Diseases associated with glycosaminoglycan metabolism

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28/02/2022
**Introduction**

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

**Literature references**


Reactome database release: 79

This document contains 16 pathways (see Table of Contents)
Diseases associated with glycosaminoglycan metabolism

Stable identifier: R-HSA-3560782

Diseases: congenital disorder of glycosylation

A number of genetic disorders are caused by mutations in the genes encoding glycosyltransferases and sulfotransferases, enzymes responsible for the synthesis of glycosaminoglycans (GAGs) as well as hexosaminidase degradation of GAGs (Mizumoto et al. 2013).

Literature references


Editions

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Defective SLC26A2 causes chondrodysplasias

**Location:** Diseases associated with glycosaminoglycan metabolism

**Stable identifier:** R-HSA-3560792

**Diseases:** achondrogenesis type IB, diastrophic dysplasia, atelosteogenesis

The SLC26A1 and 2 genes encode sulfate transporter proteins that facilitate sulfate uptake into cells, critical in cartilage for sulfation of proteoglycans and extracellular matrix organization. Defects in SLC26A2 result in impaired SO4(2-) transport leading to insufficient sulfation of cartilage proteoglycans. Defective SLC26A2 is implicated in the pathogenesis of a spectrum of autosomal recessive human chondrodysplasias. Severity of symptoms range from mild (diastrophic dysplasia; MIM:222600), intermediate (atelosteogenesis type II; MIM256050) to severe (achondrogenesis type 1B; MIM:600972) (Superti-Furga et al. 1996, Dwyer et al. 2010, Dawson & Markovich 2005).

**Literature references**


**Editions**

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Defective PAPSS2 causes SEMD-PA

Location: Diseases associated with glycosaminoglycan metabolism

Stable identifier: R-HSA-3560796

Diseases: spondyloepimeta physeal dysplasia


Literature references


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Defective B4GALT7 causes EDS, progeroid type

**Location:** Diseases associated with glycosaminoglycan metabolism

**Stable identifier:** R-HSA-3560783

**Diseases:** Ehlers-Danlos syndrome

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Ehlers-Danlos syndrome (EDS) is a group of inherited connective tissue disorders, caused by a defect in the synthesis of collagen types I or III. Abnormal collagen renders connective tissues more elastic. The severity of the mutation can vary from mild to life-threatening. There is no cure and treatment is supportive, including close monitoring of the digestive, excretory and particularly the cardiovascular systems. Defective B4GALT7, a galactosyltransferase important in proteoglycan synthesis, causes the progeroid variant of EDS (MIM:130070). Features include an aged appearance, developmental delay, short stature, generalized osteopenia, defective wound healing, hypermobile joints, hypotonic muscles, and loose but elastic skin (Okajima et al. 1999).

**Literature references**


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Defective B3GAT3 causes JDSSDHD

Location: Diseases associated with glycosaminoglycan metabolism

Stable identifier: R-HSA-3560801

Diseases: Larsen syndrome, congenital heart defect

Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferases1, 2 and 3 (B3GAT1-3) are involved in forming the linker tetrasaccharide present in heparan sulfate and chondroitin sulfate. Defects in B3GAT3 cause multiple joint dislocations, short stature, craniofacial dysmorphism, and congenital heart defects (JDSSDHD; MIM:245600). This is an autosomal recessive disease characterized by dysmorphic facies, elbow, hip and knee dislocations, clubfeet, short stature and cardiovascular defects (Steel & Kohl 1972, Bonaventure et al. 1992, Baasanjav et al. 2011). JDSSDHD has phenotypic similarities to Larsen syndrome (Larsen et al. 1950).

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Jassal, B.
Spillmann, D.
Defective CHSY1 causes TPBS

Location: Diseases associated with glycosaminoglycan metabolism

Stable identifier: R-HSA-3595177

Diseases: brachydactyly

Chondroitin sulfate synthases (CHSY) are involved in the synthesis of chondroitin sulfate, adding alternating glucuronate (GlcA) and N-acetylgalactosamine (GalNAc) to the growing chondroitin polymer (Mizumoto et al. 2013). Defects in CHSY1 cause temtamy preaxial brachydactyly syndrome (TPBS; MIM:605282), a syndrome characterized by multiple congenital anomalies, mental retardation, sensorineural deafness, growth retardation and bilateral symmetric digital anomalies mainly in the form of preaxial brachydactyly (literally, shortness of fingers and toes) and hyperphalangism (Temtamy et al. 1998, Race et al. 2010, Tian et al. 2010).

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Defective CHST3 causes SEDCJD

Location: Diseases associated with glycosaminoglycan metabolism

Stable identifier: R-HSA-3595172

Diseases: spondyloepimeta physeal dysplasia

Carbohydrate sulfotransferase 3 (CHST3) transfers sulfate (SO4(2-)) to position 6 of N-acetylgalactosamine (GalNAc) residues of chondroitin-containing proteins resulting in chondroitin sulfate (CS), the predominant glycosaminoglycan present in cartilage. Defects in CHST3 result in spondyloepiphyseal dysplasia with congenital joint dislocations (SEDCJD; MIM:143095), a bone dysplasia clinically characterized by severe progressive kyphoscoliosis (abnormal curvature of the spine), arthritic changes with joint dislocations and short stature in adulthood (Unger et al. 2010).

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Defective CHST14 causes EDS, musculocontractural type

Location: Diseases associated with glycosaminoglycan metabolism

Stable identifier: R-HSA-3595174

Diseases: Ehlers-Danlos syndrome

Carbohydrate sulfotransferase 14 (CHST14 also known as D4ST-1) mediates the transfer of sulfate to position 4 of further N-acetylgalactosamine (GalNAc) residues of dermatan sulfate (DS). Defects in CHST14 cause Ehlers-Danlos syndrome, musculocontractural type (MIM:601776). The Ehlers-Danlos syndromes (EDS) are a group of connective tissue disorders that share common features such as skin hyperextensibility, articular hypermobility and tissue fragility (Beighton et al. 1998). The musculocontractural form of EDS (MIM:601776) include distinctive characteristics such as craniofacial dysmorphism, congenital contractures of fingers and thumbs, clubfeet, severe kyphoscoliosis and muscular hypotonia (Malfait et al. 2010).

Literature references


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Defective B4GALT1 causes B4GALT1-CDG (CDG-2d)

**Location:** Diseases associated with glycosaminoglycan metabolism

**Stable identifier:** R-HSA-3656244

**Diseases:** congenital disorder of glycosylation type II

Congenital disorders of glycosylation (CDG, previously called carbohydrate-deficient glycoprotein syndromes, CDGSs), are a group of hereditary multisystem disorders. They are characterized biochemically by hypoglycosylation of glycoproteins, diagnosed by isoelectric focusing (IEF) of serum transferrin. There are two types of CDG, types I and II. Type I CDG has defects in the assembly of lipid-linked oligosaccharides or their transfer onto nascent glycoproteins, whereas type II CDG comprises defects of trimming, elongation, and processing of protein-bound glycans. Clinical symptoms are dominated by severe psychomotor and mental retardation, as well as blood coagulation abnormalities (Jaeken 2013). B4GALT1-CDG (CDG type IId) is a multisystem disease, characterized by dysmorphic features, hydrocephalus, hypotonia and blood clotting abnormalities (Hansske et al. 2002).

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Defective CHST6 causes MCDC1

Location: Diseases associated with glycosaminoglycan metabolism

Stable identifier: R-HSA-3656225

Diseases: macular corneal dystrophy

Carbohydrate sulfotransferase 6 (CHST6) catalyzes the transfer of sulfate to position 6 of non-reducing ends of N-acetylglucosamine (GlcNAc) residues on keratan sulfate (KS). KS plays a central role in maintaining corneal transparency. Defective CHST6 (Nakazawa et al. 1984) results in unsulfated keratan deposited within the intracellular space and the extracellular corneal stroma leading to macular dystrophy, corneal type I (MCDC1; MIM:217800). MCDC1 is an early-onset, ocular disease characterized by bilateral, progressive corneal opacification, and reduced corneal sensitivity (Jones & Zimmerman 1961). MCD can be subdivided into 2 types on the basis of immunohistochemical studies and serum analysis for keratan sulfate; MCD type I, in which there is a virtual absence of sulfated KS-specific antibody response in the serum and cornea and MCD type II, in which the normal KS-specific antibody response is present in cornea and serum (Yang et al. 1988).

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Defective EXT1 causes exostoses 1, TRPS2 and CHDS

**Location:** Diseases associated with glycosaminoglycan metabolism

**Stable identifier:** R-HSA-3656253

**Diseases:** hereditary multiple exostoses

Heparan sulfate (HS) is involved in regulating various body functions during development, homeostasis and pathology including blood clotting, angiogenesis and metastasis of cancer cells. Exostosin 1 and 2 (EXT1 and 2) glycosyltransferases are required to form HS. They are able to transfer N-acetylglucosamine (GlcNAc) and glucuronate (GlcA) to HS during its synthesis. The functional form of these enzymes appears to be a complex of the two located on the Golgi membrane. Defects in either EXT1 or EXT2 can cause hereditary multiple exostoses 1 (Petersen 1989) and 2 (McGaughran et al. 1995) respectively (MIM:133700 and MIM:133701), autosomal dominant disorders characterized by multiple projections of bone capped by cartilage resulting in deformed legs, forearms and hands. Trichorhinophalangeal syndrome, type II (TRPS2 aka Langer-Giedion syndrome, LGS) is a disorder that combines the clinical features of trichorhinophalangeal syndrome type I (TRPS1, MIM:190350) and multiple exostoses type I, caused by mutations in the TRPS1 and EXT1 genes, respectively (Langer et al. 1984, Ludecke et al. 1995). Defects in EXT1 may also be responsible for chondrosarcoma (CHDS; MIM:215300) (Schajowicz & Bessone 1967, Hecht et al. 1995).

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Defective EXT2 causes exostoses 2

Location: Diseases associated with glycosaminoglycan metabolism

Stable identifier: R-HSA-3656237

Diseases: hereditary multiple exostoses

Heparan sulfate (HS) is involved in regulating various body functions during development, homeostasis and pathology including blood clotting, angiogenesis and metastasis of cancer cells. Exostosin 1 and 2 (EXT1 and 2) glycosyltransferases are required to form HS. They are able to transfer N-acetylglucosamine (GlcNAc) and glucuronate (GlcA) to HS during its synthesis. The functional form of these enzymes appears to be a complex of the two located on the Golgi membrane. Defects in either EXT1 or EXT2 can cause hereditary multiple exostoses 1 (Petersen 1989) and 2 (McGaughran et al. 1995) respectively (MIM:133700 and MIM:133701), autosomal dominant disorders characterised by multiple projections of bone capped by cartilage resulting in deformed legs, forearms and hands.

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Defective HEXA causes GM2G1

Location: Diseases associated with glycosaminoglycan metabolism

Stable identifier: R-HSA-3656234

Diseases: gangliosidosis GM1

Beta-hexosaminidase (HEX) cleaves the terminal N-acetyl galactosamine (GalNAc) from glycosaminoglycans (GAGs) and any other molecules containing a terminal GalNAc. There are two forms of HEX; HEXA and B. The A form is a trimer of the subunits alpha, beta A and beta B. The B form is a tetramer of 2 beta A and 2 beta B subunits (O’Dowd et al. 1988). Defects in the two subunits cause lysosomal storage diseases marked by the accumulation of GM2 gangliosides in neuronal cells. Defects in the alpha subunits are the cause of GM2-gangliosidosis type 1 (GM2G1) (MIM:272800), also known as Tay-Sachs disease (Okada & O’Brien 1969, Nakano et al. 1988). Classical Tay-Sachs disease is characterised by infant-onset neurodegeneration followed by paralysis, dementia and blindness, Death occurs by the age of 2 or 3 (Okada et al. 1971). The two other forms of Tay-Sachs disease, juvenile- and adult-onset, are less common and severe than the infant-onset form (Suzuki et al. 1970, Johnson et al. 1982).

Literature references


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https://reactome.org
Defective HEXB causes GM2G2

**Location:** Diseases associated with glycosaminoglycan metabolism

**Stable identifier:** R-HSA-3656248

**Diseases:** gangliosidosis GM2

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Beta-hexosaminidase (HEX) cleaves the terminal N-acetyl galactosamine (GalNAc) from glycosaminoglycans (GAGs) and any other molecules containing a terminal GalNAc. There are two forms of HEX; HEXA and B. The A form is a trimer of the subunits alpha, beta A and beta B. The B form is a tetramer of 2 beta A and 2 beta B subunits (O'Dowd et al. 1988). Defects in the two subunits cause lysosomal storage diseases marked by the accumulation of GM2 gangliosides in neuronal cells.

Defects in the beta subunits are the cause of GM2-gangliosidosis type 2 (GM2G2; MIM:268800), also known as Sandhoff disease (Sandhoff et al. 1968, Banerjee et al. 1991). Sandhoff disease is an autosomal recessive lysosomal storage disease clinically indistinguishable from GM2-gangliosidosis type 1, presenting early blindness with cherry-red spots on the macula, progressive motor and mental deterioration and macrocephaly. Death usually occurs by the age of 3 years.

**Literature references**


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Defective ST3GAL3 causes MCT12 and EIEE15

Location: Diseases associated with glycosaminoglycan metabolism

Stable identifier: R-HSA-3656243

Diseases: developmental disorder of mental health

CMP-N-acetylmuraminate-beta-1,4-galactoside alpha-2,3-sialyltransferase (ST3GAL3) mediates the transfer of sialic acid from CMP-sialic acid to galactose-containing glycoproteins and forms the sialyl Lewis α epitope on proteins which are required for attaining and/or maintaining higher cognitive functions. Some defects in ST3GAL3 result in mental retardation, autosomal recessive 12 (MRT12; MIM:611090), a disorder characterised by below average general intellectual function and impaired adaptive behaviour (Najmabadi et al. 2007, Hu et al. 2011). Another defect of ST3GAL3 can cause early infantile epileptic encephalopathy-15 (EIEE15: MIM:615006), resulting in severe mental retardation (Edvardson et al. 2012).

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Defective B3GALT6 causes EDSP2 and SEMDJL1

Location: Diseases associated with glycosaminoglycan metabolism

Stable identifier: R-HSA-4420332

Diseases: Ehlers-Danlos syndrome, spondyloepimetaphyseal dysplasia

The biosynthesis of dermatan sulfate/chondroitin sulfate and heparin/heparan sulfate glycosaminoglycans (GAGs) starts with the formation of a tetrasaccharide linker sequence attached to the core protein. Beta-1,3-galactosyltransferase 6 (B3GALT6) is one of the critical enzymes involved in the formation of this linker sequence. Defects in B3GALT6 causes Ehlers-Danlos syndrome progeroid type 2 (EDSP2; MIM:615349), a severe disorder resulting in a broad spectrum of skeletal, connective tissue and wound healing problems. Defects in B3GALT6 can also cause spondyloepimetaphyseal dysplasia with joint laxity type 1 (SEMDJL1; MIM:271640), characterised by spinal deformity and lax joints, especially of the hands and respiratory compromise resulting in early death (Nakajima et al. 2013, Malfait et al. 2013).

Literature references


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