Mucopolysaccharidoses

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16/12/2019
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.

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Literature references


Reactome database release: 71

This document contains 12 pathways (see Table of Contents)

https://reactome.org
**Mucopolysaccharidoses**

**Stable identifier:** R-HSA-2206281

**Diseases:** mucopolysaccharidosis

The mucopolysaccharidoses (MPS) are a group of rare, inherited lysosomal storage disorders caused by deficiencies of enzymes catalyzing the stepwise degradation of glycosaminoglycans (GAGs, originally called mucopolysaccharides) (Neufeld & Muenzer in Scriver et al. 2001). Catabolism of the GAGs dermatan sulfate, heparan sulfate, heparin, keratan sulfate, chondroitin sulfate or hyaluronan may be blocked at one or more steps, resulting in lysosomal accumulation of GAG fragments of varying size. Over time these collect in the cells, blood and connective tissues ultimately resulting in progressive irreversible cellular damage which affects appearance, physical abilities, organ and system function, vision, and usually mental development (Lehman et al. 2011, Ashworth et al. 2006). Life expectancy is also reduced. There are 11 known enzyme deficiencies that give rise to 7 distinct MPS. These disorders are biochemically characterized by elevated levels of partially or undegraded GAGs in lysosomes, blood, urine and cerebro-spinal fluid (Muenzer 2011, Coutinho et al. 2012). The MPS are part of the lysosomal storage disease family, a group of about 50 genetic disorders caused by deficient lysosomal proteins (Ballabio & Gieselmann 2009).

**Literature references**


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MPS I - Hurler syndrome

**Location:** Mucopolysaccharidoses

**Stable identifier:** R-HSA-2206302

**Diseases:** mucopolysaccharidosis I

Mucopolysaccharidosis type I (MPS I, Hurler syndrome, Hurler's disease, gargoylism, Scheie, Hirler-Scheie syndrome; MIM:607014, 607015 and 607016) is an autosomal recessive genetic disorder where there is a deficiency of alpha-L-iduronidase (IDUA, MIM:252800), a glycosidase that removes non-reducing terminal alpha-L-iduronide residues during the lysosomal degradation of the glycosaminoglycans heparan sulphate and dermatan sulphate (McKusick 1959). In 1992, Scott and colleagues were able to clone and purify the gene that encodes this enzyme, IDUA, demonstrating that it spans approximately 19 kb and contains 14 exons (Scott et al. 1992).

Hurler syndrome is named after a German paediatrician Gertrud Hurler (1919, no reference available). The result is build up of heparan sulfate and dermatan sulfate in the body and increased urinary excretion of these GAGs. Symptoms and signs include hepatosplenomegaly, dwarfism, unique facial features, corneal clouding, retinopathy, progressive mental retardation appears during childhood and early death can occur due to organ damage (Campos & Monaga 2012). MPS I is divided into three subtypes, ranging from severe to mild phenotypes; Mucopolysaccharidosis type IH (MPSIH, Hurler syndrome, MIM:607014), mucopolysaccharidosis type IH/S (MPSIH/S, Hurler-Scheie syndrome, MIM: 607015) and mucopolysaccharidosis type IS (MPSIS, Scheie syndrome, MIM: 607016) respectively (McKusick 1972).

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Mucopolysaccharidosis II (MPS II, Hunter syndrome, MIM:309900) is an X-linked, recessive genetic disorder which therefore primarily affects males. MPS II was first described in 1917, by Major Charles Hunter (Hunter 1917) and is caused by a deficiency (or absence) of iduronate-2-sulfatase (IDS, MIM:300823), which would normally hydrolyse the 2-sulfate groups of the L-iduronate 2-sulfate units of dermatan sulfate, heparan sulfate and heparin. Without IDS, these GAGs accumulate in the body and are excessively excreted in urine. Although the disease was known since the early 1970s, being the first MPS to be defined clinically in humans, it wasn't until the 1990s that IDS was cloned. It is now known to be localized to Xq28 (Wilson et al. 1991) and contain 9 exons (Flomen et al. 1993) spanning approximately 24 kb (Wilson et al. 1993).

Build up can occur in the liver and spleen as well as in the walls and valves of the heart (reduced hepatic and cardiac function, liver/spleen hepatosplenomegaly), airways (leading to obstructive airway disease), all major joints and bones (joint stiffness and skeletal deformities) and in brain (severe mental retardation). The rate of progression and degree of severity of the disorder can be different for each person with MPS II. Severe forms of the disorder can result in death in childhood whereas those with a "milder" form can expect to live to their 20's or 30's. Some patients even survive into their fifth and sixth decades of life (Wraith et al. 2008, Beck 2011).

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MPS IIIA - Sanfilippo syndrome A

**Location:** Mucopolysaccharidoses

**Stable identifier:** R-HSA-2206307

**Diseases:** mucopolysaccharidosis III

Mucopolysaccharidosis III (MPS III, Sanfilippo syndrome) was described in 1963 by a pediatrician named Sylvester Sanfilippo (J. Pediat. 63: 837-838, 1963, no reference). Mucopolysaccharidosis IIIA (MPS IIIA, Sanfilippo syndrome A, MIM:252900) is a rare, autosomal recessive lysosomal storage disease characterised by severe CNS degeneration in early childhood leading to death between 10 and 20 years of age. A deficiency of the enzyme N-sulphoglucosamine sulphohydrolase (SGSH, MIM:605270), which normally hydrolyses the sulfate group from the terminal N-sulphoglucosamine residue of heparan sulfate (HS), leads to the build-up of HS in cells and tissues and its presence in urine (van de Kamp et al. 1981, Yogalingam & Hopwood 2001, de Ruijter et al. 2011). The gene encoding N-sulfoglucosamine sulfohydrolase, SGSH, was cloned in 1995 (Scott et al.1995) and, later, shown to contain 8 exons spanning approximately 11 kb (Karageorgos et al. 1996).

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Mucopolysaccharidosis III (Sanfilippo syndrome) was described in 1963 by a pediatrician named Sylvester Sanfilippo (J. Pediat. 63: 837838, 1963, no reference). MPS IIIB (Mucopolysaccharidosis type IIIB, MPS IIIB, Sanfilippo syndrome type B; MIM:252920) is an autosomal recessive genetic disorder due to loss of function of alpha-N-acetylglucosaminidase (NAGLU; MIM:609701), involved in the hydrolysis of terminal non-reducing N-acetylglucosamine residues in heparan sulfate (HS) The gene encoding NAGLU was cloned in 1996 by Zhao and colleagues. It contains 6 exons and spans 8.3 kb on chromosome 17q21 (Zhao et al. 1996). MPSIIIB is characterized by severe CNS retardation but only mild somatic disease and death usually occurs in the second or third decade of life (Zhao et al. 1996, Yogalingam & Hopwood 2001, de Ruijter et al. 2011). MPS IIIB shows extensive molecular heterogeneity (Schmidtchen et al. 1998).

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Mucopolysaccharidosis III (Sanfilippo syndrome) was described in 1963 by a pediatrician named Sylvester Sanfilippo (J. Pediat. 63: 837838, 1963, no reference). Mucopolysaccharidosis type III (MPS IIIC, Sanfilippo syndrome C; MIM:252930) is an autosomal recessive genetic disorder due to the loss of heparan alpha-glucosaminide N-acetyltransferase (HGSNAT; MIM:610453) that normally acetylates the non-reducing terminal alpha-glucosamine residue of heparan sulfate. The molecular defects underlying MPS IIIC remained unknown for almost three decades due to the low tissue content and instability of HGSNAT. But, during the last decade, the gene was cloned in parallel by two different groups and shown to contain 18 exons and span approximately 62Kb (Fan et al. 2006, Hrebicek et al. 2006). Loss of HGSNAT results in build up of this glycosaminglycan (GAG) in cells and tissues and is characterized by severe central nervous system degeneration but only with mild somatic disease and death occurs typically during the second or third decade of life (Kresse et al. 1978, Klein et al. 1978, Feldhammer et al. 2009, de Ruijter et al. 2011).

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Mucopolysaccharidosis III (Sanfilippo syndrome) was described in 1963 by a pediatrician named Sylvester Sanfilippo (J. Pediat. 63: 837-838, 1963, no reference). Mucopolysaccharidosis type III (MPS IIID, Sanfilippo syndrome D, MIM:252940) is an autosomal recessive genetic disorder due to the loss of N-acetyl-D-glucosamine 6-sulfatase (GNS; MIM:607664), that hydrolyses the 6-sulfate groups of the N-acetyl-D-glucosamine 6-sulfate units of the glycosaminoglycans (GAGs) heparan sulfate and keratan sulfate. GNS is localized to chromosome 12q14 and has 14 exons spanning 46 kb (Robertson et al. 1988, Mok et al. 2003). Loss of enzyme activity leads to lysosomal accumulation and urinary excretion of heparan sulfate and N-acetylglucosamine 6-sulfate residues (Mok et al. 2003). Keratan sulphate does not accumulate in MPS IIID, as beta-linked N-acetyl-D-glucosamine 6-sulphate can be cleaved by beta-hexosaminidase A (Kresse et al. 1980). This disorder is characterized by progressive mental deterioration but only moderate physical abnormalities and death during the second or third decade of life, presenting a phenotype similar to MPSIIIA (Jones et al. 1997, de Ruijter et al. 2011).

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MPS IV - Morquio syndrome A

**Location:** Mucopolysaccharidoses

**Stable identifier:** R-HSA-2206290

**Diseases:** mucopolysaccharidosis IV

Mucopolysaccharidosis IV A (MPS IVA, MPS4A, Morquio's syndrome, Morquio's; MIM:253000) is a rare, autosomal recessive mucopolysaccharide storage disease, first described simultaneously in 1929 by L Morquio (Morquio L, Sur une forme de distrophie familiale, Bull Soc Pediat, Paris, 27, 1929, 145-152) and JF Brailsford (Brailsford, JF, Chondro-osteo-dystrophy: roentgenographic and clinical features of child with dislocation of vertebrae, Am j Surg, 7, 1929, 404-410). MPSIVA is caused by a deficiency in N-acetylgalactosamine 6-sulfatase (GALNS; MIM:612222) which normally hydrolyses 6-sulfate groups of N-acetylgalactosamine 6-sulfate units of chondroitin sulfate (CS) and of galactose 6-sulfate units of keratan sulfate (KS) (Matalon et al. 1974). The result is accumulation of KS/DS in cells and overexcretion in urine. Severe osteochondrodysplasia is a commonly seen phenotype for this disease. The severity of the disease is variable but severe cases limits lifespan to their 20's or 30's (Prat et al. 2008, Tomatsu et al. 2011). The gene coding for human GALNS was mapped to chromosome 16q24.3 (Masuno et al. 1993) and its structure described at the same time by two independent groups as comprising 14 exons and spanning approximately 40-50 kb (Nakashima et al.1994, Morris et al.1994).

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MPS IV - Morquio syndrome B

Location: Mucopolysaccharidoses

Stable identifier: R-HSA-2206308

Diseases: mucopolysaccharidosis

Defects in beta-galactosidase (GLB1; MIM:611458) can result in GM1 gangliosidosis (GM1; MIM:230500) (Nishimoto et al. 1991) (not described here), with several phenotypes indicating mental deterioration, as well as in mucopolysaccharidosis IVB, a characteristic mucopolysaccharidosis with no neurological symptoms (Callahan 1999).

Mucopolysaccharidosis IVB (MPS IVB, Morquio’s syndrome B; MIM:253010) is a rare, autosomal recessive mucopolysaccharide storage disease characterized by intracellular accumulation of keratan sulfate (KS), skeletal dysplasia and corneal clouding. There is no central nervous system involvement, intelligence is normal and there is increased KS excretion in urine (Suzuki et al. "Beta-galactosidase deficiency (beta-galactosidosis): GM1 gangliosidosis and Morquio B disease", p3775-3809 in Stryer et al. 2001). MPSIVB is caused by a defect in betagalactosidase (GLB1), which normally cleaves terminal galactosyl residues from glycosaminoglycans, gangliosides and glycoproteins. The GLB1 gene spans 62.5 kb and contains 16 exons (Oshima et al.1988, Santamaria et al. 2007) and maps to chromosome 3p21.33 (Takano & Yamanouchi 1993).

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MPS VI - Maroteaux-Lamy syndrome

Location: Mucopolysaccharidoses

Stable identifier: R-HSA-2206285

Diseases: mucopolysaccharidosis VI

Mucopolysaccharidosis type VI (MPS VI, Maroteaux-Lamy syndrome, polydystrophic dwarfism; MIM:253200) is an autosomal recessive lysosomal storage disorder caused by a deficiency in arylsulfatase B (ARSB, N-acetyl-galactosamine 4-sulfatase; MIM:611542). It is named after two French physicians, Pierre Maroteaux and Maurice Emil Joseph Lamy. Maroteaux first described this disorder as a novel dysostosis associated with increased urinary excretion of chondroitin sulfates (CS; Maroteaux et al. 1963). The gene encoding ARSB is mapped to chromosome 5q11-q13 (Fidzianska et al. 1984) and contains 8 exons spanning about 206 kb (Karageorgos et al. 2007). Defective ARSB results in build up of dermatan sulfate (DS) and chondroitin sulfate (CS) in soft tissues causing compression and blockages in blood vessels, nerves, trachea, corneal clouding and disrupting normal bone development. Symptoms are similar to MPS I but with normal intelligence generally (Rapini et al. 2007, Valayannopoulos et al. 2010).

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MPS VII - Sly syndrome

Location: Mucopolysaccharidoses

Stable identifier: R-HSA-2206292

Diseases: mucopolysaccharidosis VII

Mucopolysaccharidosis type VII (MPS VII, Sly syndrome, beta-glucuronidase deficiency; MIM:253220) is an autosomal recessive lysosomal storage disease characterized by a deficiency of the enzyme beta-glucuronidase (GUSB; MIM:611499) which would normally cleave glucuronide residues from dematan sulphate, keratan sulphate and chondroitin sulphate, resulting in build up of these GAGs in cells and tissues (Sly et al. 1973). The gene encoding GUSB is 21 kb long, contains 12 exons and gives rise to two different types of cDNAs, through an alternate splicing mechanism (Miller et al. 1990). It maps to 7q11.21-q11.22 (Speleman et al. 1996). The phenotype is highly variable, ranging from severe causing death, non-immune hydrops fetalis (Vervoort et al. 1996) to mild forms with survival into adulthood (Storch et al. 2003). Most patients with the intermediate phenotype show hepatomegaly, skeletal anomalies, coarse facies, and variable degrees of mental impairment (Shipley et al. 1993, Tomatsu et al. 2009).

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MPS IX - Natowicz syndrome

Location: Mucopolysaccharidoses

Stable identifier: R-HSA-2206280

Diseases: mucopolysaccharidosis

Mucopolysaccharidosis type IX (MPS IX, Natowicz syndrome, Hyaluronidase deficiency, MIM:601492) is a rare lysosomal storage disease characterized by high hyaluronan (HA) concentration in the serum resulting from deficiency in hyaluronidase 1 (HYAL1, MIM:607071) which normally hydrolyses 1-4 linkages between N-acetylglucosamine (GlcNAc) and D-glucuronate (GlcA) residues. Symptoms of MPS IX are periodically painful soft tissue masses around the joints, acquired short stature and erosion of the hip joint, although joint movement and intelligence are normal (Natowicz et al. 1996, Triggs-Raine et al. 1999).

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