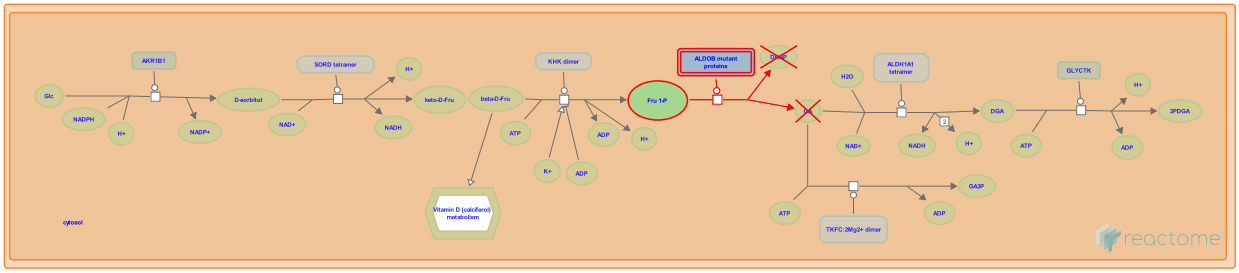
Hereditary fructose intolerance



D'Eustachio, P., Jassal, B., Timson, DJ., Tolan, DR.

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

10/04/2024

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.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

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. ↗

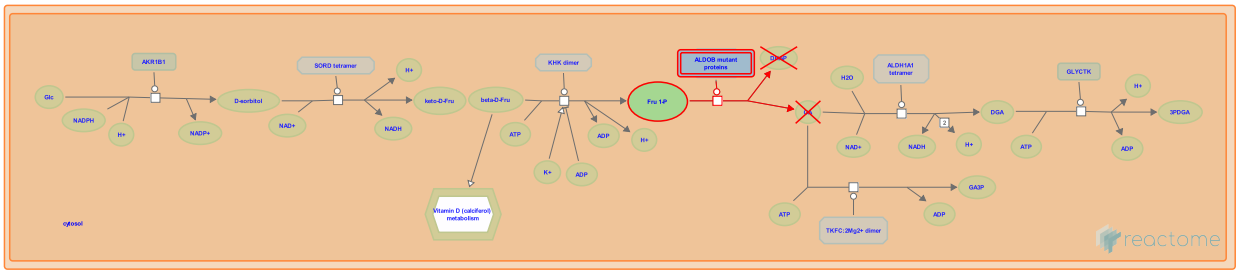
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Hereditary fructose intolerance ↗

Stable identifier: R-HSA-5657560

Diseases: hereditary fructose intolerance syndrome



Deficiencies in aldolase B arising from mutations in the aldolase B gene (ALDOB) prevent the cleavage of fructose 1-phosphate to glyceraldehyde (GA) and dihydroxyacetone phosphate (DHAP), leading to hereditary fructose intolerance (HFI). This autosomal recessive disorder is potentially fatal, but can be managed by exclusion of fructose from the diet (Cox et al. 1988; Tolan 1995).

Literature references

Tolan, DR. (1995). Molecular basis of hereditary fructose intolerance: mutations and polymorphisms in the human aldolase B gene. *Hum Mutat, 6*, 210-8. ↗

Cross, NC., Cox, TM., Tolan, DR. (1988). Catalytic deficiency of human aldolase B in hereditary fructose intolerance caused by a common missense mutation. *Cell, 53*, 881-5. ↗

Editions

2015-01-29	Authored, Edited	D'Eustachio, P.
2015-01-29	Reviewed	Jassal, B.
2015-02-17	Reviewed	Tolan, DR., Timson, DJ.

Defective ALDOB does not cleave Fru 1-P to GA and DHAP ↗

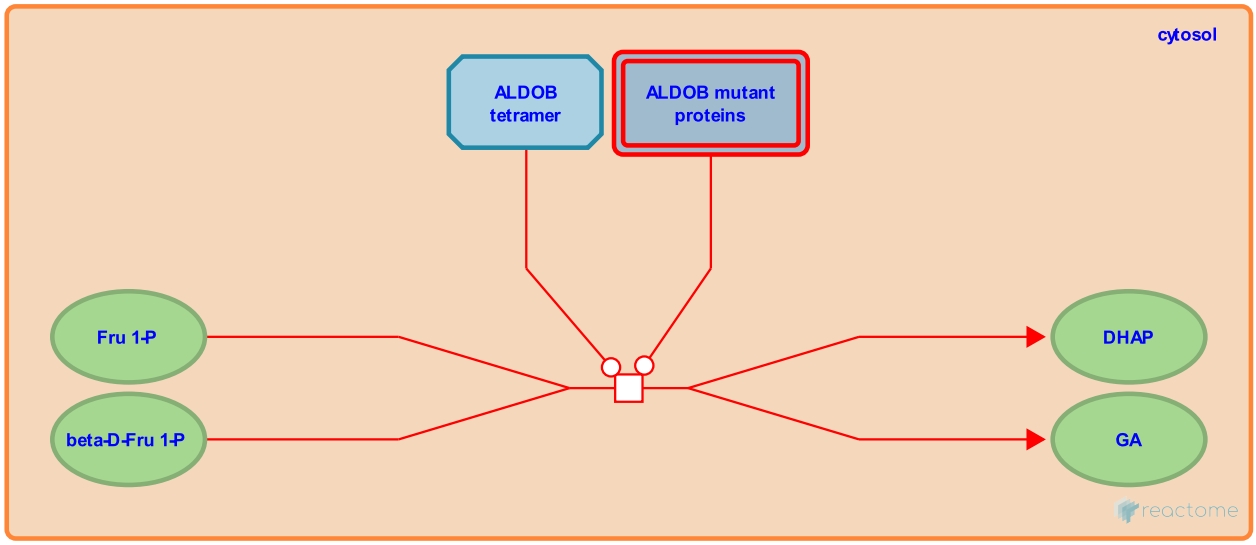
Location: Hereditary fructose intolerance

Stable identifier: R-HSA-5656438

Type: transition

Compartments: cytosol

Diseases: hereditary fructose intolerance syndrome



Mutations in ALDOB that cause deficiency of aldolase B block the cleavage of fructose 1-phosphate (Fru 1-P) to glyceraldehyde (GA) and dihydroxyacetone phosphate (DHAP) and cause hereditary fructose intolerance (HFI). The links between the enzyme deficiency and pathology are unclear at present, but may involve depletion of the cellular phosphate pool and increased levels of Fru 1-P (Oberhaensli et al, 1987; Bouteldja & Timson, 2010). Affected individuals can develop severe hypoglycemia, lactic acidosis, and other metabolic abnormalities when fed fructose; the disease can be effectively managed by complete exclusion of fructose from the diet. A large number of ALDOB variants have been described in affected individuals (e.g. Tolan 1995); the two missense mutant alleles annotated here are the most common (53% of those with HFI have one of these alleles) (Cross et al. 1988; Cross et al. 1990; Coffee et al. 2010), and encode full length aldolase B proteins whose catalytic activity is sharply reduced due to considerable loss of stability (Malay et al., 2002; Malay et al. 2005; Rellos et al., 2000 - see also PDB structures 1XDL and 1XDM). Other less common variants, not annotated here, retain activities and thermal stabilities similar to the wild-type (Esposito et al, 2010). The physiological role of aldolase B has been established from metabolic and DNA sequencing studies of patients with HFI (Ali et al. 1998) and in a mouse model for this disease (Oppelt et al. 2015).

Literature references

Tolan, DR. (1995). Molecular basis of hereditary fructose intolerance: mutations and polymorphisms in the human aldolase B gene. *Hum Mutat, 6*, 210-8. ↗

Schwarz, H., Oberhaensli, RD., Rajagopalan, B., Taylor, DJ., Collins, JE., Herschkowitz, N. et al. (1987). Study of hereditary fructose intolerance by use of 31P magnetic resonance spectroscopy. *Lancet, 2*, 931-4. ↗

Allen, KN., Malay, AD., Tolan, DR. (2005). Structure of the thermolabile mutant aldolase B, A149P: molecular basis of hereditary fructose intolerance. *J. Mol. Biol., 347*, 135-44. ↗

Sygusch, J., Cox, TM., Rellos, P. (2000). Expression, purification, and characterization of natural mutants of human aldolase B. Role of quaternary structure in catalysis. *J. Biol. Chem., 275*, 1145-51. ↗

Odièvre, M., Sebastio, G., Cox, TM., de Franchis, R., Mascali, G., Romano, C. et al. (1990). Molecular analysis of aldolase B genes in hereditary fructose intolerance. *Lancet, 335*, 306-9. ↗

Editions

2015-01-29	Authored, Edited	D'Eustachio, P.
2015-01-29	Reviewed	Jassal, B.
2015-02-17	Reviewed	Tolan, DR., Timson, DJ.

Table of Contents