Defects in cobalamin (B12) metabolism

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

17/11/2022

https://reactome.org
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


Reactome database release: 82

This document contains 13 pathways *(see Table of Contents)*

https://reactome.org
Defects in cobalamin (B12) metabolism

Stable identifier: R-HSA-3296469

Diseases: vitamin B12 deficiency

Cobalamin (Cbl, vitamin B12) is a nutrient essential for normal functioning of the brain and nervous system and for the formation of blood. Cbl-dependent methionine synthase (MTR) is required for conversion of 5-methyltetrahydrofolate (metTHF) to tetrahydrofolate (THF), in addition to its role in conversion of homocysteine to methionine. In Cbl deficiency, and in inborn errors of Cbl metabolism that affect function of methionine synthase, inability to regenerate THF from metTHF results in decreased function of folate-dependent reactions that are involved in 2 steps of purine biosynthesis and thymidylate synthesis. Cbl deficiency results in hyperhomocysteinemia (due to defects in the conversion of homocysteine to methionine which requires Cbl as a cofactor) and increased levels of methylmalonic acid (MMA). Methionine is used in myelin production, protein, neurotransmitter, fatty acid and phospholipid production and DNA methylation. Symptoms of Cbl deficiency are bone marrow promegaloblastosis (megaloblastic anemia) due to the inhibition of DNA synthesis (specifically purines and thymidine) and neurological symptoms. The defective genes involved in Cbl deficiencies are described below (Froese & Gravel 2010, Nielsen et al. 2012, Whitehead 2006, Watkins & Rosenblatt 2011, Fowler 1998).

Literature references


### Editions

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Defective CBLIF causes IFD

**Location:** Defects in cobalamin (B12) metabolism

**Stable identifier:** R-HSA-3359457

**Diseases:** megaloblastic anemia

Defects in cobalamin binding intrinsic factor CBLIF, aka gastric intrinsic factor GIF) cause hereditary intrinsic factor deficiency (IFD, aka congenital pernicious anemia; MIM:261000). IFD is an autosomal recessive disorder characterized by megaloblastic anemia (Tanner et al. 2005).

**Literature references**


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[https://reactome.org](https://reactome.org)
Defective AMN causes MGA1

**Location:** Defects in cobalamin (B12) metabolism

**Stable identifier:** R-HSA-3359462

**Diseases:** megaloblastic anemia

Defects in AMN cause recessive hereditary megaloblastic anemia 1 (RH-MGA1 aka MGA1 Norwegian type or Imerslund-Grasbeck syndrome, I-GS; MIM:261100). The Norwegian cases described by Imerslund were due to defects in AMN (Imerslund 1960). The resultant malabsorption of Cbl (vitamin B12) leads to impaired B12-dependent folate metabolism and ultimately impaired thymine synthesis and DNA replication.

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Defective CUBN causes MGA1

**Location:** Defects in cobalamin (B12) metabolism

**Stable identifier:** R-HSA-3359463

**Diseases:** megaloblastic anemia

Defects in the CUBN gene cause recessive hereditary megaloblastic anemia 1 (RH-MGA1 aka MGA1 Finnish type or Imerslund-Grasbeck syndrome, I-GS; MIM:261100). The Finnish cases described by Grasbeck et al. were caused by defects in CUBN (Grasbeck et al. 1960). The resultant malabsorption of Cbl (cobalamin, vitamin B12) leads to impaired B12-dependent folate metabolism and ultimately impaired thymine synthesis and DNA replication.

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ATP-binding cassette sub-family D member 4 (ABCD4) is thought to mediate the lysosomal export of cobalamin (Cbl aka vitamin B12) into the cytosol, making it available for the production of Cbl cofactors. Cbl is an important cofactor for correct haematological and neurological functions. Defects in ABCD4 can cause methylmalonic aciduria and homocystinuria, cblJ type (MAHCJ; MIM:614857), a genetically heterogeneous metabolic disorder of Cbl metabolism characterised by decreased levels of the coenzymes adenosylcobalamin (AdoCbl) and methylcobalamin (MeCbl). Clinically, symptoms include feeding difficulties, poor growth, hypotonia, lethargy, anaemia and delayed development (Coelho et al. 2012).

**Literature references**

Defective MMACHC causes MAHCC

**Location:** Defects in cobalamin (B12) metabolism

**Stable identifier:** R-HSA-3359474

**Diseases:** methylmalonic aciduria and homocystinuria type cblC

Defects in MMACHC cause methylmalonic aciduria and homocystinuria type cblC (MMAHCC; MIM:277400). MMAHCC is the most common disorder of cobalamin metabolism and is characterized by decreased levels of the coenzymes adenosylcobalamin (AdoCbl) and methylcobalamin (MeCbl). Affected individuals may have developmental, haematologic, neurologic, metabolic, ophthalmologic, and dermatologic clinical findings (Lerner-Ellis et al. 2006).

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Defective MMADHC causes MMAHCD

Location: Defects in cobalamin (B12) metabolism

Stable identifier: R-HSA-3359473

Diseases: methylmalonic aciduria and homocystinuria type cblD

Defects in MMADHC cause methylmalonic aciduria and homocystinuria type cblD (MMAHCD; MIM:277410), a disorder of cobalamin metabolism characterized by decreased levels of the coenzymes adenosylcobalamin (AdoCbl) and methylcobalamin (MeCbl) (Coelho et al. 2008).

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Defective MTRR causes HMAE

Location: Defects in cobalamin (B12) metabolism

Stable identifier: R-HSA-3359467

Diseases: methylmalonic aciduria and homocystinuria type cblE

Defects in MTRR cause methylcobalamin deficiency type E (cblE; methionine synthase reductase deficiency; MIM:236270) (Wilson et al. 1999). Patients with cblE exhibit megaloblastic anemia and hyperhomocysteinemia. SAM is used as a methyl donor in many biological reactions and demethylation of SAM produces S-adenosylhomocysteine, which is deadenosylated to form homocysteine. Homocysteine remethylation is carried out by MTR, which requires MTRR to maintain enzyme-bound cobalamin (Cbl) in its active form; but in cblE patients, MTR becomes inactivated and thus homocysteine accumulates.

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Watkins, D.
Defective MTR causes HMAG

Location: Defects in cobalamin (B12) metabolism

Stable identifier: R-HSA-3359469

Diseases: methylmalonic aciduria and homocystinuria type cblG


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https://reactome.org
Defective MMAB causes MMA, cblB type

**Location:** Defects in cobalamin (B12) metabolism

**Stable identifier:** R-HSA-3359471

**Diseases:** methylmalonic acidemia

Defects in MMAB cause methylmalonic aciduria type cblB (cblB aka methylmalonic aciduria type B or vitamin B12 responsive methylmalonic aciduria of cblB complementation type; MIM:251110). Affected individuals have methylmalonic aciduria and episodes of metabolic ketoacidosis, despite a functional methylmalonyl CoA mutase. In severe cases, newborns become severely acidotic and may die if acidosis is not treated promptly (Dobson et al. 2002).

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Defective MMAA causes MMA, cblA type

Location: Defects in cobalamin (B12) metabolism

Stable identifier: R-HSA-3359475

Diseases: methylmalonic acidemia

Defects in MMAA cause methylmalonic aciduria type cblA (cblA aka methylmalonic aciduria type A or vitamin B12-responsive methylmalonic aciduria of cblA complementation type; MIM:251100). Affected individuals accumulate methylmalonic acid in the blood and urine and are prone to potentially life threatening acidotic crises in infancy or early childhood (Dobson et al. 2002, Lerner-Ellis et al. 2004).

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https://reactome.org
Defective TCN2 causes TCN2 deficiency

**Location:** Defects in cobalamin (B12) metabolism

**Stable identifier:** R-HSA-3359454

**Diseases:** megaloblastic anemia

Defective transcobalamin II (produced by the TCN2 gene) results in TCN2 deficiency (MIM:275350), an autosomal recessive disorder with early-onset in infancy characterized by failure to thrive, megaloblastic anemia, and pancytopenia. If left untreated, the disorder can result in mental retardation and neurologic abnormalities (Haberle et al. 2009).

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Defective CD320 causes MMATC

Location: Defects in cobalamin (B12) metabolism

Stable identifier: R-HSA-3359485

Diseases: methylmalonic acidemia

Defects in CD320 cause methylmalonic aciduria type TCblR (MMATC aka methylmalonic aciduria; MIM:613646) resulting in elevated methylmalonic acid (MMA) and homocysteine (HCYS) in newborns (Quadros et al. 2010).

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