Supplementary Table S1. Overview of some proteoglycans and their pathophysiological involvements.

Location	Designation	Type of GAG chain	Role
Intracellular	Serglycin (SG)	Heparin/CS	Formation of intracellular storage granules in mast cells [1].
Cell surface	Syndecans	HS/CS	Regulation of vascular development and wound healing [2].
	Glypicans	HS	Regulation of Wnt and FGF signaling pathways during growth, development and cancer [3].
Extracellular matrices	Aggrecan	CS/KS	Provides the mechanical properties of cartilage [4].
	Fibromodulin	KS	Regulation of collagen fibrillogenesis, muscle cell growth, cellular reprogramming, and angiogenesis [5].
	Decorin	DS	Promotes collagen fibrillogenesis [6] and inhibits tyrosine kinase receptors [7].
	Biglycan	CS/DS	Promotes collagen fibrillogenesis [8] and promotes osteoblast differentiation and bone maturation [9].
	Collagen XVIII	HS	Structural component of the basement membranes of vascular and epithelial cells. Inhibits angiogenesis and Wnt signalling [10].

Blood	Endocan	DS	Regulation of cell adhesion, migration, proliferation, and angiogenesis in cancer and wound healing [11].
	Inter-α-trypsin inhibitor family	CS	Stabilization of extracellular matrices, anti-plasmin activity, inhibition of complement activation and protection against kidney stone formation [12].
	PG-100	CS	Inhibition of atherosclerosis formation by trapping of low-density lipoprotein [13]. Growth factor activity triggering differentiation of bone marrow cells [14].
	Apolipoprotein-O	CS	Regulation of fatty acid metabolism and oxidative stress during inflammation [15-16]

Supplementary Table S2. Proteoglycan inherited metabolic diseases: Classification and clinical aspects.

PG defect subgroup	**Mutated gene**	**Associated disorder and clinical features**
Defects of the tetrasaccharide linkage region (Linkeropathies)	*XYLT1* Initiating xylose transfer to the core protein (Xylβ1-*O*-Ser).	**- Desbuquois dysplasia type 2** (MIM - 615777): Short long bones, joint laxity and dislocations, advanced carpal/tarsal ossification, chondrodysplasia, growth retardation [17].
	XYLT2 Initiating xylose transfer to the core protein (Xylβ1-*O*-Ser).	**- Spondyloocular syndrome** (MIM - 605822): Osteopenia/osteoporosis, cataract, deafness, heart defects [18].
	B4GALT7 Transfer of the first galactose of the	**- Ehlers-Danlos syndrome (EDS) spondylodysplastic type 1** (MIM - 130070):

	linkage (Galβ1–3Galβ1–4Xylβ1-*O*-Ser).	Joint laxity, hyperelastic skin, short stature, hypotonia, poor wound healing [19].
	B3GALT6 Transfer of the second galactose of the linkage region (Galβ1–3Galβ1–4Xylβ1-*O*-Ser).	**- EDS progeroid type 2** (MIM – 615349) and **Spondyloepymetaphyseal dysplasia** (MIM – 271640): Recurrent bone fractures, epimetaphyseal dysplasia, joint laxity and dislocations, cutaneous hyperlaxity, scoliosis, intellectual disabilities, poor wound healing, hypotonia [20].
	B3GAT3 Transfer of the terminating glucuronic acid of the linkage region (GlcAβ1–3Galβ1–3Galβ1–4Xylβ1-*O*-Ser).	**Larsen-like syndrome** (MIM – 245600): Joint laxity and dislocations, scoliosis, cutis laxa, heart defects [21].
	FAM20B Phosphorylation of the xylose after the first galactose addition (Gal-Xyl(2-*O*-phosphate)-*O*-Ser).	**- Desbuquois dysplasia** (MIM - 615777) with lethal neonatal short limb dysplasia [22].
GAG elongation defects	*CSGALNACT1* First GalNAc transfer to the linkage region: initiation of CS elongation.	**Mild skeletal dysplasia with advanced bone age** (unreferenced): Skeletal dysplasia, short stature, advanced bone age, facial dysmorphism, joint laxity, monkey wrench appearance of the femur, Bell's plasy, neuropathies [23].
	CHSY1 [GlcA-GalNAc] polymerization: CS GAG elongation	**- Temtamy preaxial brachydactyly syndrome** (MIM - 605282): Characteristic digits shortening, facial dysmorphism, deafness, growth and mental retardation [24].
	EXTL3 First GlcNAc transfer to the linkage region: Initiation of HS elongation.	**- Neuro-immuno-skeletal dysplasia syndrome** (MIM - 617425): Severe immunodeficiency associated to skeletal dysplasia, developmental delay and intellectual disability [25].

	EXT1/EXT2 [GlcA-GlcNAc] polymerization: HS GAG elongation	**- Hereditary multiple exostosis syndrome** (MIM - 133700/133701): Benign osteoarticular tumors called exostosis or osteochondromas leading to skeletal dysmorphisms [26-27].
	DSE GlcA epimerization to IdoA: CS conversion to DS	**- EDS musculocontractural type 2** (MIM - 615539): Characteristic craniofacial deformities (large fontanel, hypertelorism, blue sclerae…), skin hyperextensibility, muscle hypoplasia and hypotonia, bruising [28].
GAG sulfation defects	*SLC26A2* Cell-surface inorganic sulfate transporter	**- Achondrogenesis type 1B** (MIM - 600972): Micromelia, flat face, short trunk, fetal/perinatal lethality. [29] **- Atelosteogenesis type 2** (MIM - 256050): Limb shortening, cleft palate, characteristic facial dysmorphisms, 'hitchhiker' thumbs, possible fetal/perinatal lethality.
		- Achondrogenesis type 1B (MIM - 600972): Micromelia, flat face, short trunk, fetal/perinatal lethality. **- Atelosteogenesis type 2** (MIM - 256050): Limb shortening, cleft palate, characteristic facial dysmorphisms, 'hitchhiker' thumbs, possible fetal/perinatal lethality. **- Diastrophic dysplasia** (MIM - 222600): Short and thick long bones, joint dysplasia, scoliosis, 'hitchhiker' thumbs, club feet, cleft palate, cysts on the external ear. **- Recessive multiple epiphyseal dysplasia type 4** (MIM - 226900): Flat epiphyses, hips arthritis, double layered-patella, clubfoot, brachydactyly, joint pain.

CHST3 Sulfation of GalNAc residues in the CS chains	**- Spondyloepiphyseal dysplasia with joint laxity (SEDJL) CHST3 type** (MIM - 143095): Kyphosis/scoliosis, Club feet, knees and hips dislocations, short stature [30].
CHST6 Sulfation of GlcNAc residues in KS chains	**- Macular corneal dystrophy** (MIM - 217800): Corneal opacity and thinning, photophobia, tearing, progressive vision loss [31].
CHST12, CHST13** Sulfation of GalNAc residues on the CS chain *UST** Sulfation of GlcA/IdoA residue in CS/DS chains	**- Kashin-Beck disease*** Joint pain, deformities and limited joint mobility in fingers, shoulders, ankles, knees, wrists, toes. Bone damage and short stature [32]. **Unestablished causality*
CHST14 (D4ST1) Sulfation of GalNAc residues on the DS chains	**- EDS musculocontractural type 1** (MIM - 601776): Muscle hypotonia, facial dysmorphisms, joint dislocation, skin hyperlaxity, club feet, bruising [33-34] .
PAPSS2 Synthesis of sulfate donors (PAPS)	**- Spondyloepimetaphyseal dysplasia Pakistani type** (MIM - 612847): Short stature, scoliosis, osteoarthritis, mild brachydactyly [35]. **- Brachyolmia** (MIM - 271530): Short stature, short trunk, platyspondyly, vertebral deformities,, calcification of costal cartilage, and hormonal disturbances [36-37].

	IMPAD1 (inositol monophosphatase domain-containig 1) Hydrolysis of PAP released from sulfation reactions	**- Chondrodysplasia with joint dislocations, gPAPP type** (MIM - 614078): Short stature, chondrodysplasia with brachydactyly, joint dislocations, micrognathia, cleft palate and facial dysmorphism [38]. **- Catel-Manzke syndrome** (MIM - 616145): Growth retardation, cleft palate with micrognathia, isolated knee hyperlaxity, abnormally shaped phalanges and carpal synostosis [39].
Defects in UDP-sugar synthesis and transport	*SLC35D1* Transport of UDP-GlcA, UDP-GalNAc, UDP-GlcNAc, UDP-Gal, and UDP-Xyl in the ER.	**- Schneckenbecken dysplasia** (MIM - 269250): Lethal chondrodysplasia, snail-like pelvis, flattened hypoplastic vertebral bodies, short ribs, short and wide fibulae, short and broad long bones with a dumbbell-like appearance, and precocious ossification of the tarsus [40].
	SLC35A3 UDP-GlcNAc transport in the Golgi appararus	**- SLC35A3-CDG - Autism spectrum disorder-epilepsy-arthrogryposis syndrome** (MIM - 615553): Arthrogryposis, retromicrognathia, hypotonia, delayed psychomotor development, autism, seizures, microcephaly, and intellectual disability [41].
	SLC35A2 UDP-Gal transport in the Golgi apparatus	**- SLC35A2-CDG** (MIM - 3000896): Epilepsy, delayed psychomotor development, hypotonia, skeletal abnormalities, facial dysmorphism, inverted nipples, vision and hearing abnormalities, cardiac diseases [42].

	CANT1 (Calcium activated nucleotidase) ER/Golgi protein involved in the hydrolysis of the UDP released after the glycosylation reactions	**- Desbuquois dysplasia type 1** (MIM - 613165): Severe growth retardation, joint laxity, short extremities, scoliosis, short long bones with metaphyseal splay, 'Swedish key' appearance of the proximal femur and advanced carpal and tarsal ossification [43].
	TGDS Unknown function (possible involvement in UDP-sugar biosynthesis)	**- Catel-Manzke syndrome** (MIM:616145): Pierre robin sequence (cleft palate, glossoptosis, micrognatia, breathing difficulties), hyperphalangy, joint hypermobility, short long bones [44].
	UGDH Synthesis of UDP-GlcA from UDP-glucose	**- Epileptic encephalopathy with developmental delay (MIM – 603370/618792)** Severe developmental delay, epileptic encephalopathy, facial dysmorphisms [45].
Defects linked to impaired Golgi homeostasis	*TMEM165* Golgi localized Ca^{2+} - Mn^{2+} / H^{+} antiporter	**- TMEM165-CDG** (MIM:614727): Psychomotor and growth retardation, facial dysmorphism, skeletal dysplasia with osteoporosis, scoliosis [46].
	COG4 (Conserved oligomeric Golgi - subunit 4) Tethering complex involved in the retrograde trafficking from the Golgi apparatus to the ER	**- Saul Wilson syndrome** (MIM:606976): Short stature, characteristic craniofacial dysmorphisms, prominent forehead, cataract, microencephaly, clubfoot, brachydactyly, irregularities of the vertebral bodies [47].

SLC10A7 Ca^{2+} influx regulation across intracellular membranes	**- Skeletal dysplasia and amelogenesis imperfecta** (unreferenced): Short stature, microretrognathia, dislocations, monkey wrench appearance of the femora, short long bones, advanced carpal and tarsal ossification, severe tooth abnormalities [48].
GORAB (Golgin Rab6-interacting protein) Trans-Golgi protein involved in retrograde trafficking	**- Gerodermia osteodysplastica** (MIM:231070): Lax and wrinkled skin, osteoporosis with spontaneous fractures, short stature, joint dislocations, and intellectual disabilities [49].
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