Defective GGT1 does not hydrolyse glutamate from AFXBO-SG, AFNBO-SG

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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. ↗

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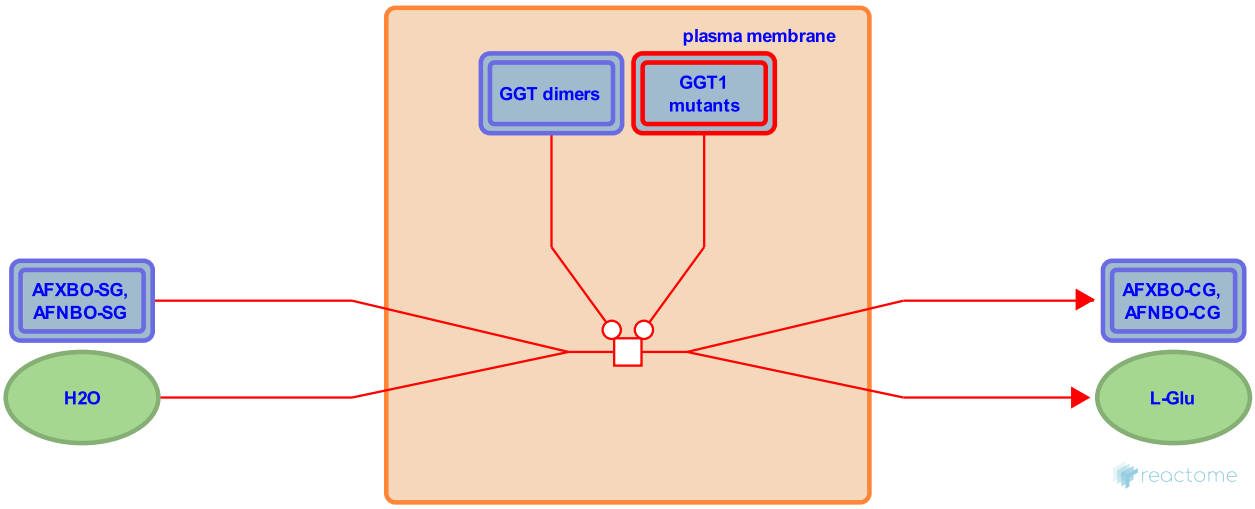
Stable identifier: R-HSA-5602984

Type: transition

Compartments: plasma membrane, extracellular region

Diseases: inherited metabolic disorder



To be excreted in urine, glutathione conjugates undergo several hydrolysis steps to form mercapturic acids which are readily excreted. The first step is the hydrolysis of a gamma-glutamyl residue from the conjugate catalysed by gamma-glutamyltransferases (GGTs). These are membrane-bound, heterodimeric enzymes composed of light and heavy peptide chains. Aflatoxin conjugates (AFXBO-SG, AFNBO-SG) can be hydrolysed in this way. Defects in GGT1 can cause glutathionuria (GLUTH; MIM:231950), an autosomal recessive disorder characterised by increased GSH concentration in the plasma and urine. Mutations that cause GLUTH can occur in both chains of the GGT1 dimer. R107H and R107Q in the heavy chain play a significant role in substrate binding rather than catalysis (Ikeda et al. 1993). S451A, S452A, D423A and D423E mutations in the light, catalytic chain of GGT1 completely or almost completely result in loss of function of the enzyme (Ikeda et al. 1995, Ikeda et al. 1995b).

Literature references

Fujii, J., Anderson, ME., Meister, A., Taniguchi, N., Ikeda, Y. (1995). Involvement of Ser-451 and Ser-452 in the catalysis of human gamma-glutamyl transpeptidase. *J. Biol. Chem., 270*, 22223-8. ↗

Fujii, J., Meister, A., Taniguchi, N., Ikeda, Y. (1995). Human gamma-glutamyl transpeptidase mutants involving conserved aspartate residues and the unique cysteine residue of the light subunit. *J. Biol. Chem., 270*, 12471-5. ↗

Fujii, J., Taniguchi, N., Ikeda, Y. (1993). Significance of Arg-107 and Glu-108 in the catalytic mechanism of human gamma-glutamyl transpeptidase. Identification by site-directed mutagenesis. *J. Biol. Chem., 268*, 3980-5. ↗

Editions

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