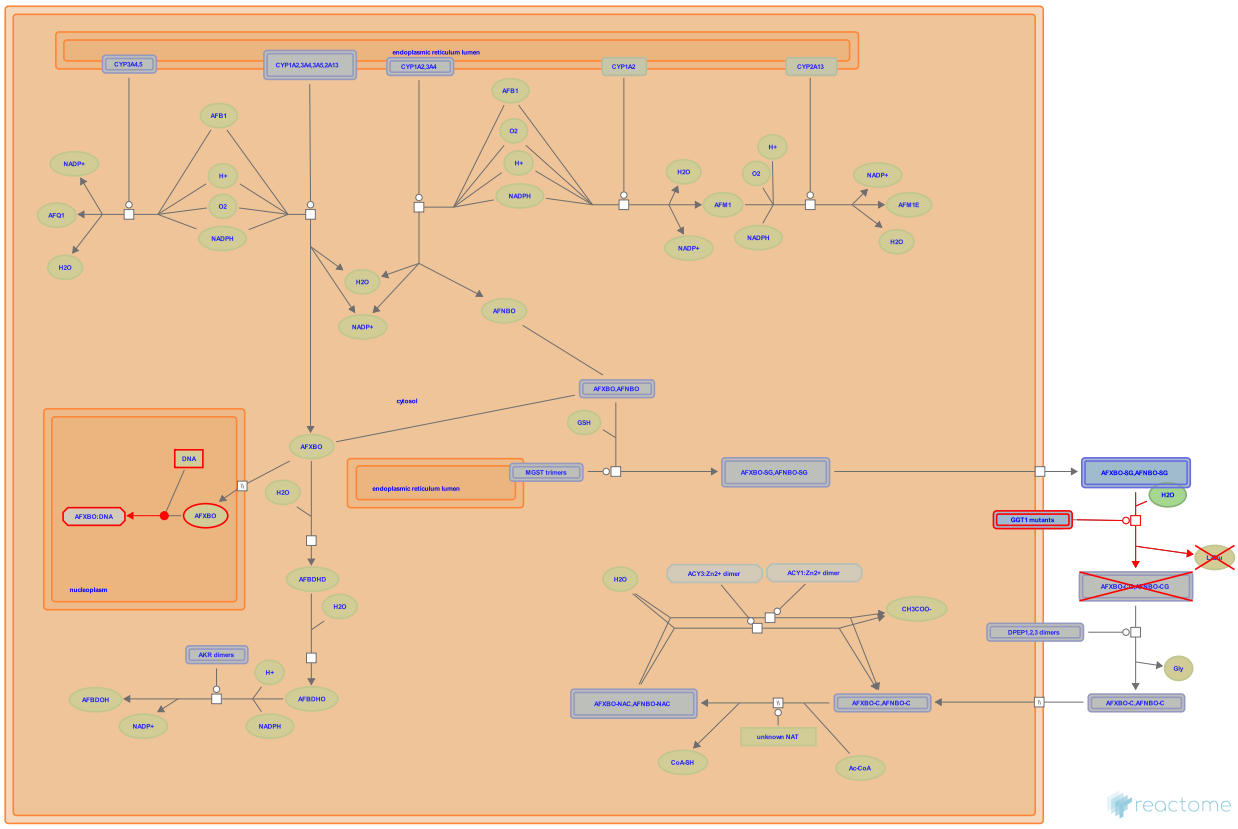
Defective GGT1 in aflatoxin detoxification causes GLUTH



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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

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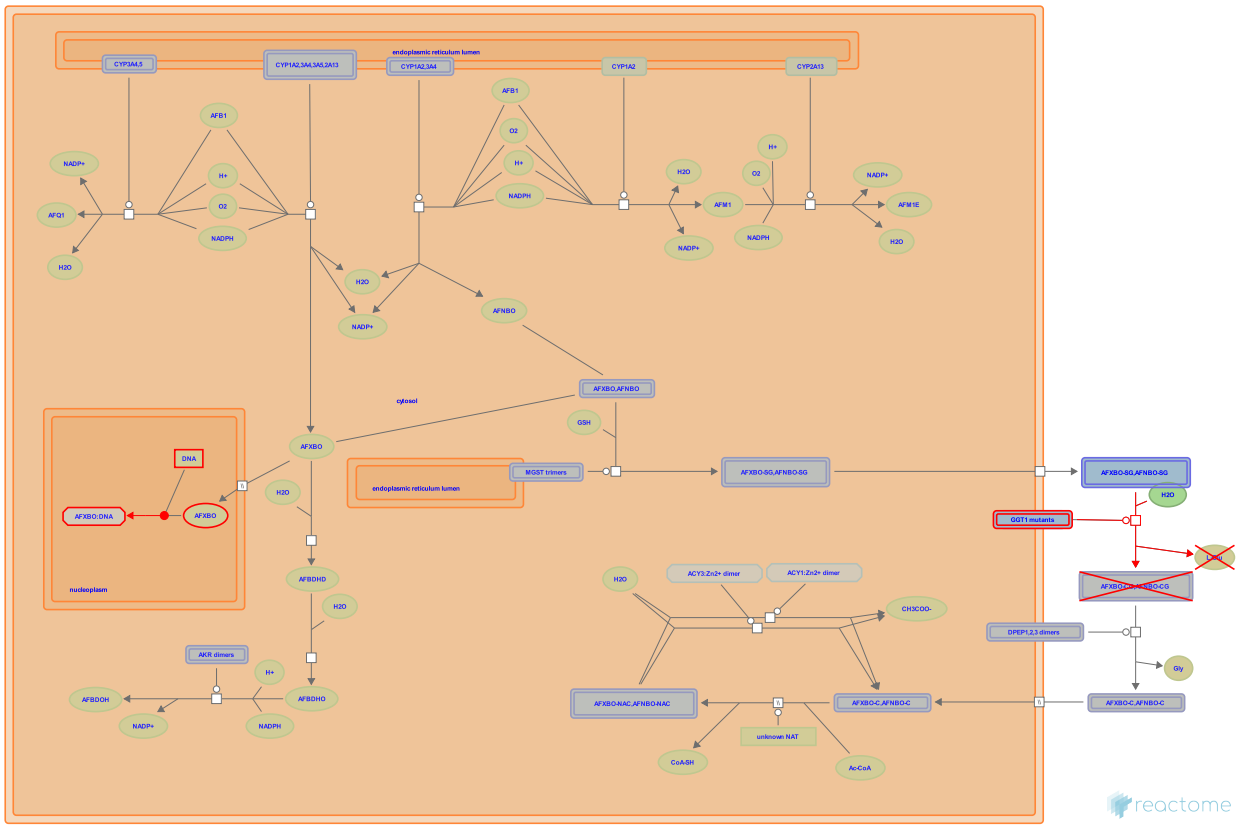
Defective GGT1 in aflatoxin detoxification causes GLUTH ↗

Stable identifier: R-HSA-9035968

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. Extracellular glutathione (GSH) or its conjugates can be hydrolysed to give cysteinylglycine (CG, or CG conjugates) and free glutamate (L-Glu). Hydrolysis of GSH provides cells with a local cysteine supply and contributes to intracellular GSH levels (Heisterkamp et al. 2008). 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 (Heisterkamp et al. 2008, Aoyama & Nakaki 2013).

Literature references

Groffen, J., Sneddon, TP., Heisterkamp, N., Warburton, D. (2008). The human gamma-glutamyltransferase gene family. *Hum Genet, 123*, 321-32. ↗

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

Editions

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2014-11-03	Reviewed	Nakaki, T.

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

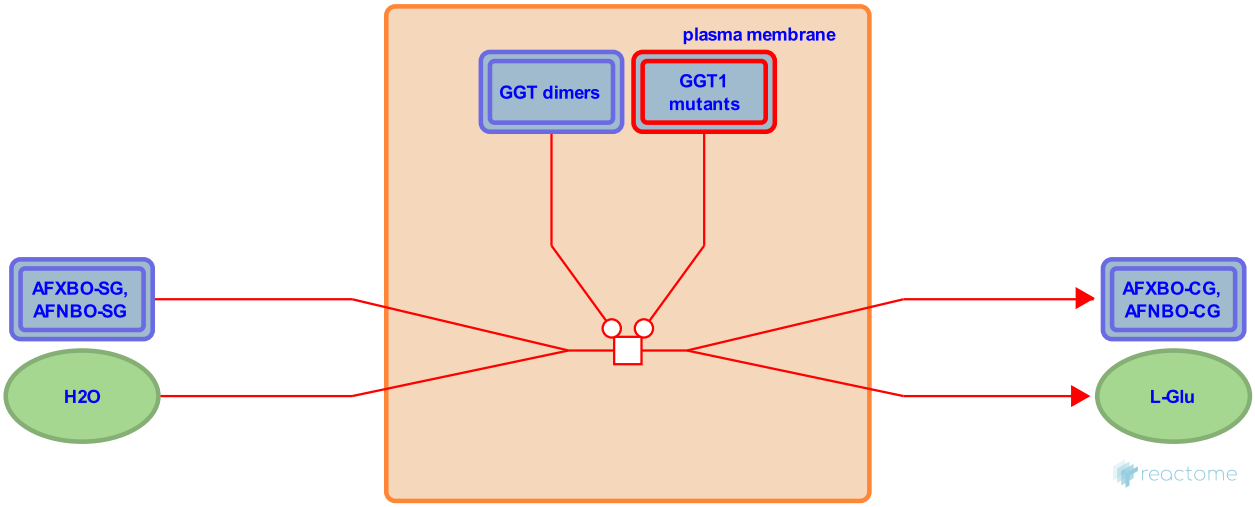
Location: Defective GGT1 in aflatoxin detoxification causes GLUTH

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

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Editions

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