Defects in biotin (Btn) metabolism

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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


Reactome database release: 79

This document contains 3 pathways (see Table of Contents)

https://reactome.org
Defects in biotin (Btn) metabolism

Stable identifier: R-HSA-3323169

Diseases: vitamin metabolic disorder

Biotin (Btn, vitamin B7, vitamin H, coenzyme R) is an essential cofactor for five biotin-dependent carboxylase enzymes, involved in the synthesis of fatty acids, isoleucine, valine and in gluconeogenesis. Thus, Btn is necessary for cell growth, fatty acid synthesis and the metabolism of fats and amino acids. Inherited metabolic disorders characterized by deficient activities of all five biotin dependent carboxylases are termed multiple carboxylase deficiencies. Two congenital defects in biotin metabolism leading to multiple carboxylase deficiency are known, holocarboxylase synthetase deficiency (MIM 609018) and biotinidase deficiency (MIM 253260). In both scenarios symptoms include ketolactic acidosis, organic aciduria, hyperammonemia, skin rashes, hypotonia, seizures, developmental delay, alopecia, and coma. As humans are auxotrophic for Btn, the micronutrient must be obtained from external sources such as intestinal microflora and dietary forms. Accordingly, severe malnutrition can also give rise to biotin deficiency and multiple carboxylase deficiency. Biotin deficiency can also be induced by the excessive consumption of raw egg white that contains the biotin-binding protein avidin. Holocarboxylase synthetase deficiency arises when all five biotin-dependent enzymes are not biotinylated leading to their reduced activities. The defective genes causing these conditions are described here (Pendini et al. 2008, Suzuki et al. 2005). Biotinidase deficiency is caused by defects in the recycling of Btn. General symptoms include decreased appetite and growth, dermatitis and perosis. The defective genes causing these conditions are described here (Procter et al. 2013).

Literature references


### Editions

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Defective HLCS causes multiple carboxylase deficiency

**Location:** Defects in biotin (Btn) metabolism

**Stable identifier:** R-HSA-3371599

**Diseases:** vitamin metabolic disorder

Defects in HLCS causes holocarboxylase synthetase deficiency (HLCS deficiency aka early onset multiple carboxylase deficiency; MIM:253270). HLCS deficiency is an autosomal recessive disorder whereby deficient HLCS activity results in reduced activity of all five biotin-dependent carboxylases. Symptoms include metabolic acidosis, organic aciduria, lethargy, hypotonia, convulsions and dermatitis (Suzuki et al. 2005). Patients can present symptoms shortly after birth to up to early childhood and will be prescribed oral biotin supplements, typically 10-20 mg daily. Two classes of HLCS deficiency have been reported depending on whether patients respond to biotin therapy. Most patients respond favourably to treatment and show complete reversal of biochemical and clinical symptoms (Morrone et al. 2002, Dupuis et al. 1999). Here mutations in the HLCS active site cause a reduced affinity for biotin that can be overcome by pharmacological doses of the vitamin (Pendini et al. 2008). Patients who display incomplete responsiveness to biotin therapy have a poor long-term prognosis (Bailey et al. 2008). Here mutations that reside outside of the enzyme's active site have no effect on biotin binding but do compromise the protein-protein interaction between the HLCS and its substrates, resulting in reduced biotinylation of all five carboxylases thus reducing their enzymatic activity (Mayende et al. 2012).

**Literature references**


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Defective BTD causes biotidinase deficiency

**Location:** Defects in biotin (Btn) metabolism

**Stable identifier:** R-HSA-3371598

**Diseases:** vitamin metabolic disorder

BTD deficiency is an autosomal recessive disorder in which the body is unable to recycle and reuse biotin (Btn). This results in a secondary Btn deficiency that leads to juvenile-onset multiple carboxylase deficiency (MIM:253260) (Wolf 2012, Wolf et al. 1983). Patients present with neurological and cutaneous symptoms, including seizures, hypotonia, skin rash, and alopecia, usually between the second and fifth months of life (Wolf 2010). Children with profound BTD deficiency are treated with pharmacological doses of biotin (5-20 mg daily). Neonatal screening for BTD deficiency is performed in most states of the United States and many other countries.

**Literature references**

Wolf, B. (2012). Biotinidase deficiency: "if you have to have an inherited metabolic disease, this is the one to have". *Genet. Med.*, 14, 565-75.


**Editions**

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