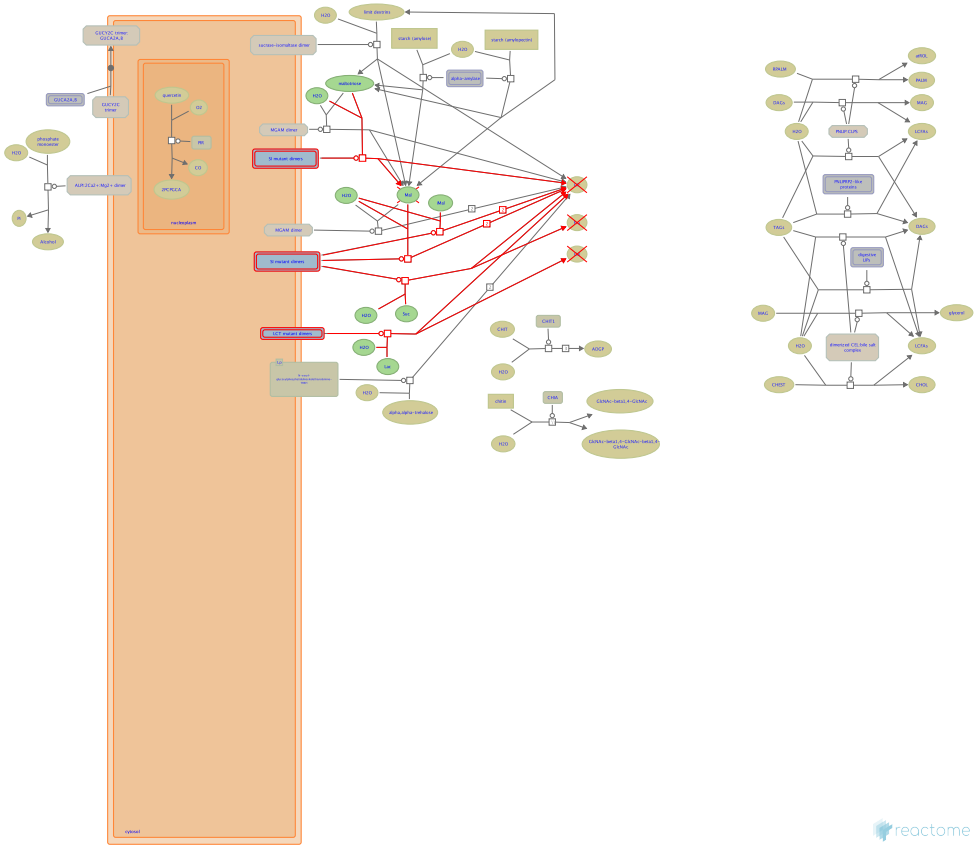
Intestinal saccharidase deficiencies



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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. ↗

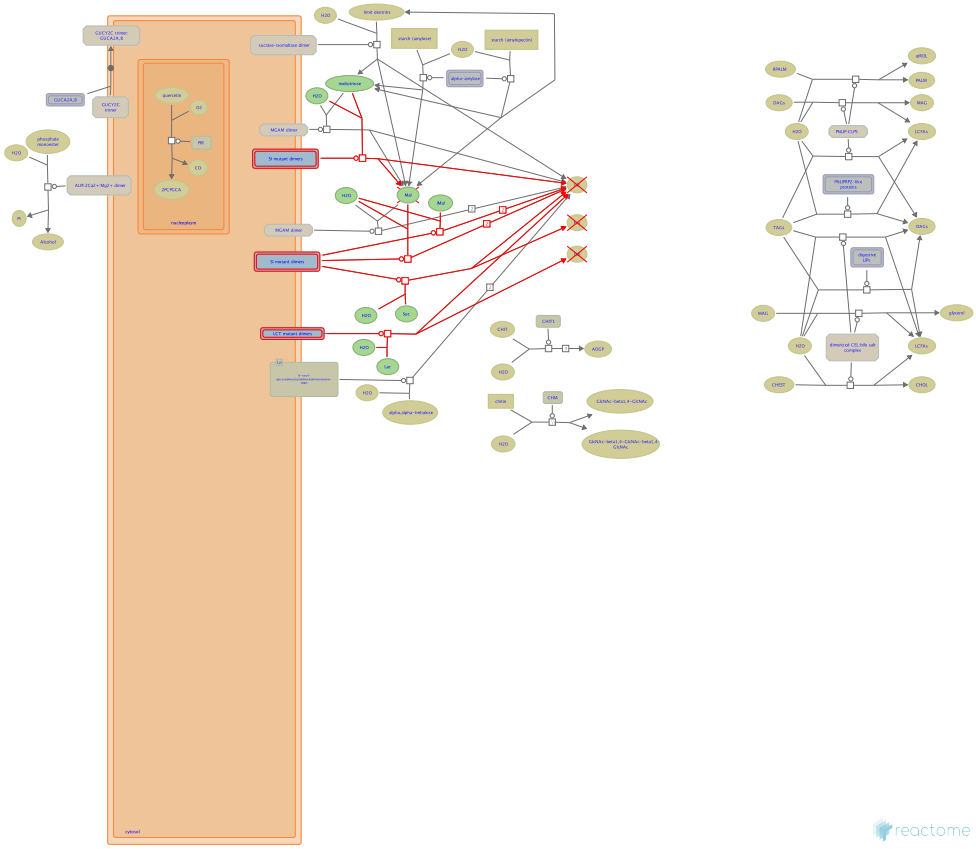
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Intestinal saccharidase deficiencies ↗

Stable identifier: R-HSA-5659898

Diseases: intestinal disaccharidase deficiency



Defects in in two enzymes required for intestinal digestion of dietary carbohydrate, lactase (LCT, a domain of lactase-phlorizin hydrolase protein) and sucrase-isomaltase (SI), are annotated here. The first affects nursing infants; the second affects individuals after weaning.

The disaccharide lactose is a major constituent of human breast milk. To be taken up from the gut in the nursing infant, this sugar must first be hydrolyzed by LCT present on the external face of enterocytes in microvilli of the small intestine. Mutations that disrupt LCT activity are associated with acute illness in newborn children as lactose fermentation by gut bacteria leads to severe diarrhea. The condition is effectively treated by feeding affected infants a lactose-free formula. This congenital disease is distinct from the down-regulation of LCT expression after weaning in many human populations that is associated with a milder form of lactose intolerance in adults (Jarvela et al. 2009).

The starch in a post-weaning diet is digested by amylases to di- and oligosaccharides that must be further digested to monosaccharides in order to be taken up from the lumen of the small intestine into endothelial cells of the intestinal brush border. If they are not digested, a process in which enterocyte-associated SI plays a central role, they remain in the gut lumen and are fermented by gut bacteria, leading to osmotic and fermentative diarrhea (Naim et al. 2012; Van Beers et al. 1995).

Literature references

Naim, HY., Heine, M., Zimmer, KP. (2012). Congenital sucrase-isomaltase deficiency: heterogeneity of inheritance, trafficking, and function of an intestinal enzyme complex. *J. Pediatr. Gastroenterol. Nutr., 55*, S13-20. ↗

Van Beers, EH., Büller, HA., Grand, RJ., Einerhand, AW., Dekker, J. (1995). Intestinal brush border glycohydrolases: structure, function, and development. *Crit. Rev. Biochem. Mol. Biol., 30*, 197-262. ↗

Järvelä, I., Torniainen, S., Kolho, KL. (2009). Molecular genetics of human lactase deficiencies. *Ann. Med., 41*, 568-75. ↗

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2015-01-29	Reviewed	Jassal, B.
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Defective SI does not hydrolyze Mal ↗

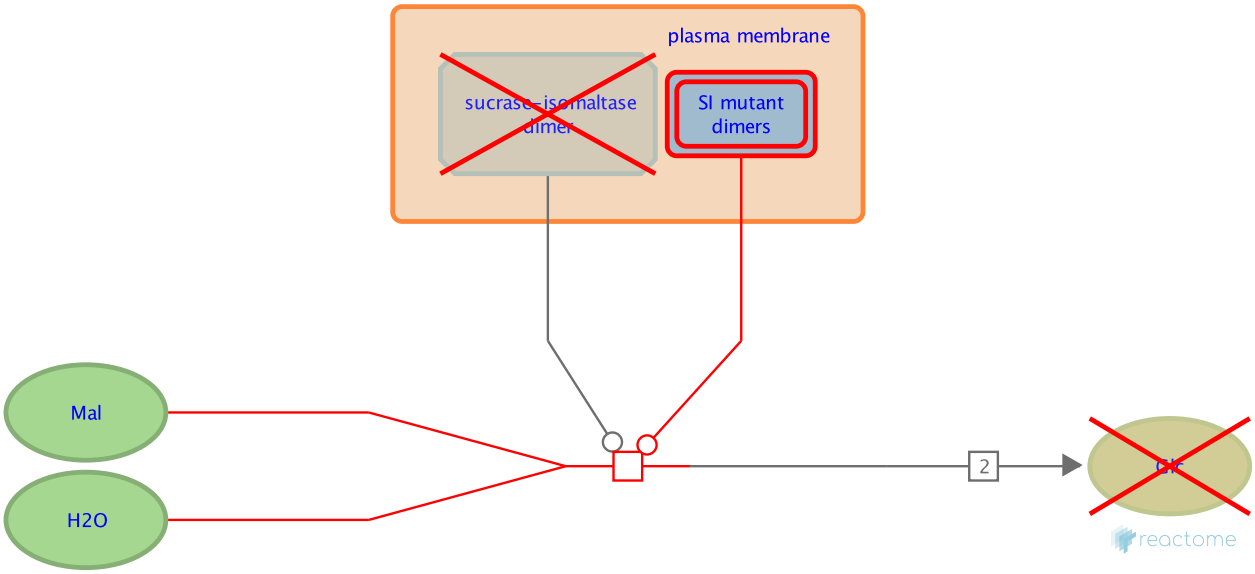
Location: Intestinal saccharidase deficiencies

Stable identifier: R-HSA-5659922

Type: transition

Compartments: extracellular region, plasma membrane

Diseases: intestinal disaccharidase deficiency



Mutations that disrupt the catalytic activity or strongly interfere with proper folding, glycosylation and transport of SI (sucrase-isomaltase) block the cleavage of maltose (Mal) to glucose in the gut lumen. Affected individuals can develop severe diarrhea; this symptom is managed by excluding indigestible sugars from the diet (Gray et al. 1976; Ritz et al. 2003; Semenza et al. 1965). A variety of SI mutant alleles have been described. Three missense mutations that are associated with severe loss of SI activity in vivo are annotated here (Alfalah et al. 2009;,Ouwendijk et al. 1996; Sander et al. 2006; Spodsberg et al. 2001). All missense mutant alleles that have been characterized to date encode proteins that fail to reach the lumenal plasma membrane or cannot associate stably with it; one missense mutation not annotated here encodes a polypeptide that undergoes an intracellular cleavage and is secreted as the active enzyme (Jacob et al. 2000).

Literature references

Alfalah, M., Keiser, M., Leeb, T., Zimmer, KP., Naim, HY. (2009). Compound heterozygous mutations affect protein folding and function in patients with congenital sucrase-isomaltase deficiency. *Gastroenterology, 136*, 883-92. ↗

Gray, GM., Conklin, KA., Townley, RR. (1976). Sucrase-isomaltase deficiency. Absence of an inactive enzyme variant. *N. Engl. J. Med., 294*, 750-3. ↗

Jacob, R., Zimmer, KP., Schmitz, J., Naim, HY. (2000). Congenital sucrase-isomaltase deficiency arising from cleavage and secretion of a mutant form of the enzyme. *J. Clin. Invest., 106*, 281-7. ↗

Ouwendijk, J., Moolenaar, CE., Peters, WJ., Hollenberg, CP., Ginsel, LA., Fransen, JA. et al. (1996). Congenital sucrase-isomaltase deficiency. Identification of a glutamine to proline substitution that leads to a transport block of sucrase-isomaltase in a pre-Golgi compartment. *J. Clin. Invest., 97*, 633-41. ↗

Ritz, V., Alfalah, M., Zimmer, KP., Schmitz, J., Jacob, R., Naim, HY. (2003). Congenital sucrase-isomaltase deficiency because of an accumulation of the mutant enzyme in the endoplasmic reticulum. *Gastroenterology, 125*, 1678-85. ↗

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Defective SI does not hydrolyze iMal ↗

Location: Intestinal saccharidase deficiencies

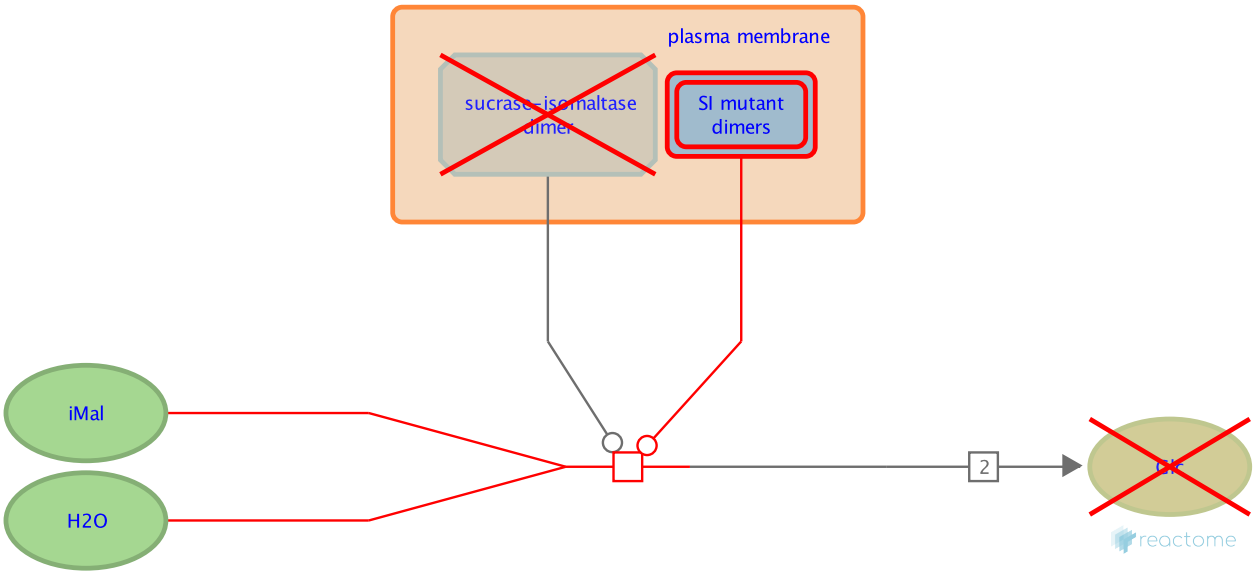
Stable identifier: R-HSA-5659879

Type: transition

Compartments: extracellular region, plasma membrane

Diseases: intestinal disaccharidase deficiency

Inferred from: Defective SI does not hydrolyze Mal (Homo sapiens)



Mutations that disrupt the catalytic activity or strongly interfere with proper folding, glycosylation and transport of SI (sucrase-isomaltase) are inferred to block the cleavage of isomaltose (iMal) to glucose, based on the experimentally demonstrated failure of these SI mutant proteins to hydrolyze maltose (e.g., Sander et al. 2006) and the broad substrate specificity of the normal enzyme (Sim et al. 2010).

Literature references

Sander, P., Alfalah, M., Keiser, M., Korponay-Szabo, I., Kovács, JB., Leeb, T. et al. (2006). Novel mutations in the human sucrase-isomaltase gene (SI) that cause congenital carbohydrate malabsorption. *Hum. Mutat., 27*, 119. ↗

Sim, L., Willemsma, C., Mohan, S., Naim, HY., Pinto, BM., Rose, DR. (2010). Structural basis for substrate selectivity in human maltase-glucoamylase and sucrase-isomaltase N-terminal domains. *J. Biol. Chem., 285*, 17763-70. ↗

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Defective SI does not hydrolyze Suc ↗

Location: Intestinal saccharidase deficiencies

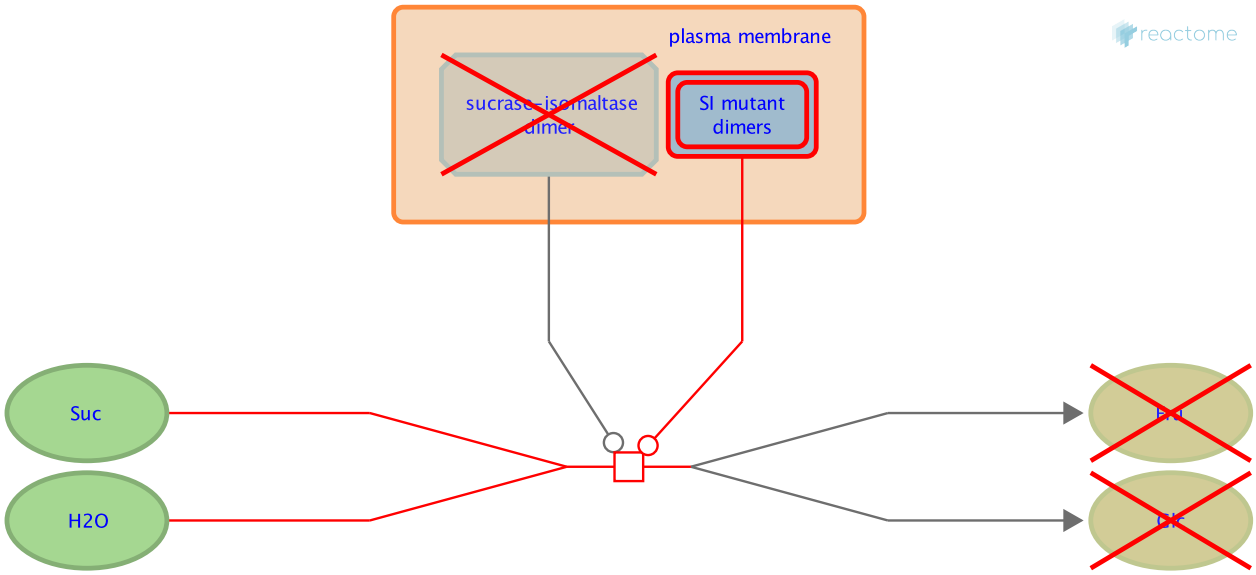
Stable identifier: R-HSA-5659926

Type: transition

Compartments: extracellular region, plasma membrane

Diseases: intestinal disaccharidase deficiency

Inferred from: Defective SI does not hydrolyze Mal (Homo sapiens)



Mutations that disrupt the catalytic activity or strongly interfere with proper folding, glycosylation and transport of SI (sucrase-isomaltase) are inferred to block the cleavage of sucrose (Suc) to glucose and fructose, based on the experimentally demonstrated failure of these SI mutant proteins to hydrolyze maltose (e.g., Sander et al. 2006) and the broad substrate specificity of the normal enzyme (Sim et al. 2010).

Literature references

Sander, P., Alfalah, M., Keiser, M., Korponay-Szabo, I., Kovács, JB., Leeb, T. et al. (2006). Novel mutations in the human sucrase-isomaltase gene (SI) that cause congenital carbohydrate malabsorption. *Hum. Mutat., 27*, 119. ↗

Sim, L., Willemsma, C., Mohan, S., Naim, HY., Pinto, BM., Rose, DR. (2010). Structural basis for substrate selectivity in human maltase-glucoamylase and sucrase-isomaltase N-terminal domains. *J. Biol. Chem., 285*, 17763-70. ↗

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Defective SI does not hydrolyze maltotriose ↗

Location: Intestinal saccharidase deficiencies

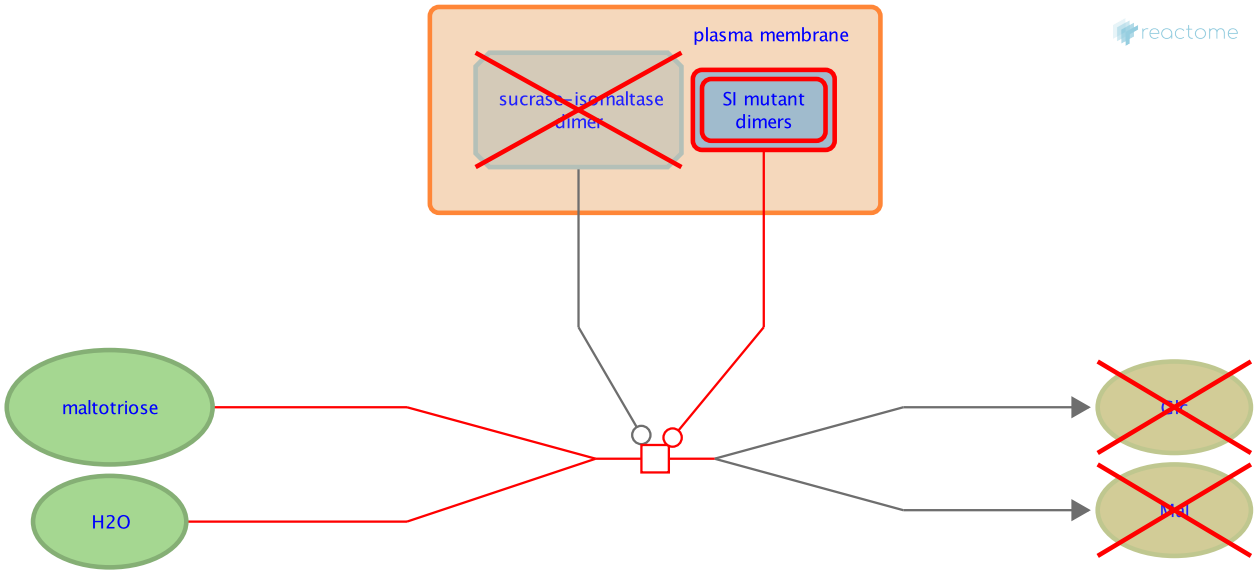
Stable identifier: R-HSA-5659899

Type: transition

Compartments: extracellular region, plasma membrane

Diseases: intestinal disaccharidase deficiency

Inferred from: Defective SI does not hydrolyze Mal (Homo sapiens)



Mutations that disrupt the catalytic activity or strongly interfere with proper folding, glycosylation and transport of SI (sucrase-isomaltase) are inferred to block the cleavage of maltotriose to maltose and glucose, based on the experimentally demonstrated failure of these SI mutant proteins to hydrolyze maltose (e.g., Sander et al. 2005) and the broad substrate specificity of the normal enzyme (Sim et al. 2010).

Literature references

Sander, P., Alfalah, M., Keiser, M., Korponay-Szabo, I., Kovács, JB., Leeb, T. et al. (2006). Novel mutations in the human sucrase-isomaltase gene (SI) that cause congenital carbohydrate malabsorption. *Hum. Mutat., 27*, 119. ↗

Sim, L., Willemsma, C., Mohan, S., Naim, HY., Pinto, BM., Rose, DR. (2010). Structural basis for substrate selectivity in human maltase-glucoamylase and sucrase-isomaltase N-terminal domains. *J. Biol. Chem., 285*, 17763-70. ↗

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Defective LCT does not hydrolyze Lac ↗

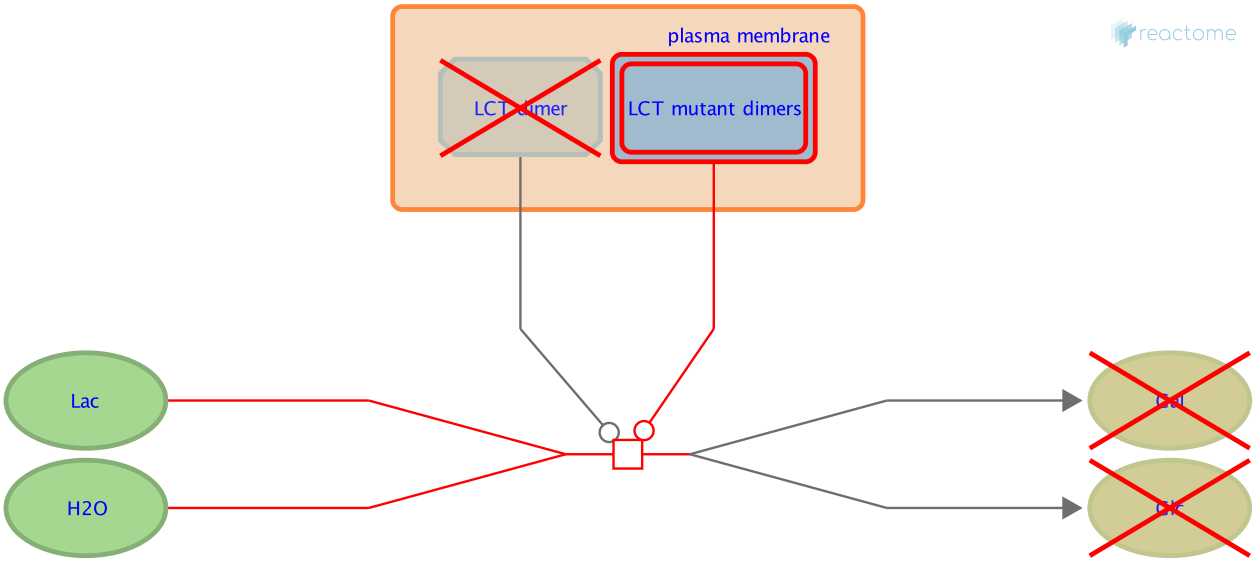
Location: Intestinal saccharidase deficiencies

Stable identifier: R-HSA-5658001

Type: transition

Compartments: extracellular region, plasma membrane

Diseases: lactose intolerance



Mutations that disrupt the catalytic activity of LCT (lactase) block the cleavage of lactose (Lac) to galactose and glucose in the gut lumen and cause lactose intolerance in nursing infants. Affected individuals can develop severe diarrhea; the disease can be effectively managed by complete exclusion of lactose from the diet. A variety of LCT mutant alleles have been described. Two missense mutations that are associated with severe loss of lactase activity in vivo are annotated here (Kuokkanen et al. 2006; Torniainen et al. 2009).

Literature references

Kuokkanen, M., Kokkonen, J., Enattah, NS., Ylisaukko-Oja, T., Komu, H., Varilo, T. et al. (2006). Mutations in the translated region of the lactase gene (LCT) underlie congenital lactase deficiency. *Am. J. Hum. Genet., 78*, 339-44. ↗

Torniainen, S., Freddara, R., Routi, T., Gijsbers, C., Catassi, C., Höglund, P. et al. (2009). Four novel mutations in the lactase gene (LCT) underlying congenital lactase deficiency (CLD). *BMC Gastroenterol, 9*, 8. ↗

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