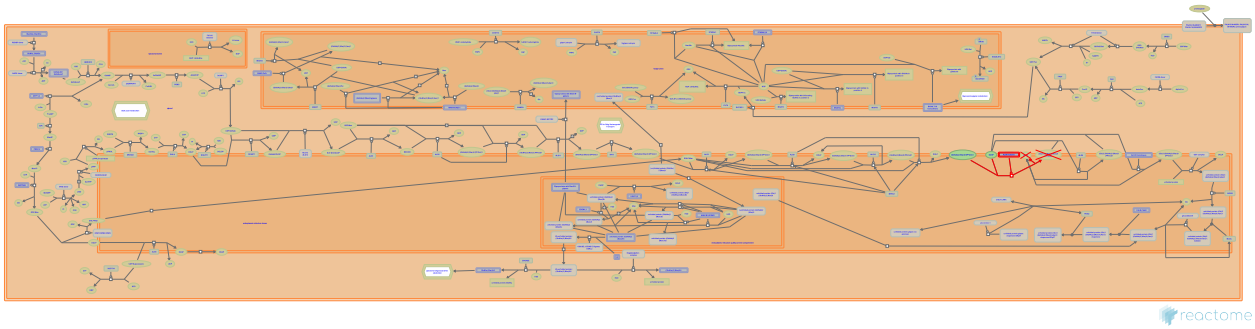
Defective ALG6 causes CDG-1c



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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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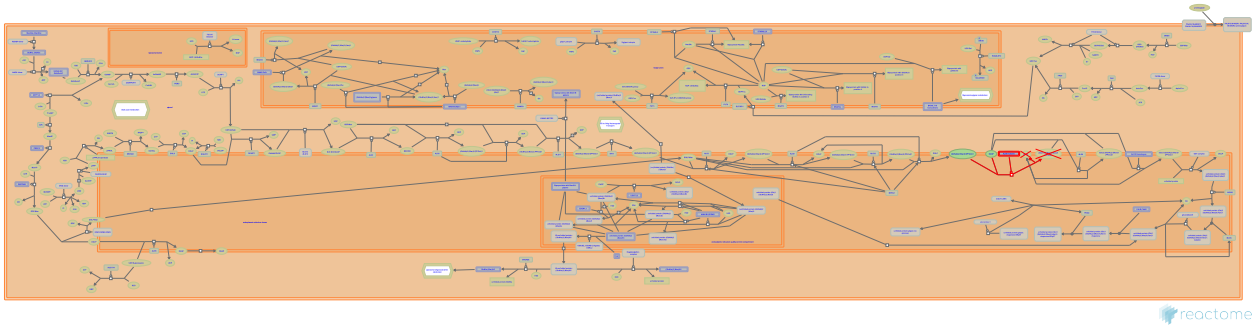
Defective ALG6 causes CDG-1c ↗

Stable identifier: R-HSA-4724289

Diseases: congenital disorder of glycosylation type I



Dolichyl pyrophosphate Man9GlcNAc2 alpha-1,3-glucosyltransferase (ALG6) normally adds the first glucose moiety to the lipid-linked oligosaccharide precursor (LLO aka N-glycan precursor) which is required for subsequent N-glycosylation of proteins (Imbach et al. 1999). Defects in ALG6 can cause congenital disorder of glycosylation 1c (ALG6-CDG, CDG-1c; MIM:603147), a multisystem disorder characterised by under-glycosylated serum glycoproteins (Imbach et al. 1999, Imbach et al. 2000, Westphal et al. 2000, Sun et al. 2005). ALG6 deficiency is accompanied by an accumulation of the N-glycan precursor (GlcNAc)2 (Man)9 (PP-Dol)1 and is the second most common CDG disease subtype after PMM2-CDG (CDG-1a) (Imbach et al. 1999). 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

Hennet, T., Wevers, RA., Burda, P., Berger, EG., Imbach, T., Aebi, M. et al. (1999). A mutation in the human ortholog of the Saccharomyces cerevisiae ALG6 gene causes carbohydrate-deficient glycoprotein syndrome type-Ic. *Proc Natl Acad Sci U S A, 96*, 6982-7. ↗

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Editions

2013-10-23	Authored, Edited	Jassal, B.
2014-10-31	Reviewed	Belaya, K.

Defective ALG6 does not add glucose to the N-glycan precursor ↗

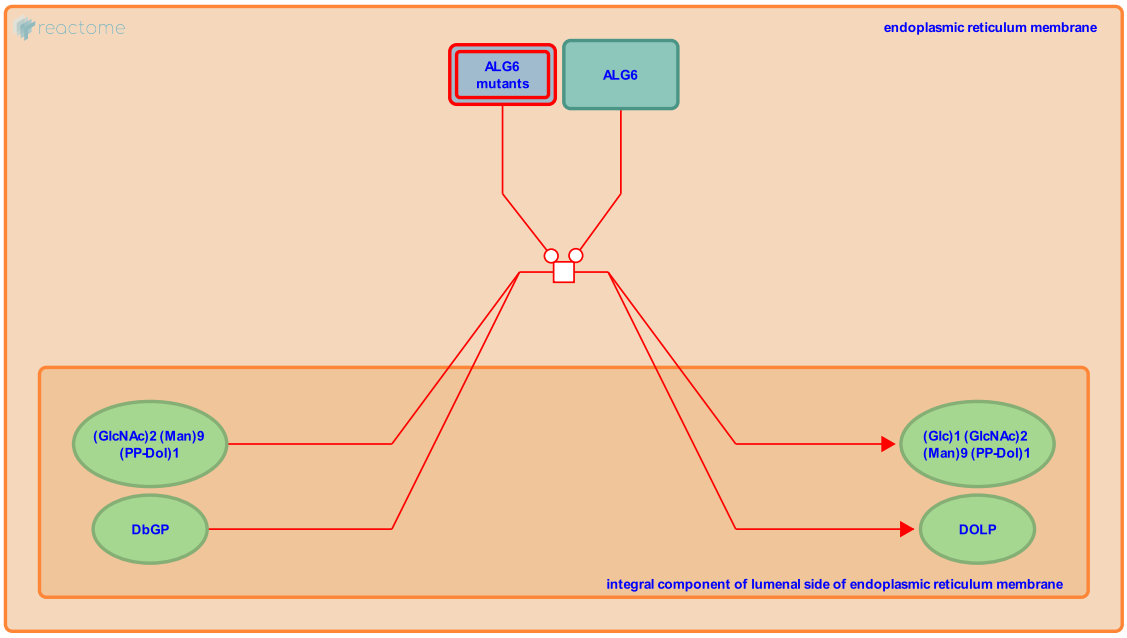
Location: Defective ALG6 causes CDG-1c

Stable identifier: R-HSA-4724291

Type: transition

Compartments: endoplasmic reticulum membrane, integral component of lumenal side of endoplasmic reticulum membrane

Diseases: congenital disorder of glycosylation type I



Dolichyl pyrophosphate Man9GlcNAc2 alpha-1,3-glucosyltransferase (ALG6) normally adds the first glucose moiety to the lipid-linked oligosaccharide precursor (LLO aka N-glycan precursor) which is required for subsequent N-glycosylation of proteins (Imbach et al. 1999). Defects in ALG6 can cause congenital disorder of glycosylation 1c (ALG6-CDG, CDG-1c; MIM:603147), a multisystem disorder characterised by under-glycosylated serum glycoproteins (Imbach et al. 1999, Imbach et al. 2000, Westphal et al. 2000, Sun et al. 2005). ALG6 deficiency is accompanied by an accumulation of the N-glycan precursor (GlcNAc)2 (Man)9 (PP-Dol)1 (Imbach et al. 1999). 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. Mutations that can cause ALG6-CDG are A333V and S478P. The A333V mutation is the most commom mutation seen in ALG6-CDG patients. These mutations result in altered activity of ALG6 but don't completely abolish its activity (Imbach et al. 1999, Imbach et al. 2000, Dercksen et al. 2013). A c.257+5G>A splice site mutation (not shown here) that causes exon 3 skipping leads to a nonfunctional protein (Imbach et al. 2000, Westphal et al. 2000). Two more mutations can cause the build up of the N-glycan precursor (GlcNAc)2 (Man)9 (PP-Dol)1; a three bp deletion (897-899delAAT) in exon 9 and an intronic
mutation (680+2T>G) in intron 7 (neither shown here). Transduction of patient fibroblasts with a lentivirus carrying wildtype hALG6 improved the biochemical phenotype of the cells, confirming that these two mutations are disease-causing (Sun et al. 2005).

Literature references

Hennet, T., Wevers, RA., Burda, P., Berger, EG., Imbach, T., Aebi, M. et al. (1999). A mutation in the human ortholog of the Saccharomyces cerevisiae ALG6 gene causes carbohydrate-deficient glycoprotein syndrome type-Ic. *Proc Natl Acad Sci U S A, 96*, 6982-7. ↗

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2013-10-23	Authored, Edited	Jassal, B.
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