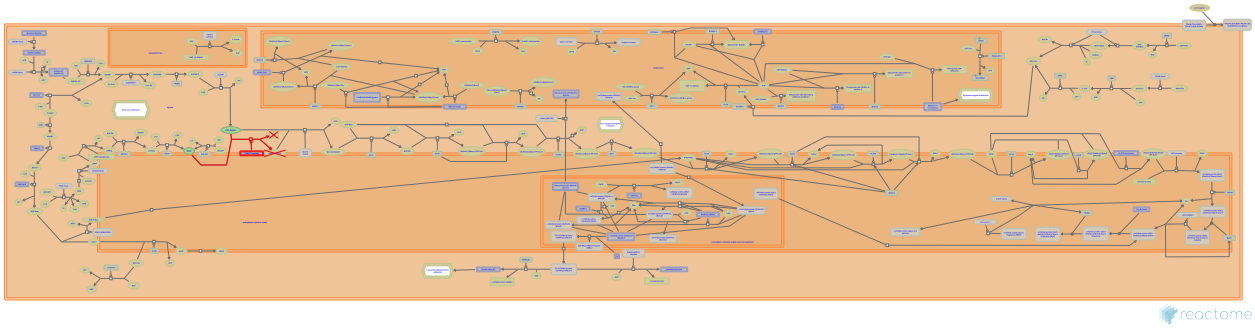
Defective DPAGT1 causes DPAGT1-CDG (CDG-1j) and CMSTA2



Belaya, K., Jassal, B.

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

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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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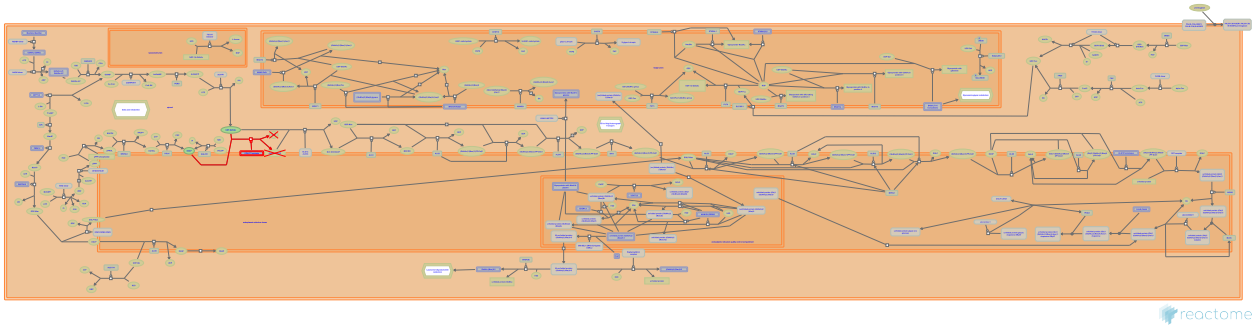
Defective DPAGT1 causes DPAGT1-CDG (CDG-1j) and CMSTA2 ↗

Stable identifier: R-HSA-4549356

Diseases: congenital disorder of glycosylation type I



UDP-N-acetylglucosamine--dolichyl-phosphate N-acetylglucosaminephosphotransferase (DPAGT1) catalyses the initial committed step in the biosynthesis of dolichyl pyrophosphate-oligosaccharides. Defects in DPAGT1 cause congenital disorder of glycosylation 1j (DPAGT1-CDG, previously known as CDG-1j; MIM:608093), a multisystem disorder characterised by under-glycosylated serum glycoproteins (Wu et al. 2003, Timal et al. 2012). Congenital disorders of glycosylation 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. Defects in DPAGT1 can also cause myasthenic syndrome, congenital, with tubular aggregates, 2 (CMSTA2; MIM:614750), characterised by muscle weakness of mainly the proximal limb muscles, with tubular aggregates present on muscle biopsy. Sufferers find walking difficult and fall frequently. Younger sufferers show hypotonia and poor head control. A disorder of neuromuscular transmission is detected on electromyography (Belaya et al. 2012, Finlayson et al. 2013).

Literature references

Belaya, K., Finlayson, S., Slater, CR., Cossins, J., Liu, WW., Maxwell, S. et al. (2012). Mutations in DPAGT1 cause a limb-girdle congenital myasthenic syndrome with tubular aggregates. *Am. J. Hum. Genet., 91*, 193-201. ↗

Wu, X., Rush, JS., Karaoglu, D., Krasnewich, D., Lubinsky, MS., Waechter, CJ. et al. (2003). Deficiency of UDP-GlcNAc:Dolichol Phosphate N-Acetylglucosamine-1 Phosphate Transferase (DPAGT1) causes a novel congenital disorder of Glycosylation Type Ij. *Hum Mutat, 22*, 144-50. ↗

Timal, S., Hoischen, A., Lehle, L., Adamowicz, M., Huijben, K., Sykut-Cegielska, J. et al. (2012). Gene identification in the congenital disorders of glycosylation type I by whole-exome sequencing. *Hum. Mol. Genet., 21*, 4151-61. ↗

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Editions

2013-09-12	Authored, Edited	Jassal, B.
2014-10-31	Reviewed	Belaya, K.

Defective DPAGT1 does not transfer GlcNAc to DOLP ↗

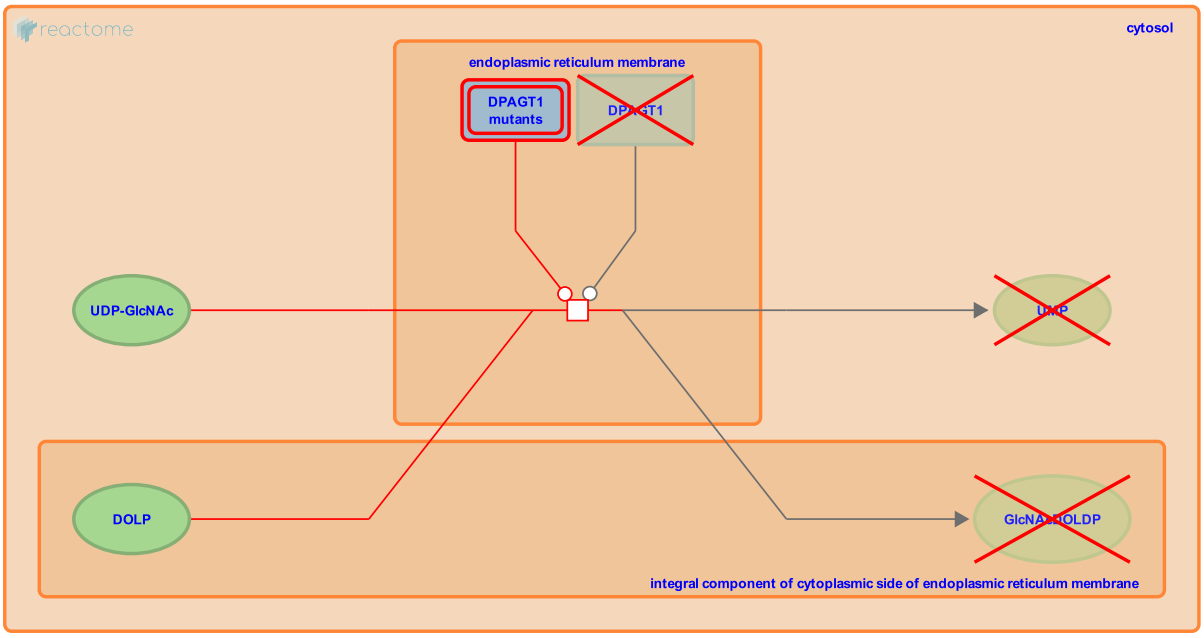
Location: Defective DPAGT1 causes DPAGT1-CDG (CDG-1j) and CMSTA2

Stable identifier: R-HSA-4549334

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol, integral component of cytoplasmic side of endoplasmic reticulum membrane

Diseases: congenital disorder of glycosylation type I



In the first committed step of N-glycan precursor (LLO) synthesis, UDP-N-acetylglucosamine--dolichyl-phosphate N-acetylglucosaminephosphotransferase (DPAGT1) normally catalyses the transfer of N-acetylglucosamine (GlcNAc), via an alpha-1,3 linkage, to a molecule of dolichyl phosphate (DOLP). Defects in DPAGT1 can cause congenital disorder of glycosylation, type 1j (DPAGT1-CDG, previously called CDG1j; MIM:608093), a multisystem disorder characterised by under-glycosylated serum glycoproteins. Clinical features include defective nervous system development, psychomotor retardation, coagulation diorders and immunodeficiency. Mutations causing DPAGT1-CDG include Y170C, I69N and a G-A transition in intron 1 (not shown here) which results in degradation of the mutant mRNA (Wu et al. 2003, Timal et al. 2012). Defects in DPAGT1 can also cause myasthenic syndrome, congenital, with tubular aggregates, 2 (CMSTA2; MIM:614750 a syndrome that arises from impaired neuromuscular transmission and characterised by muscle weakness, especially of the limb-girdle. Mutations causing CMSTA2 include V117I, M108I, L120M, T234Hfs*116 and V264G (Belaya et al. 2012).

Literature references

Wu, X., Rush, JS., Karaoglu, D., Krasnewich, D., Lubinsky, MS., Waechter, CJ. et al. (2003). Deficiency of UDP-GlcNAc:Dolichol Phosphate N-Acetylglucosamine-1 Phosphate Transferase (DPAGT1) causes a novel congenital disorder of Glycosylation Type Ij. *Hum Mutat, 22*, 144-50. ↗

Timal, S., Hoischen, A., Lehle, L., Adamowicz, M., Huijben, K., Sykut-Cegielska, J. et al. (2012). Gene identification in the congenital disorders of glycosylation type I by whole-exome sequencing. *Hum. Mol. Genet., 21*, 4151-61. ↗

Belaya, K., Finlayson, S., Slater, CR., Cossins, J., Liu, WW., Maxwell, S. et al. (2012). Mutations in DPAGT1 cause a limb-girdle congenital myasthenic syndrome with tubular aggregates. *Am. J. Hum. Genet., 91*, 193-201. ↗

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