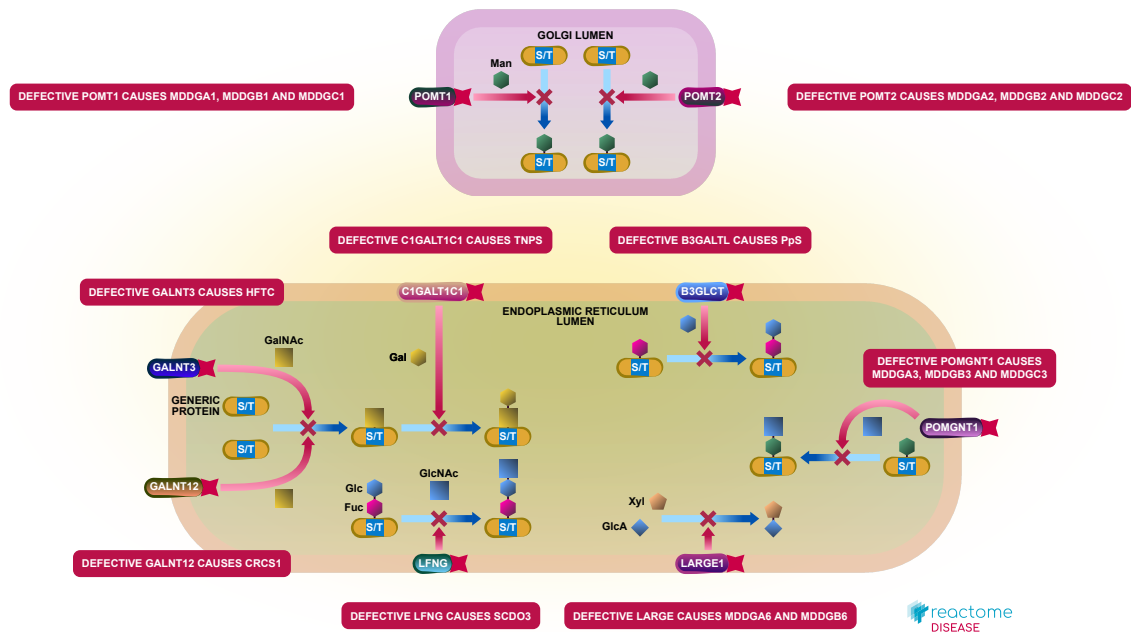


# Diseases associated with O-glycosylation of proteins



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.

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of [Creative Commons Attribution 4.0 International \(CC BY 4.0\) License](https://creativecommons.org/licenses/by/4.0/). For more information see our [license](https://reactome.org/about/licenses).

This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the [Reactome Textbook](https://reactome.org/textbook).

23/04/2024

## 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. [↗](#)

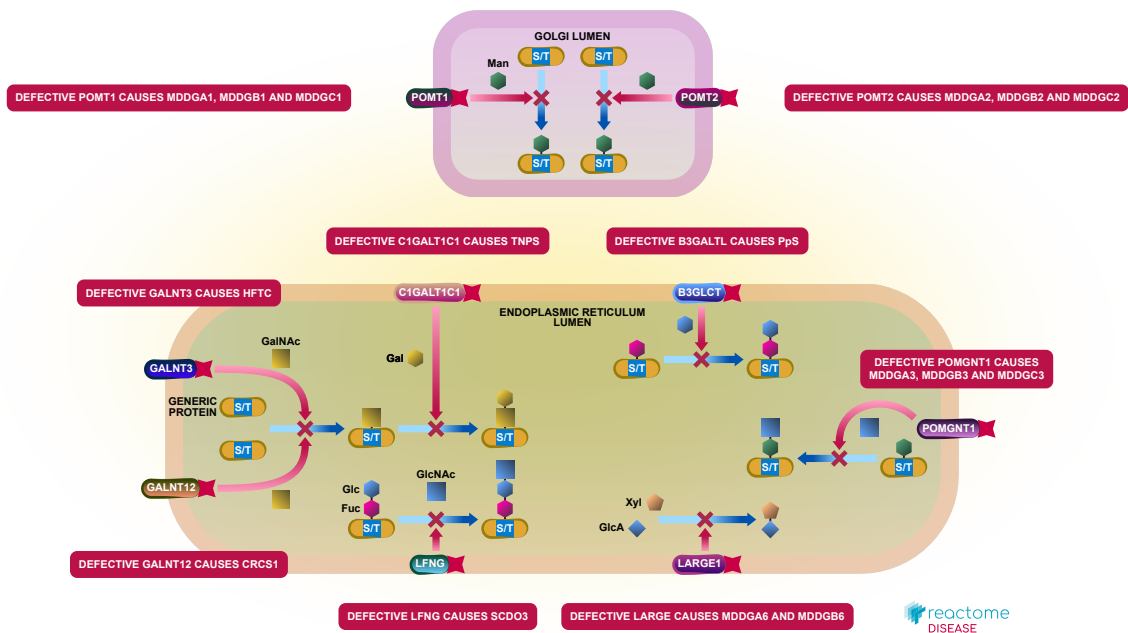
Reactome database release: 88

This document contains 10 pathways ([see Table of Contents](#))

## Diseases associated with O-glycosylation of proteins ↗

**Stable identifier:** R-HSA-3906995

**Diseases:** congenital disorder of glycosylation



Glycosylation is the most abundant modification of proteins, variations of which occur in all living cells. Glycosylation can be further categorized into N-linked (where the oligosaccharide is conjugated to Asparagine residues) and O-linked glycosylation (where the oligosaccharide is conjugated to Serine, Threonine and possibly Tyrosine residues). Within the family of O-linked glycosylation, the oligosaccharides attached can be further categorized according to their reducing end residue: GalNAc (often described as mucin-type, due to the abundance of this type of glycosylation on mucins), Mannose and Fucose. This section reviews currently known congenital disorders of glycosylation associated with defects of protein O-glycosylation (Cylwik et al. 2013, Freeze et al. 2014).

### Literature references

- Chong, JX., Bamshad, MJ., Freeze, HH., Ng, BG. (2014). Solving glycosylation disorders: fundamental approaches reveal complicated pathways. *Am. J. Hum. Genet.*, 94, 161-75. ↗
- Chrostek, L., Lipartowska, K., Cylwik, B., Gruszewska, E. (2013). Congenital disorders of glycosylation. Part II. Defects of protein O-glycosylation. *Acta Biochim. Pol.*, 60, 361-8. ↗

### Editions

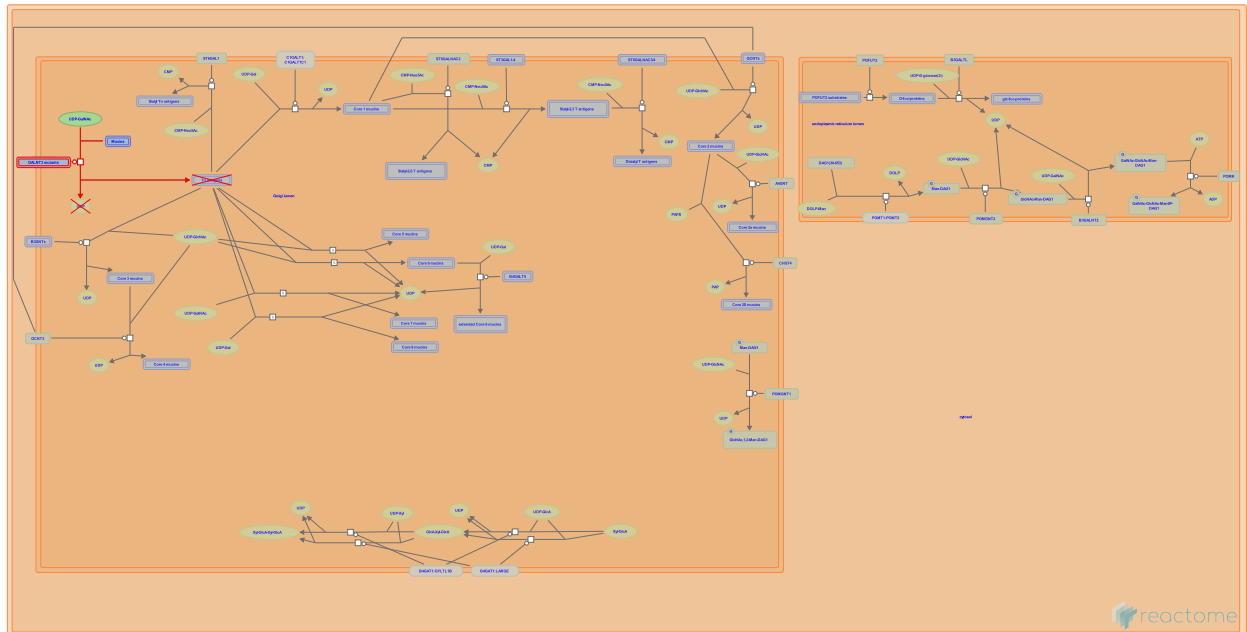
2013-07-17	Authored, Edited	Jassal, B.
2015-12-18	Reviewed	Joshi, HJ., Hansen, L.

## Defective GALNT3 causes HFTC ↗

**Location:** Diseases associated with O-glycosylation of proteins

**Stable identifier:** R-HSA-5083625

**Diseases:** hyperphosphatemia



The family of UDP GalNAc:polypeptide N acetylgalactosaminyltransferases (GalNAc transferases, GALNTs) carry out the addition of N acetylgalactosamine (GalNAc) on serine, threonine or possibly tyrosine residues on a wide variety of proteins, most commonly associated with mucins. This is the initial reaction in the biosynthesis of GalNAc-type O linked oligosaccharides (Wandall et al. 1997). This reaction takes place in the Golgi apparatus (Röttger et al. 1998). There are 20 known members of the GALNT family, 15 of which have been characterised and 5 candidate members which are thought to belong to this family based on sequence similarity (Bennett et al. 2012). The GALNT-family is classified as belonging to CAZy family GT27. Defects in one of the GALNT family genes, GALNT3 (MIM:601756), can cause familial hyperphosphatemic tumoral calcinosis (HFTC; MIM:211900). HFTC is a rare autosomal recessive severe metabolic disorder characterised by the progressive deposition of calcium phosphate crystals in the skin, soft tissues and sometimes bone (Chefetz et al. 2005). The biochemical observation is hyperphosphatemia, caused by increased renal absorption of phosphate (Chefetz et al. 2005, Ichikawa et al. 2005). Some patients manifest recurrent, transient, painful swellings of the long bones with radiological evidence of periosteal reaction and cortical hyperostosis (Frishberg et al. 2005).

### Literature references

- Fritz, TA., Mandel, U., Bennett, EP., Tabak, LA., Gerken, TA., Clausen, H. (2012). Control of mucin-type O-glycosylation: a classification of the polypeptide GalNAc-transferase gene family. *Glycobiology*, 22, 736-56. ↗
- Whitehouse, C., White, J., Bennett, EP., Olivo, JC., Röttger, S., Berger, EG. et al. (1998). Localization of three human polypeptide GalNAc-transferases in HeLa cells suggests initiation of O-linked glycosylation throughout the Golgi apparatus. *J Cell Sci*, 111, 45-60. ↗
- Koerber, F., Galli-Tsinopoulou, A., Topaz, O., Chefetz, I., Richard, G., Schoenau, E. et al. (2005). A novel homozygous missense mutation in FGF23 causes Familial Tumoral Calcinosis associated with disseminated visceral calcification. *Hum. Genet.*, 118, 261-6. ↗
- Burchell, J., Bennett, EP., Hassan, H., Taylor-Papadimitriou, J., Roepstorff, P., Hollingsworth, MA. et al. (1997). Substrate specificities of three members of the human UDP-N-acetyl-alpha-D-galactosamine:Polypeptide N-acetylgalactosaminyltransferase family, GalNAc-T1, -T2, and -T3. *J Biol Chem*, 272, 23503-14. ↗
- Lyles, KW., Ichikawa, S., Econs, MJ. (2005). A novel GALNT3 mutation in a pseudoautosomal dominant form of tumoral calcinosis: evidence that the disorder is autosomal recessive. *J. Clin. Endocrinol. Metab.*, 90, 2420-3. ↗

## Editions

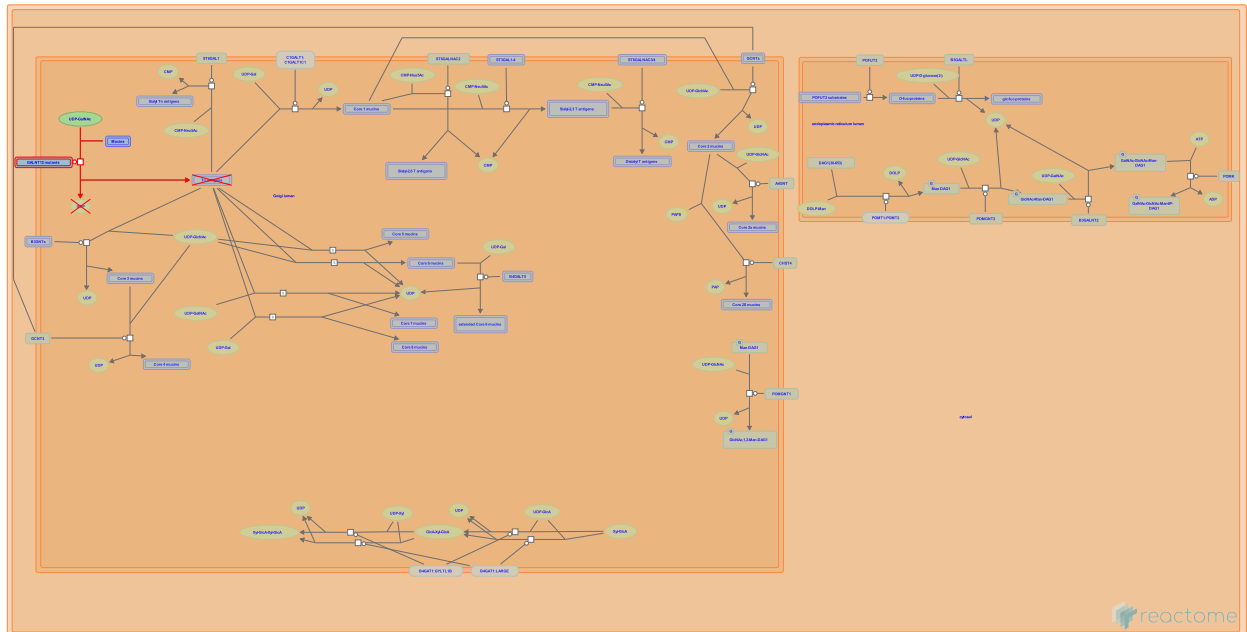
2013-11-07	Authored, Edited	Jassal, B.
2015-12-18	Reviewed	Joshi, HJ., Hansen, L.

## Defective GALNT12 causes CRC1 ↗

**Location:** Diseases associated with O-glycosylation of proteins

**Stable identifier:** R-HSA-5083636

**Diseases:** colorectal cancer



The family of UDP GalNAc:polypeptide N acetylgalactosaminyltransferases (GalNAc transferases, GALNTs) carry out the addition of N acetylgalactosamine on serine, threonine or possibly tyrosine residues on a wide variety of proteins, and most commonly associated with mucins (Wandall et al. 1997). This reaction takes place in the Golgi apparatus (Rottger et al. 1998). There are 20 known members of the GALNT family, 15 of which have been characterised and 5 candidate members which are thought to belong to this family based on sequence similarity (Bennett et al. 2012). The GALNT-family is classified as belonging to CAZy family GT27. Defects in one of the GALNT family, GALNT12 (Guo et al. 2002) (MIM: 610290) can result in decreased glycosylation of mucins, mainly expressed in the digestive organs such as the stomach, small intestine and colon, and may play a role in colorectal cancer 1 (CRC1; MIM:608812). CRC1 is a complex disease characterised by malignant lesions arising from the inner walls of the colon and rectum (Guda et al. 2009, Clarke et al. 2012).

### Literature references

- Fritz, TA., Mandel, U., Bennett, EP., Tabak, LA., Gerken, TA., Clausen, H. (2012). Control of mucin-type O-glycosylation: a classification of the polypeptide GalNAc-transferase gene family. *Glycobiology*, 22, 736-56. ↗
- Whitehouse, C., White, J., Bennett, EP., Olivo, JC., Röttger, S., Berger, EG. et al. (1998). Localization of three human polypeptide GalNAc-transferases in HeLa cells suggests initiation of O-linked glycosylation throughout the Golgi apparatus. *J Cell Sci*, 111, 45-60. ↗
- Parfrey, PS., Younghusband, HB., Clarke, E., Mahoney, K., Green, RC., Green, JS. et al. (2012). Inherited deleterious variants in GALNT12 are associated with CRC susceptibility. *Hum. Mutat.*, 33, 1056-8. ↗
- Papadopoulos, N., Lowe, JB., Lawrence, E., Wiesner, GL., Willis, J., Moinova, H. et al. (2009). Inactivating germ-line and somatic mutations in polypeptide N-acetylgalactosaminyltransferase 12 in human colon cancers. *Proc. Natl. Acad. Sci. U.S.A.*, 106, 12921-5. ↗
- Burchell, J., Bennett, EP., Hassan, H., Taylor-Papadimitriou, J., Roepstorff, P., Hollingsworth, MA. et al. (1997). Substrate specificities of three members of the human UDP-N-acetyl-alpha-D-galactosamine:Polypeptide N-acetylgalactosaminyltransferase family, GalNAc-T1, -T2, and -T3. *J Biol Chem*, 272, 23503-14. ↗

### Editions

2013-11-07

Authored, Edited

Jassal, B.

2015-12-18

Reviewed

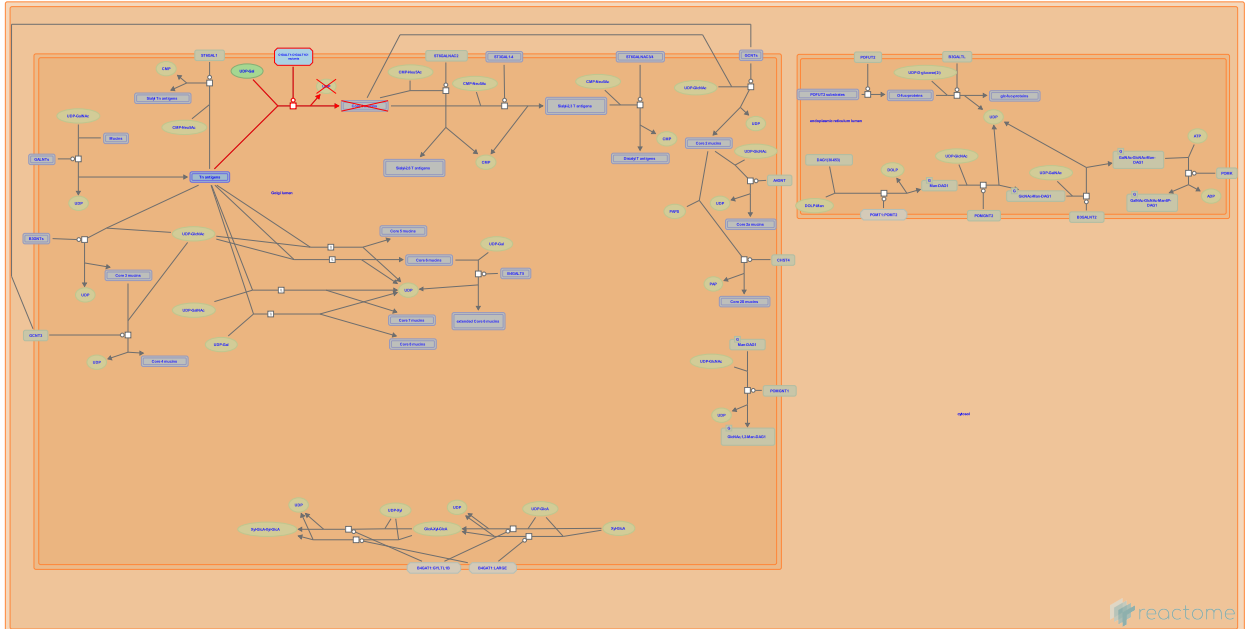
Joshi, HJ., Hansen, L.

## Defective C1GALT1C1 causes TNPS ↗

**Location:** Diseases associated with O-glycosylation of proteins

**Stable identifier:** R-HSA-5083632

**Diseases:** carcinoma



Glycoprotein-N-acetylgalactosamine 3-beta-galactosyltransferase 1 (C1GALT1; MIM:610555) mediates the transfer of Galactose (Gal) from UDP-galactose to single O-linked GalNAc residues (Tn antigens) to form Core 1 structures on glycoproteins. C1GALT1 is active when in complex with the molecular chaperone C1GALT1C1 (aka COSMC; MIM:300611) which assists the folding and/or stability of C1GALT1. Defects in C1GALT1C1 causes somatic Tn polyagglutination syndrome (TNPS; MIM:300622), characterised by the polyagglutination of erythrocytes by naturally occurring anti-Tn antibodies following exposure of the Tn antigen on their surface. Defects in C1GALT1C1 render C1GALT1 inactive and results in the accumulation of the incompletely glycosylated Tn antigen. The Tn antigen is tumour-associated, found in a majority of human carcinomas, and is not normally expressed in peripheral tissues or blood cells (Crew et al. 2008, Ju et al. 2014). C1GALT1 and C1GALT1C1 belong to the CAZy family GT31 ([www.cazy.org](http://www.cazy.org)).

### Literature references

Aryal, RP., Cummings, RD., Ju, T., Wang, Y., Kudelka, MR. (2014). The Cosmc connection to the Tn antigen in cancer . *Cancer Biomark*, 14, 63-81. ↗

Daniels, G., Singleton, BK., Parsons, SF., Green, C., Anstee, DJ., Crew, VK. (2008). New mutations in C1GALT1C1 in individuals with Tn positive phenotype. *Br. J. Haematol.*, 142, 657-67. ↗

### Editions

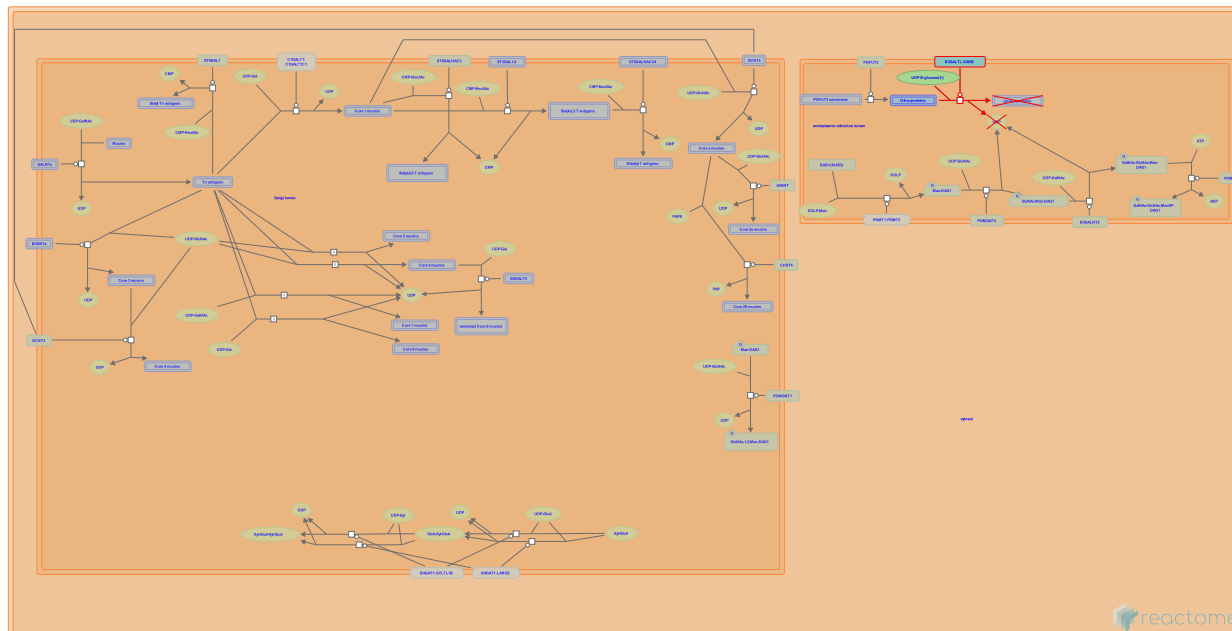
2013-11-07	Authored, Edited	Jassal, B.
2015-12-18	Reviewed	Joshi, HJ., Hansen, L.

## Defective B3GALTL causes PpS ↗

**Location:** Diseases associated with O-glycosylation of proteins

**Stable identifier:** R-HSA-5083635

**Diseases:** eye disease, orofacial cleft



Human beta-1,3-glucosyltransferase like protein (B3GALTL, HGNC Approved Gene Symbol: B3GLCT; MIM:610308; CAZy family GT31), localised on the ER membrane, glucosylates O-fucosylated proteins. The resultant glc-beta-1,3-fuc disaccharide modification on thrombospondin type 1 repeat (TSR1) domain-containing proteins is thought to assist in the secretion of many of these proteins from the ER lumen, and mediate an ER quality-control mechanism of folded TSRs (Vasudevan et al. 2015). Defects in B3GALTL can cause Peters plus syndrome (PpS; MIM:261540), an autosomal recessive disorder characterised by anterior eye chamber defects, short stature, delay in growth and mental developmental and cleft lip and/or palate (Heinonen & Maki 2009).

### Literature references

Vasudevan, D., Haltiwanger, RS., Johar, SS., Takeuchi, H., Majerus, E. (2015). Peters plus syndrome mutations disrupt a noncanonical ER quality-control mechanism. *Curr. Biol.*, 25, 286-95. ↗

Maki, M., Heinonen, TY. (2009). Peters'-plus syndrome is a congenital disorder of glycosylation caused by a defect in the beta1,3-glucosyltransferase that modifies thrombospondin type 1 repeats. *Ann. Med.*, 41, 2-10. ↗

### Editions

2013-11-07	Authored, Edited	Jassal, B.
2015-12-18	Reviewed	Joshi, HJ., Hansen, L.

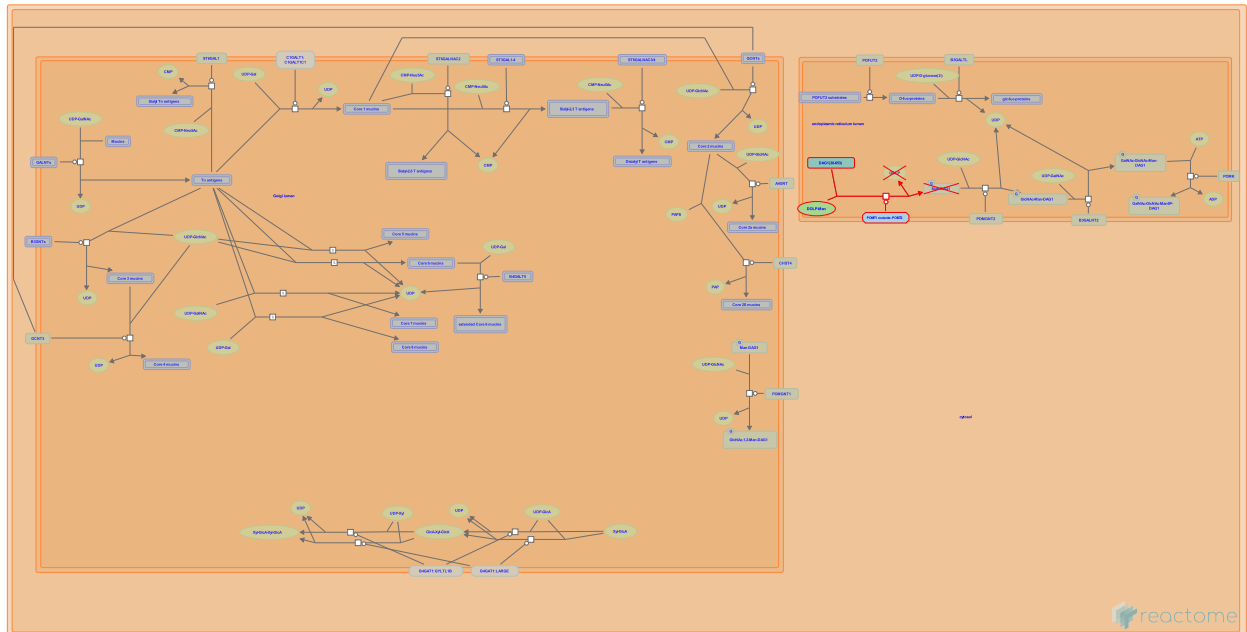


## Defective POMT1 causes MDDGA1, MDDGB1 and MDDGC1 ↗

**Location:** Diseases associated with O-glycosylation of proteins

**Stable identifier:** R-HSA-5083633

**Diseases:** muscular dystrophy-dystroglycanopathy



Co-expression of both protein O-mannosyl-transferases 1 and 2 (POMT1 and POMT2; CAZy family GT39) is necessary for enzyme activity, 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). 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 POMT1 (MIM:607423) results in defective glycosylation of DAG1 and can cause severe congenital muscular dystrophy-dystroglycanopathies ranging from a severe type A, MDDGA1 (brain and eye abnormalities; MIM:236670), through a less severe type B, MDDGB1 (congenital form with mental retardation; MIM:613155) to a milder type C, MDDGC1 (limb girdle form; MIM:609308) (Bertini et al. 2011, Wells 2013).

### Literature references

- Wells, L. (2013). The o-mannosylation pathway: glycosyltransferases and proteins implicated in congenital muscular dystrophy. *J. Biol. Chem.*, 288, 6930-5. ↗
- Gualandi, F., D'Amico, A., Petrini, S., Bertini, E. (2011). Congenital muscular dystrophies: a brief review. *Semin Pediatr Neurol*, 18, 277-88. ↗

### Editions

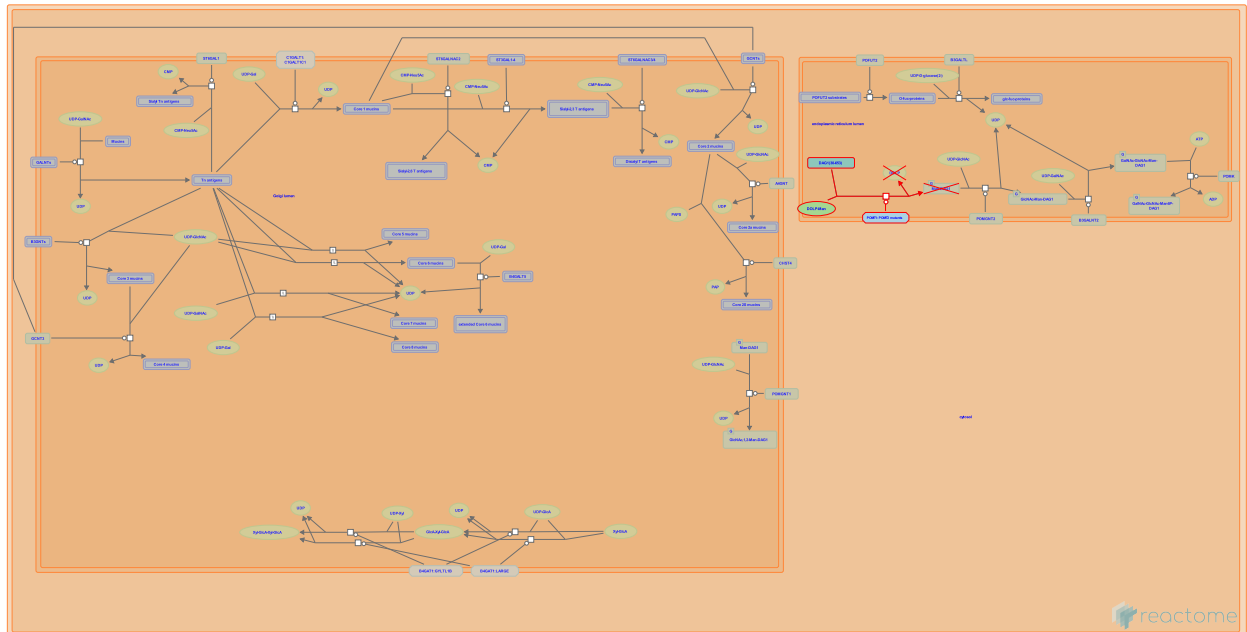
2013-11-07	Authored, Edited	Jassal, B.
2015-12-18	Reviewed	Joshi, HJ., Hansen, L.

## Defective POMT2 causes MDDGA2, MDDGB2 and MDDGC2 ↗

**Location:** Diseases associated with O-glycosylation of proteins

**Stable identifier:** R-HSA-5083629

**Diseases:** muscular dystrophy-dystroglycanopathy



Co-expression of both protein O-mannosyl-transferases 1 and 2 (POMT1 and POMT2; CAZy family GT39) is necessary for enzyme activity, 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). 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

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

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

### Editions

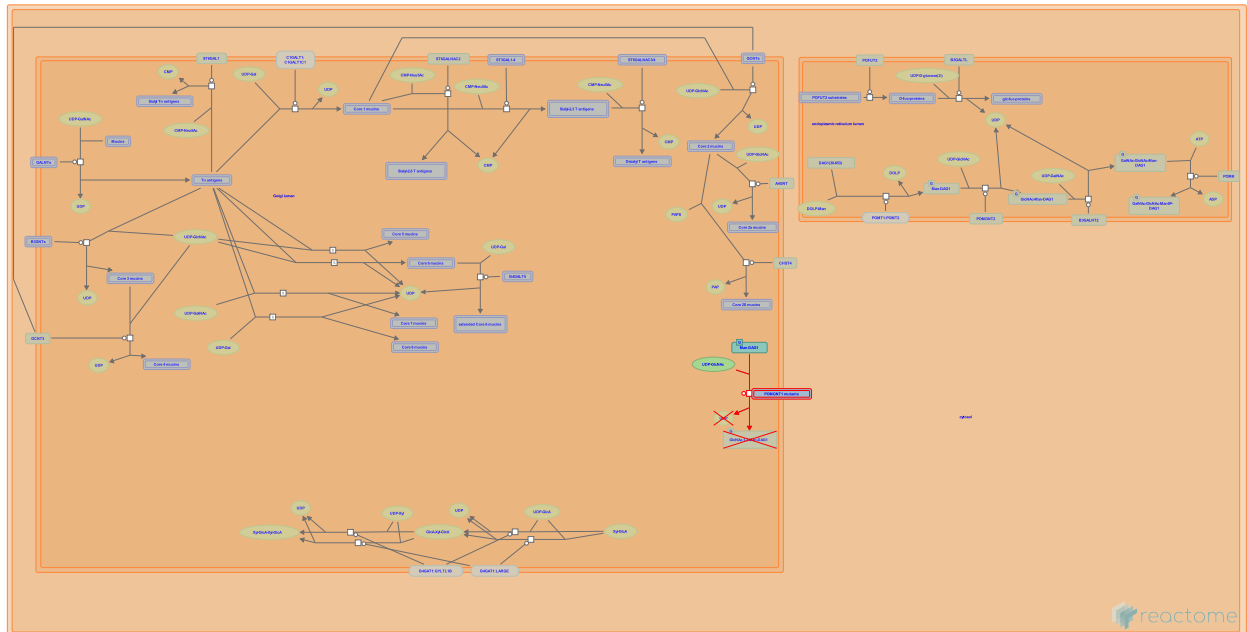
2013-11-07	Authored, Edited	Jassal, B.
2015-12-18	Reviewed	Joshi, HJ., Hansen, L.

## Defective POMGNT1 causes MDDGA3, MDDGB3 and MDDGC3 ↗

**Location:** Diseases associated with O-glycosylation of proteins

**Stable identifier:** R-HSA-5083628

**Diseases:** muscular dystrophy-dystroglycanopathy



Protein O-linked-mannose beta-1,2-N-acetylglucosaminyltransferase 1 (POMGNT1; CAZy family GT61; MIM:606822) mediates the transfer of N-acetylglucosaminyl (GlcNAc) residues to mannosylated proteins such as mannose-O-serine-dystroglycan (man-O-Ser-DAG1). 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 POMGNT1 (MIM:606822) result in disrupted glycosylation of DAG1 and can cause severe congenital muscular dystrophy-dystroglycanopathies ranging from a severe type A3 (MDDGA3; MIM:253280), through a less severe type B3 (MDDGB3; MIM:613151) to a milder type C3 (MDDGC3; MIM:613157) (Bertini et al. 2011, Wells 2013).

### Literature references

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

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

### Editions

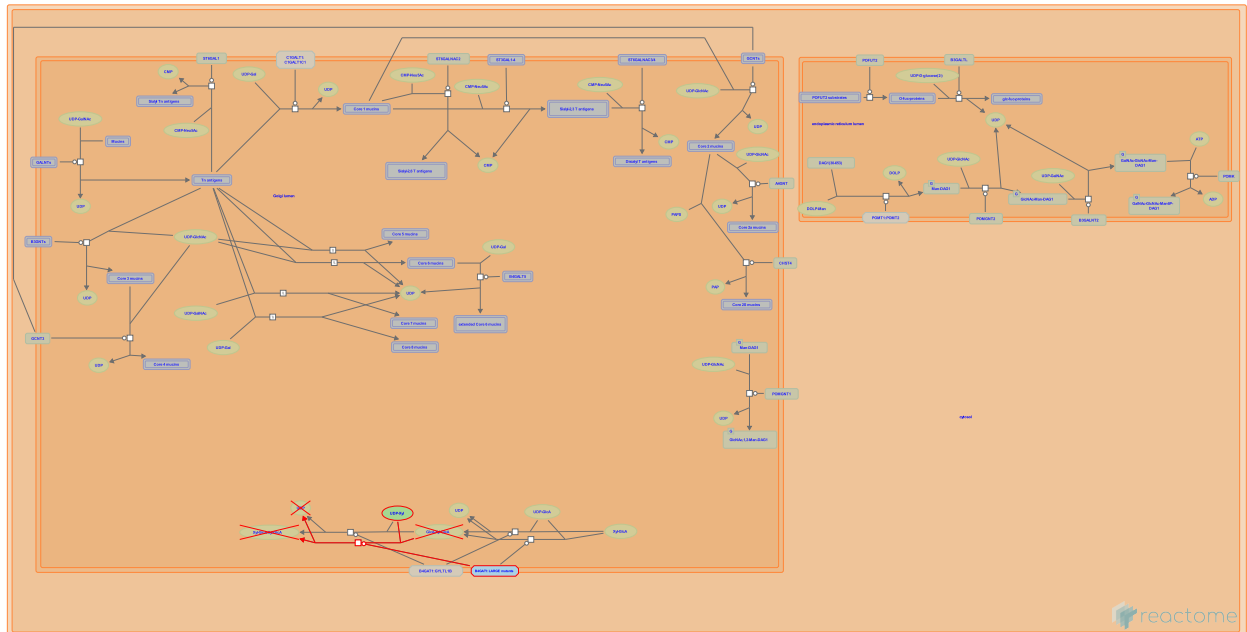
2013-11-07	Authored, Edited	Jassal, B.
2015-12-18	Reviewed	Joshi, HJ., Hansen, L.

## Defective LARGE causes MDDGA6 and MDDGB6 ↗

**Location:** Diseases associated with O-glycosylation of proteins

**Stable identifier:** R-HSA-5083627

**Diseases:** congenital muscular dystrophy



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, a structure present in alpha-dystroglycan (DAG1; MIM:128239) which plays a key role in skeletal muscle function and regeneration. LARGE contains two substrate-specific GT-domains and belongs to the CAZy glycosyltransferase families GT8 and GT49. Defects in LARGE result in hypoglycosylation of DAG1 and cause several congenital muscular dystrophies (CMDs). Muscular dystrophy-dystroglycanopathy congenital with brain and eye anomalies A6 (MDDGA6; MIM:613154) is associated with brain anomalies, eye malformations, profound mental retardation, and death usually in the first years of life (Clement et al. 2008, Mercuri et al. 2009). Muscular dystrophy-dystroglycanopathy congenital with mental retardation B6 (MDDGB6; MIM:608840) is associated with profound mental retardation, white matter changes and structural brain abnormalities (Longman et al. 2003).

### Literature references

- Scuderi, C., Mottarelli, E., Morandi, L., Laverda, A., Saredi, S., Moggio, M. et al. (2009). Congenital muscular dystrophies with defective glycosylation of dystroglycan: a population study. *Neurology*, 72, 1802-9. ↗
- Talim, B., Smith, J., Rutherford, M., Abbs, S., Cowan, F., Godfrey, C. et al. (2008). Brain involvement in muscular dystrophies with defective dystroglycan glycosylation. *Ann. Neurol.*, 64, 573-82. ↗
- Merlini, L., Brown, SC., Kennedy, C., Brockington, M., Torelli, S., Muntoni, F. et al. (2003). Mutations in the human LARGE gene cause MDC1D, a novel form of congenital muscular dystrophy with severe mental retardation and abnormal glycosylation of alpha-dystroglycan. *Hum. Mol. Genet.*, 12, 2853-61. ↗

### Editions

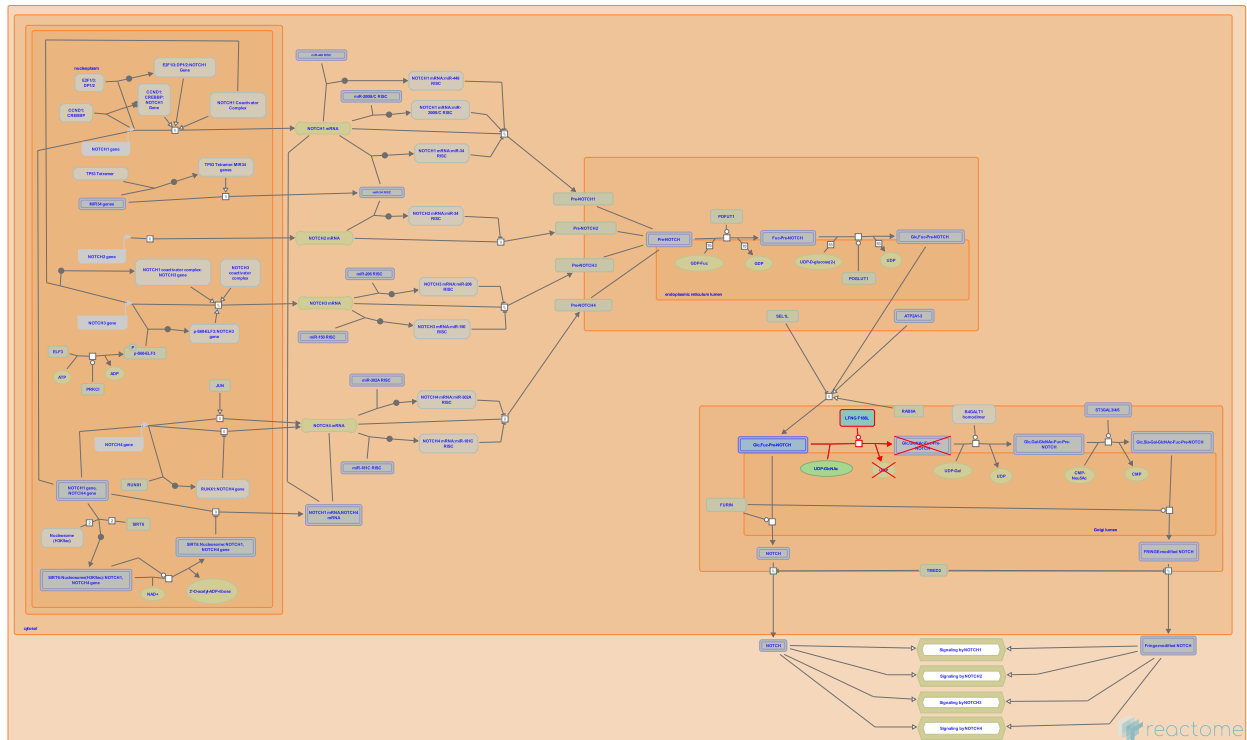
2013-11-07	Authored, Edited	Jassal, B.
2015-12-18	Reviewed	Joshi, HJ., Hansen, L.

## Defective LFNG causes SCDO3 ↗

**Location:** Diseases associated with O-glycosylation of proteins

**Stable identifier:** R-HSA-5083630

**Diseases:** spondylocostal dysostosis



The Fringe family (CAZy family GT31) of glycosyltransferases in mammals includes LFNG (lunatic fringe; MIM:602576), MFNG (manic fringe; MIM:602577) and RFNG (radical fringe; MIM:602578). Fringe enzymes function in the Golgi apparatus where they initiate the elongation of O-linked fucose on fucosylated peptides by the addition of a beta 1,3 N-acetylglucosaminyl group (GlcNAc) (Moloney et al. 2000). Fringe enzymes elongate conserved O fucosyl residues conjugated to EGF repeats of NOTCH, modulating NOTCH activity (Cohen et al. 1997, Johnston et al. 1997) by decreasing the affinity of NOTCH extracellular domain for JAG ligands (Brückner et al. 2000).

The spondylocostal dysostoses (SCDs) are a group of disorders that arise during embryonic development by a disruption of somitogenesis. The Notch signalling pathway is essential for somitogenesis, the precursors of vertebra and associated musculature. Defects in one of the Fringe enzymes, beta-1,3-N-acetylglucosaminyltransferase lunatic fringe (LFNG), can cause spondylocostal dysostosis, autosomal recessive 3 (SCDO3, MIM:609813), a condition of variable severity associated with vertebral and rib segmentation defects (Sparrow et al. 2006).

## Literature references

- Chapman, G., Sillence, D., Whittock, NV., Wouters, MA., Dunwoodie, SL., Turnpenny, PD. et al. (2006). Mutation of the LUNATIC FRINGE gene in humans causes spondylocostal dysostosis with a severe vertebral phenotype. *Am. J. Hum. Genet.*, 78, 28-37. ↗
- Brückner, K., Cohen, S., Perez, L., Clausen, H. (2000). Glycosyltransferase activity of Fringe modulates Notch-Delta interactions. *Nature*, 406, 411-5. ↗
- Bashirullah, A., Whiting, E., Phillips, RA., Boulianne, G., Egan, SE., Campbell, C. et al. (1997). Fringe boundaries coincide with Notch-dependent patterning centres in mammals and alter Notch-dependent development in *Drosophila*. *Nat Genet*, 16, 283-8. ↗
- Prabhakaran, B., Johnston, SH., Irvine, KD., Rauskolb, C., Wilson, R., Vogt, TF. (1997). A family of mammalian Fringe genes implicated in boundary determination and the Notch pathway. *Development*, 124, 2245-54. ↗

## Editions

2013-11-07	Authored, Edited	Jassal, B.
2015-12-18	Reviewed	Joshi, HJ., Hansen, L.

# Table of Contents

Introduction	1
❖ Diseases associated with O-glycosylation of proteins	2
❖ Defective GALNT3 causes HFTC	3
❖ Defective GALNT12 causes CRCS1	5
❖ Defective C1GALT1C1 causes TNPS	6
❖ Defective B3GALTL causes PpS	7
❖ Defective POMT1 causes MDDGA1, MDDGB1 and MDDGC1	8
❖ Defective POMT2 causes MDDGA2, MDDGB2 and MDDGC2	9
❖ Defective POMGNT1 causes MDDGA3, MDDGB3 and MDDGC3	10
❖ Defective LARGE causes MDDGA6 and MDDGB6	11
❖ Defective LFNG causes SCDO3	12
Table of Contents	14