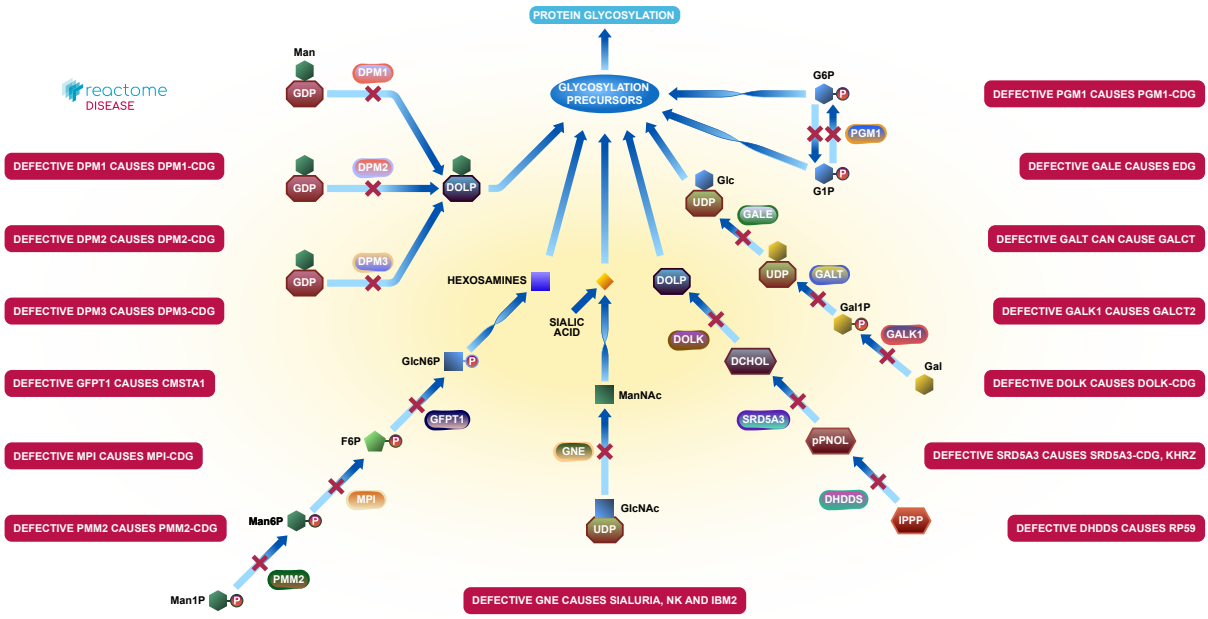
Diseases associated with glycosylation precursor biosynthesis



Jassal, B., Spillmann, D., Timson, DJ.

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

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.

25/04/2024

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. ↗

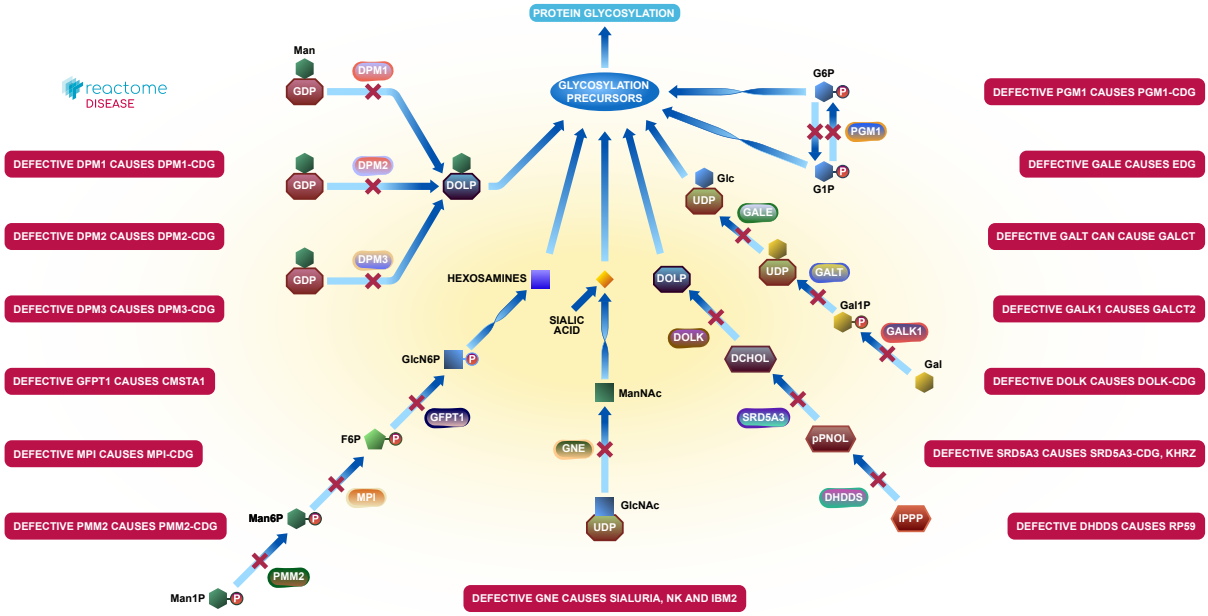
Reactome database release: 88

This document contains 15 pathways (see Table of Contents)

Diseases associated with glycosylation precursor biosynthesis ↗

Stable identifier: R-HSA-5609975

Diseases: congenital disorder of glycosylation



Glycosylation diseases associated with the enzymes that mediate the biosynthesis of glycosylation precursors are curated in this section (Jaeken & Matthijs 2007, Freeze et al. 2015).

Literature references

Freeze, HH., Ng, BG., Eklund, EA., Patterson, MC. (2015). Neurological Aspects of Human Glycosylation Disorders. *Annu. Rev. Neurosci.*. ↗

Matthijs, G., Jaeken, J. (2007). Congenital disorders of glycosylation: a rapidly expanding disease family. *Annu Rev Genomics Hum Genet, 8*, 261-78. ↗

Editions

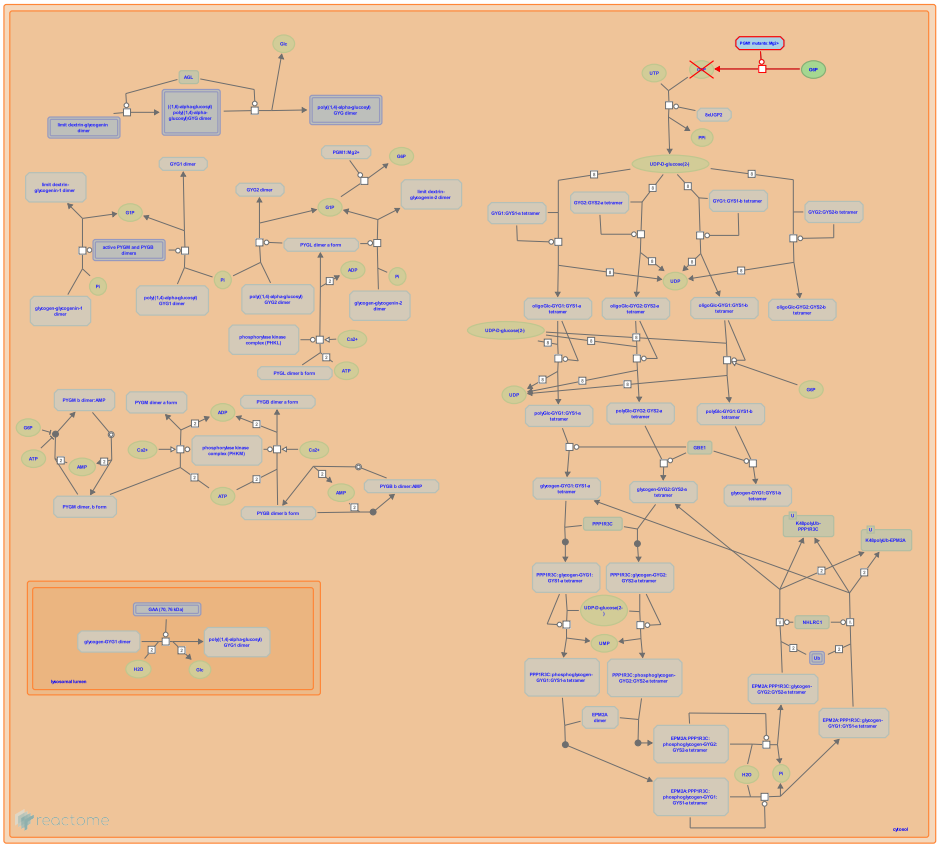
2014-07-09	Reviewed	Spillmann, D.
2014-07-18	Authored, Edited	Jassal, B.
2015-02-25	Reviewed	Timson, DJ.

Defective PGM1 causes PGM1-CDG ↗

Location: Diseases associated with glycosylation precursor biosynthesis

Stable identifier: R-HSA-5609974

Diseases: congenital disorder of glycosylation



Phosphoglucomutases 1 and 2 (PGM1, 2) are involved in the cytosolic biosynthesis of nucleotide sugars needed for glycan biosynthesis, specifically, the isomerisation of glucose-6-phosphate (G6P) into glucose-1-phosphate (G1P). Defects in PGM1 can cause congenital disorder of glycosylation 1t (CDG1t, now known as PGM1-CDG; MIM:614921), a broad spectrum disorder characterised by under-glycosylated serum glycoproteins (Timal et al. 2012, Tegtmeyer et al. 2014). CDGs result in a wide variety of clinical features such as defects in nervous system development, psychomotor retardation, dysmorphic features, hypotonia, coagulation disorders, and immunodeficiency.

Literature references

Paprocka, J., Thiel, C., Morava, E., Rodenburg, RJ., Hoischen, A., Timal, S. et al. (2012). Gene identification in the congenital disorders of glycosylation type I by whole-exome sequencing. *Hum. Mol. Genet., 21*, 4151-61. ↗

Tegtmeyer, LC., Debus, V., Seyyedi, S., Rymen, D., Ficicioglu, C., He, P. et al. (2014). Multiple phenotypes in phosphoglucomutase 1 deficiency. *N. Engl. J. Med., 370*, 533-42. ↗

Editions

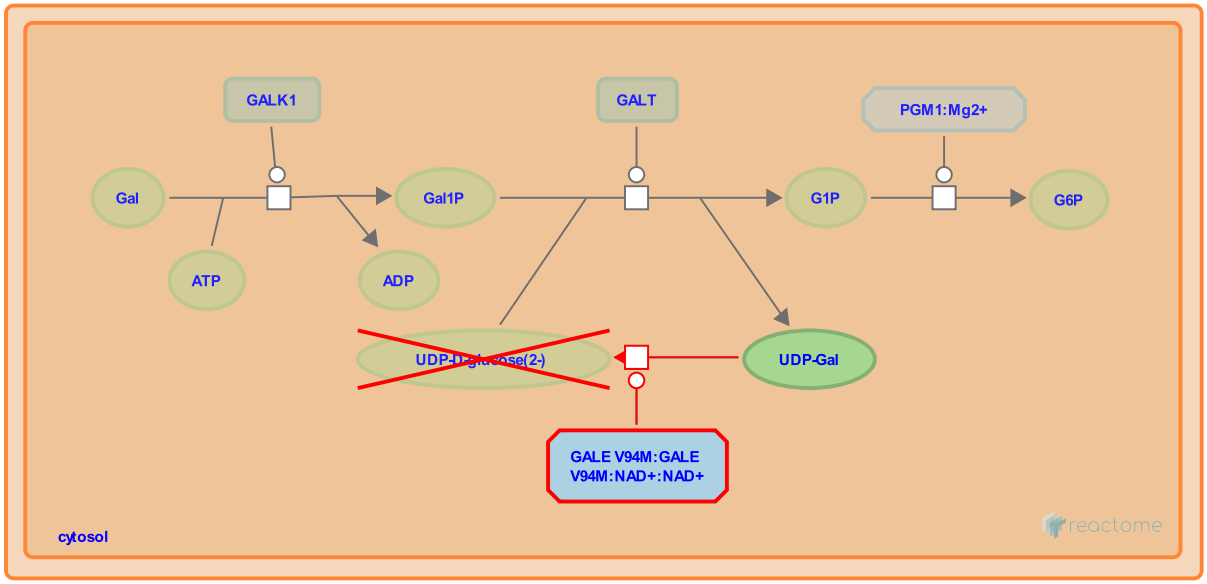
2014-07-18	Authored, Edited	Jassal, B.
2015-04-30	Reviewed	Spillmann, D.

Defective GALE causes EDG ↗

Location: Diseases associated with glycosylation precursor biosynthesis

Stable identifier: R-HSA-5609977

Diseases: galactosemia



Cytosolic UDP-galactose 4'-epimerase (GALE) catalyses the reversible interconversion of UDP-D-galactose (UDP-Gal) and UDP-glucose (UDP-Glc), the third reacton in the Leloir pathway of galactose metabolism. GALE can also catalyse the epimerisation of UDP-N-acetylglucosamine to UDP-N-acetylgalactosamine. The active form of the enzyme is a homodimer with one molecule of bound NAD per monomer (GALE:NAD+ dimer). Defects in GALE can cause Epimerase-deficiency galactosemia (EDG; MIM:230350), or type III galactosemia (diseases of galactose metabolism) whose clinical features include early-onset cataracts, liver damage, deafness and mental retardation. Historically, it was considered that there were two forms of GALE deficidency; a benign ("peripheral") form where there is no GALE activity in red blood cells and characterised by mild symptoms (Gitzelmann 1972) and a rarer "generalised" form with no detectable GALE activity in all tissues resulting in more severe symptoms (Holton et al. 1981). The disease is now considered to be a continuum (Openo et al. 2006).

Literature references

Gitzelmann, R. (1972). Deficiency of uridine diphosphate galactose 4-epimerase in blood cells of an apparently healthy infant. Preliminary communication. *Helv Paediatr Acta, 27*, 125-30. ↗

Yu, C., Scaglia, F., Fridovich-Keil, JL., Schnur, RE., Lamance, K., Schroer, RJ. et al. (2006). Epimerase-deficiency galactosemia is not a binary condition. *Am. J. Hum. Genet., 78*, 89-102. ↗

Young, R., Holton, JB., Gillett, MG., MacFaul, R. (1981). Galactosaemia: a new severe variant due to uridine diphosphate galactose-4-epimerase deficiency. *Arch. Dis. Child., 56*, 885-7. ↗

Editions

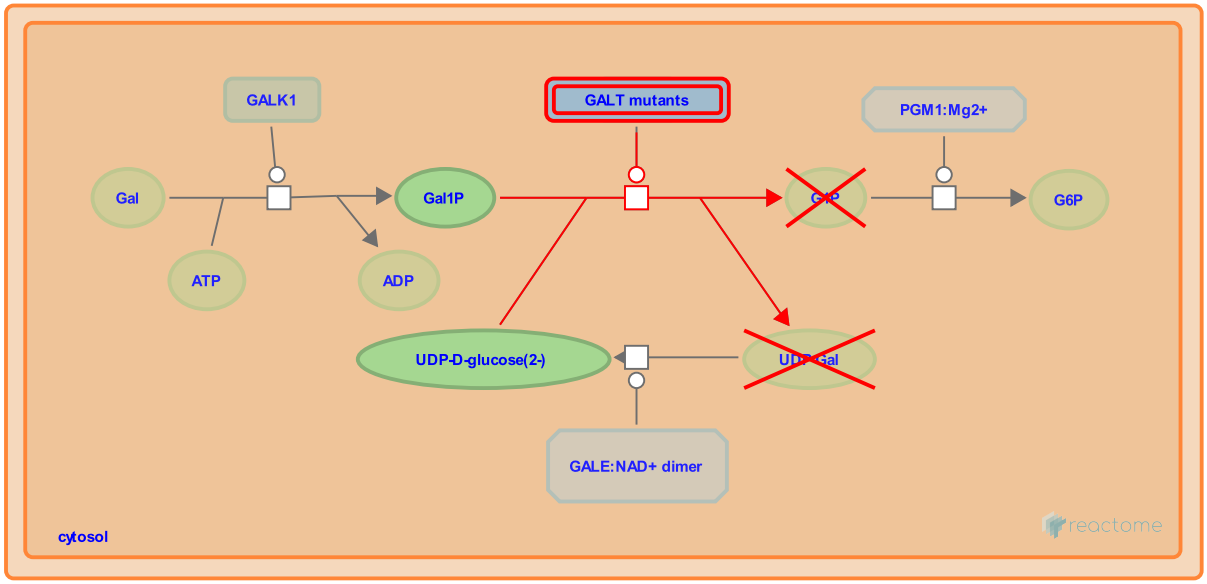
2014-07-18	Authored, Edited	Jassal, B.
2015-02-25	Reviewed	Timson, DJ.

Defective GALT can cause GALCT ↗

Location: Diseases associated with glycosylation precursor biosynthesis

Stable identifier: R-HSA-5609978

Diseases: galactosemia



Galactose-1-phosphate uridylyltransferase (GALT) is one of the enzymes involved in galactose metabolism in the Leloir pathway. GALT catalyses the transfer of uridine monophosphate (UMP) from UDP-glucose (UDP-Glc) to galactose-1-phosphate (Gal1P) to form UDP-galactose (UDP-Gal) and glucose 1-phosphate. Defects in GALT can cause Galactosemia (GALCT; MIM:230400), an autosomal recessive disorder of galactose metabolism presenting in neonatals that causes jaundice, cataracts and mental retardation (Bosch 2006).

Literature references

Bosch, AM. (2006). Classical galactosaemia revisited. *J. Inherit. Metab. Dis., 29,* 516-25. ↗

Editions

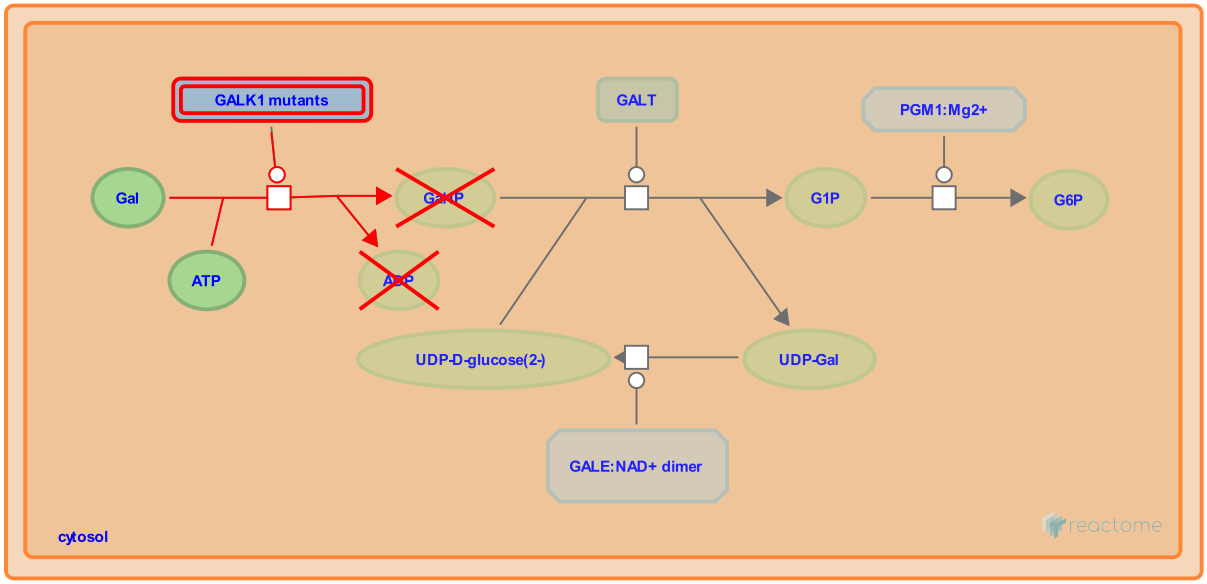
2014-07-18	Authored, Edited	Jassal, B.
2015-02-25	Reviewed	Timson, DJ.

Defective GALK1 causes GALCT2 ↗

Location: Diseases associated with glycosylation precursor biosynthesis

Stable identifier: R-HSA-5609976

Diseases: galactokinase deficiency



Cytosolic galactokinase (GALK1) catalyses the first committed step in the Leloir pathway of galactose metabolism. GALK1 catalyses the phosphorylation of D-galactose (Gal) to form D-galactose 1-phosphate (Gal1P). Defects in GALK1 can cause type II galactosemia (GALCT2; MIM:230200), an autosomal recessive deficiency characterised by congenital cataracts during infancy and presenile cataracts in the adult population. Galactitol accumulation in the lens is the cause of these cataracts (Bosch et al. 2002).

Literature references

Wijburg, FA., Bakker, HD., van Gennip, AH., Wanders, RJA., Bosch, AM., van Kempen, JV. (2002). Clinical features of galactokinase deficiency: a review of the literature. *J. Inherit. Metab. Dis., 25*, 629-34. ↗

Editions

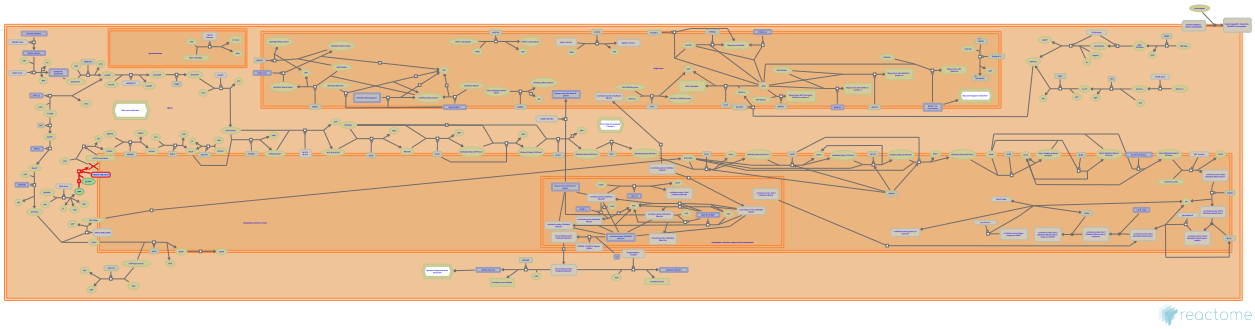
2014-07-18	Authored, Edited	Jassal, B.
2015-02-25	Reviewed	Timson, DJ.

Defective DHDDS causes RP59 ↗

Location: Diseases associated with glycosylation precursor biosynthesis

Stable identifier: R-HSA-4755609

Diseases: retinitis pigmentosa



The ER membrane-associated enzyme dehydrodolichyl diphosphate synthase (DHDDS) (Endo et al. 2003) normally mediates the sequential head-to-tail cis addition of multiple isopentyl pyrophosphate (IPP) molecules to farnesyl pyrophosphate (E,E-FPP) to produce polyprenol pyrophosphate (pPPP) (Shridas et al. 2003). Dolichol in humans contain homologues ranging from 17-23 isoprene units, the most common homologues contain 19 or 20 isoprene units (Freeman et al. 1980). Dolichol is an important substrate in the N-glycosylation of proteins, including rhodopsin.

Defects in DHDDS cause retinitis pigmentosa 59 (RP59; MIM:613861), a pigment retinopathy, characterised by retinal pigment deposits (visible on fundus examination) and primary loss of rod photoreceptors followed by secondary loss of cone photoreceptors. Sufferers typically have night vision blindness and loss of mid to peripheral vision. As the condition progresses, they lose far peripheral vision and eventually central vision (Zuchner et al. 2011).

Literature references

Rupar, CA., Carroll, KK., Freeman, DJ. (1980). Analysis of dolichol in human tissues by high pressure liquid chromatography. *Lipids, 15*, 191-3. ↗

Züchner, S., Buxbaum, JD., Wen, R., Vance, JM., Farooq, A., Pericak-Vance, MA. et al. (2011). Whole-exome sequencing links a variant in DHDDS to retinitis pigmentosa. *Am. J. Hum. Genet., 88*, 201-6. ↗

Shridas, P., Waechter, CJ., Rush, JS. (2003). Identification and characterization of a cDNA encoding a long-chain cis-isoprenyltranferase involved in dolichyl monophosphate biosynthesis in the ER of brain cells. *Biochem. Biophys. Res. Commun., 312*, 1349-56. ↗

Zhang, YW., Koyama, T., Takahashi, S., Endo, S. (2003). Identification of human dehydrodolichyl diphosphate synthase gene. *Biochim. Biophys. Acta, 1625*, 291-5. ↗

Editions

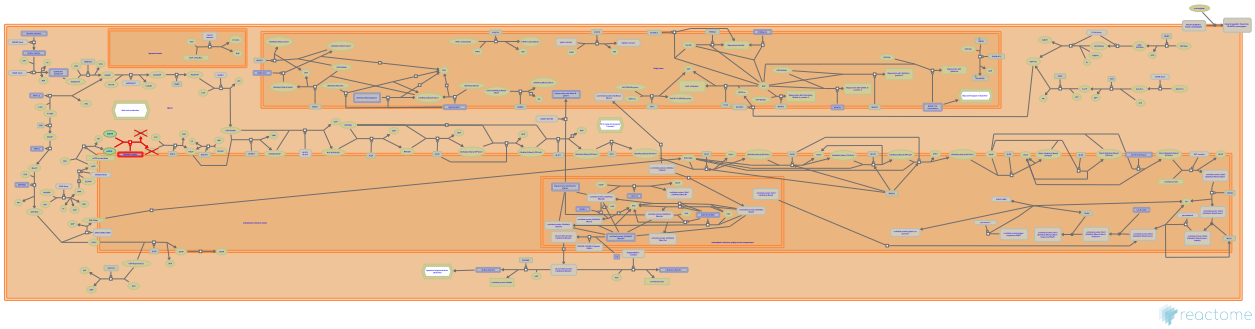
2013-10-25	Authored, Edited	Jassal, B.
2015-04-30	Reviewed	Spillmann, D.

Defective SRD5A3 causes SRD5A3-CDG, KHRZ ↗

Location: Diseases associated with glycosylation precursor biosynthesis

Stable identifier: R-HSA-4755579

Diseases: congenital disorder of glycosylation type I



Polyprenol reductase (SRD5A3), resident on the endoplasmic reticulum membrane, normally mediates the reduction of the alpha-isoprene unit of polyprenol (pPNOL) to form dolichol (DCHOL) in a NADPH-dependent manner (Cantagrel et al. 2010). DCHOLs are substrates required for the synthesis of the lipid-linked oligosaccharide (LLO) precursor used for N-glycosylation. Defects in SRD5A3 cause congenital disorder of glycosylation 1q (SRD5A3-CDG, CDG1q; MIM:612379), a neurodevelopmental disorder characterised by under-glycosylated serum glycoproteins resulting in nervous system development, psychomotor retardation, hypotonia, coagulation disorders and immunodeficiency (Cantagrel et al. 2010, Kasapkara et al. 2012). Defects in SRD5A3 can also cause Kahrizi syndrome (KHRZ; MIM:612713), a neurodevelopmental disorder characterised by mental retardation, cataracts, holes in eye structures, pathological curvature of the spine, and coarse facial features (Kahrizi et al. 2011).

Literature references

Kuss, AW., Chen, W., Ullmann, R., Kahrizi, K., Tzschach, A., Garshasbi, M. et al. (2011). Next generation sequencing in a family with autosomal recessive Kahrizi syndrome (OMIM 612713) reveals a homozygous frameshift mutation in SRD5A3. *Eur. J. Hum. Genet., 19*, 115-7. ↗

Swistun, D., Ali, BR., De Brouwer, AP., Morava, E., Freeze, HH., Ng, BG. et al. (2010). SRD5A3 is required for converting polyprenol to dolichol and is mutated in a congenital glycosylation disorder. *Cell, 142*, 203-17. ↗

Kasapkara, CS., Hasanoğlu, A., Tümer, L., Ezgü, FS., Matthijs, G., Race, V. et al. (2012). SRD5A3-CDG: a patient with a novel mutation. *Eur. J. Paediatr. Neurol., 16*, 554-6. ↗

Editions

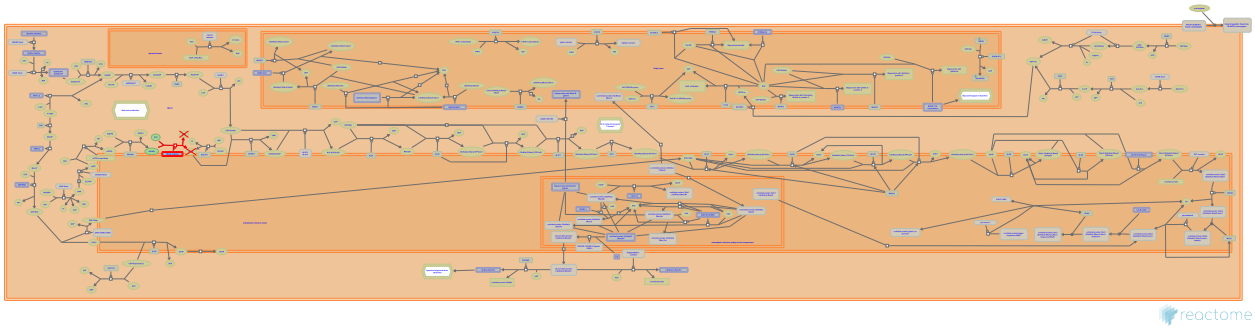
2013-10-25	Authored, Edited	Jassal, B.
2015-04-30	Reviewed	Spillmann, D.

Defective DOLK causes DOLK-CDG ↗

Location: Diseases associated with glycosylation precursor biosynthesis

Stable identifier: R-HSA-4755583

Diseases: congenital disorder of glycosylation type I



Dolichol kinase (DOLK, TMEM15) normally mediates the phosphorylation of dolichol (DCHOL) to form dolichyl phosphate (DOLP) in the ER membrane (Fernandez et al. 2002). DOLP is an important substrate in the synthesis of N- and O-glycosylated proteins and GPI anchors. Defects in DOLK cause congenital disorder of glycosylation type 1m (DOLK-CDG, CDG1m, also known as dolichol kinase deficiency; MIM:610768), a severe mutisystem disorder characterised by under-glycosylated serum glycoproteins. This disorder has a very severe phenotype and death can occur in early life (Kranz et al. 2007).

Literature references

Denecke, J., Jungeblut, C., Grobe, H., Debus, V., Reichel, S., Hammersen, G. et al. (2007). A defect in dolichol phosphate biosynthesis causes a new inherited disorder with death in early infancy. *Am J Hum Genet, 80*, 433-40. ↗

Shridas, P., Fernandez, F., Jiang, S., Waechter, CJ., Aebi, M. (2002). Expression and characterization of a human cDNA that complements the temperature-sensitive defect in dolichol kinase activity in the yeast sec59-1 mutant: the enzymatic phosphorylation of dolichol and diacylglycerol are catalyzed by separate CTP-mediated kinase activities in Saccharomyces cerevisiae. *Glycobiology, 12*, 555-62. ↗

Editions

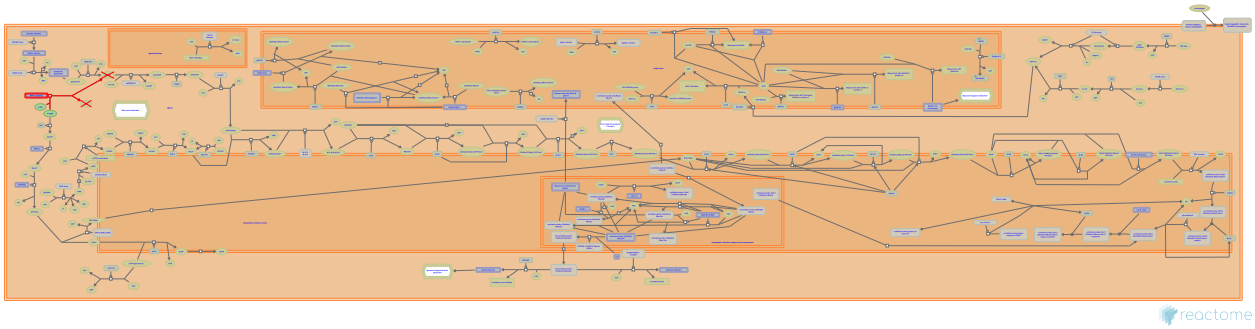
2013-10-25	Authored, Edited	Jassal, B.
2015-04-30	Reviewed	Spillmann, D.

Defective GFPT1 causes CMSTA1 ↗

Location: Diseases associated with glycosylation precursor biosynthesis

Stable identifier: R-HSA-4085023

Diseases: congenital disorder of glycosylation type I



Glucosamine-fructose 6-phosphate aminotransferases 1 and 2 (GFPT1,2) are the first and rate-limiting enzymes in the hexosamine synthesis pathway, and thus formation of hexosamines like N-acetylglucosamine (GlcNAc). These enzymes probably play a role in limiting the availability of substrates for the N- and O-linked glycosylation of proteins. GFPT1 and 2 are required for normal functioning of neuromuscular synaptic transmission. Defects in GFPT1 lead to myasthenia, congenital, with tubular aggregates 1 (CMSTA1; MIM:610542), characterised by altered muscle fibre morphology and impaired neuromuscular junction development. Sufferers of CMSTA1 show a good response to acetylcholinesterase inhibitors (Senderek et al. 2011). The missense mutations observed do not always result in significant reduction in enzyme activity, but biopsies show reduced amounts of GFPT1 protein suggesting increased turnover or defective translation (Senderek et al. 2011).

Literature references

Abicht, A., Dusl, M., Nilipour, Y., Straub, V., Colomer, J., Laval, SH. et al. (2011). Hexosamine biosynthetic pathway mutations cause neuromuscular transmission defect. *Am J Hum Genet, 88*, 162-72. ↗

Editions

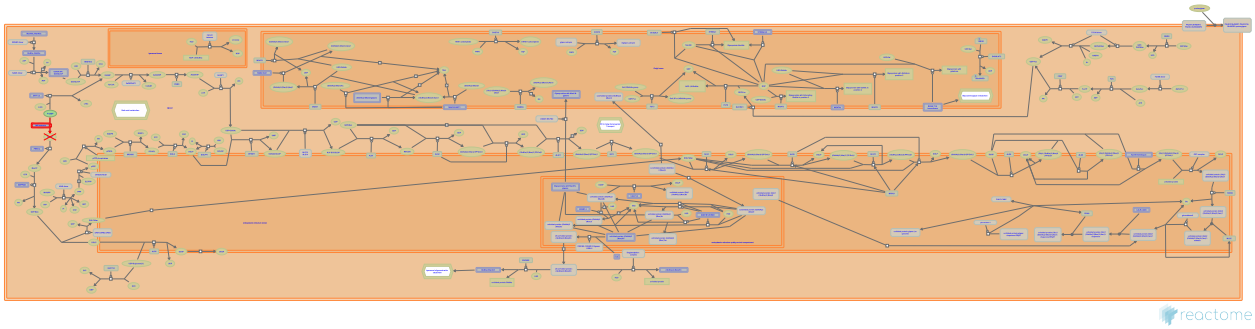
2013-08-01	Authored, Edited	Jassal, B.
2015-04-30	Reviewed	Spillmann, D.

Defective MPI causes MPI-CDG ↗

Location: Diseases associated with glycosylation precursor biosynthesis

Stable identifier: R-HSA-4043916

Diseases: congenital disorder of glycosylation type I



Mannose 6-phosphate isomerase (MPI) normally isomerises fructose 6-phosphate (Fru6P) to mannose 6-phosphate (Man6P) in the cytosol. Man6P is a precursor in the synthesis of GDP-mannose and dolichol-phosphate-mannose, required for mannosyl transfer reactions in the N-glycosylation of proteins. Defects in MPI cause congenital disorder of glycosylation 1b (MPI-CDG, previously known as CDG1b,; MIM:602579), a multisystem disorder characterised by under-glycosylated serum glycoproteins (Schollen et al. 2000). Unlike PMM2-CDG (CDG1a), there is no neurological involvement with MPI-CDG. Instead, patients present predominantly with diarrhoea, failure to thrive and protein-losing enteropathy (Pelletier et al. 1986). MPI-CDG is one of two CDGs that can be treated with oral mannose supplementation, but can be fatal if left untreated (Marquardt & Denecke 2003).

Literature references

Denecke, J., Marquardt, T. (2003). Congenital disorders of glycosylation: review of their molecular bases, clinical presentations and specific therapies. *Eur. J. Pediatr., 162*, 359-79. ↗

Brochu, P., Pelletier, VA., Morin, CL., Galéano, N., Roy, CC., Weber, AM. (1986). Secretory diarrhea with protein-losing enteropathy, enterocolitis cystica superficialis, intestinal lymphangiectasia, and congenital hepatic fibrosis: a new syndrome. *J. Pediatr., 108*, 61-5. ↗

Freeze, H., Huijmans, JG., Schollen, E., Patterson, M., Pronicka, E., Babovic-Vuksanovic, D. et al. (2000). Genomic organization of the human phosphomannose isomerase (MPI) gene and mutation analysis in patients with congenital disorders of glycosylation type Ib (CDG-Ib). *Hum Mutat, 16*, 247-52. ↗

Editions

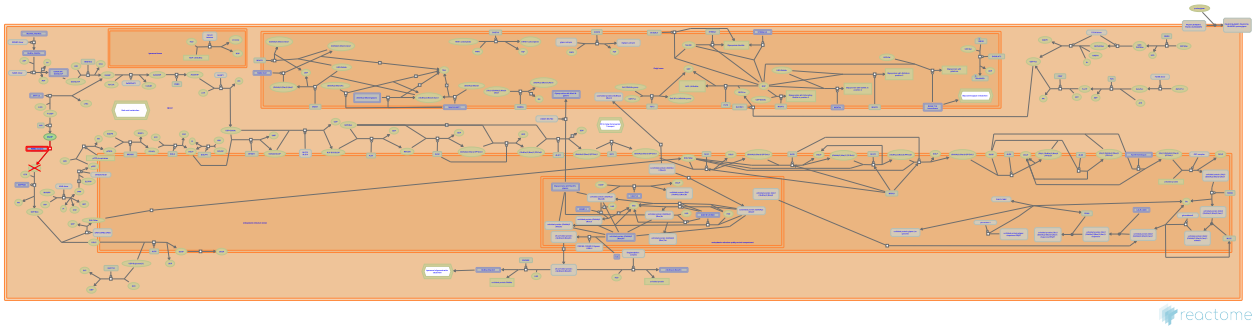
2013-07-29	Authored, Edited	Jassal, B.
2015-04-30	Reviewed	Spillmann, D.

Defective PMM2 causes PMM2-CDG ↗

Location: Diseases associated with glycosylation precursor biosynthesis

Stable identifier: R-HSA-4043911

Diseases: congenital disorder of glycosylation type I



Phosphomannomutase 2 (PMM2) normally catalyses the isomerisation of mannose 6-phosphate (Man6P) to mannose 1-phosphate (Man1P) in the cytosol of cells. Man1P is a precursor in the synthesis of GDP-mannose and dolichol-phosphate-mannose, required for critical mannosyl transfer reactions in the N-glycosylation of proteins. Mutations in the PMM2 gene are one of the causes of Jaeken syndrome, a congenital disorder of glycosylation type 1a (PMM2-CDG, previously CDG-1a) (Matthijs et al. 1997). PMM2-CDG was first described in Belgian identical twin sisters, characterized by psychomotor retardation and multiple serum glycoprotein abnormalities. Serum and CSF transferrin were found to be deficient in sialic acid (Jaeken et al. 1984). PMM2-CDG is the most common CDG disease subtype.

Literature references

Cassiman, JJ., Matthijs, G., Veiga-da-Cunha, M., Schollen, E., Jaeken, J., Van Schaftingen, E. et al. (1997). Mutations in PMM2, a phosphomannomutase gene on chromosome 16p13, in carbohydrate-deficient glycoprotein type I syndrome (Jaeken syndrome). *Nat Genet, 16*, 88-92. ↗

Eeckels, R., Corbeel, L., van der Heul, C., Eggermont, E., van Eijk, HG., Jaeken, J. (1984). Sialic acid-deficient serum and cerebrospinal fluid transferrin in a newly recognized genetic syndrome. *Clin. Chim. Acta, 144*, 245-7. ↗

Editions

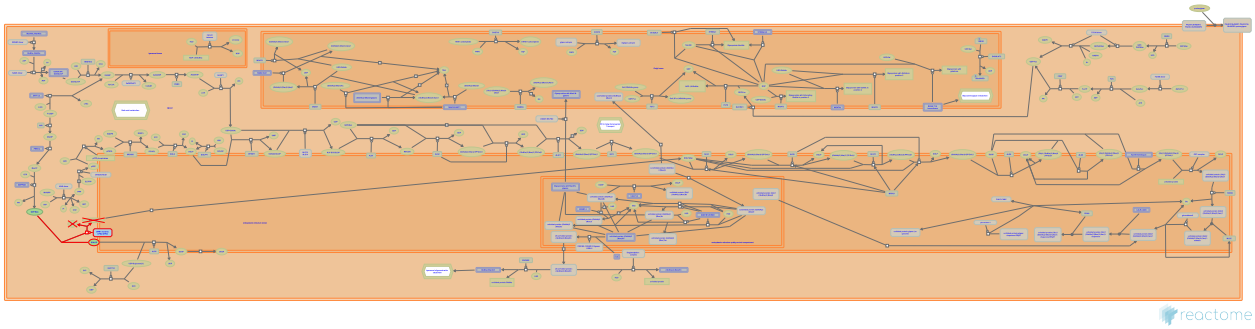
2013-07-29	Authored, Edited	Jassal, B.
2015-04-30	Reviewed	Spillmann, D.

Defective DPM1 causes DPM1-CDG ↗

Location: Diseases associated with glycosylation precursor biosynthesis

Stable identifier: R-HSA-4717374

Diseases: congenital disorder of glycosylation type I



Dolichyl-phosphate mannosyltransferase (DPM), a heterotrimeric protein embedded in the endoplasmic reticulum membrane, mediates the transfer of mannose (from cytosolic GDP-mannose) to dolichyl phosphate (DOLP) to form dolichyl-phosphate-mannose (DOLPman). The first subunit of the heterotrimer (DPM1) appears to be the actual catalyst, and the other two subunits (DPM2 and 3) appear to stabilise it (Maeda et al. 2000). Defects in DPM1 can cause congenital disorder of glycosylation 1e (DPM1-CDG, CDG-1e; MIM:608799), a multisystem disorder caused by a defect in glycoprotein biosynthesis and characterised by under-glycosylated serum glycoproteins (Kim et al. 2000, Imbach et al. 2000, Garcia-Silva et al. 2004).

Literature references

Kinoshita, T., Kangawa, K., Hino, J., Tanaka, S., Maeda, Y. (2000). Human dolichol-phosphate-mannose synthase consists of three subunits, DPM1, DPM2 and DPM3. *EMBO J, 19*, 2475-82. ↗

Stutz, A., Imbach, T., Aebi, M., Matthijs, G., King, MD., Schenk, B. et al. (2000). Deficiency of dolichol-phosphate-mannose synthase-1 causes congenital disorder of glycosylation type Ie. *J. Clin. Invest., 105*, 233-9. ↗

Westphal, V., Kim, S., Filiano, J., Peterson, S., Mehta, DP., Srikrishna, G. et al. (2000). Dolichol phosphate mannose synthase (DPM1) mutations define congenital disorder of glycosylation Ie (CDG-Ie). *J. Clin. Invest., 105*, 191-8. ↗

Sanchez del Pozo, J., Martí Herreros, M., Schollen, E., Martín Hernández, E., Hennet, T., García-Silva, MT. et al. (2004). Congenital disorder of glycosylation (CDG) type Ie. A new patient. *J. Inherit. Metab. Dis., 27*, 591-600. ↗

Editions

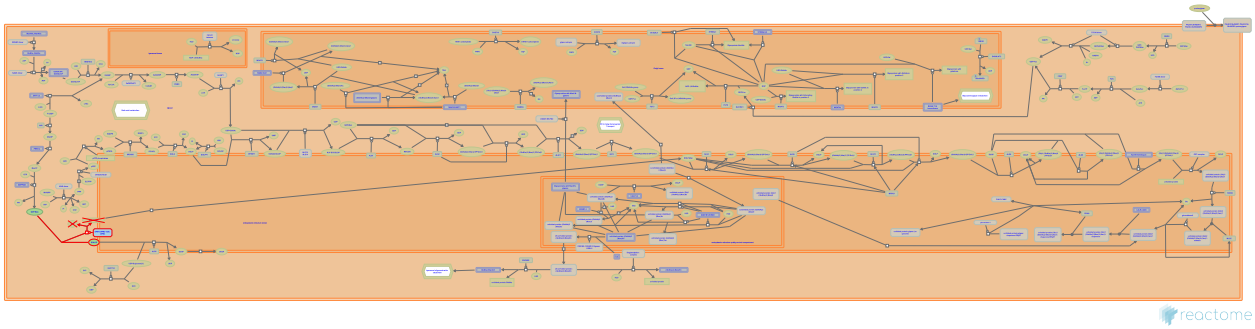
2013-10-17	Authored, Edited	Jassal, B.
2015-04-30	Reviewed	Spillmann, D.

Defective DPM2 causes DPM2-CDG ↗

Location: Diseases associated with glycosylation precursor biosynthesis

Stable identifier: R-HSA-4719377

Diseases: congenital disorder of glycosylation type I



Dolichyl-phosphate mannosyltransferase (DPM), a heterotrimeric protein embedded in the endoplasmic reticulum membrane, mediates the transfer of mannose (from cytosolic GDP-mannose) to dolichyl phosphate (DOLP) to form dolichyl-phosphate-mannose (DOLPman). The first subunit of the heterotrimer (DPM1) appears to be the actual catalyst, and the other two subunits (DPM2 and 3) appear to stabilise it (Maeda et al. 2000). Defects in DPM2 can cause congenital disorder of glycosylation 1u (DPM2-CDG, CDG1u; MIM:615042), a multisystem disorder caused by a defect in glycoprotein biosynthesis and characterised by under-glycosylated serum glycoproteins (Barone et al. 2012). CDG type 1 diseases result in a wide variety of clinical features, such as defects in the nervous system development, psychomotor retardation, dysmorphic features, hypotonia, coagulation disorders, and immunodeficiency.

Literature references

Kinoshita, T., Kangawa, K., Hino, J., Tanaka, S., Maeda, Y. (2000). Human dolichol-phosphate-mannose synthase consists of three subunits, DPM1, DPM2 and DPM3. *EMBO J, 19*, 2475-82. ↗

Passarelli, C., Morava, E., Barone, R., Sturiale, L., Foulquier, F., Race, V. et al. (2012). DPM2-CDG: a muscular dystrophy-dystroglycanopathy syndrome with severe epilepsy. *Ann. Neurol., 72*, 550-8. ↗

Editions

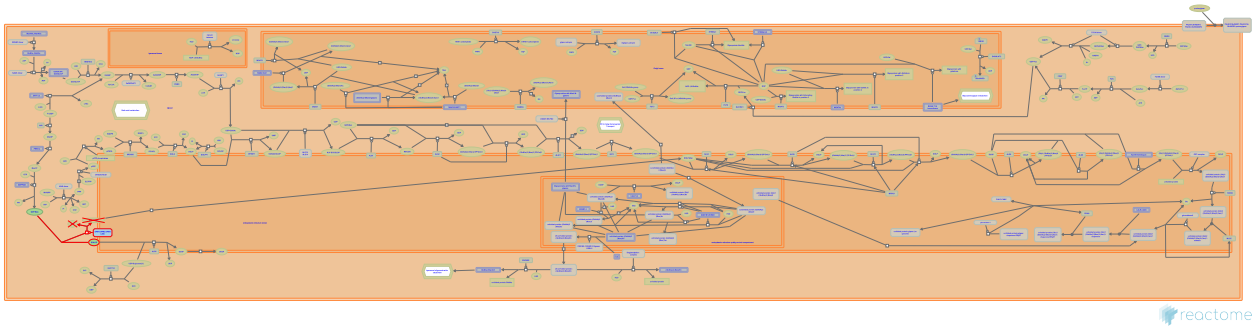
2013-10-18	Authored, Edited	Jassal, B.
2015-04-30	Reviewed	Spillmann, D.

Defective DPM3 causes DPM3-CDG ↗

Location: Diseases associated with glycosylation precursor biosynthesis

Stable identifier: R-HSA-4719360

Diseases: congenital disorder of glycosylation type I



Dolichyl-phosphate mannosyltransferase (DPM), a heterotrimeric protein embedded in the endoplasmic reticulum membrane, mediates the transfer of mannose (from cytosolic GDP-mannose) to dolichyl phosphate (DOLP) to form dolichyl-phosphate-mannose (DOLPman). The first subunit of the heterotrimer (DPM1) appears to be the actual catalyst, and the other two subunits (DPM2 and 3) appear to stabilise it (Maeda et al. 2000). Defects in DPM3 can cause congenital disorder of glycosylation 1o (DPM3-CDG, CDG1o; MIM:612937), a multisystem disorder caused by a defect in glycoprotein biosynthesis and characterised by under-glycosylated serum glycoproteins. CDG type 1 diseases result in a wide variety of clinical features, such as defects in the nervous system development, psychomotor retardation, dysmorphic features, hypotonia, coagulation disorders, and immunodeficiency (Lefeber et al. 2009).

Four biosynthetic pathways depend on DOLPman; N-glycosylation, O-mannosylation, C-Mannosylation and GPI-anchor biosynthesis. A defect in DPM3 strongly reduces O-mannosylation of alpha-dystroglycan, explaining the clinical phenotype of muscular dystrophy and linking the congenital disorders of glycosylation with the dystroglycanopathies (Lefeber et al. 2009).

Literature references

Ashida, H., Hess, D., Klein, D., Grünewald, S., Huyben, KM., Morava, E. et al. (2009). Deficiency of Dol-P-Man synthase subunit DPM3 bridges the congenital disorders of glycosylation with the dystroglycanopathies. *Am. J. Hum. Genet., 85*, 76-86. ↗

Kinoshita, T., Kangawa, K., Hino, J., Tanaka, S., Maeda, Y. (2000). Human dolichol-phosphate-mannose synthase consists of three subunits, DPM1, DPM2 and DPM3. *EMBO J, 19*, 2475-82. ↗

Editions

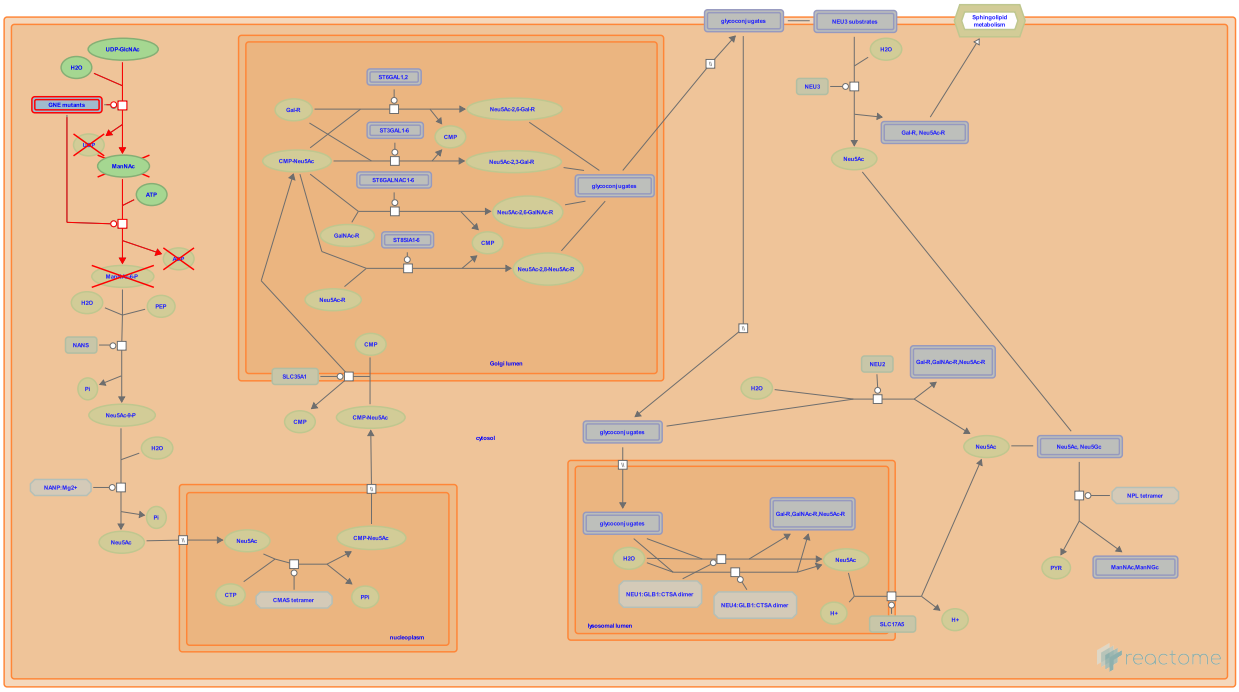
2013-10-18	Authored, Edited	Jassal, B.
2015-04-30	Reviewed	Spillmann, D.

Defective GNE causes sialuria, NK and IBM2 ↗

Location: Diseases associated with glycosylation precursor biosynthesis

Stable identifier: R-HSA-4085011

Diseases: sialuria, inclusion body myositis



Sialuria (MIM:269921) is caused by a metabolic defect where the UDP?N?acetylglucosamine 2?epimerase, N?acetylmannosamine kinase (GNE) gene lacks feedback inhibition resulting in constitutive overproduction of free sialic acid (Neu5Ac) (Montreuil et al. 1968, Fontaine et al. 1968). Sialuria is characterised by a large cytoplasmic accumulation and urinary excretion of Neu5Ac (Kamerling et al. 1979). Sialurias differ from sialidoses, in which there is storage and excretion of 'bound' Neu5Ac. Defects in GNE also cause Nonaka myopathy (NK; MIM:605820), an early adult-onset disorder characterised by muscle weakness and wasting of distal muscles, especially the anterior tibial muscles (Nonaka et al. 1981, Asaka et al. 2001). Defects in GNE also cause inclusion body myopathy 2 (IBM2; MIM:600737), an autosomal recessive disorder with a similar phenotype to Nonaka myopathy (NK). IBM2 is an adult-onset, proximal and distal muscle weakness and wasting disorder. Muscle biospsy reveals from sufferers shows a rimmed vacuole myopathy and the degenerating muscle fibers contained abnormal amounts of beta-amyloid protein such as that found in neurodegenerative diorders. However, there is no neurological symptoms in these patients (Argov & Yarom 1984).

Literature references

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Editions

2013-08-01	Authored, Edited	Jassal, B.
2015-04-30	Reviewed	Spillmann, D.

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