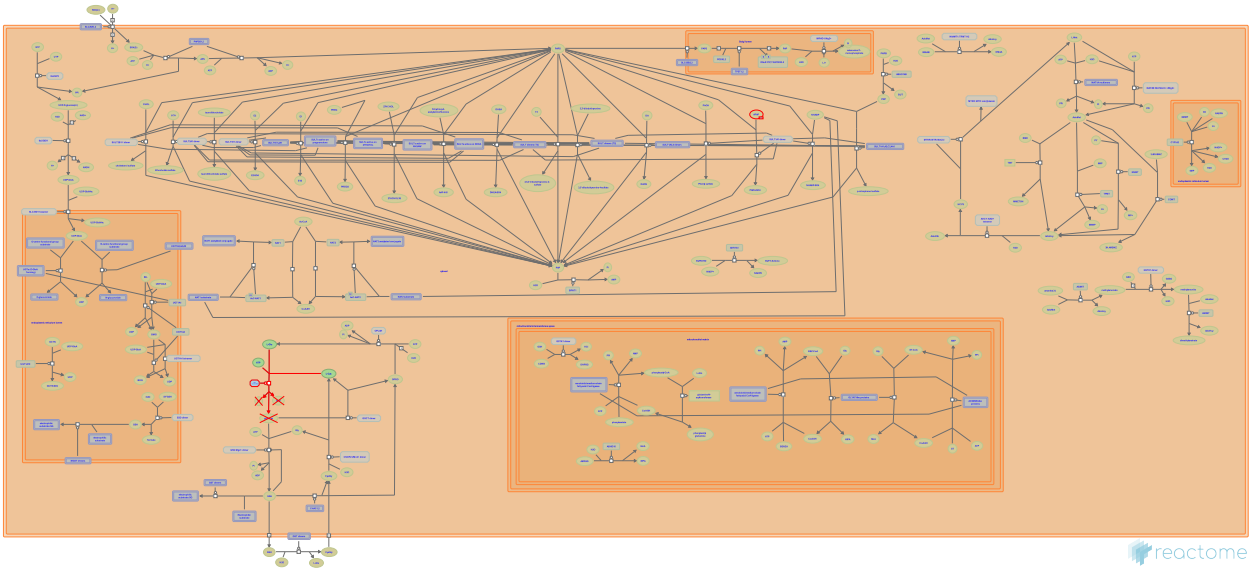
Defective GCLC causes HAGGSD



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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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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. ↗

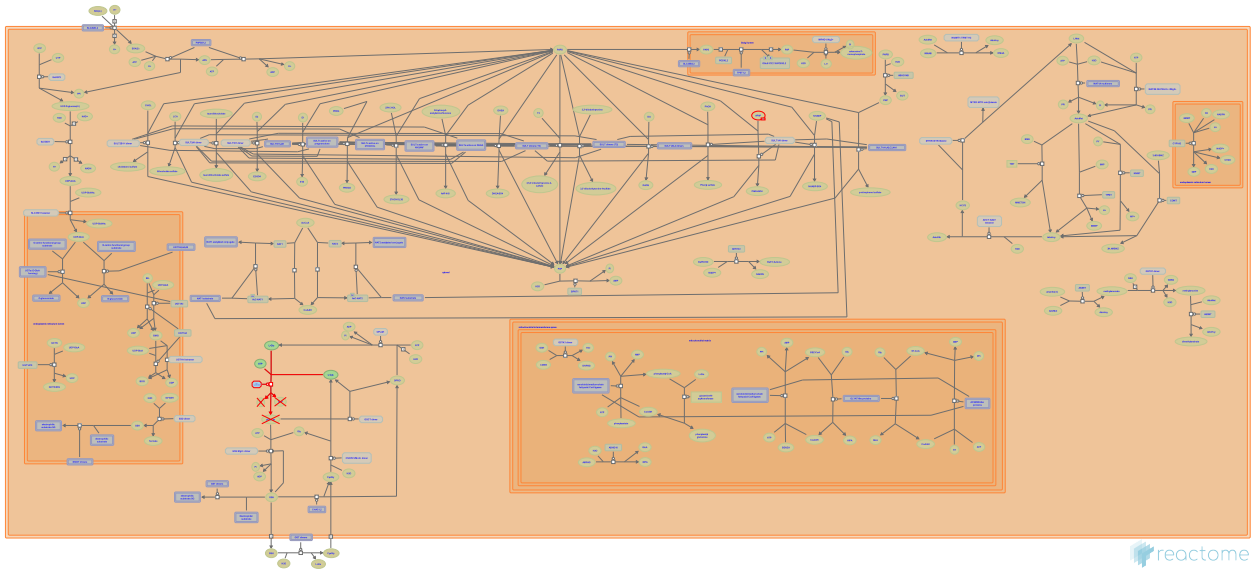
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Defective GCLC causes HAGGSD

Stable identifier: R-HSA-5578999

Diseases: hemolytic anemia



In mammalian cells, many antioxidant defence systems exist which protect cells from subsequent exposure to oxidant stresses. One antioxidant is glutathione (GSH), a tripeptide present in virtually all cells that regulates the intracellular redox state and protects cells from oxidative injury. It is metabolised via the gamma-glutamyl cycle, which is catalysed by six enzymes. In man, hereditary deficiencies have been found in five of the six enzymes. Gamma-glutamylcysteine ligase (GCL) catalyses the first and rate-limiting step in GSH biosynthesis. GCL is a heterodimer of a catalytic heavy chain (GCLC) and a regulatory light chain (GCLM). Defects in the catalytic GCLC can cause hemolytic anemia due to gamma-glutamylcysteine synthetase deficiency (HAGGSD; MIM:230450), a disease characterised by hemolytic anemia, glutathione deficiency, myopathy, late-onset spinocerebellar degeneration, and peripheral neuropathy (Ristoff & Larsson 2007, Aoyama & Nakaki 2013).

Literature references

Nakaki, T., Aoyama, K. (2013). Impaired glutathione synthesis in neurodegeneration. *Int J Mol Sci, 14*, 21021-44.

Larsson, A., Ristoff, E. (2007). Inborn errors in the metabolism of glutathione. *Orphanet J Rare Dis, 2*, 16.

Editions

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2014-11-03	Reviewed	Nakaki, T.

Defective GCLC does not ligate L-Glu to L-Cys ↗

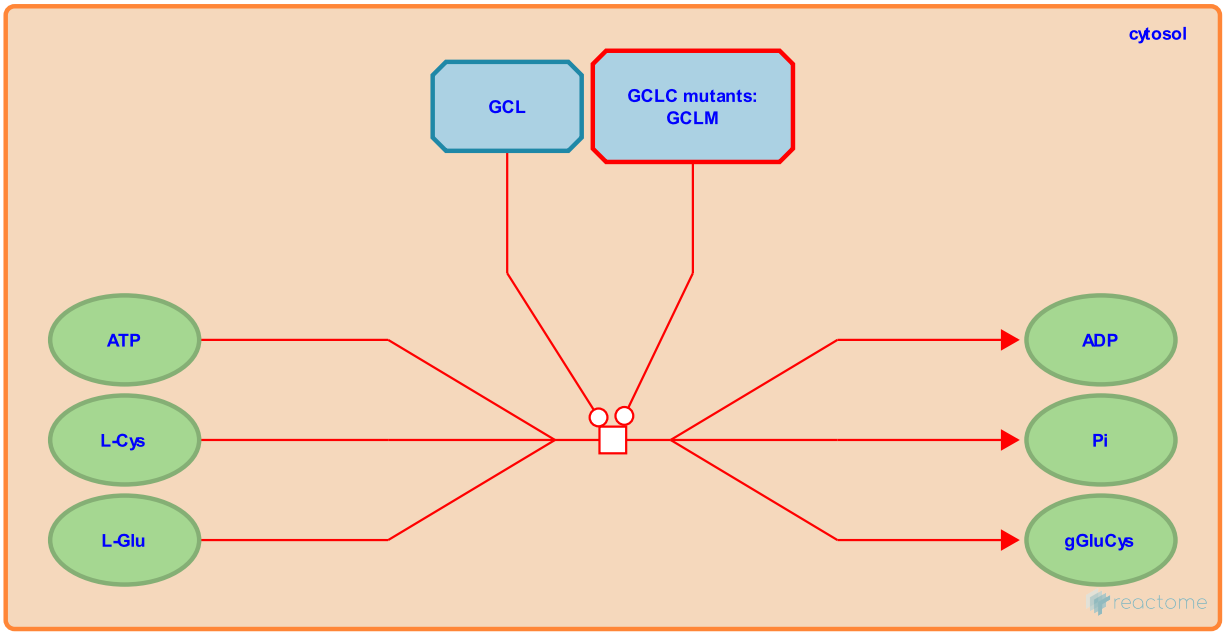
Location: Defective GCLC causes HAGGSD

Stable identifier: R-HSA-5602892

Type: transition

Compartments: cytosol

Diseases: hemolytic anemia



Gamma-glutamylcysteine ligase (GCL) catalyses the first and rate-limiting step in GSH biosynthesis. GCL is a heterodimer of a catalytic heavy chain (GCLC) and a regulatory light chain (GCLM). Defects in the catalytic GCLC can cause hemolytic anemia due to gamma-glutamylcysteine synthetase deficiency (HAGGSD; MIM:230450), a disease characterised by hemolytic anemia, glutathione deficiency, myopathy, late-onset spinocerebellar degeneration, and peripheral neuropathy. Mutations causing HAGGSD are H370L, P185L and R127C (Beutler et al. 1999, Ristoff et al. 2000, Hamilton et al. 2003).

Literature references

Alaoui-Jamali, M., Wu, JH., Batist, G., Hamilton, D. (2003). A novel missense mutation in the gamma-glutamyl-cysteine synthetase catalytic subunit gene causes both decreased enzymatic activity and glutathione production. *Blood, 102*, 725-30. ↗

Beutler, E., Matsunaga, AT., Kondo, T., Gelbart, T. (1999). The molecular basis of a case of gamma-glutamylcysteine synthetase deficiency. *Blood, 94*, 2890-4. ↗

Roos, D., Larsson, A., Weening, RS., Andersson, K., de Rijk, T., van Zwieten, R. et al. (2000). A missense mutation in the heavy subunit of gamma-glutamylcysteine synthetase gene causes hemolytic anemia. *Blood, 95*, 2193-6. ↗

Editions

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