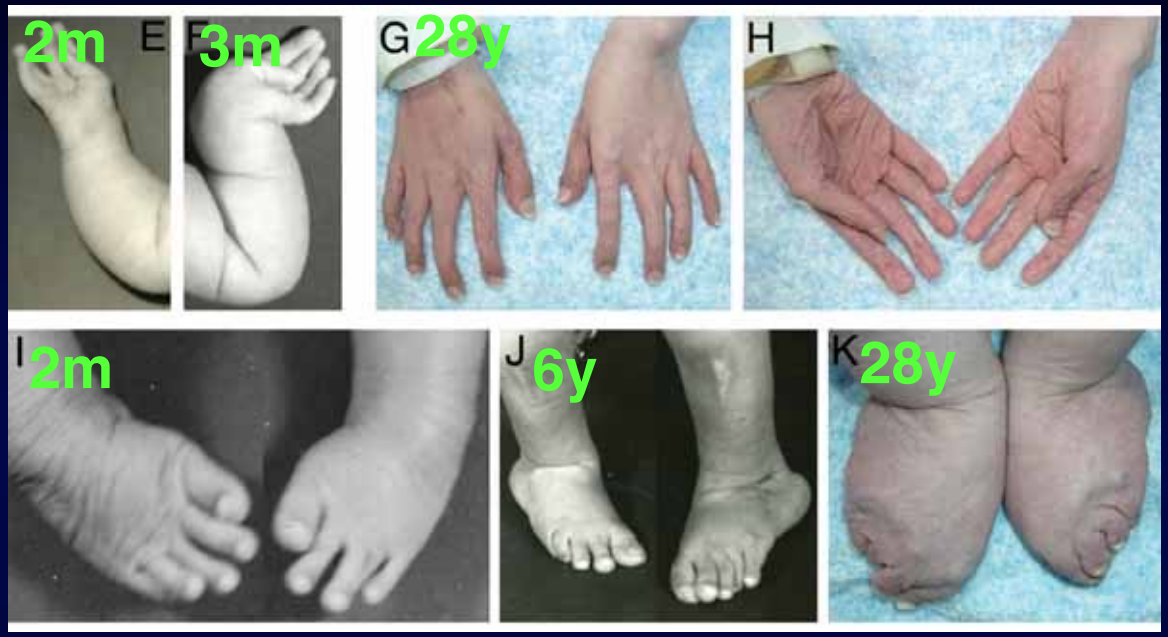
Ehlers-Danlos syndrome

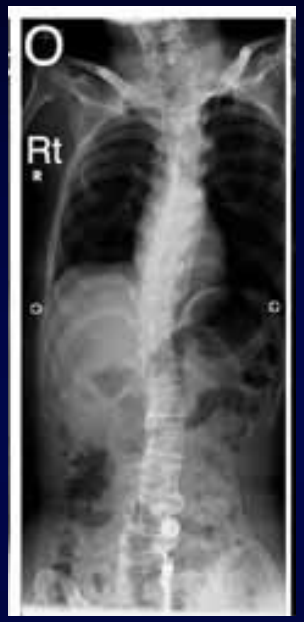
- **A heritable connective tissue disorder characterized by joint and skin laxity as well as tissue fragility.**
  (aged appearance, hypermobile joints, short stature, craniofacial dysmorphism etc.)

- Previously, the Ehlers-Danlos syndromes were classified in a system of six subtypes as follows.

Types	Affected genes
Classic type	*COL5A1, COL5A2*
Vascular type	*COL3A1*
Arthrochalasia type	*COL1A1, COL1A2*
Dermatosparaxis type	*ADAMTS2*
Hypermobility type	*TenescinXB*
Kyphoscoliosis type	*Lysyl hydroxylase*

Clinical symptoms of Ehlers-Danlos syndrome (Kosho type)





Others:

Skin hyperextension

Wrinkled skin

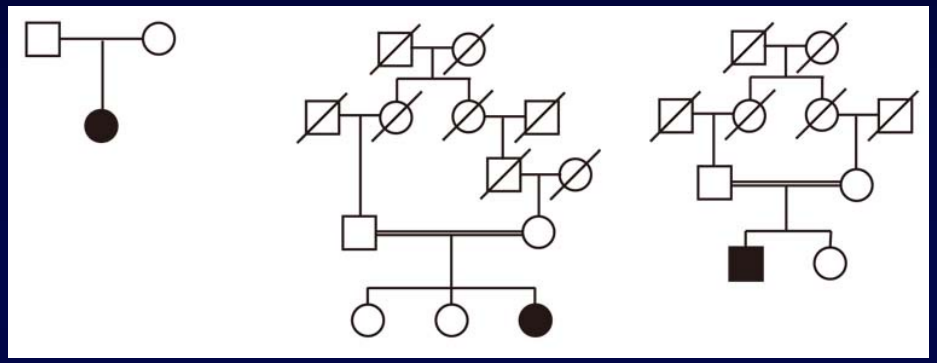
Defective heart valve

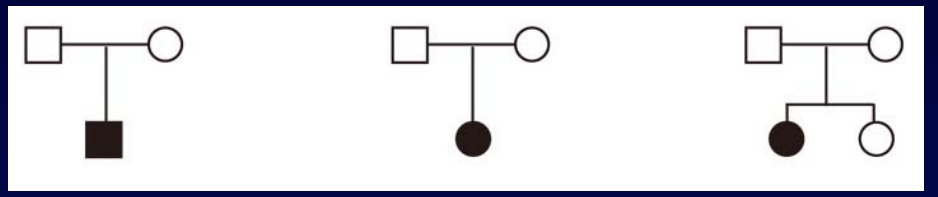
Subcutaneous hematoma

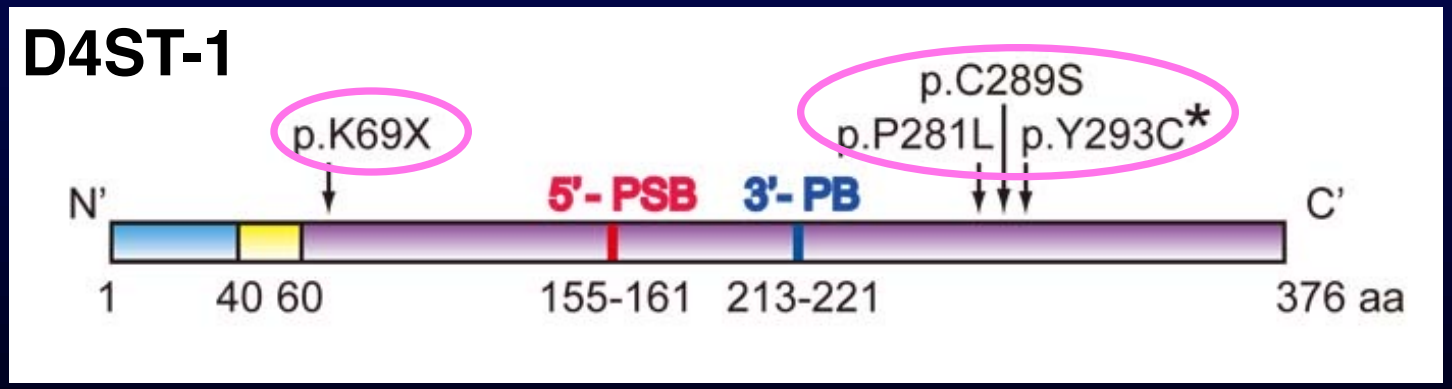
Kosho *et al.*, Am. J. Med. Genet. (2010)

Identification of the mutations in Ehlers-Danlos syndrome

P281L Y293C | P281L (homo) | P281L (homo) | K69X P281L | P281L C289S | P281L Y293C







5'-PSB, 5'-phosposulfate binding motif
3'-PB, 3'-phospo binding motif

Ehlers-Danlos syndrome

- **A heritable connective tissue disorder characterized by joint and skin laxity as well as tissue fragility.**
  (aged appearance, hypermobile joints, short stature, craniofacial dysmorphism etc.)

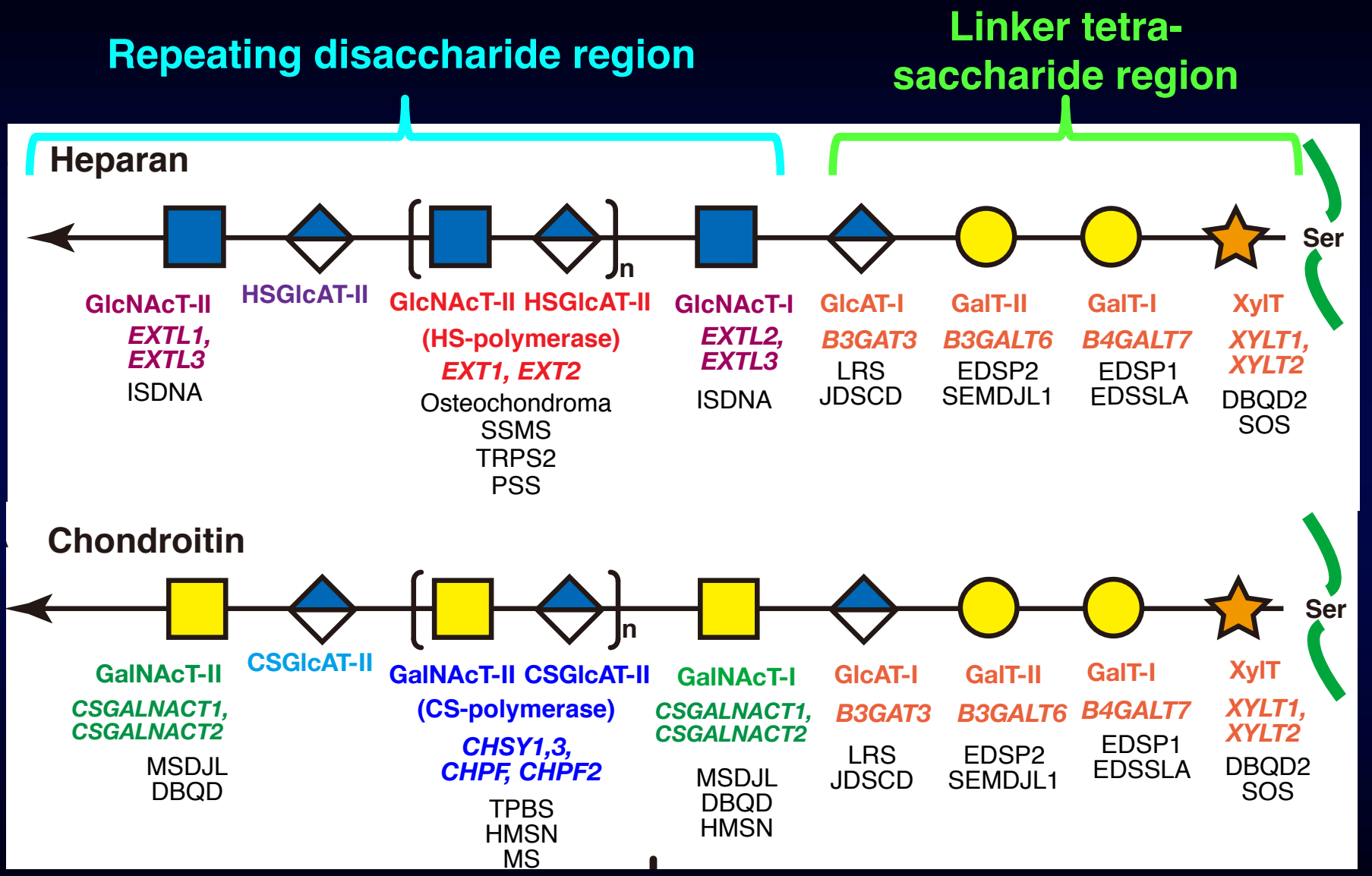
Types	Affected genes
Classic type	*COL5A1, COL5A2*
Vascular type	*COL3A1*
Arthrochalasia type	*COL1A1, COL1A2*
Dermatosparaxis type	*ADAMTS2*
Hypermobility type	*TenescinXB*
Kyphoscoliosis type	*Lysyl hydroxylase*

Ehlers-Danlos syndrome

- The International EDS Consortium proposes a revised EDS classification, which recognizes 13 subtypes. (Malfait *et al.* American Journal of Medical Genetics, 2017)

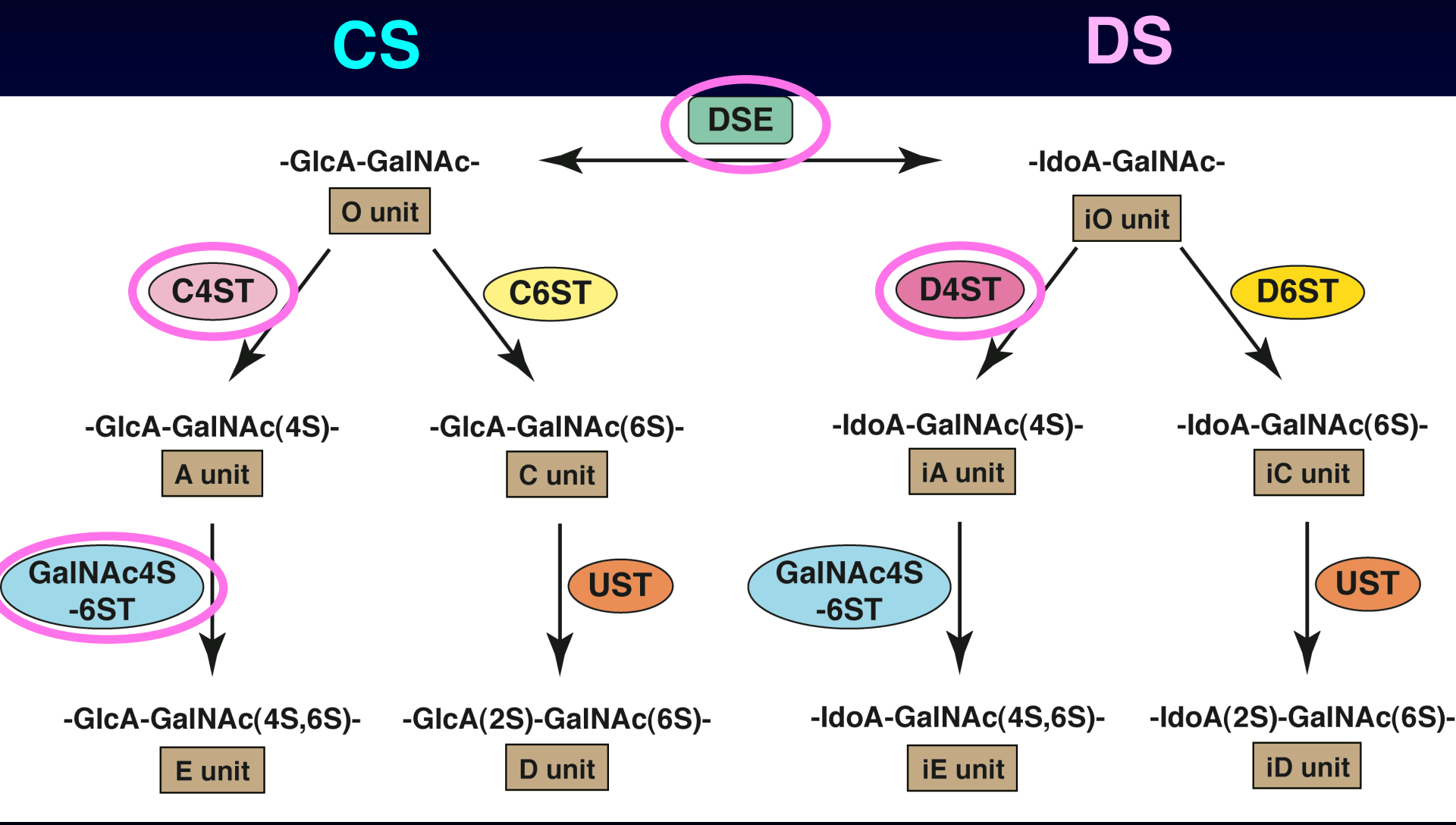
New Types	Affected genes
Classical-like type	*TenescinXB*
Cardiac-valvular type	*COL1A2*
Brittle Corbea Syndrome	*ZNF469, PRDM5*
Spondylodysplastic type	*B4GALT7, B3GALT6, SLC39A13*
Musculocontractural type	*DSE, D4ST-1*
Myopathic type	*COL12A1*
Periodontal type	*C1R*

Biosynthesis of HS and CS backbones

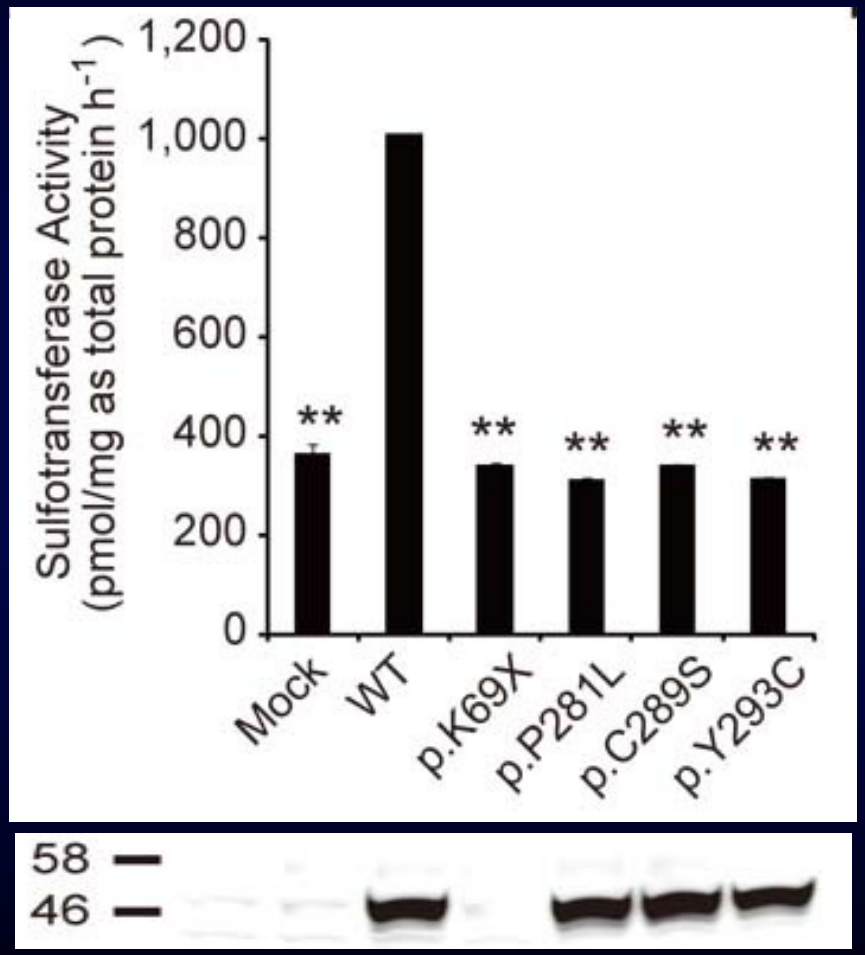


Shuji Mizumoto, Shuhei Yamada
Trends in Glycoscience and Glycotechnology, 2020, 32, E45-E51

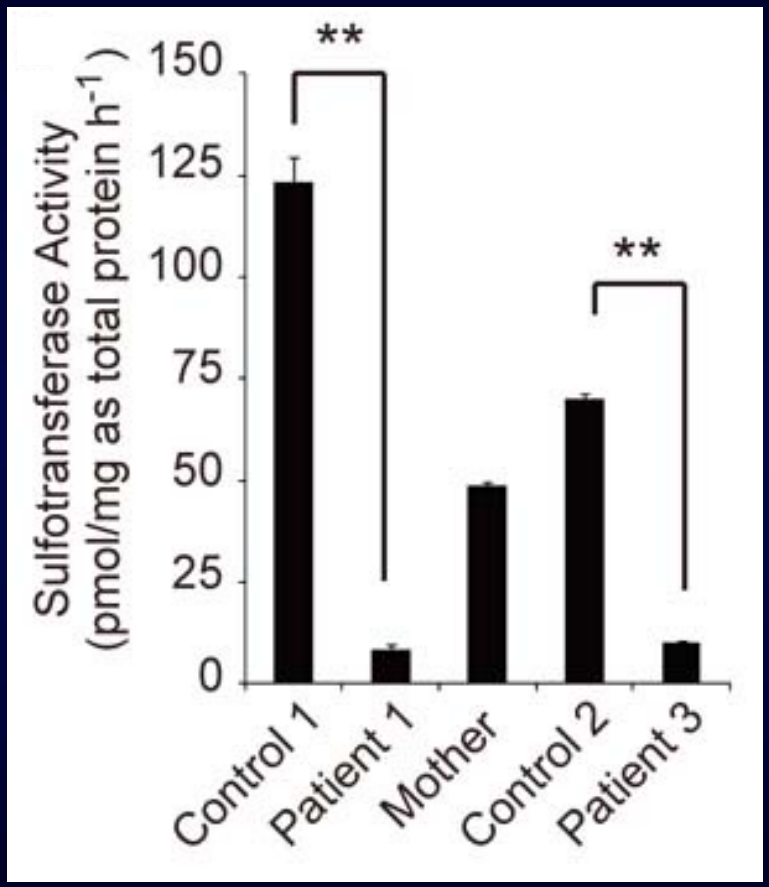
Schematic pathways of the modifications of CS and DS



Sulfotransferase activities of the recombinant D4ST-1 and the fibroblasts from patients



** $P < 0.001$

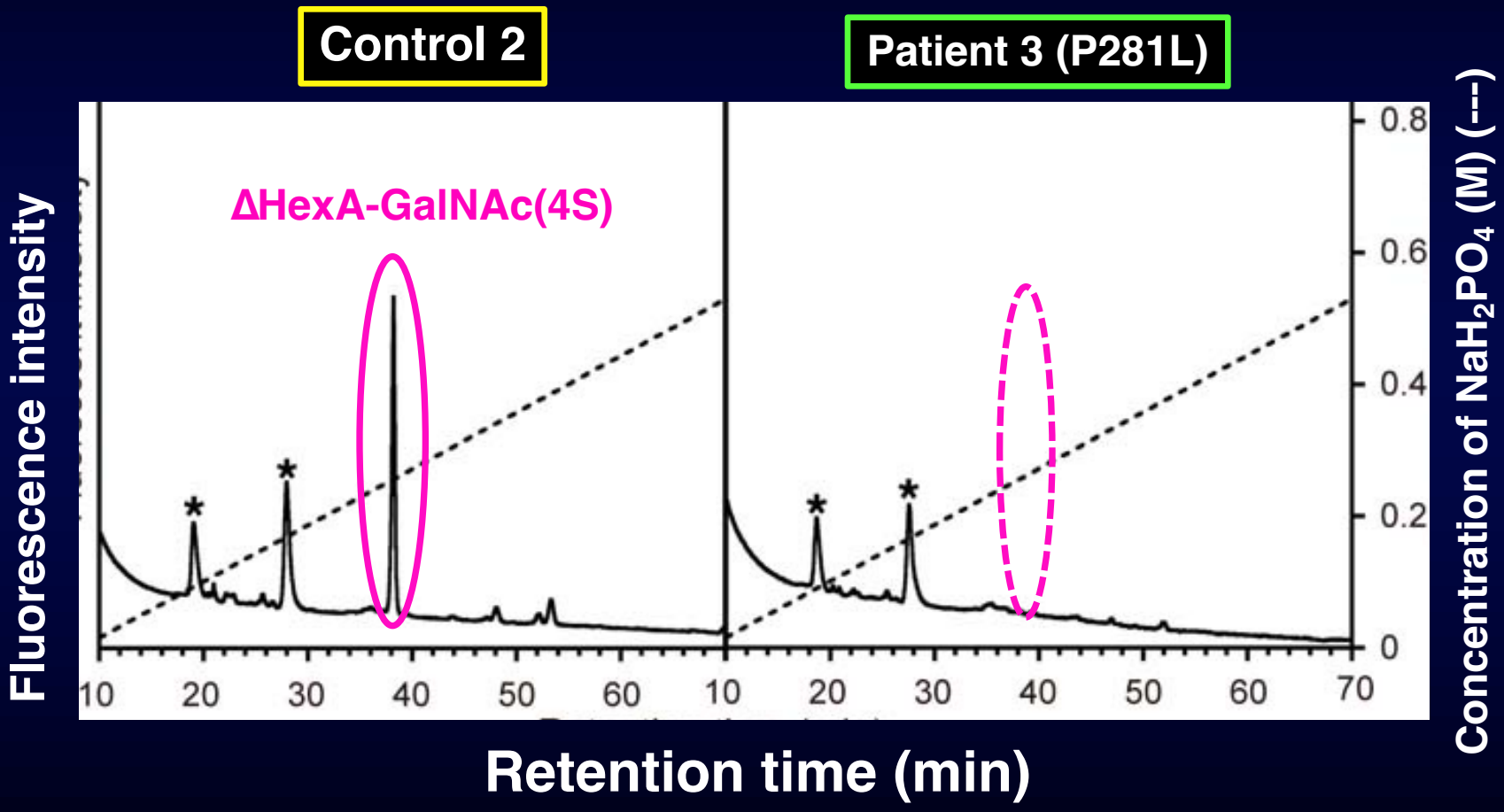


Patient 1, P281L/Y293C

Patient 3, P281L (homo)

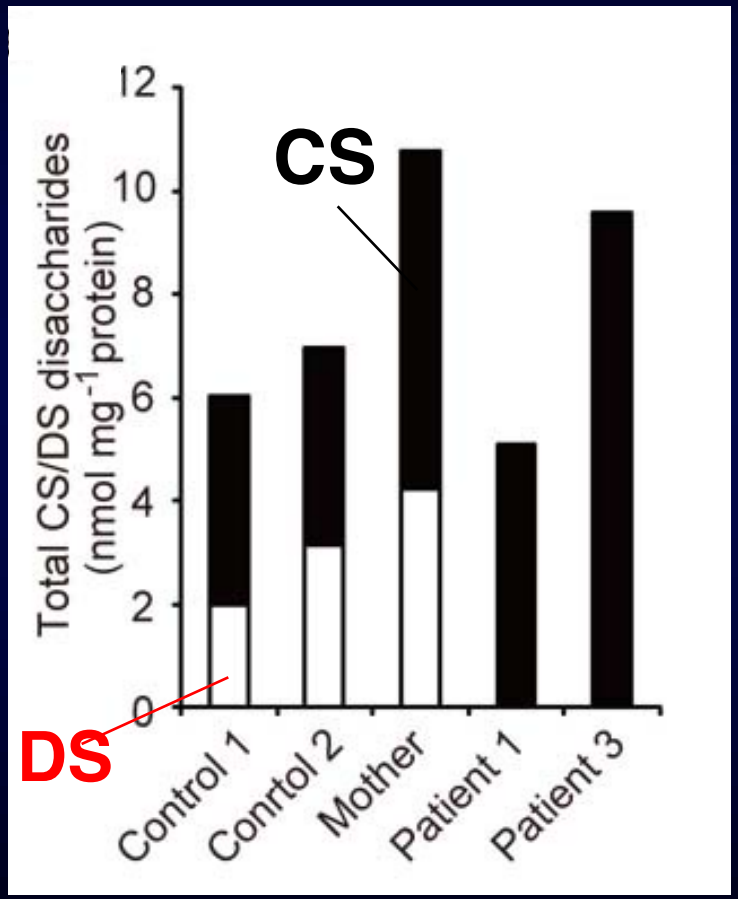
** $P < 0.001$

Chromatograms of the DS disaccharide from the skin fibroblasts



*, impurity

Total amount of CS and DS in fibroblasts from patients and healthy subjects



CS –GlcA–GalNAc(4S or 6S)–

C4ST-1 or C6ST-1

Chondroitin –GlcA–GalNAc–

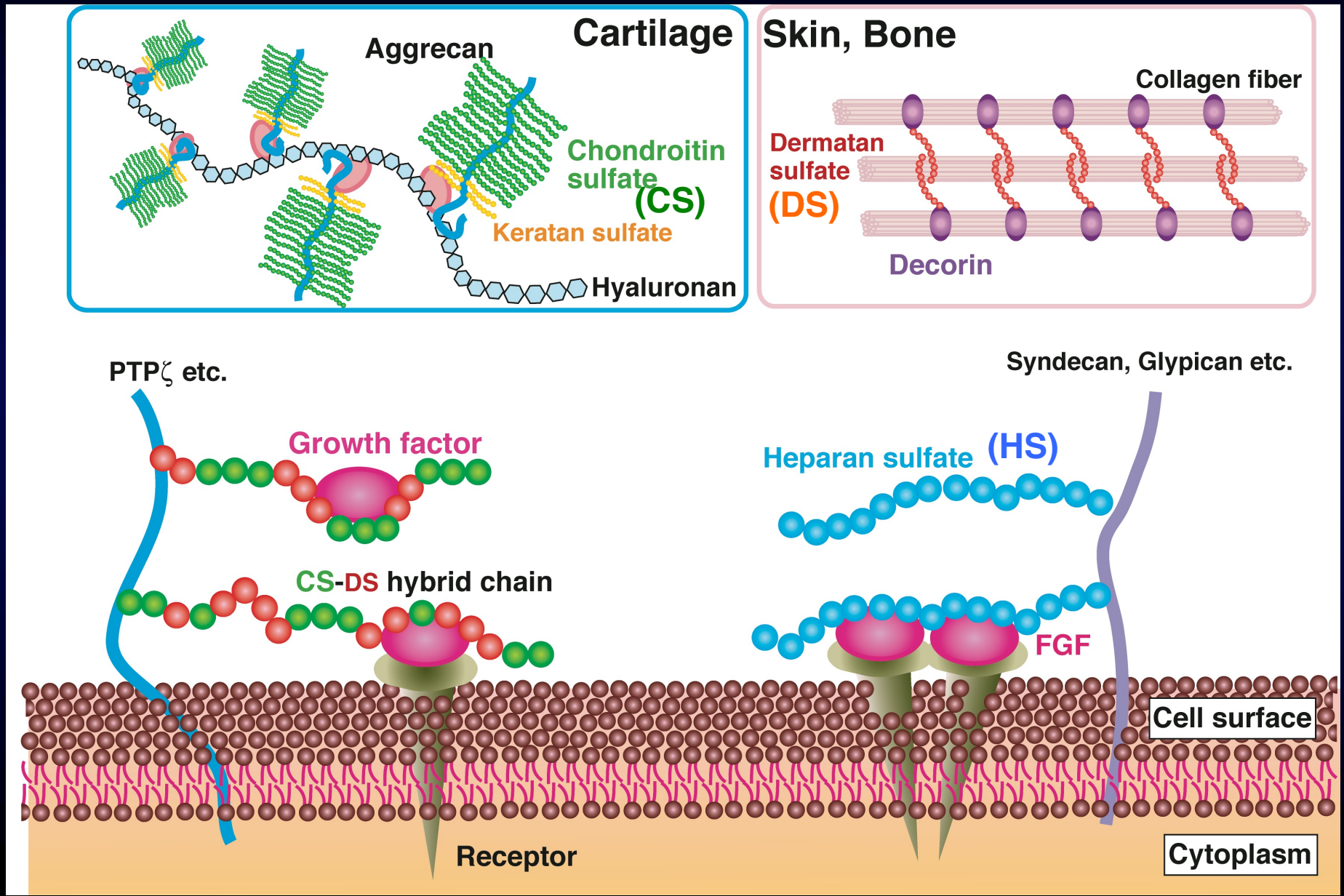
DSE

Dermatan –IdoA–GalNAc–

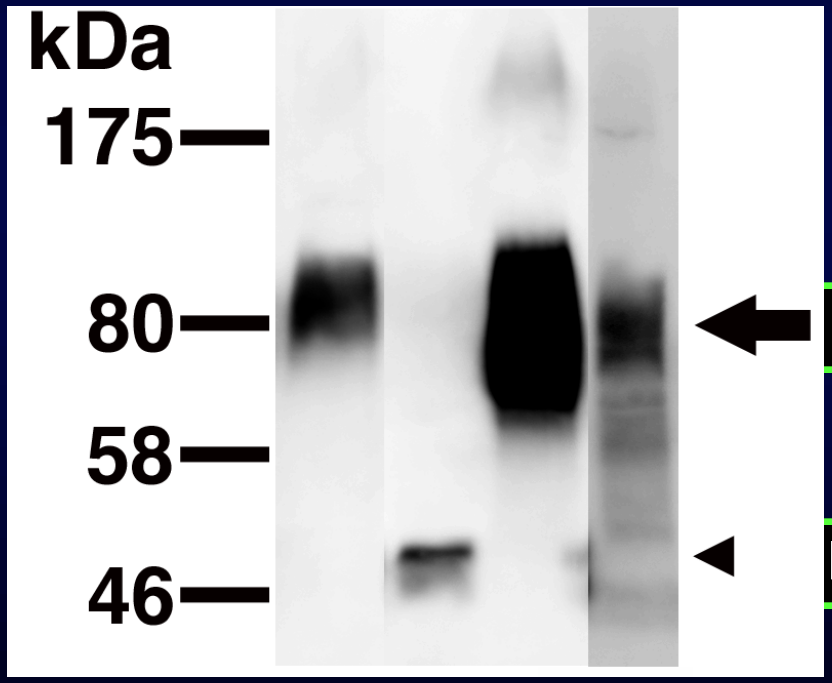
D4ST-1

DS –IdoA–GalNAc(4S)–

Various functions of CS, DS, and HS-proteoglycans at cell surfaces and in extracellular matrix



Western blotting of decorin proteoglycan (PG) secreted by fibroblasts from a patient



Detected by anti-decorin antibody

Decorin-PG

Decorin

Control

Patient

DS

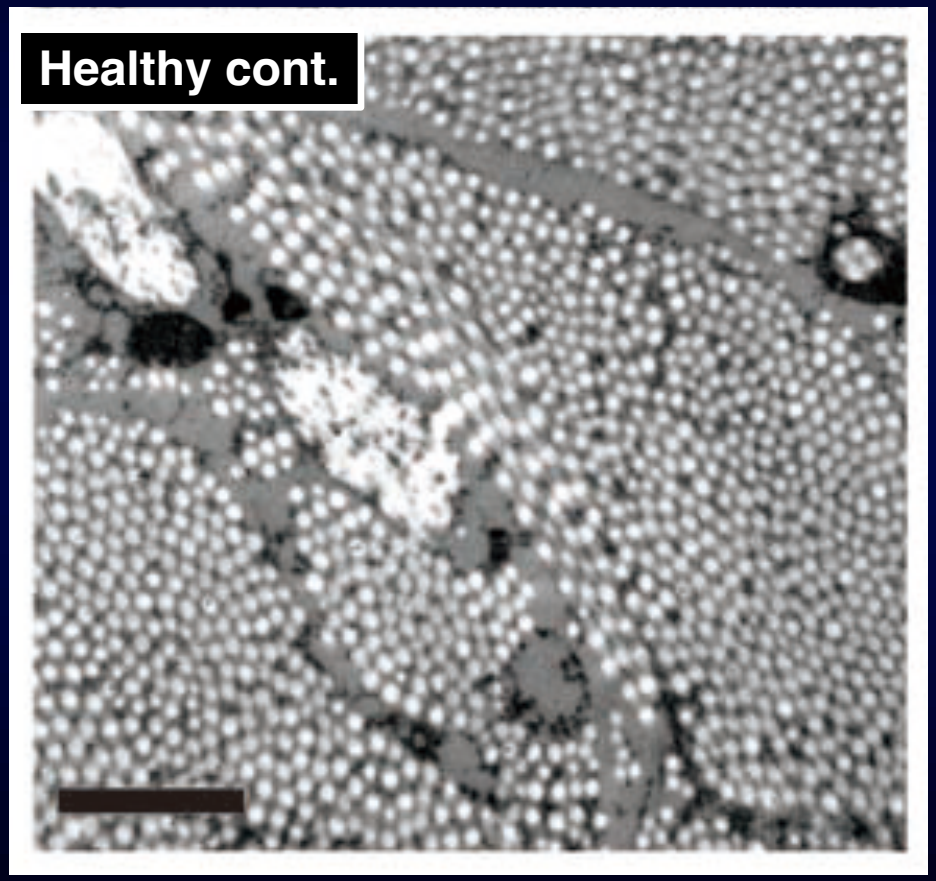
CS

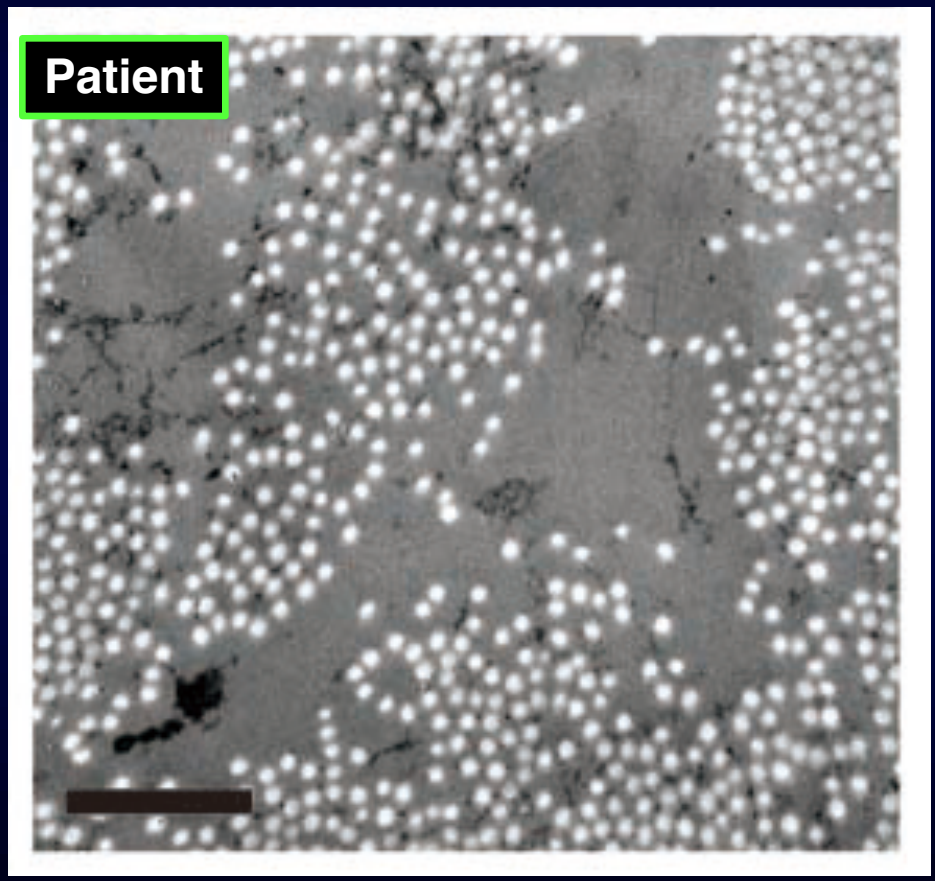
DS-specific lyase

Chondroitinase B
(CSase B)

The collagen fibers in the patient

Electron microscopy



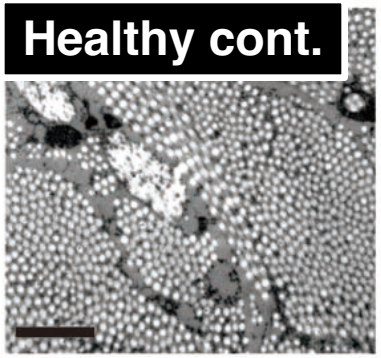


The collagen fibers in the patient

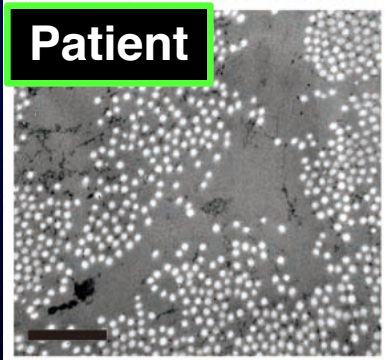
Electron microscopy

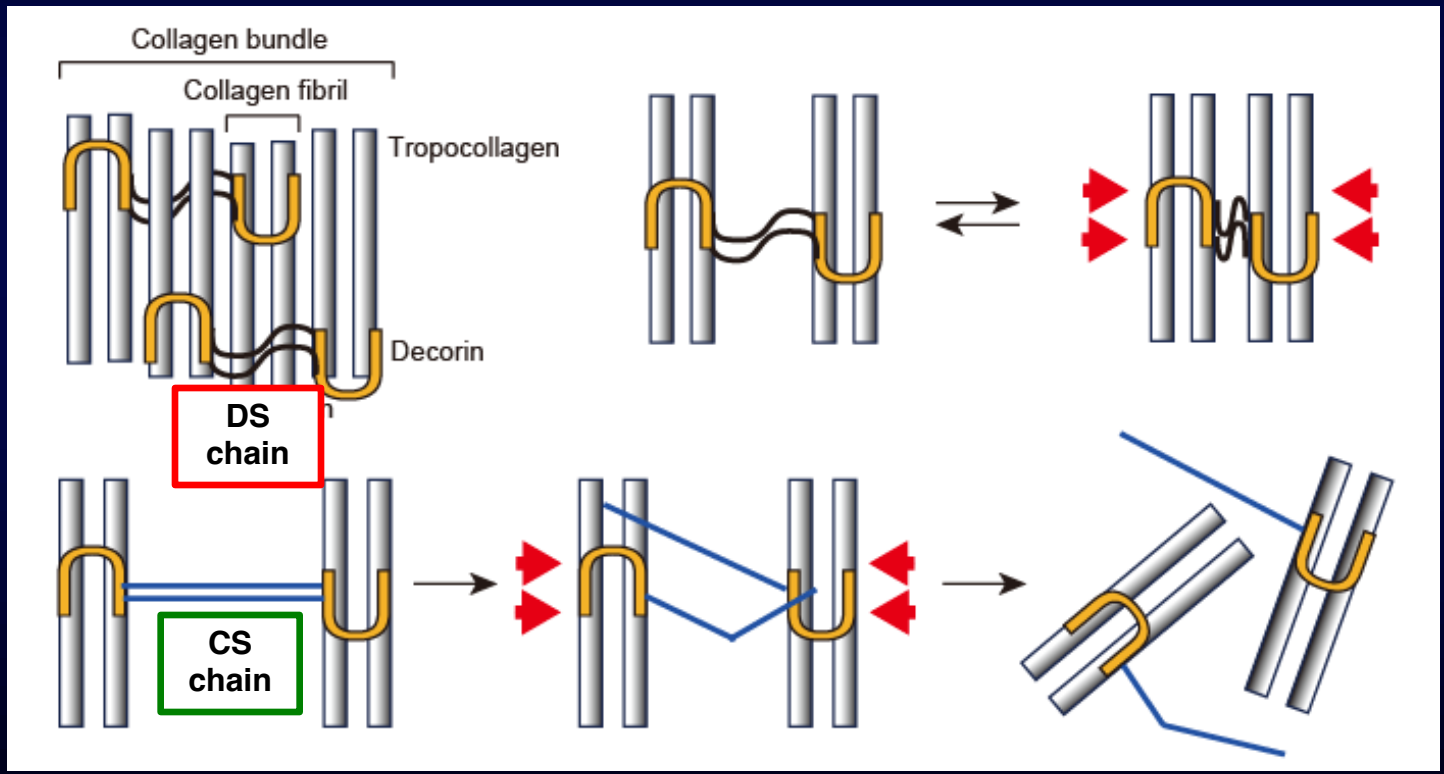
The structural alterations of collagen fibers by mechanical compression in normal and affected states

Healthy cont.



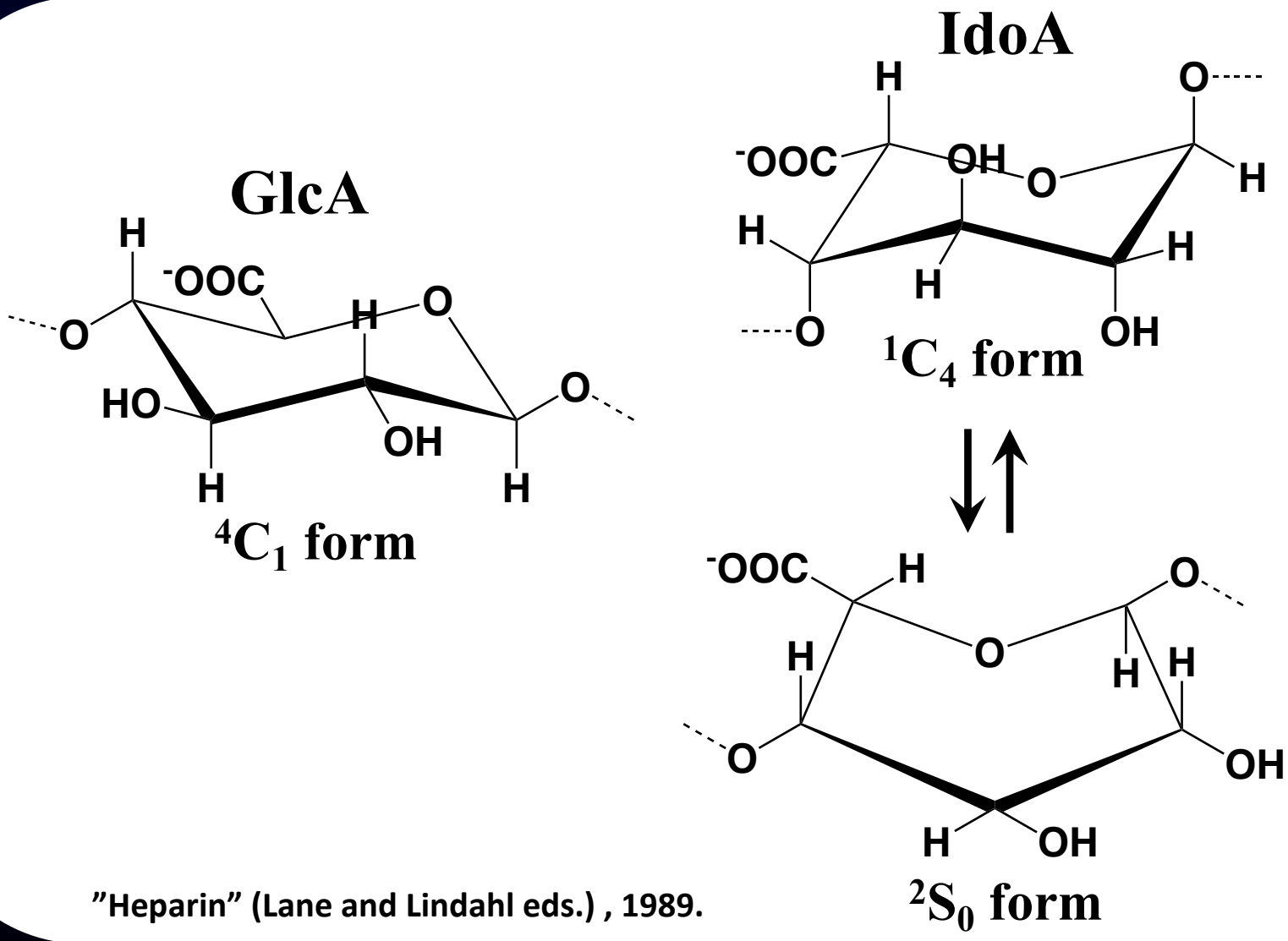
Patient





Miyake, Kosho, Mizumoto, Yamada *et al.*, Human Mutation, 2010

Conformation of GlcA and IdoA



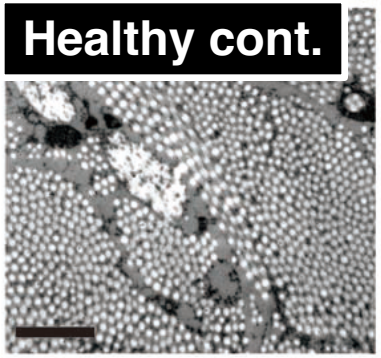
”Heparin” (Lane and Lindahl eds.) , 1989.

The collagen fibers in the patient

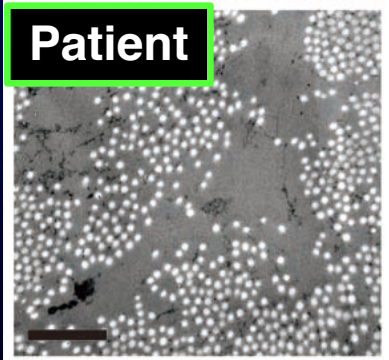
Electron microscopy

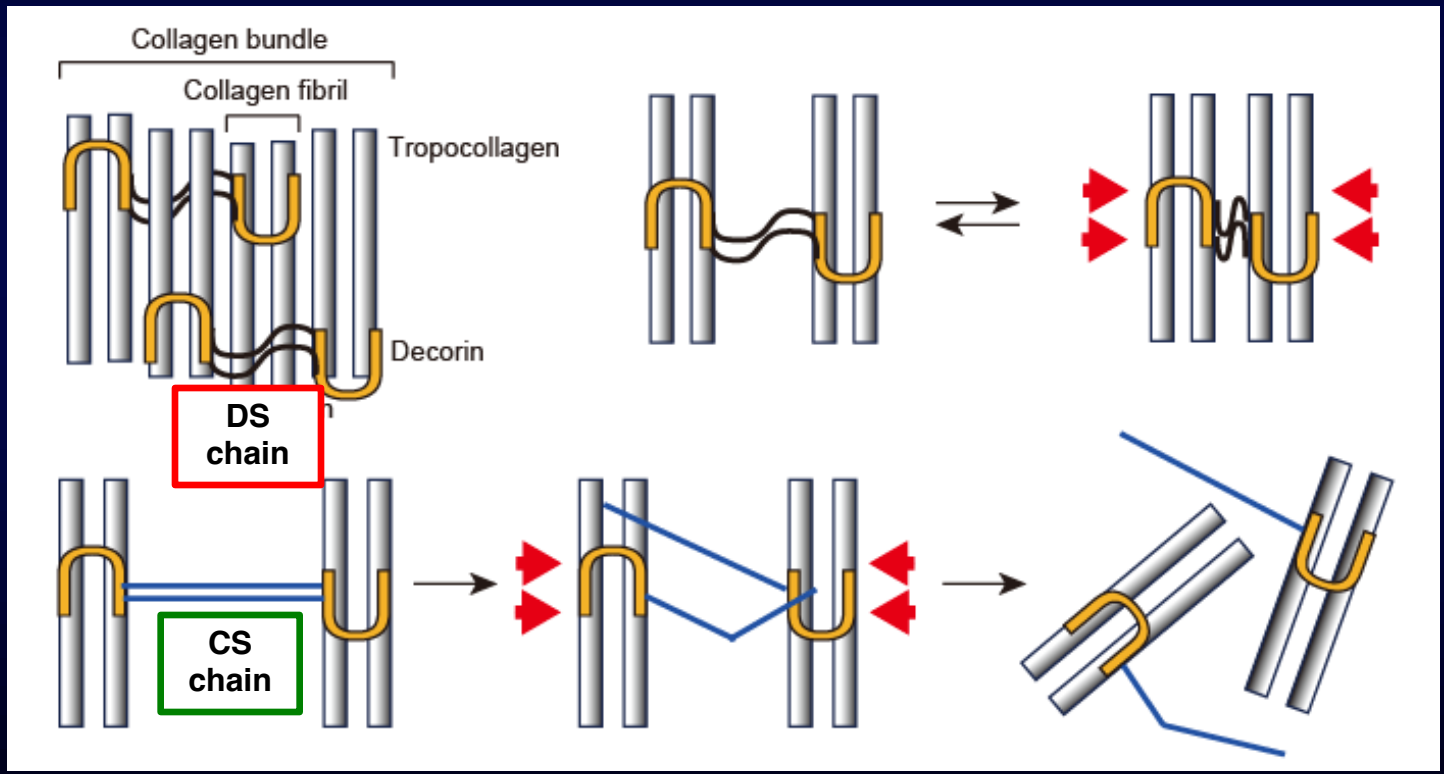
The structural alterations of collagen fibers by mechanical compression in normal and affected states

Healthy cont.



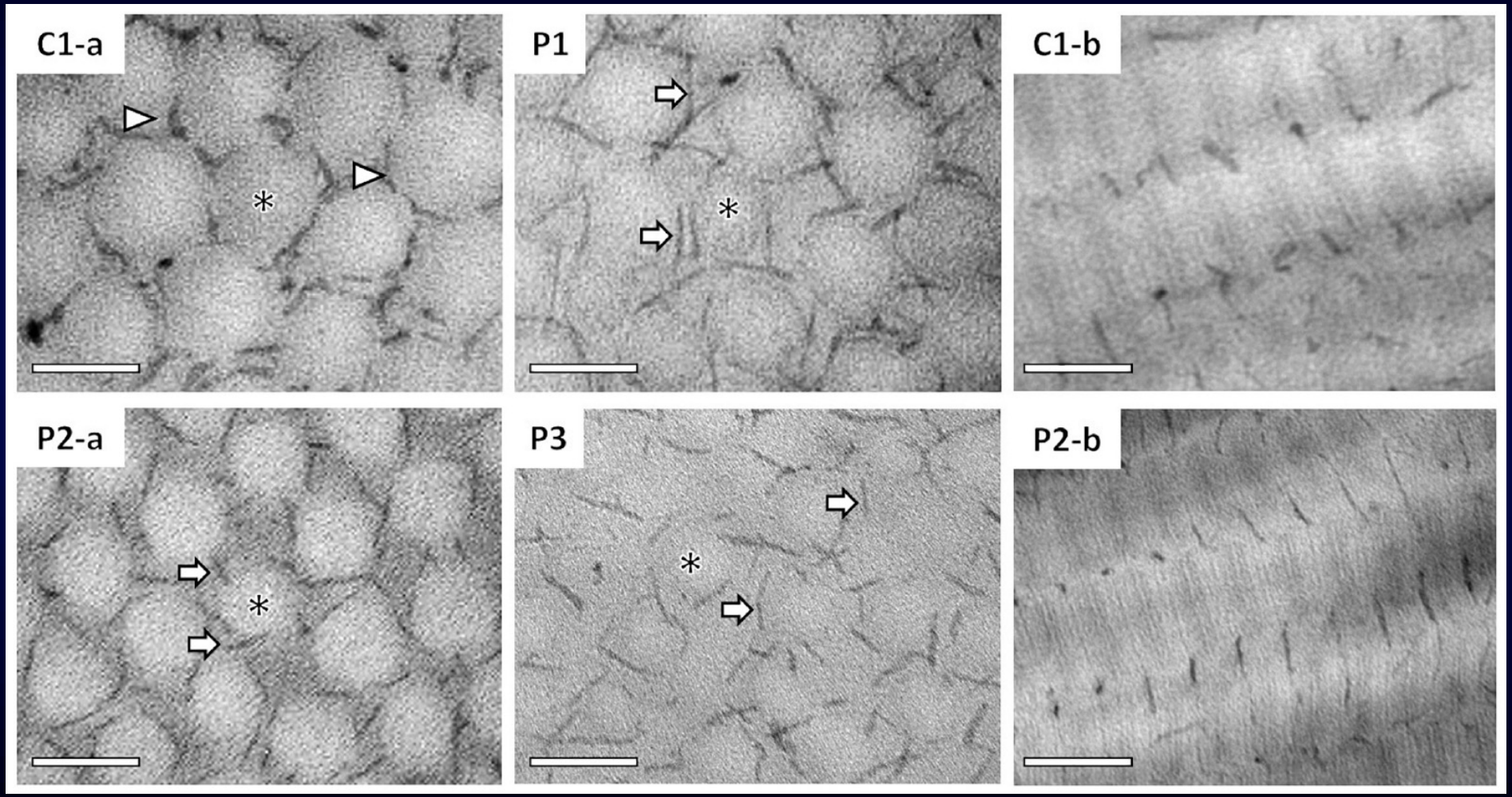
Patient





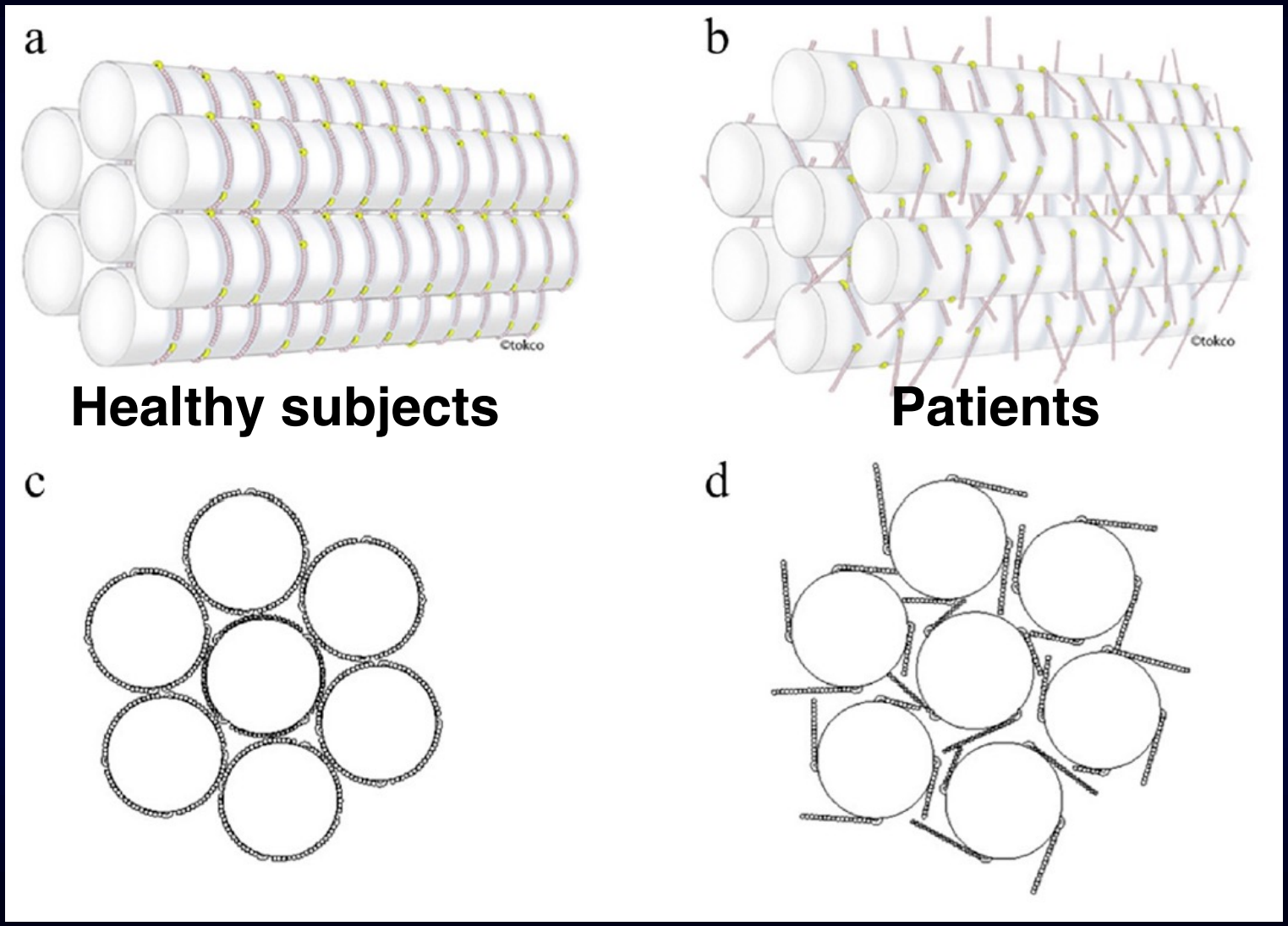
Miyake, Kosho, Mizumoto, Yamada *et al.*, Human Mutation, 2010

Structural alteration of glycosaminoglycan side chains in the skins of patients



Hirose, Mizumoto, Yamada *et al*., BBA General Subjects, 2019

Structure of collagen fibrils and GAG chains in the skin of healthy individuals and patients



Healthy subjects

Patients

DS chains adhere to collagen fibrils.

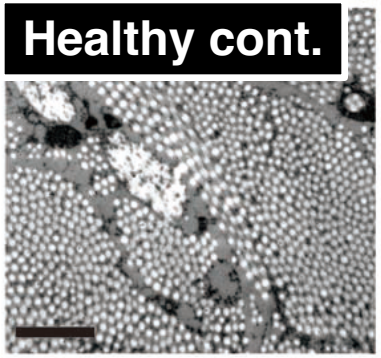
CS chains spread across interfibrillar spaces.

The collagen fibers in the patient

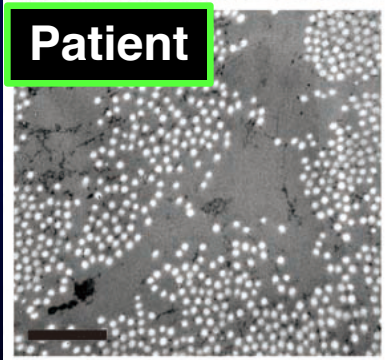
Electron microscopy

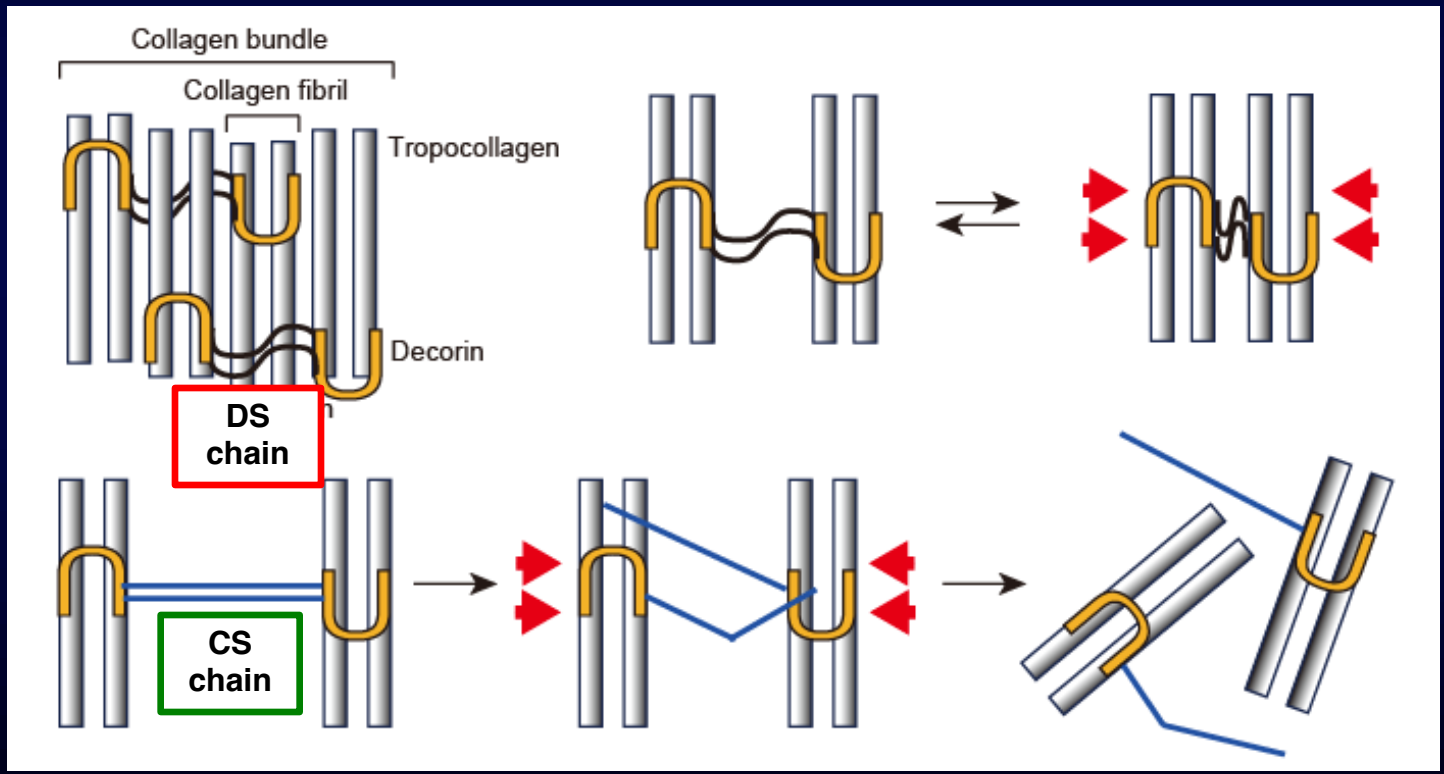
The structural alterations of collagen fibers by mechanical compression in normal and affected states

Healthy cont.



Patient





Miyake, Kosho, Mizumoto, Yamada *et al.*, Human Mutation, 2010

Urine samples from EDS patients with mutation in *D4ST1*

Patient	Age (y)	Sex	D4ST1	References
1	11	F	P281L/Y293C	P1 in Kosho *et al*. AJMG 2010
2	29	F	P281L/P281L	P2 in 〃
3	32	M	P281L/P281L	P3 in 〃
4	20	F	P281L/C289S	P5 in 〃
5	4	F	P281L/Y293C	P6 in 〃
6	41	F	F209S/P281L	Kono *et al*. Acta Derm Venereol 2016
7	10	M	F209S/P281L	P2 in Shumizu *et al*. AJMG 2011
8	3m	M	F209S/P281L	Brother of patient 7

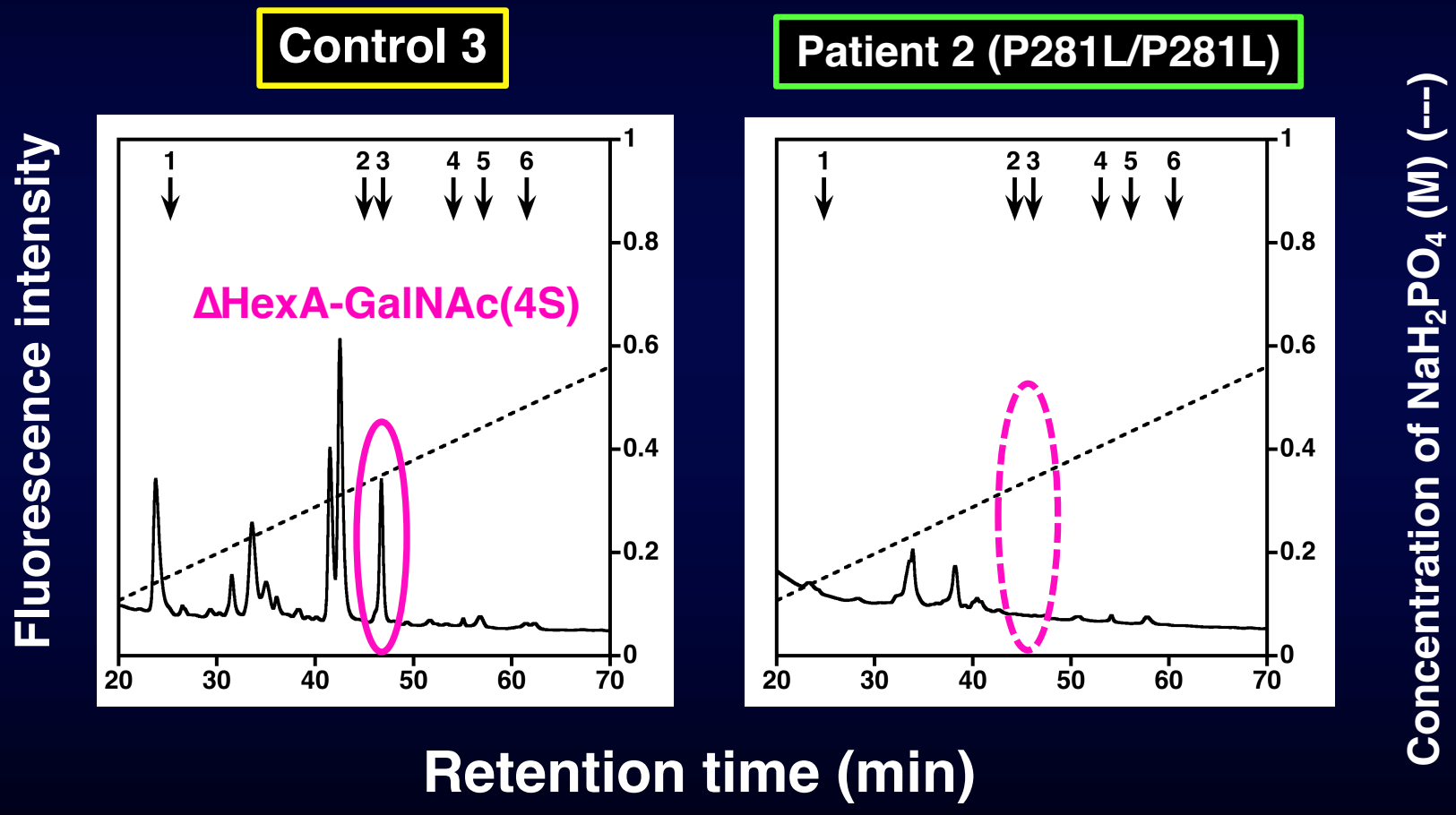
Urines from healthy subjects (15 samples)

M：6m, 10, 11, 30, 31y

F：3, 10, 12, 18, 21, 29, 39, 43y

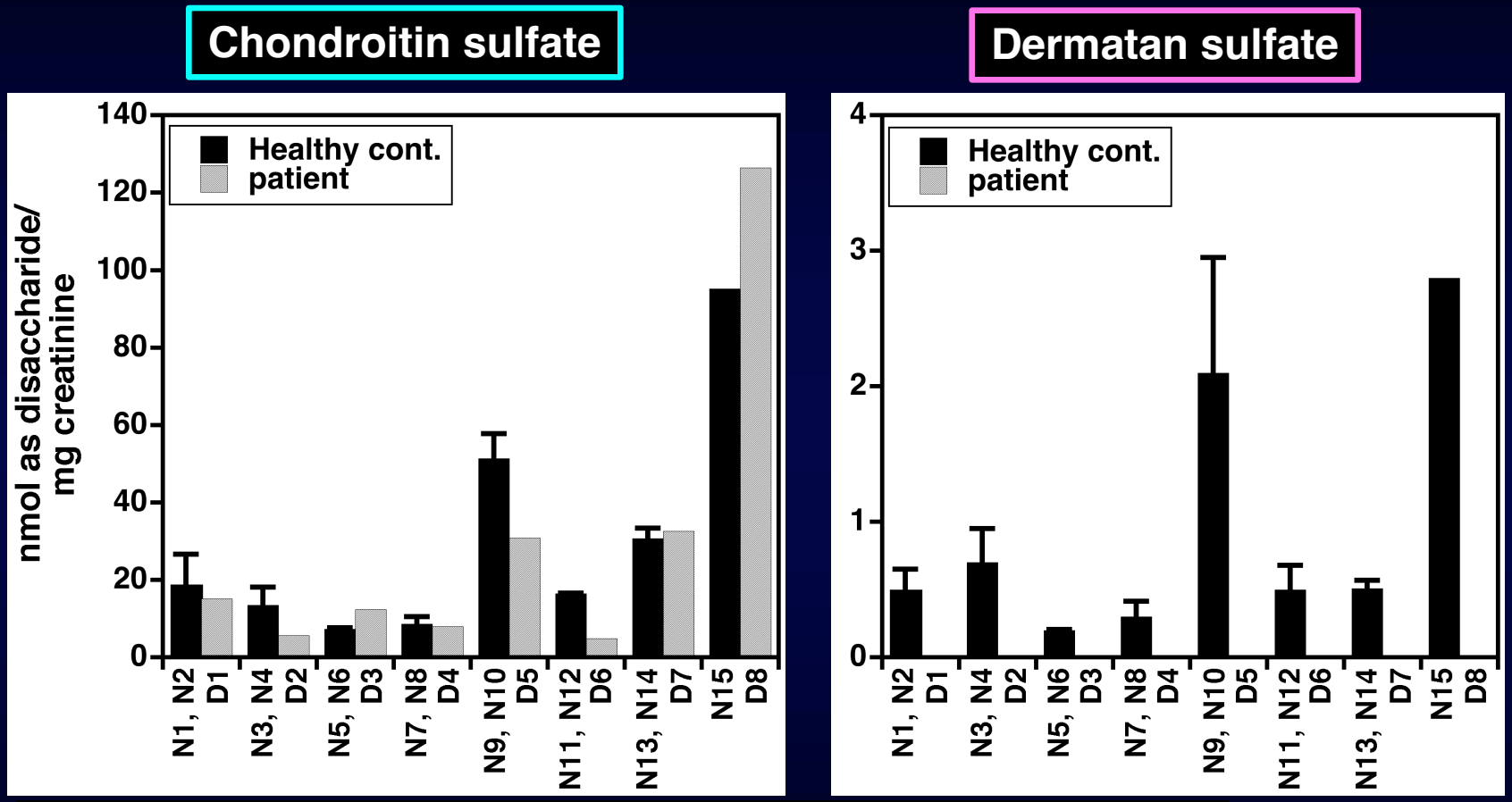
Mizumoto *et al*., Clinical Biochemistry, 50, 670, 2017.

Analysis of DS in urine from a patient and a healthy subject



Mizumoto *et al*., Clinical Biochemistry, 50, 670, 2017.

Total disaccharides of urinary CS and DS from the EDS patients with mutation in *D4ST1*



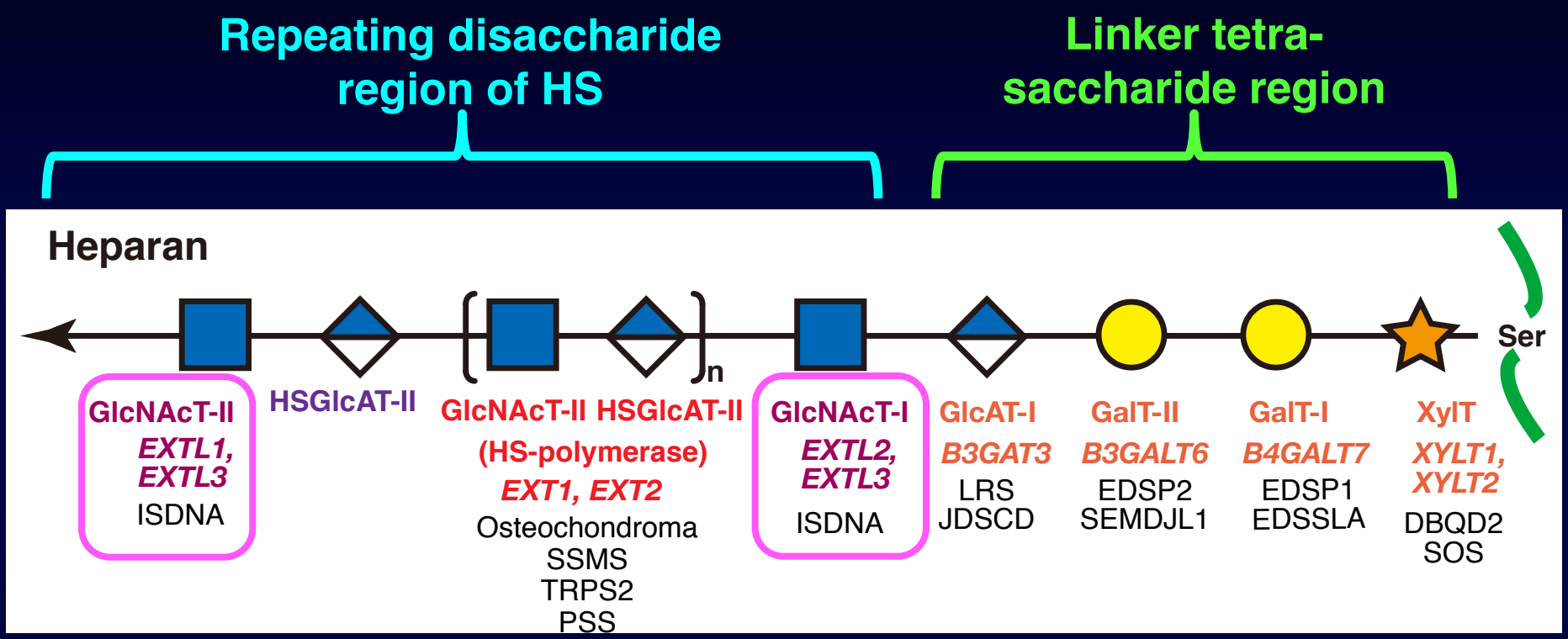
This result proposes the usefulness of a urinary disaccharide compositional analysis of CS/DS chains as a non-invasive screening method for this disorder.

Mizumoto *et al*., Clinical Biochemistry, 50, 670, 2017.

① Ehlers-Danlos syndrome caused by mutations in D4ST-1

② A novel type of spondylo-epi-metaphyseal dysplasia caused by mutations in EXTL3

Biosynthesis of HS backbone



Human tumor suppressor *EXT* gene family members *EXTL1* and *EXTL3* encode α1,4-*N*-acetylglucosaminyltransferases that likely are involved in heparan sulfate/heparin biosynthesis

Byung-Taek Kim, Hiroshi Kitagawa, Jun-ichi Tamura, Toshiyuki Saito, Marion Kusche-Gullberg, Ulf Lindahl, and Kazuyuki Sugahara

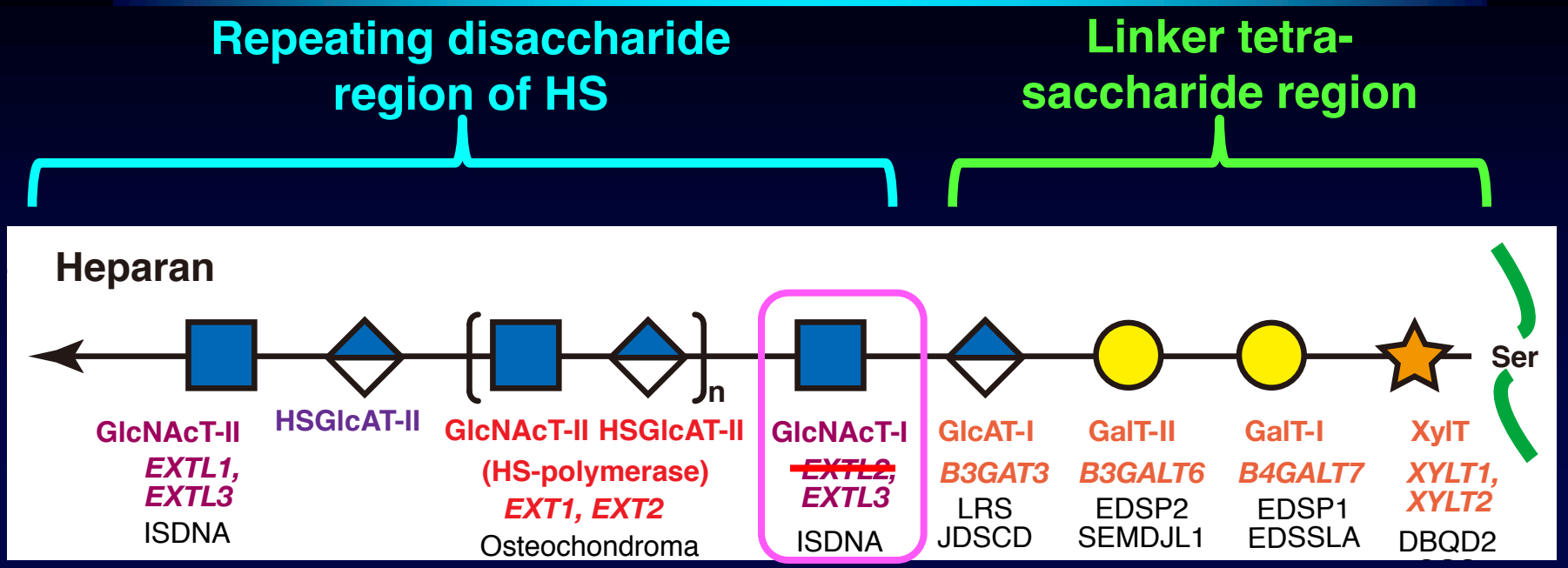
7176–7181 PNAS June 19, 2001 vol. 98 no. 13

Systemic *Extl3*-knockout mice are embryonic lethal

	Extl3$^{+/+}$	*Extl3*$^{+/-}$	*Extl3*$^{-/-}$	Total
E6.5	3 (19 %)	8 (50 %)	5 (31 %)	16
E7.5	4 (33 %)	4 (33 %)	4 (33 %)	12
E8.5	6 (22 %)	16 (59 %)	5 (19 %)	27
E9.5	12 (26 %)	33 (69 %)	1 (2 %)	46
E10.5	10 (31 %)	22 (69 %)	0	32
5-9 weeks (male)	21 (31 %)	47 (69 %)	0	68
5-9 weeks (female)	14 (31 %)	31 (69 %)	0	45

Takahashi, Yamada, Mizumoto *et al.* Biochem. Biophys. Res. Commun., 2009

Biosynthesis of HS backbone



EXTL3 seems to be responsible for initiating the chain elongation of HS polysaccharides.

Congenital diseases caused by mutations in the human EXTL3 gene

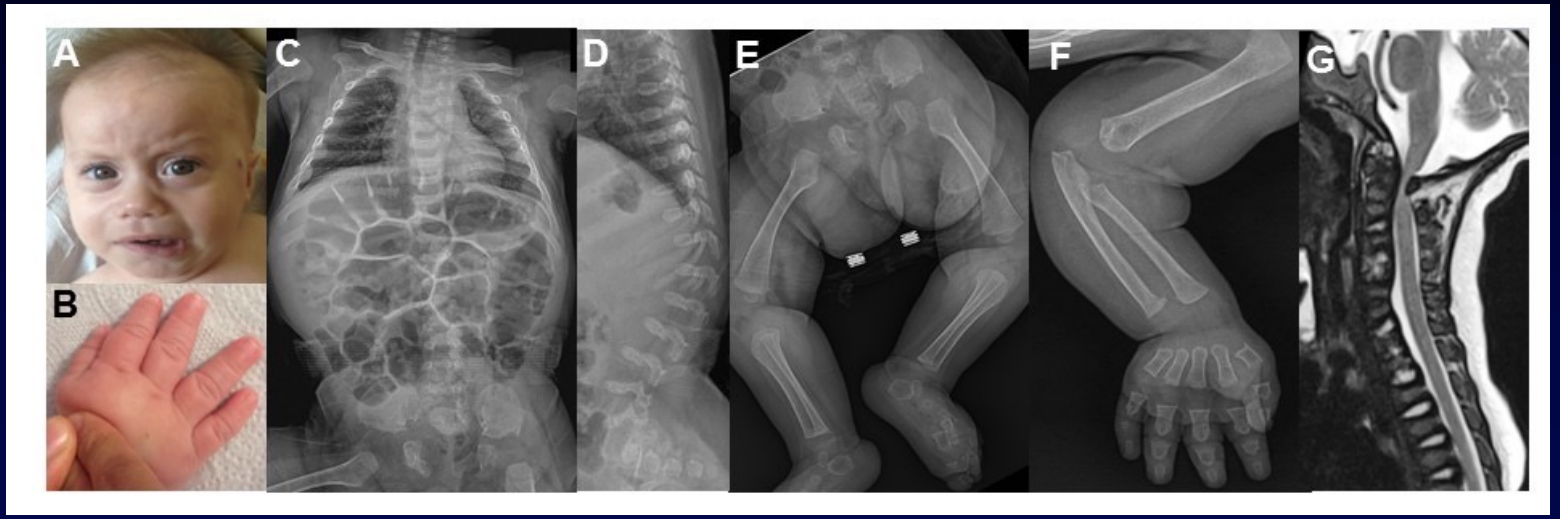
Guo *et al*., J Hum Genet, 2017
Oud *et al*., Am J Hum Genet, 2017
Volpi *et al*., J Exp Med, 2017

Affected individuals presented with

1) **various skeletal abnormalities,**
2) **neurodevelopmental defects, and**
3) **T-cell immunodeficiencies.**

Spondyloepimetaphyseal dysplasia (SEMD) with immunodeficiency/ Neuro-immuno-skeletal dysplasia syndrome caused by mutation in *EXTL3*

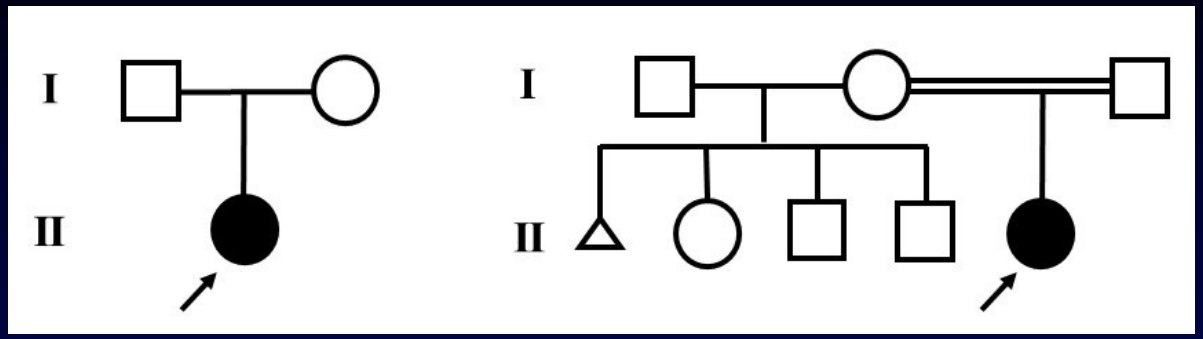
Patient 1
(5 months)

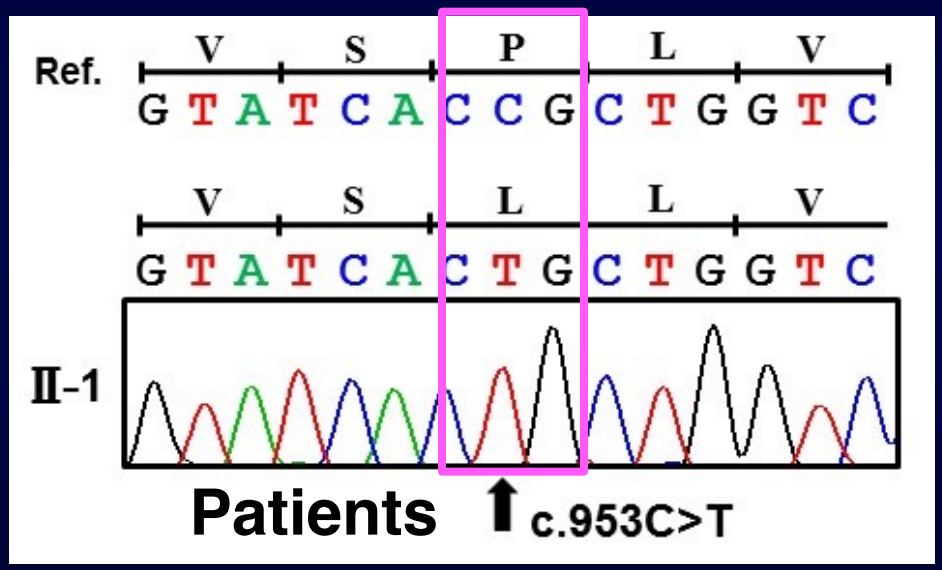


- Clinical pictures (A, B): frontal bossing, prominent eye, depressed nasal bridge, micrognathia and severe brachydactyly
- Radiographs (G-G): broad thorax, severe platyspondyly with kyphosis, broad ilia, broad ischia and pubes, broad metaphyses of the long tubular bones

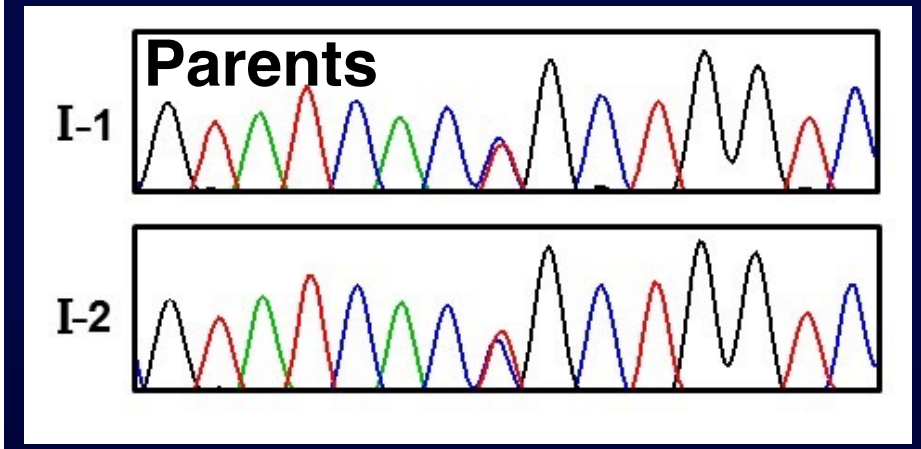
Guo, Mizumoto, Yamada *et al*. Journal of Human Genetics, 62, 797, 2017.

EXTL3 mutation



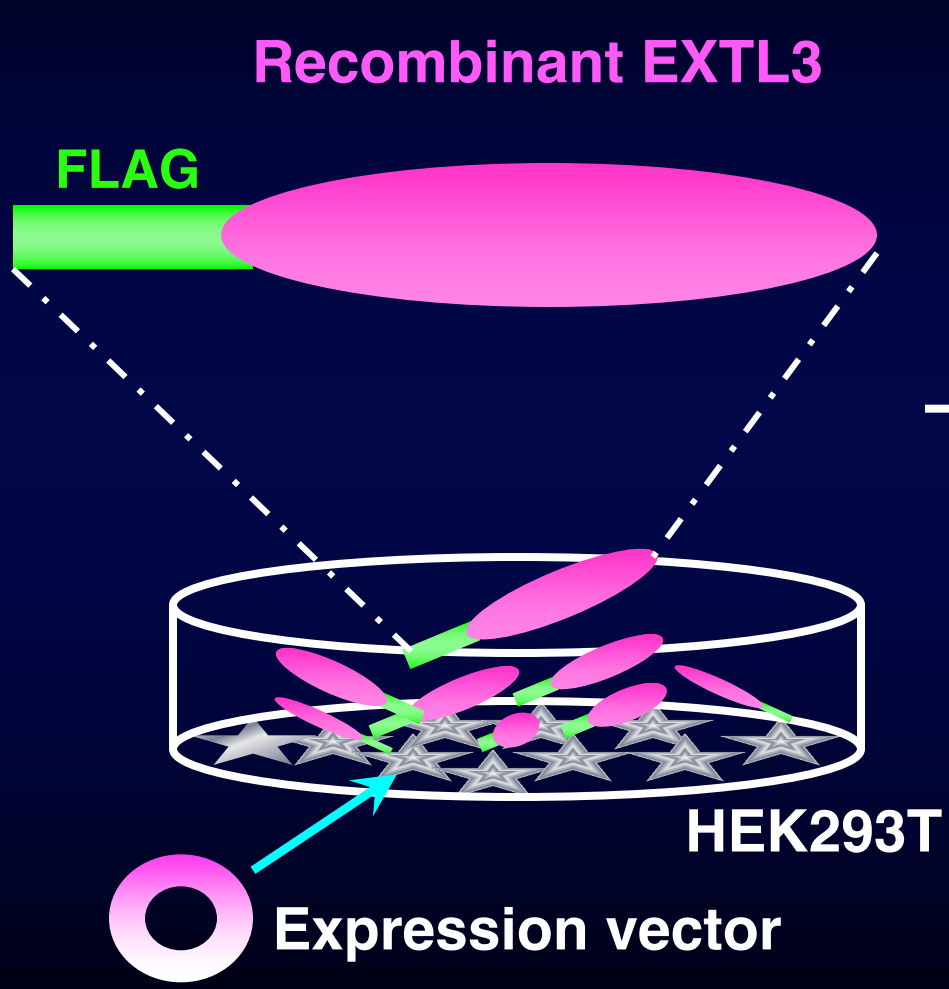


EXTL3



P318L

Expression of recombinant EXTL3 (Wild-type, P318L) and measurement of the enzyme activity



Purified EXTL3	10 μL
UDP-[^{3}H]GlcNAc	8.3 μM
Heparan sulfate	10 μg
MES-NaOH (pH 6.5)	50 mM
ATP	0.17 mM
$MnCl_2$	10 mM
Total	30 μL

37 ˚C for 2h

↓

Gel filtration

↓

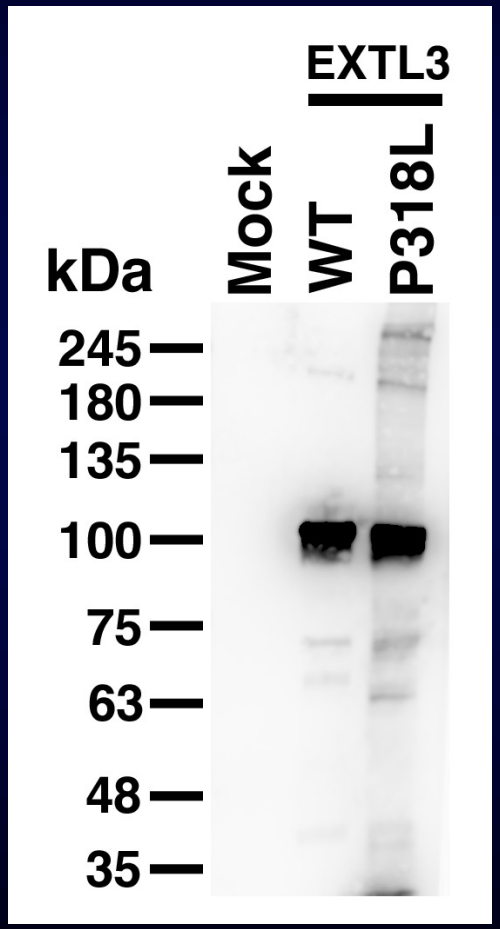
[^{3}H]GlcNAc-HS polymer

↓

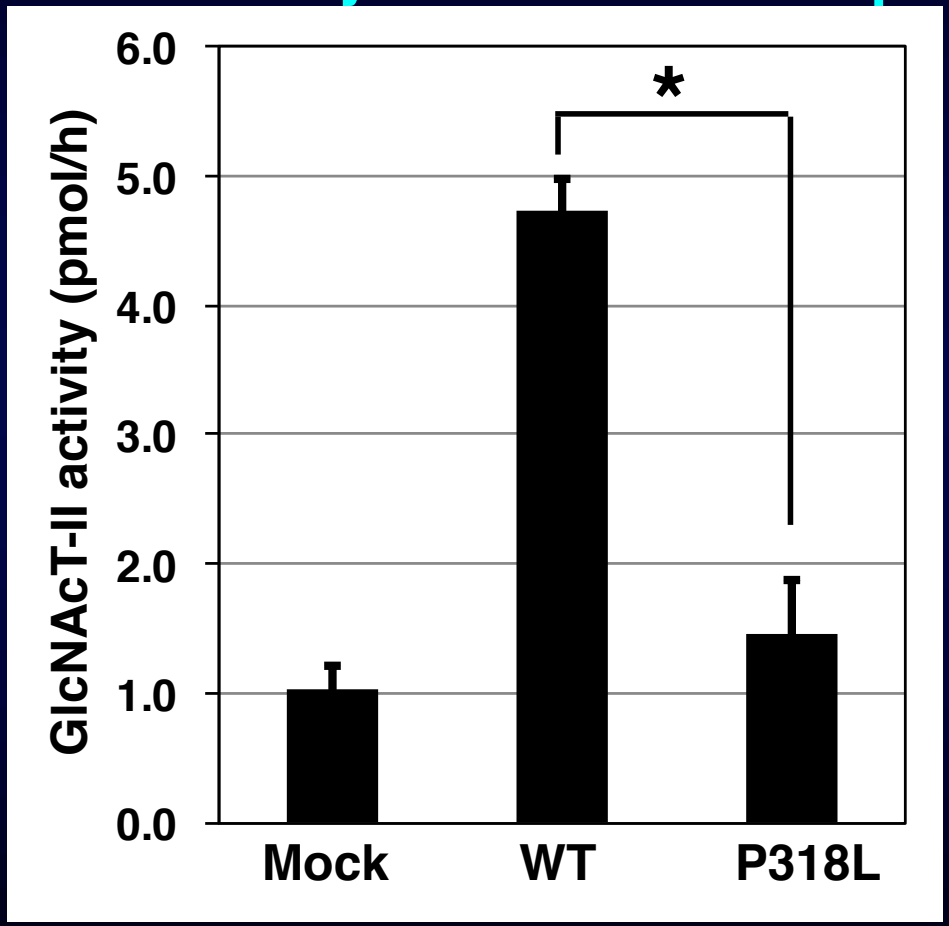
Liquid Scintillation Counting

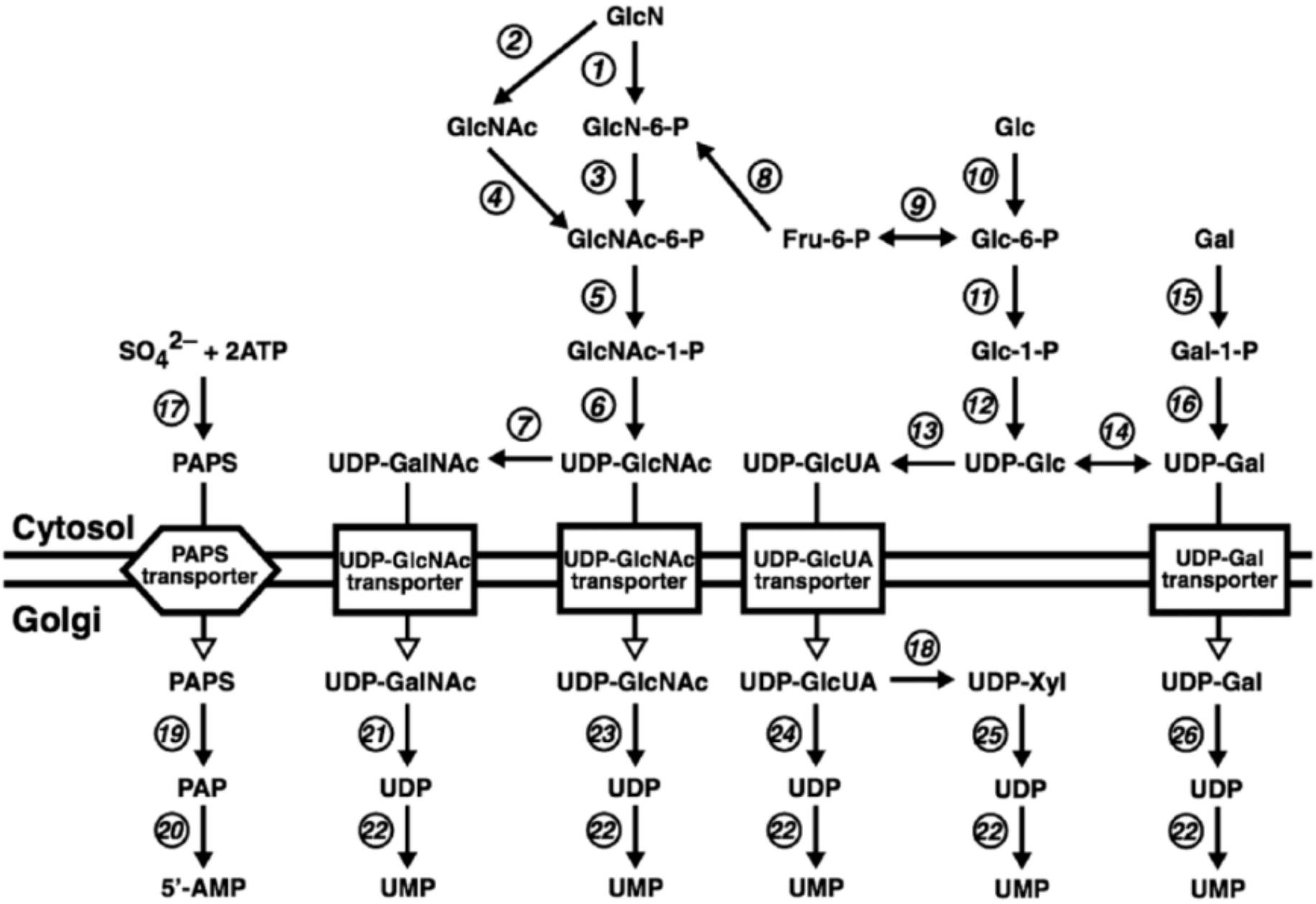
GlcNAc-transferase activity of recombinant EXTL3 (Wild-type, P318L)

Western blotting



GlcNAc-T activity of recombinant proteins




GlcN
GlcNAc
GlcN-6-P
Glc
GlcNAc-6-P
Fru-6-P
Glc-6-P
Gal
SO_4^{2-} + 2ATP
GlcNAc-1-P
Glc-1-P
Gal-1-P
PAPS
UDP-GalNAc
UDP-GlcNAc
UDP-GlcUA
UDP-Glc
UDP-Gal
Cytosol
Golgi
PAPS transporter
UDP-GlcNAc transporter
UDP-GlcNAc transporter
UDP-GlcUA transporter
UDP-Gal transporter
PAPS
UDP-GalNAc
UDP-GlcNAc
UDP-GlcUA
UDP-Xyl
UDP-Gal
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CONCLUSIONS

- Glycosaminoglycans are involved in various diseases including cancer, spinal cord injury, and infectious diseases.

- Genetic disorders caused by deficiency of catabolism of glycosaminoglycans (mucopolysaccharidoses) have been well investigated.

- Genetic disorders caused by deficiency of anabolism of glycosaminoglycans have recently been found one by one.

- There is an urgent need to develop treatments for such genetic diseases.

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Atsushi HATAMOCHI (Dokkyo Med. Univ.)
Takafumi WATANABE (Rakuno Gakuen Univ.)
Nursel ELCIOGLU (Marmara Univ. Med. Sch., Istanbul, Turkey)

Shiro IKEGAWA (RIKEN)