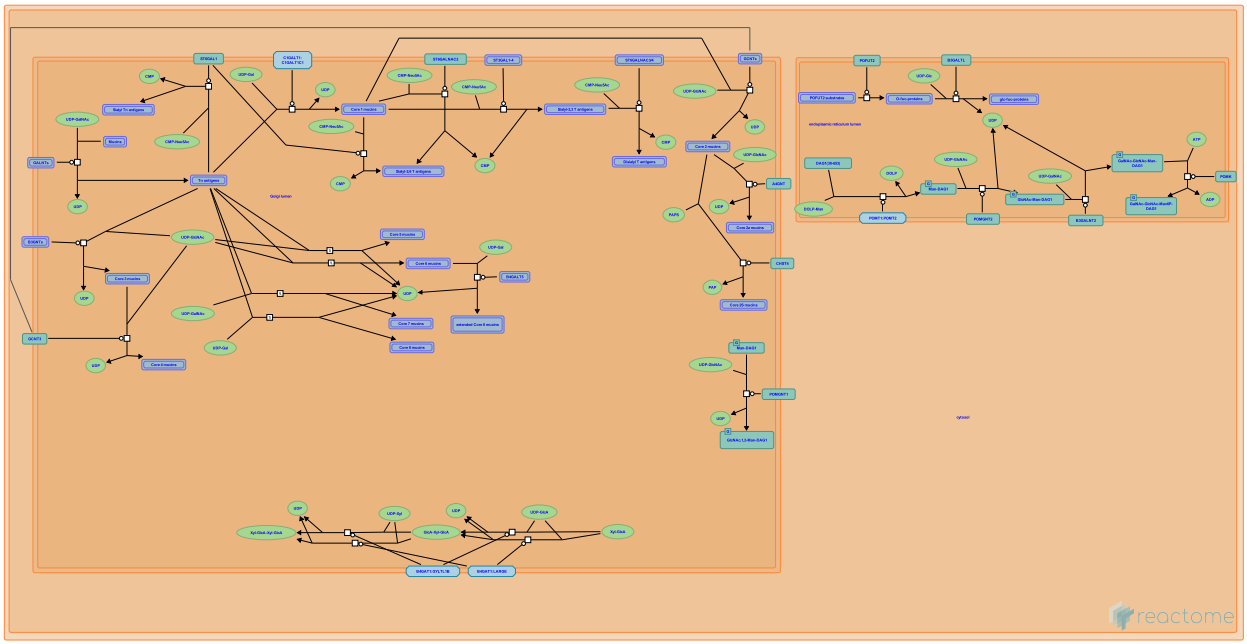
O-linked glycosylation



D'Eustachio, P., Ferrer, A., Hansen, L., Jassal, B., Joshi, HJ.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

22/10/2020

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

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

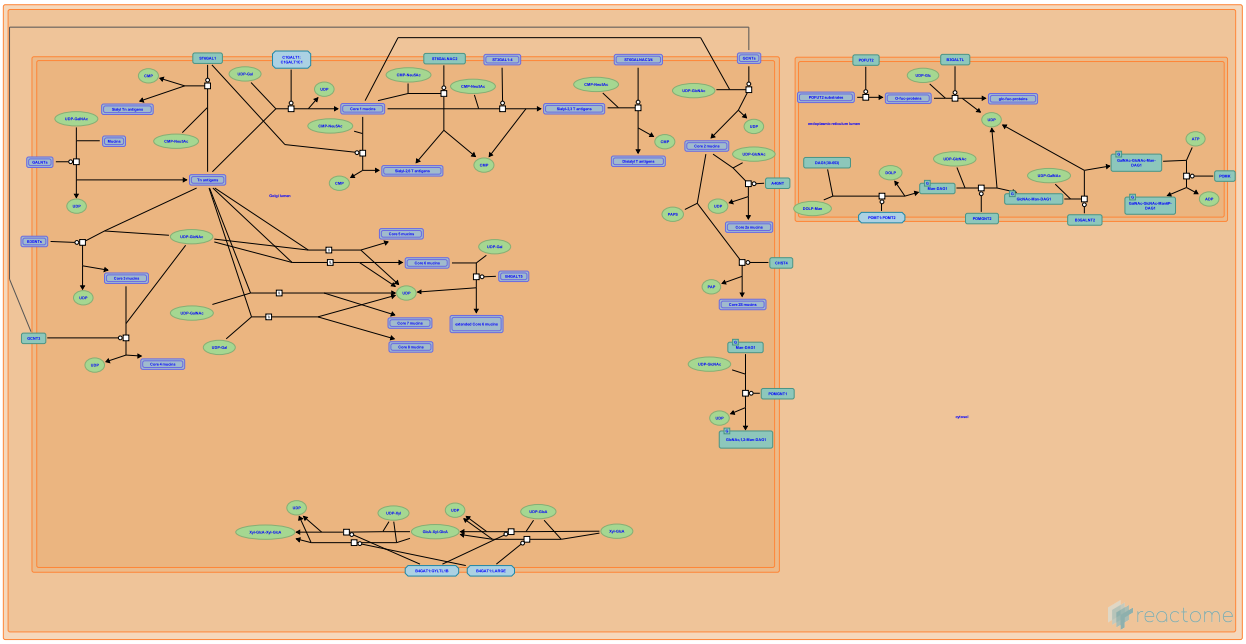
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

O-linked glycosylation ↗

Stable identifier: R-HSA-5173105



O-glycosylation is an important post-translational modification (PTM) required for correct functioning of many proteins (Van den Steen et al. 1998, Moremen et al. 2012). The O-glycosylation of proteins containing thrombospondin type 1 repeat (TSR) domains and O-glycosylation of mucins are currently described here.

Literature references

Van den Steen, P., Rudd, PM., Dwek, RA., Opdenakker, G. (1998). Concepts and principles of O-linked glycosylation. *Crit. Rev. Biochem. Mol. Biol., 33*, 151-208. ↗

Moremen, KW., Tiemeyer, M., Nairn, AV. (2012). Vertebrate protein glycosylation: diversity, synthesis and function. *Nat. Rev. Mol. Cell Biol., 13*, 448-62. ↗

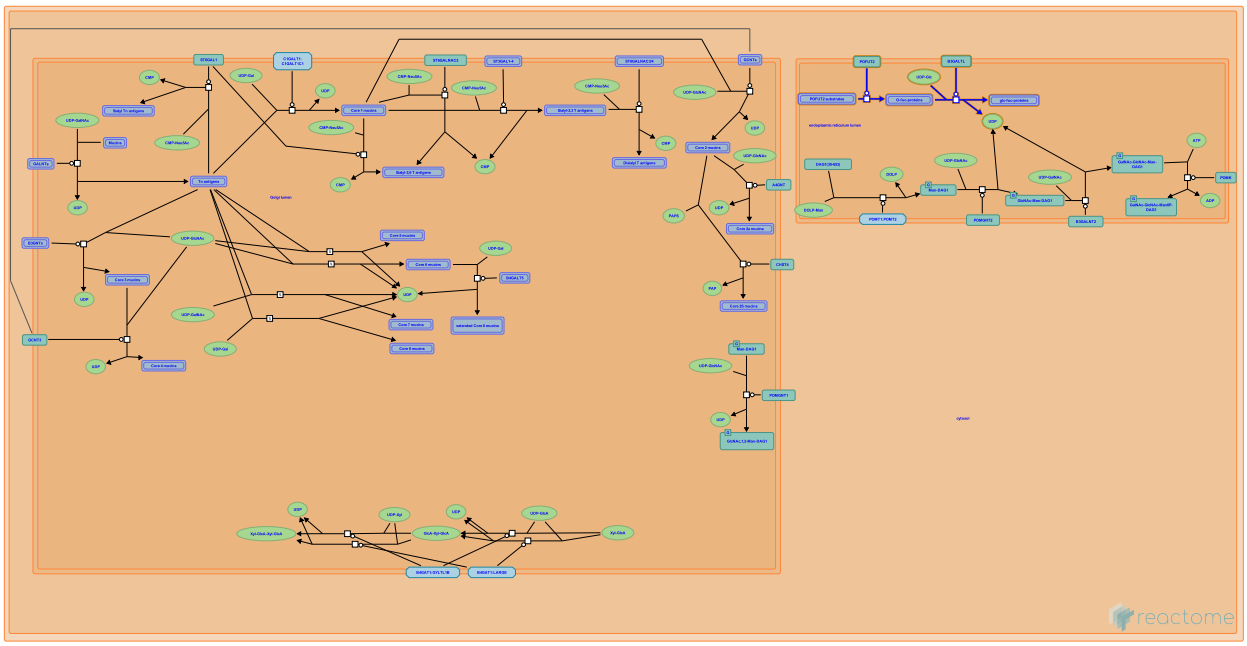
Editions

2013-11-25	Authored, Edited	Jassal, B.
2014-02-07	Reviewed	D'Eustachio, P.

O-glycosylation of TSR domain-containing proteins ↗

Location: O-linked glycosylation

Stable identifier: R-HSA-5173214



The O-fucosylation of proteins containing thrombospondin type 1 repeat (TSR) domains is an important PTM, regulating many biological processes such as Notch signalling, inflammation, wound healing, angiogenesis amd neoplasia (Adams & Tucker 2000, Moremen et al. 2012). Fucose addition is carried out by two protein fucosyltransferases, POFUT1 and 2. Only POFUT2 recognises the consensus sequence CSXS/TCG found in TSR1 domains and the fucosyl residue is attached to the hydroxyl group of conserved serine (S) or threonine (T) residues within the consensus sequence. The modification was first demonstrated on thrombospondin 1, found in platelets and the ECM (Hofsteenge et al. 2001, Luo et al. 2006). The resulting O-fucosyl-protein is subsequently a substrate for beta-1,3-glucosyltransferase-like protein (B3GALTL), which adds a glucosyl moiety to form the rare disaccharide modification Glc-beta-1,3-Fuc. More than 60 human proteins contain TSR1 domains, The disaccharide modification has been demonstrated on a small number of these TSR1 domain-containing proteins such as thrombospondin 1 (Hofsteenge et al. 2001, Luo et al. 2006), properdin (Gonzalez de Peredo et al. 2002) and F-spondin (Gonzalez de Peredo et al. 2002). The ADAMTS (a disintegrin-like and metalloprotease domain with thrombospondin type-1 repeats) superfamily consists of 19 secreted metalloproteases (ADAMTS proteases) and at lease five ADAMTS-like proteins in humans. Five members of the ADAMTS superfamily have also had experimental confirmation of the disaccharide modification. Examples are ADAMTS13 (Ricketts et al. 2007) and ADAMTSL1 (Wang et al. 2007). In the two reactions described here, the TSR1 domain-containing proteins with similarity to the experimentally confirmed ones are included as putative substrates.

Literature references

Adams, JC., Tucker, RP. (2000). The thrombospondin type 1 repeat (TSR) superfamily: diverse proteins with related roles in neuronal development. *Dev. Dyn., 218*, 280-99. ↗

Moremen, KW., Tiemeyer, M., Nairn, AV. (2012). Vertebrate protein glycosylation: diversity, synthesis and function. *Nat. Rev. Mol. Cell Biol., 13*, 448-62. ↗

Hofsteenge, J., Huwiler, KG., Macek, B., Hess, D., Lawler, J., Mosher, DF. et al. (2001). C-mannosylation and O-fucosylation of the thrombospondin type 1 module. *J. Biol. Chem., 276*, 6485-98. ↗

Luo, Y., Nita-Lazar, A., Haltiwanger, RS. (2006). Two distinct pathways for O-fucosylation of epidermal growth factor-like or thrombospondin type 1 repeats. *J. Biol. Chem., 281*, 9385-92. ↗

Ricketts, LM., Dlugosz, M., Luther, KB., Haltiwanger, RS., Majerus, EM. (2007). O-fucosylation is required for ADAMTS13 secretion. *J. Biol. Chem., 282*, 17014-23. ↗

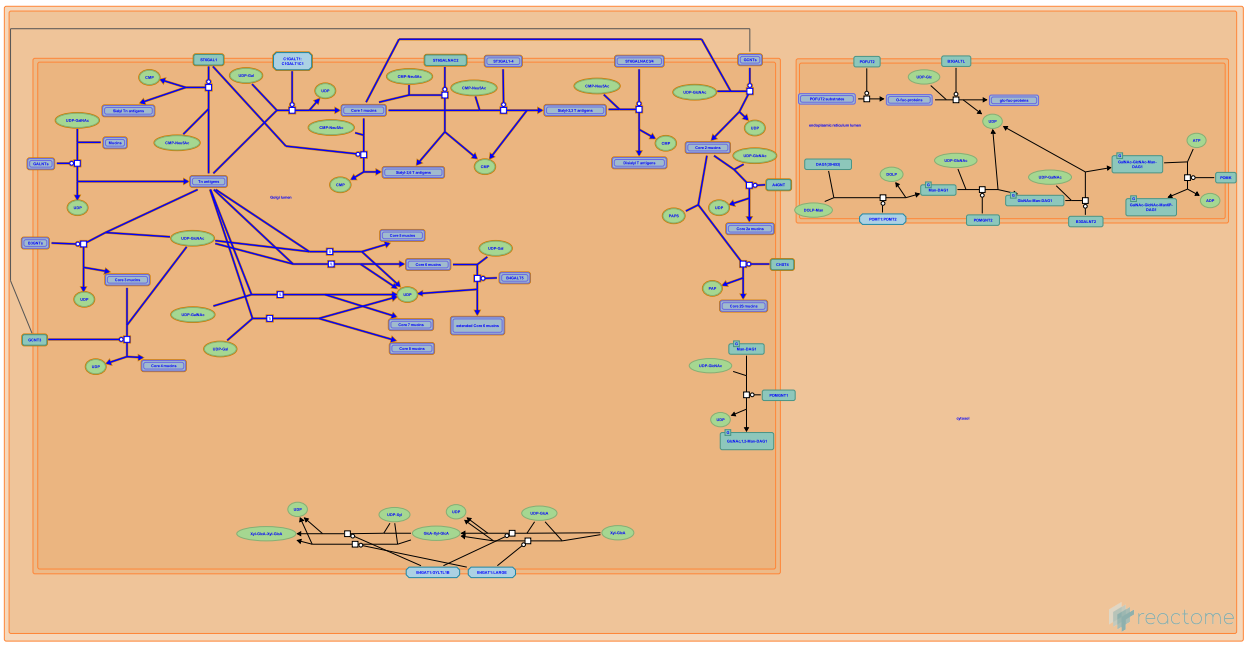
Editions

2013-11-25	Authored, Edited	Jassal, B.
2014-02-07	Reviewed	D'Eustachio, P.

O-linked glycosylation of mucins ↗

Location: O-linked glycosylation

Stable identifier: R-HSA-913709



Mucins are a family of high molecular weight, heavily glycosylated proteins (glycoconjugates) produced by epithelial tissues in most metazoa. Mucins' key characteristic is their ability to form gels; therefore they are a key component in most gel-like secretions, serving functions from lubrication to cell signalling to forming chemical barriers. To date, there are approximately 20 genes that express mucins. Mature mucins are composed of two distinct regions:

(1) The amino- and carboxy-terminal regions are very lightly glycosylated, but rich in cysteines. The cysteine residues participate in establishing disulfide linkages within and among mucin monomers.

(2) A large central region rich in serine, threonine and proline residues called the variable number of tandem repeat (VNTR) region which can become heavily O-glycosylated with hundreds of O-GalNAc glycans.

N-acetyl-galactosamine (GalNAc) is the first glycan to be attached, forming the simplest mucin O-glycan. After this, several different pathways are possible generating "core" structures. Four core structures are commonly formed, several others are possible but infrequent. O-linked glycans are often capped by the addition of a sialic acid residue, terminating the addition of any more O-glycans (Brockhausen et al, 2009; Tarp and Clausen, 2008).

Literature references

Tarp, MA., Clausen, H. (2008). Mucin-type O-glycosylation and its potential use in drug and vaccine development. *Biochim Biophys Acta, 1780*, 546-63. ↗

Brockhausen, I., Schachter, H., Stanley, P., Stanley, P., Varki, A., Cummings, RD. et al. (2009). O-GalNAc Glycans.

Editions

2010-07-19	Authored, Edited	Jassal, B.
2011-11-04	Reviewed	Ferrer, A.

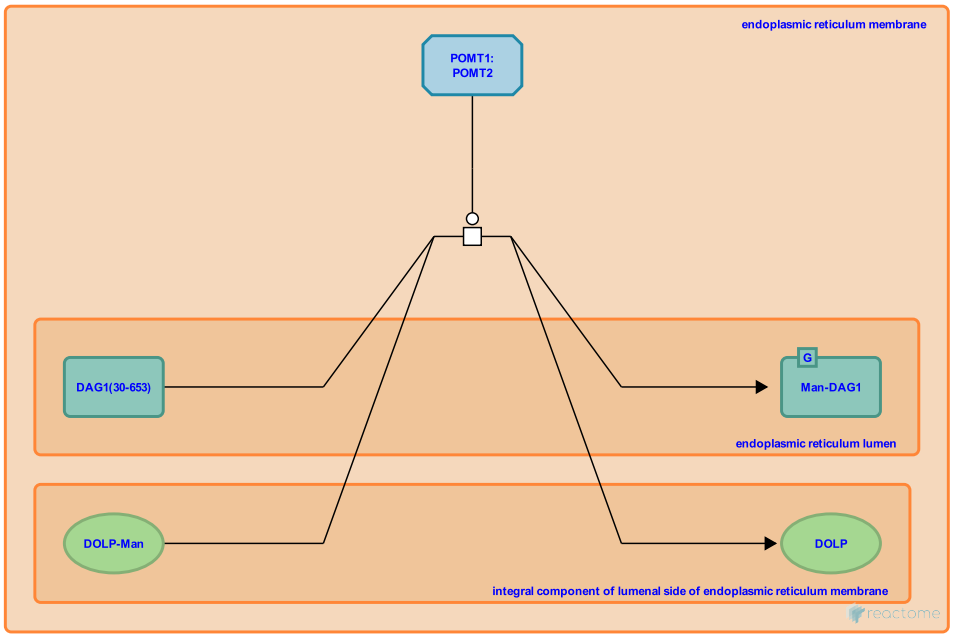
POMT1:POMT2 transfers Man from Dol-P-Man to DAG1(30-653) ↗

Location: O-linked glycosylation

Stable identifier: R-HSA-5615637

Type: transition

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen



Co-expression of both protein O-mannosyl-transferases 1 and 2 (POMT1 and POMT2; CAZy family GT39) is necessary for enzyme activity (Manya et al. 2004), that is mediating the transfer of mannosyl residues to the hydroxyl group of serine or threonine residues of proteins such as alpha-dystroglycan (DAG1; MIM:128239). This process occurs in the ER lumen and both POMT isozymes are ER membrane residents. DAG1 is a cell surface protein that plays an important role in the assembly of the extracellular matrix in muscle, brain, and peripheral nerves by linking the basal lamina to cytoskeletal proteins. Defects in POMT2 (MIM:607439) results in defective glycosylation of DAG1 and can cause severe congenital muscular dystrophy dystroglycanopathies ranging from a severe type A, MDDGA2 (brain and eye abnormalities; MIM:613150), through a less severe type B, MDDGB2 (congenital form with mental retardation; MIM:613156) to a milder type C, MDDGC2 (limb girdle form; MIM:603158) (Bertini et al. 2011, Wells 2013).

Literature references

Manya, H., Chiba, A., Yoshida, A., Wang, X., Chiba, Y., Jigami, Y. et al. (2004). Demonstration of mammalian protein O-mannosyltransferase activity: coexpression of POMT1 and POMT2 required for enzymatic activity. *Proc. Natl. Acad. Sci. U.S.A., 101*, 500-5. ↗

Bertini, E., D'Amico, A., Gualandi, F., Petrini, S. (2011). Congenital muscular dystrophies: a brief review. *Semin Pediatr Neurol, 18*, 277-88. ↗

Wells, L. (2013). The o-mannosylation pathway: glycosyltransferases and proteins implicated in congenital muscular dystrophy. *J. Biol. Chem., 288*, 6930-5. ↗

Editions

2014-07-25	Authored, Edited	Jassal, B.
2015-12-18	Reviewed	Joshi, HJ., Hansen, L.

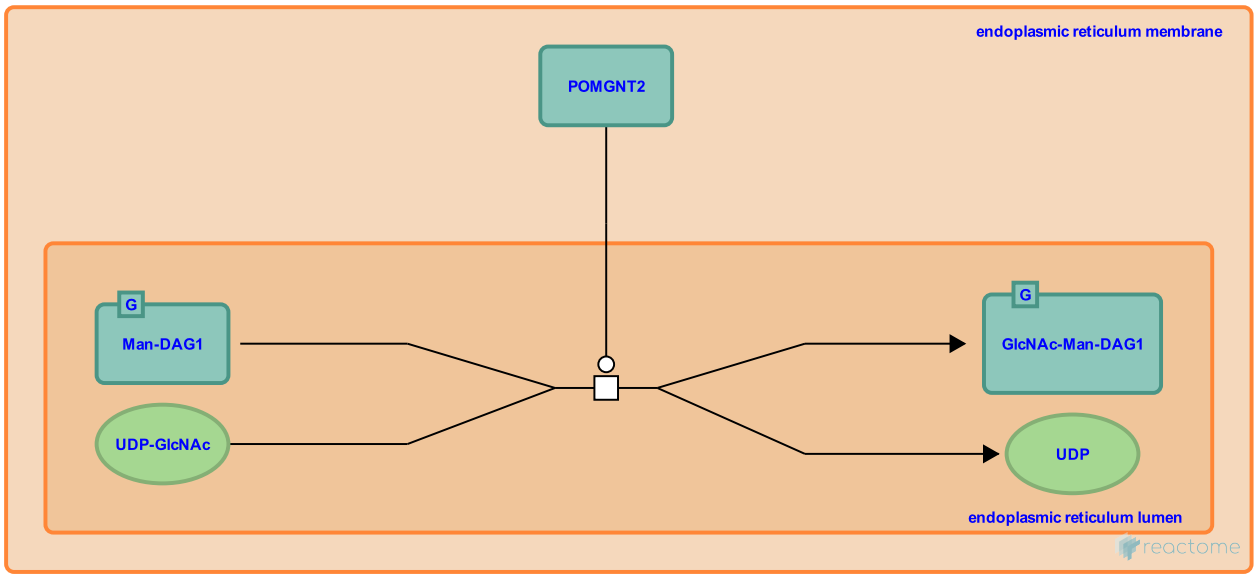
POMGNT2 transfers GlcNAc to Man-DAG1 ↗

Location: O-linked glycosylation

Stable identifier: R-HSA-8879117

Type: transition

Compartments: endoplasmic reticulum lumen, endoplasmic reticulum membrane



Three enzymes are involved in the biosynthesis of a phosphorylated O-mannosyl trisaccharide structure (N-acetylgalactosamine-beta-1,3-N-acetylglucosamine-beta-1,4-(phosphate-6-)mannose) present in alpha-dystroglycan (DAG1), which is required for binding laminin G-like domain-containing extracellular proteins with high affinity. Defects in any of these enzymes can lead to congenital muscular dystrophy.

In the first step, protein O-linked-mannose beta-1,4-N-acetylglucosaminyltransferase 2 (POMGNT2) transfers N-acetyl-D-glucosamine (GlcNAc) to the 4-position of mannosylated DAG1 to generate N-acetyl-D-glucosamine-beta-1,4-O-D-mannosyl-DAG1 (Yoshida-Moriguchi et al. 2013). Defects in POMGNT2 can cause muscular dystrophy-dystroglycanopathy congenital with brain and eye anomalies A8 (MDDGA8), a congenital muscular dystrophy that severely affects the development of the brain, eyes, and muscle, profound mental retardation, and death usually in the first years of life. This phenotype is also described as Walker-Warburg syndrome (WWS), which represents the most severe end of a phenotypic spectrum of dystroglycanopathies (Manzini et al. 2012).

Literature references

Yoshida-Moriguchi, T., Willer, T., Anderson, ME., Venzke, D., Whyte, T., Muntoni, F. et al. (2013). SGK196 is a glycosylation-specific O-mannose kinase required for dystroglycan function. *Science, 341*, 896-9. ↗

Manzini, MC., Tambunan, DE., Hill, RS., Yu, TW., Maynard, TM., Heinzen, EL. et al. (2012). Exome sequencing and functional validation in zebrafish identify GTDC2 mutations as a cause of Walker-Warburg syndrome. *Am. J. Hum. Genet., 91*, 541-7. ↗

Editions

2016-07-15	Authored, Edited	Jassal, B.
2016-08-12	Reviewed	D'Eustachio, P.

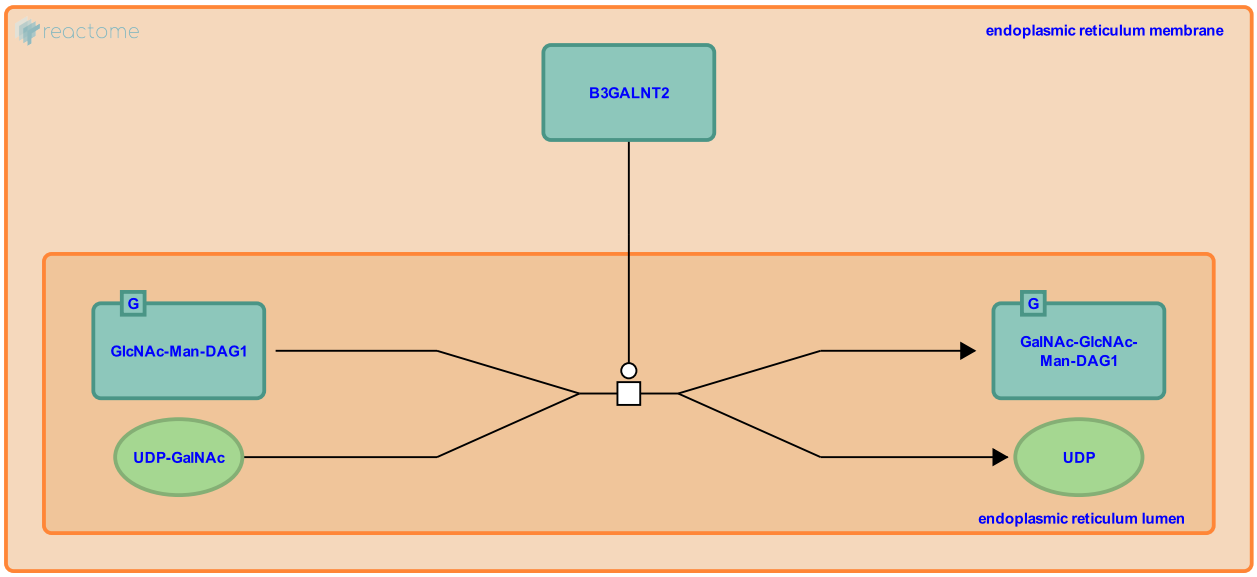
B3GALNT2 transfers GalNAc to GlcNAc-Man-DAG1 ↗

Location: O-linked glycosylation

Stable identifier: R-HSA-8931648

Type: transition

Compartments: endoplasmic reticulum lumen, endoplasmic reticulum membrane



Three enzymes are involved in the biosynthesis of a phosphorylated O-mannosyl trisaccharide structure (N-acetylgalactosamine-beta-1,3-N-acetylglucosamine-beta-1,4-(phosphate-6-)mannose) present in alpha-dystroglycan (DAG1), which is required for binding laminin G-like domain-containing extracellular proteins with high affinity. Defects in any of these enzymes can lead to congenital muscular dystrophy.

The second step is catalysed by UDP-GalNAc:beta-1,3-N-acetylgalactosaminyltransferase 2 (B3GALNT2), an ER membrane-associated enzyme that transfers N-acetylgalactosamine (GalNAc) to GlcNAc-Man-DAG1 via a 1-3 glycosidic bond (Hiruma et al. 2004, Yoshida-Moriguchi et al. 2013). Defects in B3GALNT2 can cause muscular dystrophy-dystroglycanopathy congenital with brain and eye anomalies A11 (MDDGA11), a hypoglycosylation defect resulting in a reduced ability of DAG1 to bind laminin and other extracellular matrix ligands. The disorder is characterised by dystroglycanopathy with muscle and brain anomolies (Stevens et al. 2013).

Literature references

Yoshida-Moriguchi, T., Willer, T., Anderson, ME., Venzke, D., Whyte, T., Muntoni, F. et al. (2013). SGK196 is a glycosylation-specific O-mannose kinase required for dystroglycan function. *Science, 341*, 896-9. ↗

Hiruma, T., Togayachi, A., Okamura, K., Sato, T., Kikuchi, N., Kwon, YD. et al. (2004). A novel human beta1,3-N-acetylgalactosaminyltransferase that synthesizes a unique carbohydrate structure, GalNAcbeta1-3GlcNAc. *J. Biol. Chem., 279*, 14087-95. ↗

Stevens, E., Carss, KJ., Cirak, S., Foley, AR., Torelli, S., Willer, T. et al. (2013). Mutations in B3GALNT2 cause congenital muscular dystrophy and hypoglycosylation of α-dystroglycan. *Am. J. Hum. Genet., 92*, 354-65. ↗

Editions

2016-07-18	Authored, Edited	Jassal, B.
2016-08-12	Reviewed	D'Eustachio, P.

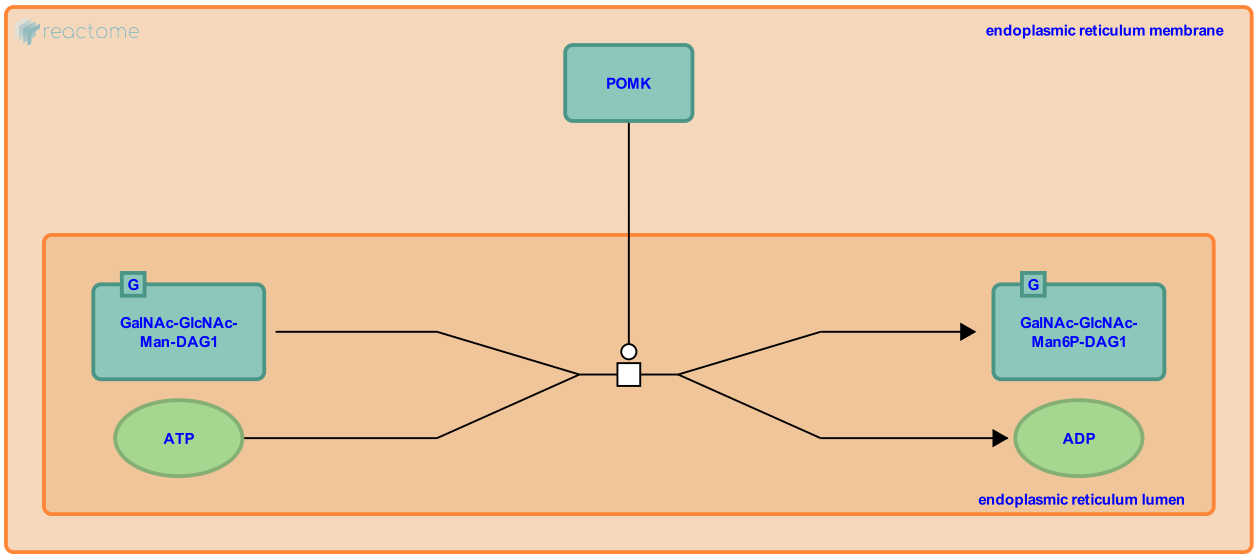
POMK 6-phosphorylates Mannose in GalNAc-GlcNAc-Man-DAG1 ↗

Location: O-linked glycosylation

Stable identifier: R-HSA-8931653

Type: transition

Compartments: endoplasmic reticulum lumen, endoplasmic reticulum membrane



Three enzymes are involved in the biosynthesis of a phosphorylated O-mannosyl trisaccharide structure (N-acetylgalactosamine-beta-1,3-N-acetylglucosamine-beta-1,4-(phosphate-6-)mannose) present in alpha-dystroglycan (DAG1), which is required for binding laminin G-like domain-containing extracellular proteins with high affinity. Defects in any of these enzymes can lead to congenital muscular dystrophy.

Once the mannosyl residue attached to DAG1 has had GlcNAc and GalNAc added to it by POMGNT2 and B3GALNT2 respectively, protein O-mannose kinase (POMK, SGK196) can phosphorylate position 6 of the mannosyl residue (Yoshida-Moriguchi et al. 2013). Defects in POMK can cause muscular dystrophy-dystroglycanopathy congenital with brain and eye anomalies A12 (MDDGA12), a congenital muscular dystrophy that disrupts normal muscle development leading to locomotor dysfuction (Di Costanzo et al. 2014).

Literature references

Yoshida-Moriguchi, T., Willer, T., Anderson, ME., Venzke, D., Whyte, T., Muntoni, F. et al. (2013). SGK196 is a glycosylation-specific O-mannose kinase required for dystroglycan function. *Science, 341*, 896-9. ↗

Di Costanzo, S., Balasubramanian, A., Pond, HL., Rozkalne, A., Pantaleoni, C., Saredi, S. et al. (2014). POMK mutations disrupt muscle development leading to a spectrum of neuromuscular presentations. *Hum. Mol. Genet., 23*, 5781-92. ↗

Editions

2016-07-18	Authored, Edited	Jassal, B.
2016-08-12	Reviewed	D'Eustachio, P.

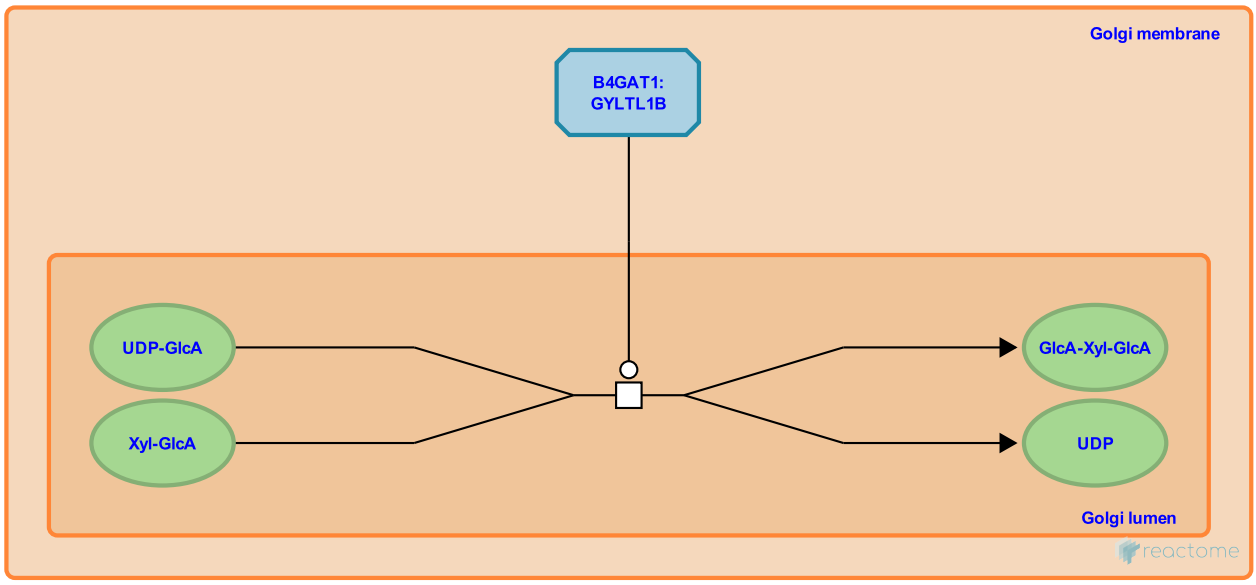
B4GAT1:GYLTL1B transfers GlcA from UDP-GlcA to Xyl-GlcA ↗

Location: O-linked glycosylation

Stable identifier: R-HSA-5617143

Type: transition

Compartments: Golgi lumen, Golgi membrane



Glycosyltransferase-like protein LARGE2 (GYLTL1B) is a bifunctional glycosyltransferases with both xylosyltransferase and beta-1,3-glucuronyltransferase activities which can form polymeric Xyl-GlcA repeats. GYLTL1B is involved in the physiological function of alpha-dystroglycan (DAG1) which plays a key role in skeletal muscle function and regeneration (Inamori et al. 2013, Wells 2013, Inamori et al. 2014).

Literature references

Inamori, K., Hara, Y., Willer, T., Anderson, ME., Zhu, Z., Yoshida-Moriguchi, T. et al. (2013). Xylosyl- and glucuronyltransferase functions of LARGE in ?-dystroglycan modification are conserved in LARGE2. *Glycobiology, 23*, 295-302. ↗

Wells, L. (2013). The o-mannosylation pathway: glycosyltransferases and proteins implicated in congenital muscular dystrophy. *J. Biol. Chem., 288*, 6930-5. ↗

Inamori, K., Willer, T., Hara, Y., Venzke, D., Anderson, ME., Clarke, NF. et al. (2014). Endogenous glucuronyltransferase activity of LARGE or LARGE2 required for functional modification of α-dystroglycan in cells and tissues. *J. Biol. Chem., 289*, 28138-48. ↗

Editions

2014-07-31	Authored, Edited	Jassal, B.
2015-12-18	Reviewed	Joshi, HJ., Hansen, L.

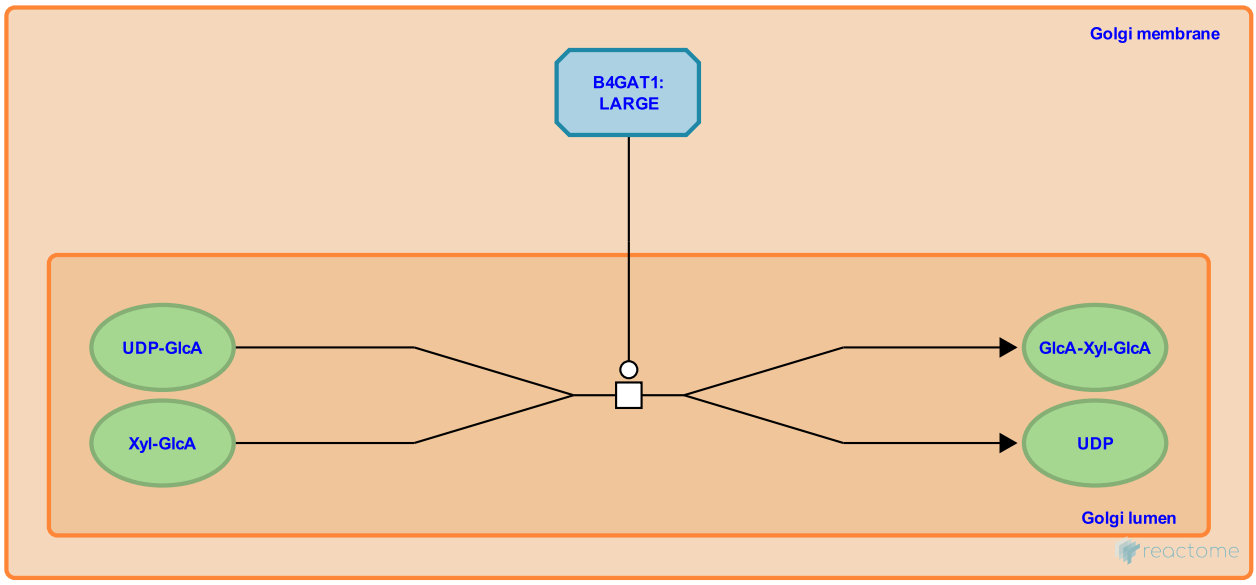
B4GAT1:LARGE transfers GlcA from UDP-GlcA to Xyl-GlcA ↗

Location: O-linked glycosylation

Stable identifier: R-HSA-9638097

Type: transition

Compartments: Golgi lumen, Golgi membrane



Glycosyltransferase-like protein LARGE is a bifunctional glycosyltransferases with both xylosyltransferase and beta-1,3-glucuronyltransferase activities which can form polymeric Xyl-GlcA repeats. LARGE is involved in the physiological function of alpha-dystroglycan (DAG1) which plays a key role in skeletal muscle function and regeneration (Inamori et al. 2013, Wells 2013, Inamori et al. 2014).

Literature references

Inamori, K., Hara, Y., Willer, T., Anderson, ME., Zhu, Z., Yoshida-Moriguchi, T. et al. (2013). Xylosyl- and glucuronyltransferase functions of LARGE in ?-dystroglycan modification are conserved in LARGE2. *Glycobiology, 23*, 295-302. ↗

Wells, L. (2013). The o-mannosylation pathway: glycosyltransferases and proteins implicated in congenital muscular dystrophy. *J. Biol. Chem., 288*, 6930-5. ↗

Inamori, K., Willer, T., Hara, Y., Venzke, D., Anderson, ME., Clarke, NF. et al. (2014). Endogenous glucuronyltransferase activity of LARGE or LARGE2 required for functional modification of α-dystroglycan in cells and tissues. *J. Biol. Chem., 289*, 28138-48. ↗

Editions

2014-07-31	Authored, Edited	Jassal, B.
2015-12-18	Reviewed	Joshi, HJ., Hansen, L.

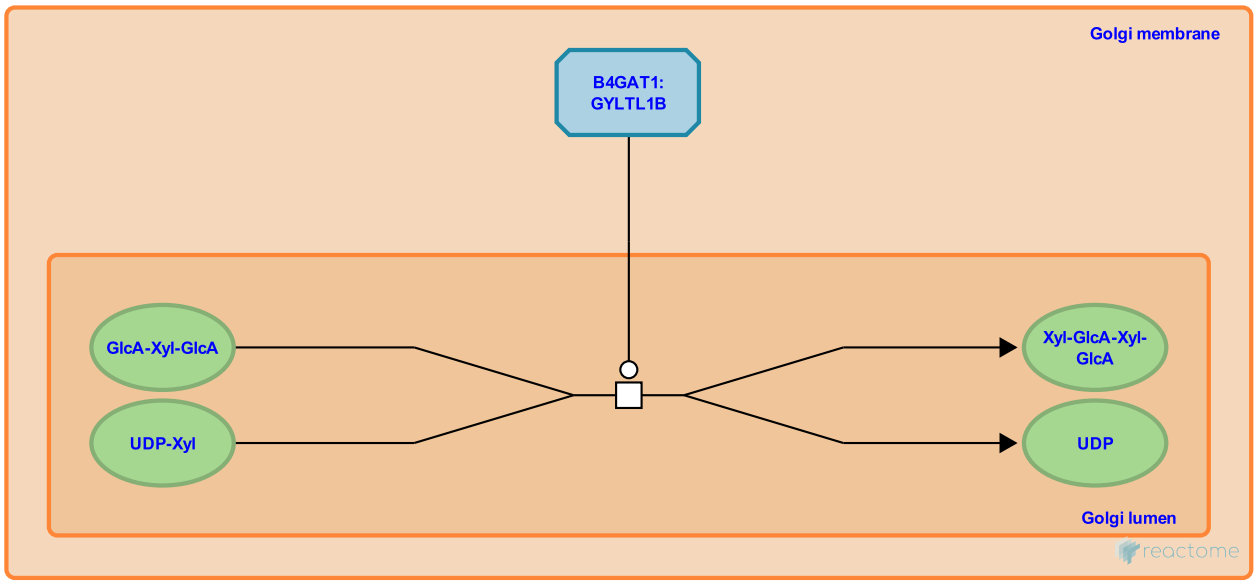
B4GAT1:GYLTL1B transfers Xyl from UDP-Xyl to GlcA-Xyl-GlcA ↗

Location: O-linked glycosylation

Stable identifier: R-HSA-5617138

Type: transition

Compartments: Golgi lumen, Golgi membrane



Glycosyltransferase-like protein LARGE2 (GYLTL1B; MIM:609709) is a bifunctional glycosyltransferase with both xylosyltransferase and beta-1,3-glucuronyltransferase activities involved in the biosynthesis of a phosphorylated O-mannosyl trisaccharide (N-acetylgalactosamine-beta-3-N-acetylglucosamine-beta-4-(phosphate-6-)mannose), a structure present in alpha-dystroglycan (DAG1) which plays a key role in skeletal muscle function and regeneration (Inamori et al. 2012, Inamori et al. 2013, Wells 2013). LARGE2 belongs to the CAZy glycosyltransferase families GT8 and GT49.

Literature references

Inamori, K., Hara, Y., Willer, T., Anderson, ME., Zhu, Z., Yoshida-Moriguchi, T. et al. (2013). Xylosyl- and glucuronyltransferase functions of LARGE in ?-dystroglycan modification are conserved in LARGE2. *Glycobiology, 23*, 295-302. ↗

Wells, L. (2013). The o-mannosylation pathway: glycosyltransferases and proteins implicated in congenital muscular dystrophy. *J. Biol. Chem., 288*, 6930-5. ↗

Inamori, K., Yoshida-Moriguchi, T., Hara, Y., Anderson, ME., Yu, L., Campbell, KP. (2012). Dystroglycan function requires xylosyl- and glucuronyltransferase activities of LARGE. *Science, 335*, 93-6. ↗

Editions

2014-07-31	Authored, Edited	Jassal, B.
2015-12-18	Reviewed	Joshi, HJ., Hansen, L.

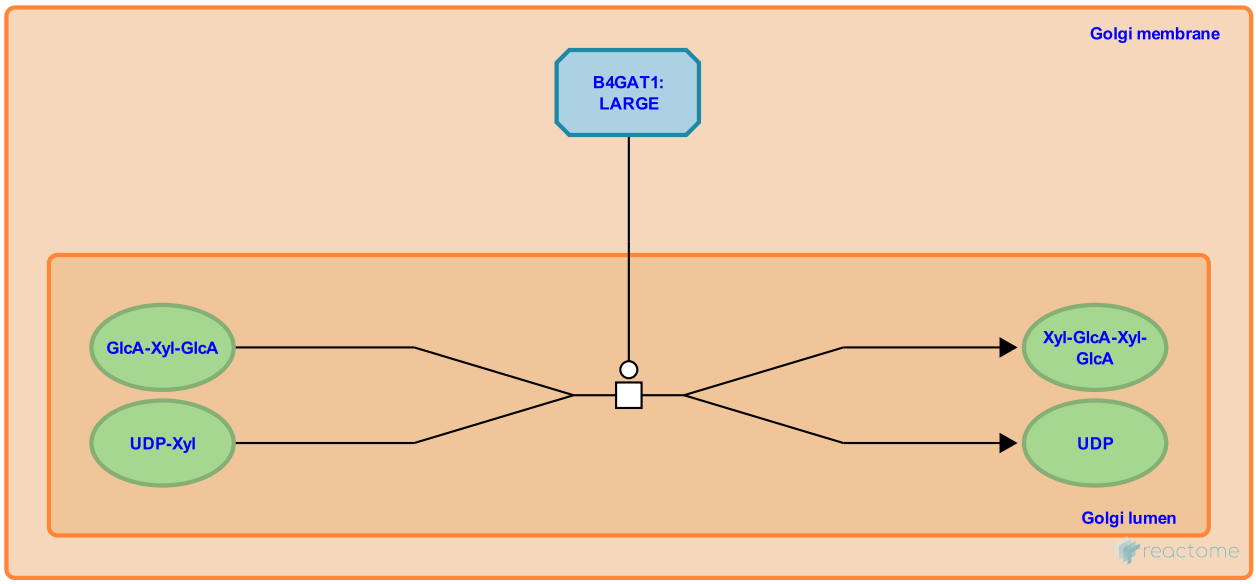
B4GAT1:LARGE transfers Xyl from UDP-Xyl to GlcA-Xyl-GlcA ↗

Location: O-linked glycosylation

Stable identifier: R-HSA-9638090

Type: transition

Compartments: Golgi lumen, Golgi membrane



Glycosyltransferase-like protein LARGE (MIM:603590) is a bifunctional glycosyltransferase with both xylosyltransferase and beta-1,3-glucuronyltransferase activities involved in the biosynthesis of a phosphorylated O-mannosyl trisaccharide (N-acetylgalactosamine-beta-3-N-acetylglucosamine-beta-4-(phosphate-6-)mannose), a structure present in alpha-dystroglycan (DAG1) which plays a key role in skeletal muscle function and regeneration (Inamori et al. 2012, Inamori et al. 2013, Wells 2013). LARGE belongs to the CAZy glycosyltransferase families GT8 and GT49.

Literature references

Inamori, K., Hara, Y., Willer, T., Anderson, ME., Zhu, Z., Yoshida-Moriguchi, T. et al. (2013). Xylosyl- and glucuronyltransferase functions of LARGE in ?-dystroglycan modification are conserved in LARGE2. *Glycobiology, 23*, 295-302. ↗

Wells, L. (2013). The o-mannosylation pathway: glycosyltransferases and proteins implicated in congenital muscular dystrophy. *J. Biol. Chem., 288*, 6930-5. ↗

Inamori, K., Yoshida-Moriguchi, T., Hara, Y., Anderson, ME., Yu, L., Campbell, KP. (2012). Dystroglycan function requires xylosyl- and glucuronyltransferase activities of LARGE. *Science, 335*, 93-6. ↗

Editions

2014-07-31	Authored, Edited	Jassal, B.
2015-12-18	Reviewed	Joshi, HJ., Hansen, L.

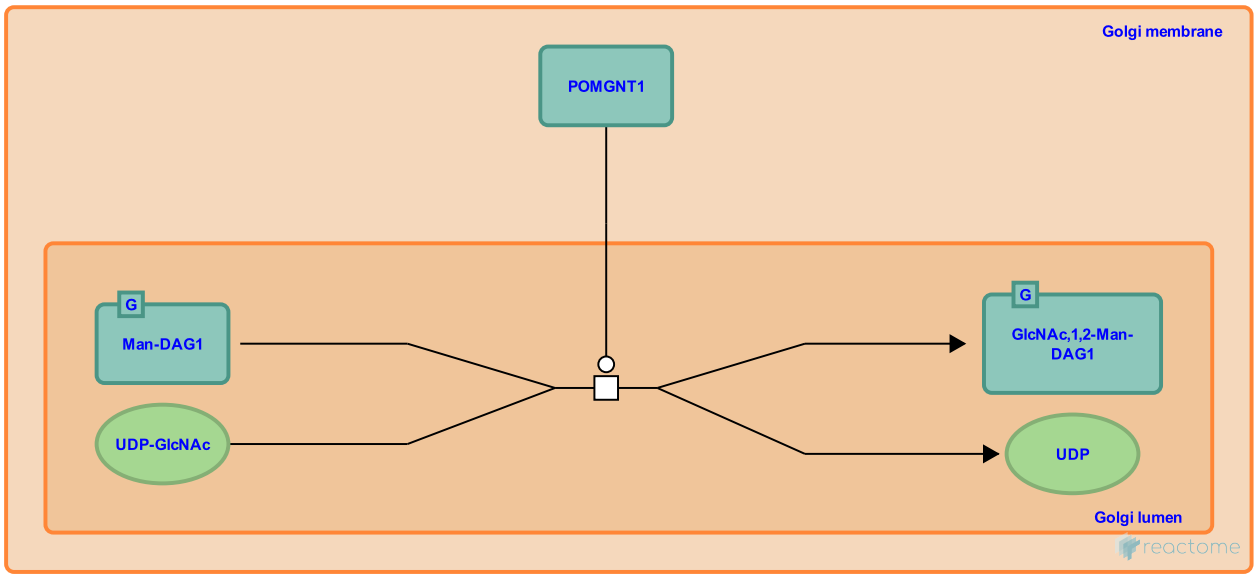
POMGNT1 transfers GlcNAc from UDP-GlcNAc to Man-O-Ser-DAG1 ↗

Location: O-linked glycosylation

Stable identifier: R-HSA-5617037

Type: transition

Compartments: Golgi lumen, Golgi membrane



Golgi membrane resident protein O-linked-mannose beta-1,2-N-acetylglucosaminyltransferase 1 (POMGNT1; MIM:606822) mediates the transfer of N-acetylglucosaminyl (GlcNAc) residues to mannosylated proteins in the Golgi lumen. It can transfer GlcNAc to mannose-O-serine-dystroglycan (Man-DAG1) with a beta-1,2 linkage. Defects in POMGNT1 result in disrupted glycosylation of DAG1 and can cause congenital muscular dystrophy-dystroglycanopathies of varying severity (Yoshida et al. 2001).

Literature references

Yoshida, A., Kobayashi, K., Manya, H., Taniguchi, K., Kano, H., Mizuno, M. et al. (2001). Muscular dystrophy and neuronal migration disorder caused by mutations in a glycosyltransferase, POMGnT1. *Dev. Cell, 1*, 717-24. ↗

Editions

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