# Defects in cobalamin (B12) metabolism


Jassal, B., Shukla, S., Watkins, D.

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



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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.

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. ↗

Reactome database release: 77

This document contains 14 pathways (see Table of Contents)

## 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


Watkins, D., Rosenblatt, DS. (2011). Inborn errors of cobalamin absorption and metabolism. *Am J Med Genet C Semin Med Genet, 157*, 33-44. ↗

Froese, DS., Gravel, RA. (2010). Genetic disorders of vitamin B12 metabolism: eight complementation groups--eight genes. *Expert Rev Mol Med, 12*, e37. ↗

Nielsen, MJ., Rasmussen, MR., Andersen, CB., Nexø, E., Moestrup, SK. (2012). Vitamin B12 transport from food to the body's cells--a sophisticated, multistep pathway. *Nat Rev Gastroenterol Hepatol, 9*, 345-54. ↗

Fowler, B. (1998). Genetic defects of folate and cobalamin metabolism. *Eur. J. Pediatr., 157*, S60-6. ↗

Whitehead, VM. (2006). Acquired and inherited disorders of cobalamin and folate in children. *Br. J. Haematol., 134*, 125-36. ↗

## Editions

| | | |
|---|---|---|
| 2013-04-18 | Authored, Edited | Jassal, B. |
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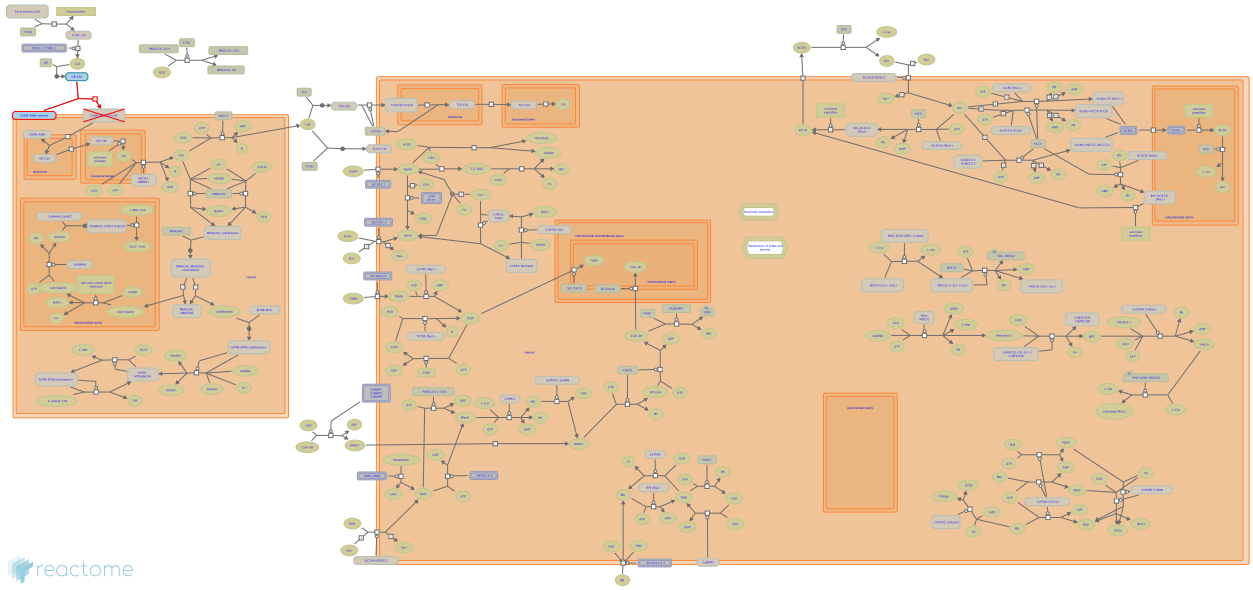
## Defective AMN causes hereditary megaloblastic anemia 1 ↗

**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.

## Literature references

IMERSLUND, O. (1960). Idiopathic chronic megaloblastic anemia in children. *Acta Paediatr Suppl, 49*, 1-115. ↗

## Editions

| | | |
|---|---|---|
| 2013-05-13 | Authored, Edited | Jassal, B. |
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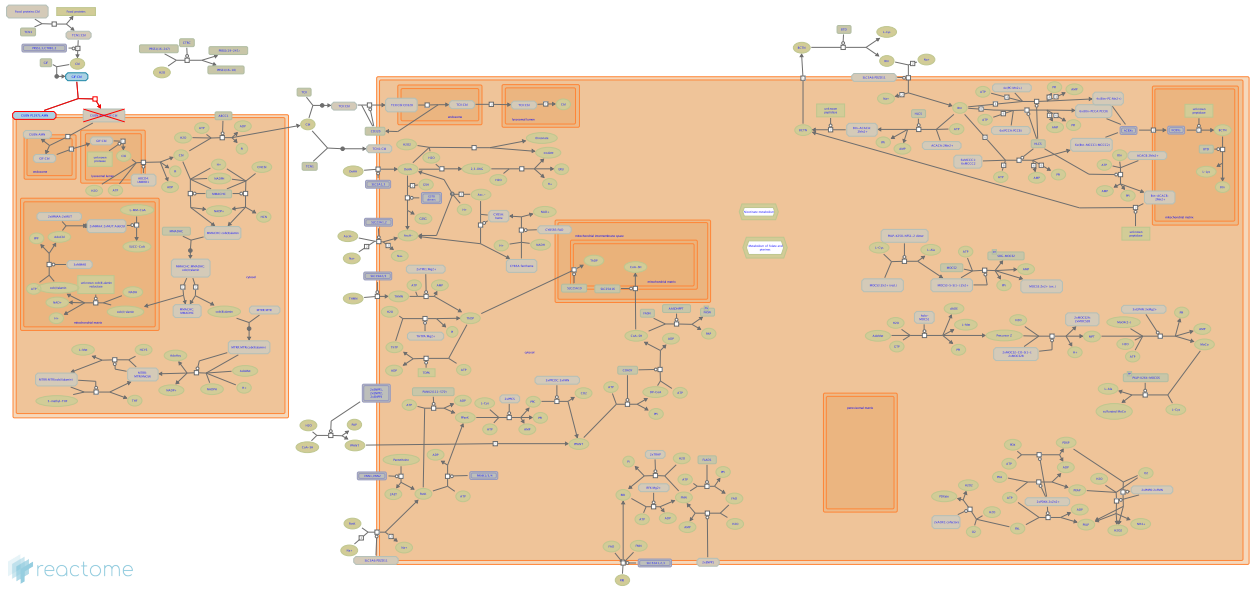
## Defective CUBN causes hereditary megaloblastic anemia 1 ↗

**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.

## Literature references

GRASBECK, R., GORDIN, R., KANTERO, I., KUHLBACK, B. (1960). Selective vitamin B12 malabsorption and proteinuria in young people. A syndrome. *Acta Med Scand, 167*, 289-96. ↗

## Editions

| | | |
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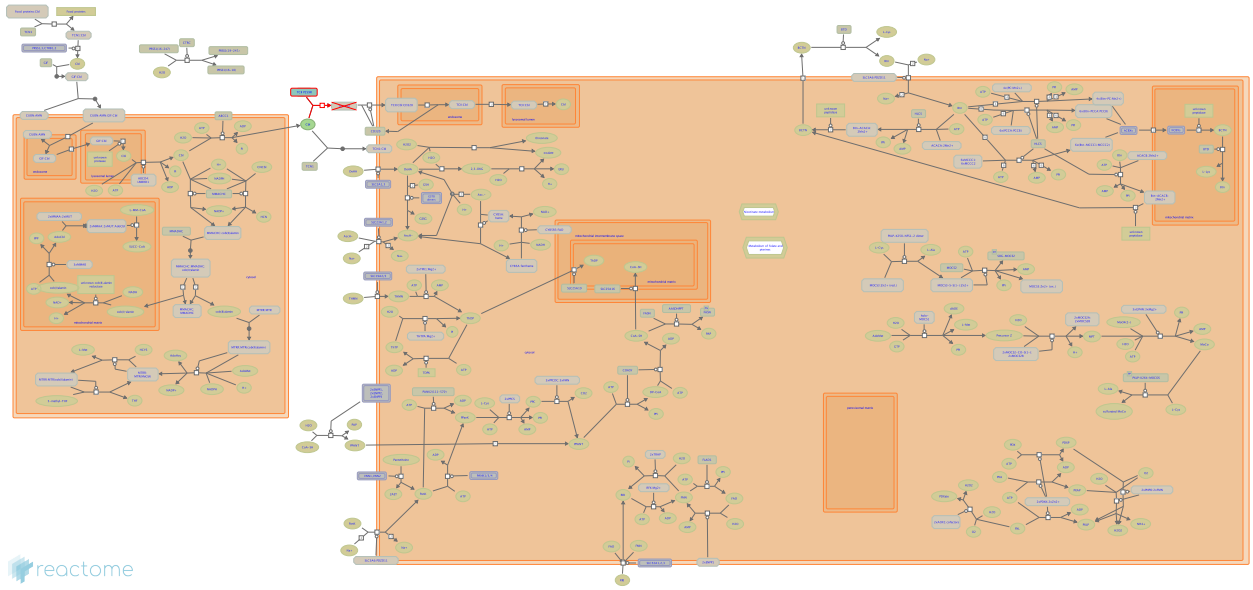
## Defective TCN2 causes hereditary megaloblastic anemia ↗

**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).

## Literature references

Häberle, J., Pauli, S., Berning, C., Koch, HG., Linnebank, M. (2009). TC II deficiency: avoidance of false-negative molecular genetics by RNA-based investigations. *J. Hum. Genet., 54*, 331-4. ↗

## Editions

| | | |
|---|---|---|
| 2013-05-13 | Authored, Edited | Jassal, B. |
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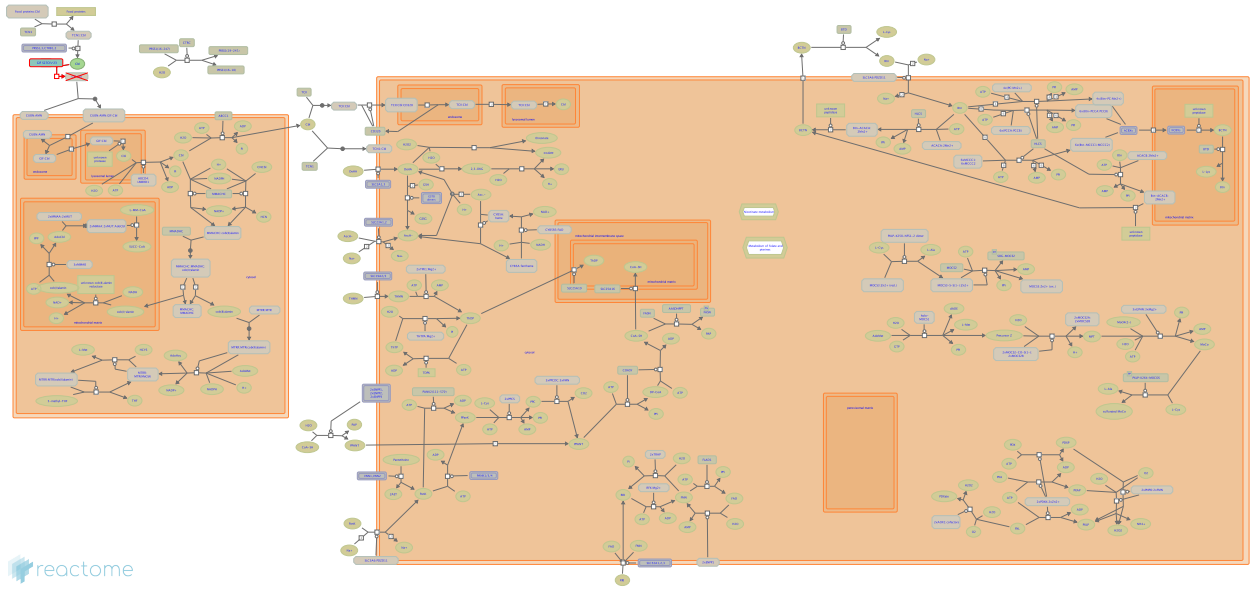
## Defective GIF causes intrinsic factor deficiency ↗

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

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

**Diseases:** megaloblastic anemia



Defects in 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


Tanner, SM., Li, Z., Perko, JD., Oner, C., Cetin, M., Altay, C. et al. (2005). Hereditary juvenile cobalamin deficiency caused by mutations in the intrinsic factor gene. *Proc. Natl. Acad. Sci. U.S.A., 102*, 4130-3. ↗


## Editions

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|---|---|---|
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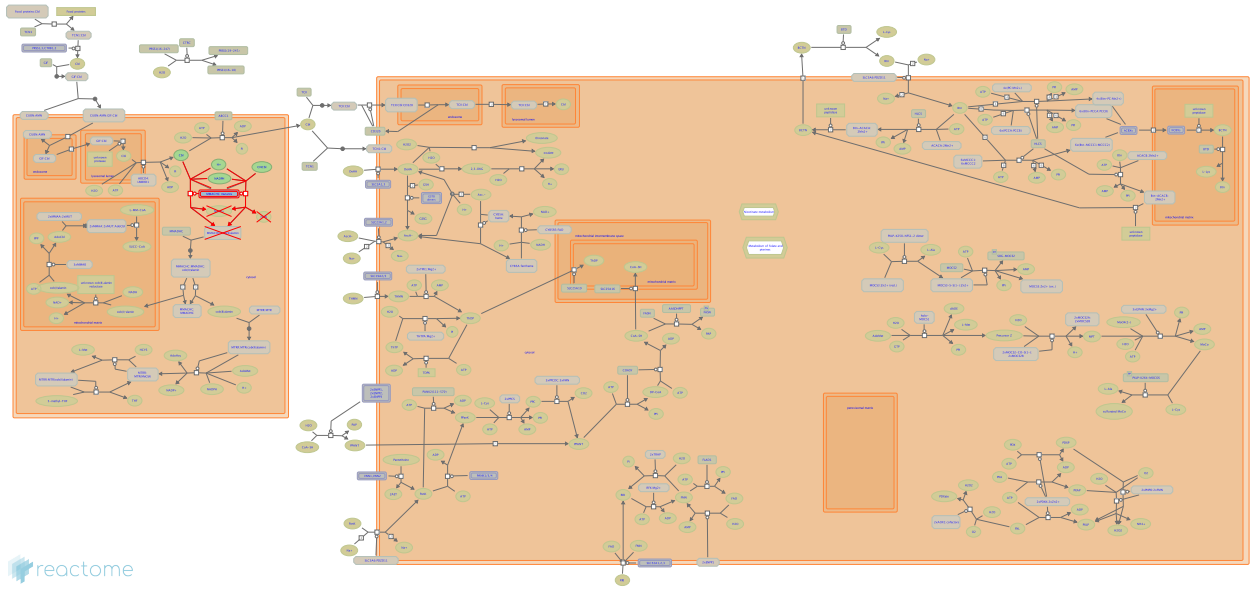
## Defective MMACHC causes methylmalonic aciduria and homocystinuria type cblC ↗

**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).

## Literature references


Lerner-Ellis, JP., Tirone, JC., Pawelek, PD., Doré, C., Atkinson, JL., Watkins, D. et al. (2006). Identification of the gene responsible for methylmalonic aciduria and homocystinuria, cblC type. *Nat. Genet., 38*, 93-100. ↗


## Editions

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|---|---|---|
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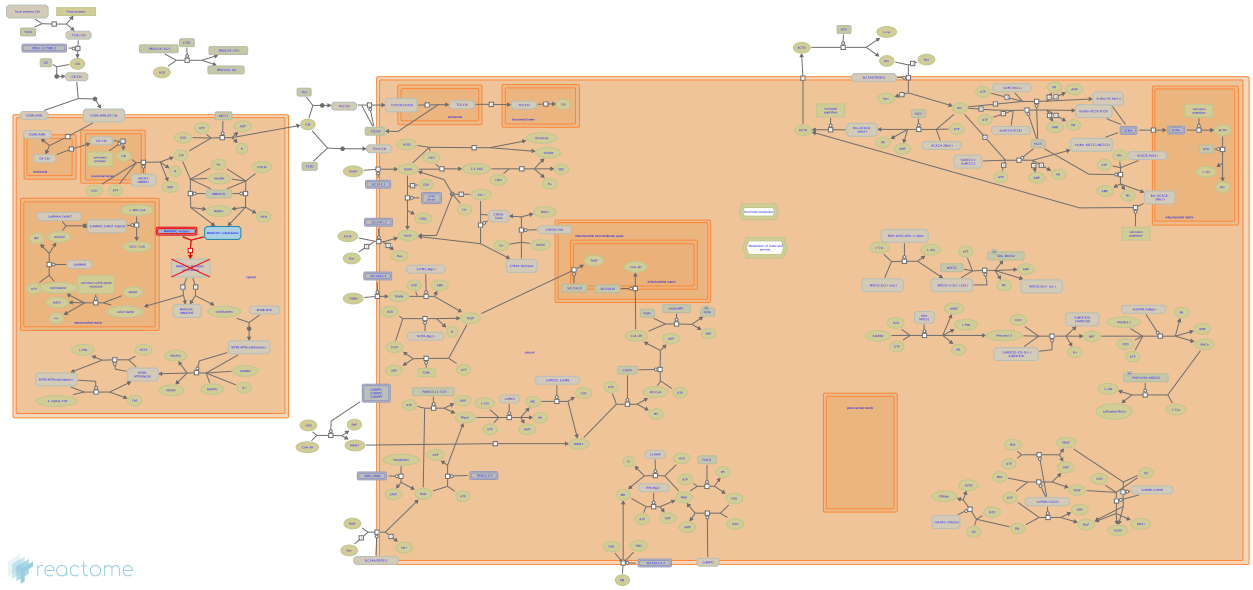
## Defective MMADHC causes methylmalonic aciduria and homocystinuria type cblD ↗

**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).

### Literature references


Coelho, D., Suormala, T., Stucki, M., Lerner-Ellis, JP., Rosenblatt, DS., Newbold, RF. et al. (2008). Gene identification for the cblD defect of vitamin B12 metabolism. *N. Engl. J. Med., 358*, 1454-64. ↗


### Editions

| | | |
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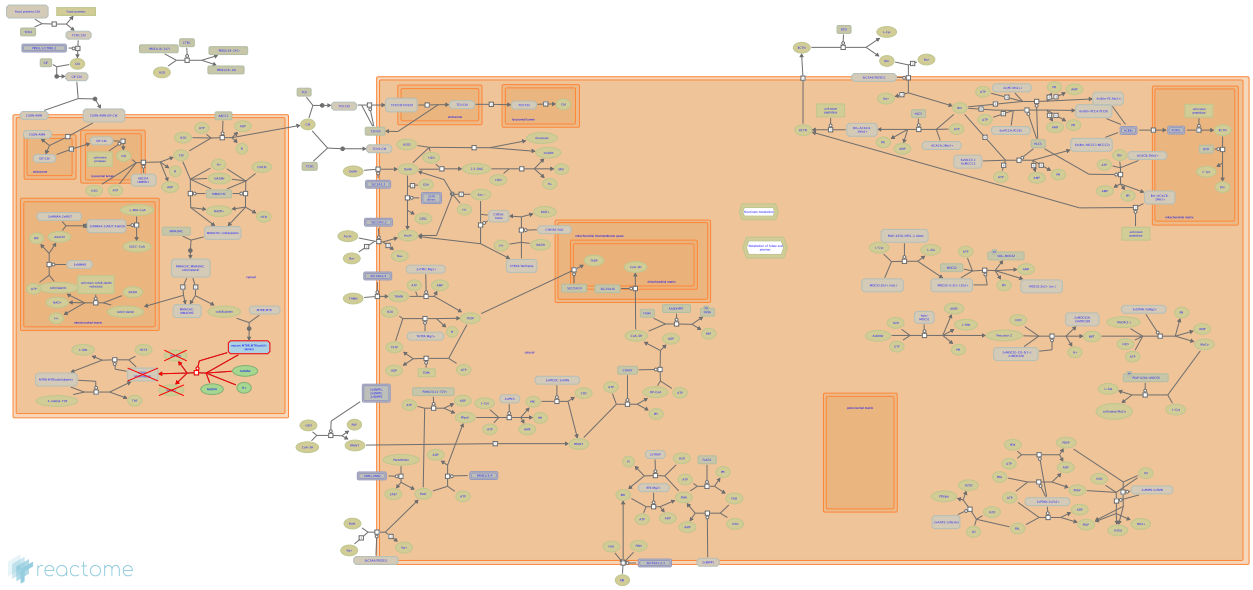
## Defective MTRR causes methylmalonic aciduria and homocystinuria type cblE ↗

**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.

## Literature references


Wilson, A., Leclerc, D., Rosenblatt, DS., Gravel, RA. (1999). Molecular basis for methionine synthase reductase deficiency in patients belonging to the cblE complementation group of disorders in folate/cobalamin metabolism. *Hum. Mol. Genet., 8*, 2009-16. ↗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|---|---|---|
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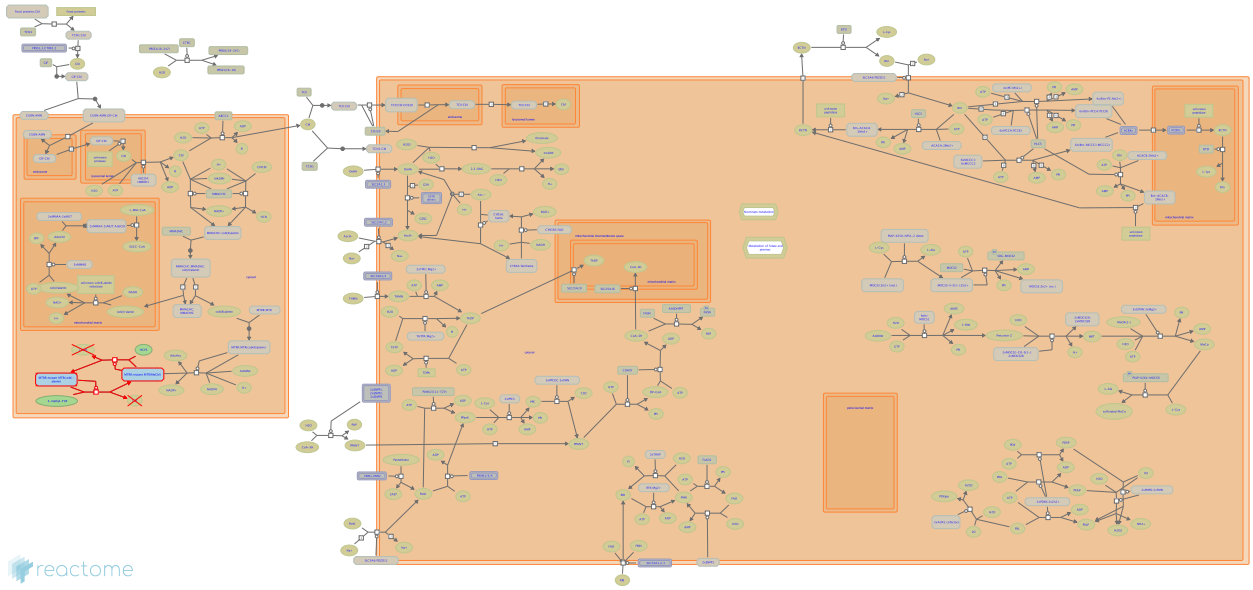
## Defective MTR causes methylmalonic aciduria and homocystinuria type cblG ↗

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

**Stable identifier:** R-HSA-3359469

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



Defects in MTR cause methylcobalamin deficiency type G (cblG; MIM:250940), an autosomal recessive inherited disease that causes mental retardation, macrocytic anemia, and homocystinuria (Leclerc et al. 1996, Gulati et al. 1996, Watkins et al. 2002).

## Literature references


Gulati, S., Baker, P., Li, YN., Fowler, B., Kruger, W., Brody, LC. et al. (1996). Defects in human methionine synthase in cblG patients. *Hum. Mol. Genet., 5*, 1859-65. ↗

Leclerc, D., Campeau, E., Goyette, P., Adjalla, CE., Christensen, B., Ross, M. et al. (1996). Human methionine synthase: cDNA cloning and identification of mutations in patients of the cblG complementation group of folate/-cobalamin disorders. *Hum Mol Genet, 5*, 1867-74. ↗

Watkins, D., Ru, M., Hwang, HY., Kim, CD., Murray, A., Philip, NS. et al. (2002). Hyperhomocysteinemia due to methionine synthase deficiency, cblG: structure of the MTR gene, genotype diversity, and recognition of a common mutation, P1173L. *Am. J. Hum. Genet., 71*, 143-53. ↗


## Editions

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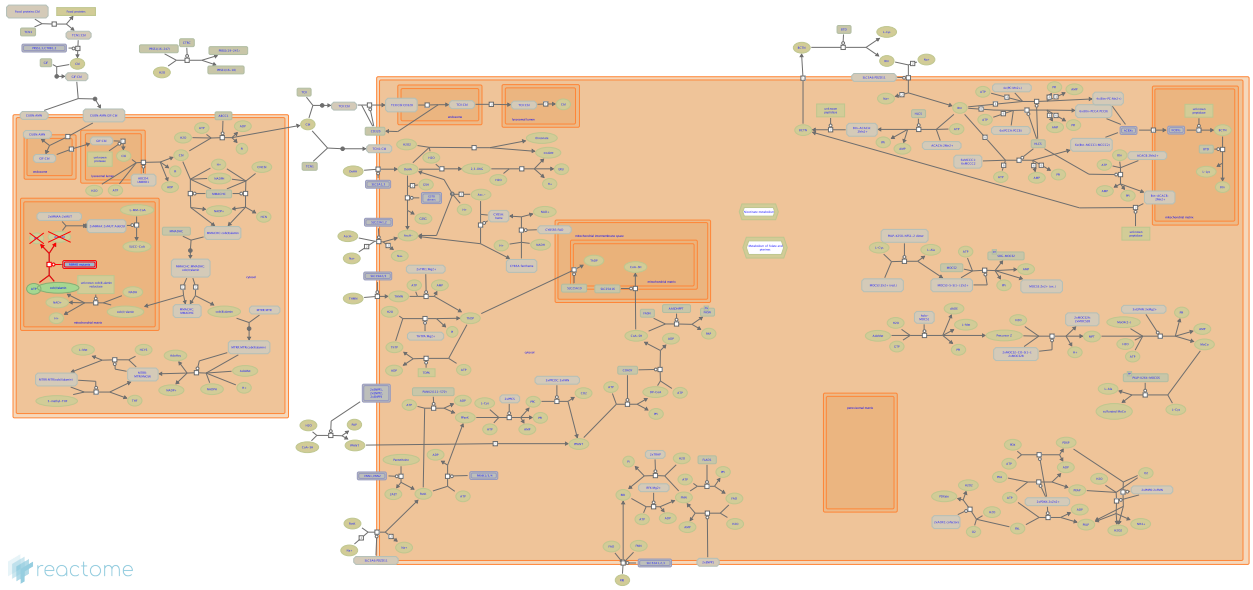
## Defective MMAB causes methylmalonic aciduria type cblB ↗

**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 methylmalonicaciduria 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).

## Literature references

Dobson, CM., Wai, T., Leclerc, D., Kadir, H., Narang, M., Lerner-Ellis, JP. et al. (2002). Identification of the gene responsible for the cblB complementation group of vitamin B12-dependent methylmalonic aciduria. *Hum. Mol. Genet., 11*, 3361-9. ↗

## Editions

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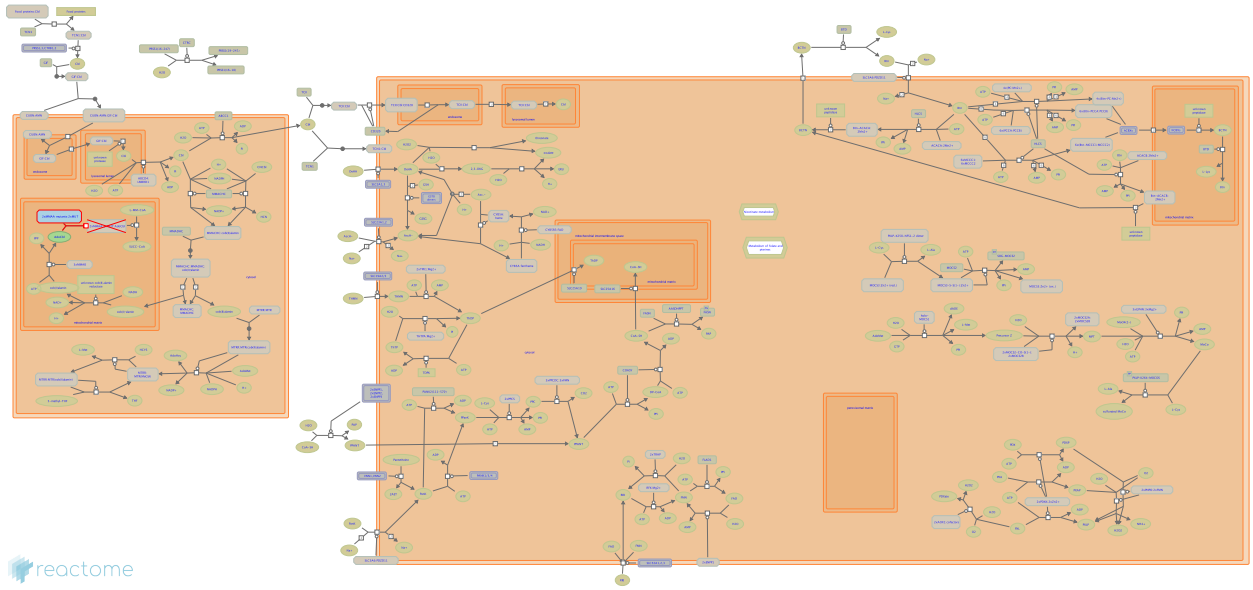
## Defective MMAA causes methylmalonic aciduria type cblA ↗

**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).

## Literature references


Dobson, CM., Wai, T., Leclerc, D., Wilson, A., Wu, X., Doré, C. et al. (2002). Identification of the gene responsible for the cblA complementation group of vitamin B12-responsive methylmalonic acidemia based on analysis of prokaryotic gene arrangements. *Proc. Natl. Acad. Sci. U.S.A., 99*, 15554-9. ↗

Lerner-Ellis, JP., Dobson, CM., Wai, T., Watkins, D., Tirone, JC., Leclerc, D. et al. (2004). Mutations in the MMAA gene in patients with the cblA disorder of vitamin B12 metabolism. *Hum. Mutat., 24*, 509-16. ↗


## Editions

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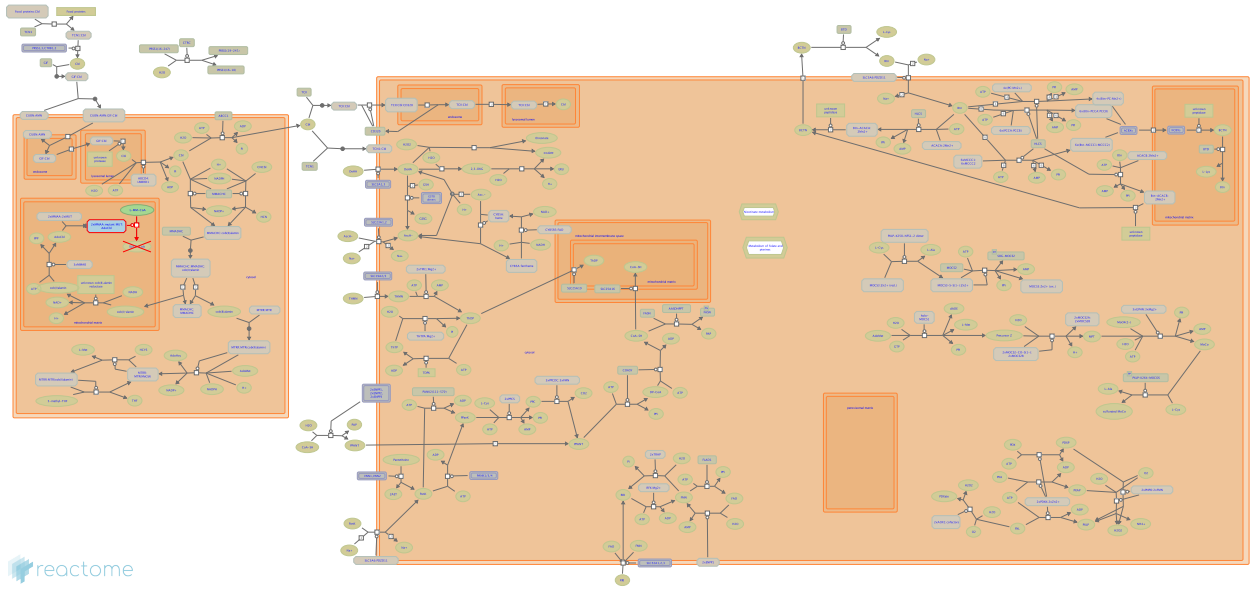
## Defective MUT causes methylmalonic aciduria mut type ↗

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

**Stable identifier:** R-HSA-3359478

**Diseases:** methylmalonic acidemia



Defects in MUT cause methylmalonic aciduria, mut type (MMAM; MIM:251000), an often fatal disorder of organic acid metabolism (Worgan et al. 2006).

## Literature references


Worgan, LC., Niles, K., Tirone, JC., Hofmann, A., Verner, A., Sammak, A. et al. (2006). Spectrum of mutations in mut methylmalonic acidemia and identification of a common Hispanic mutation and haplotype. *Hum. Mutat., 27*, 31-43. ↗


## Editions

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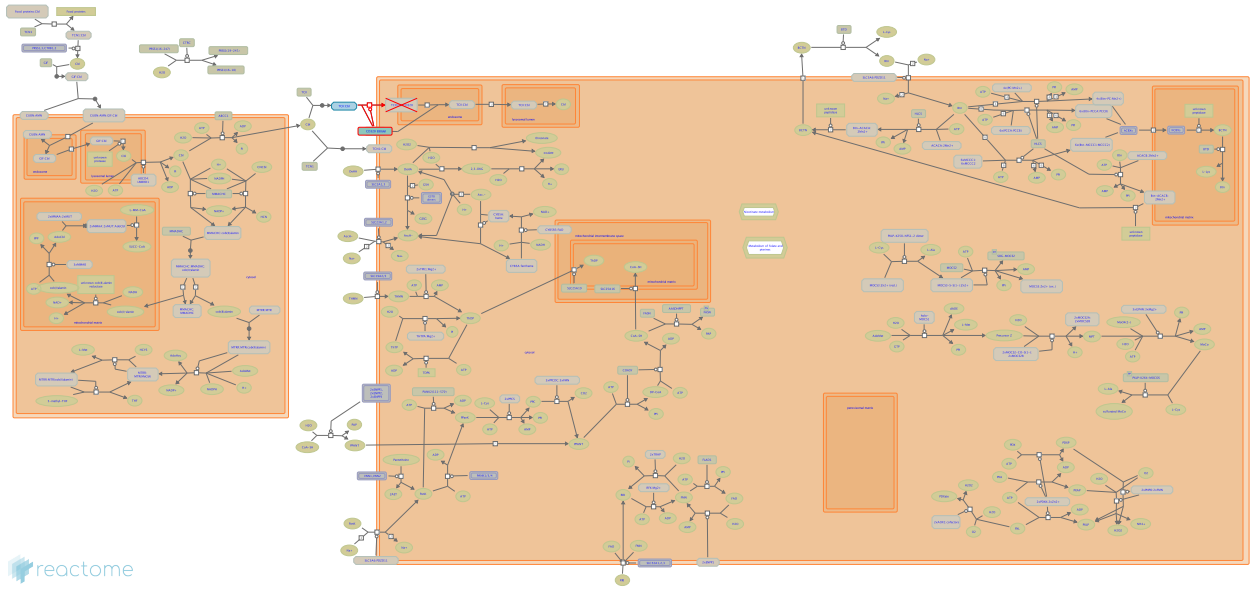
## Defective CD320 causes methylmalonic aciduria ↗

**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).

## Literature references


Quadros, EV., Lai, SC., Nakayama, Y., Sequeira, JM., Hannibal, L., Wang, S. et al. (2010). Positive newborn screen for methylmalonic aciduria identifies the first mutation in TCblR/CD320, the gene for cellular uptake of transcobalamin-bound vitamin B(12). *Hum. Mutat., 31*, 924-9. ↗


## Editions

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|---|---|---|
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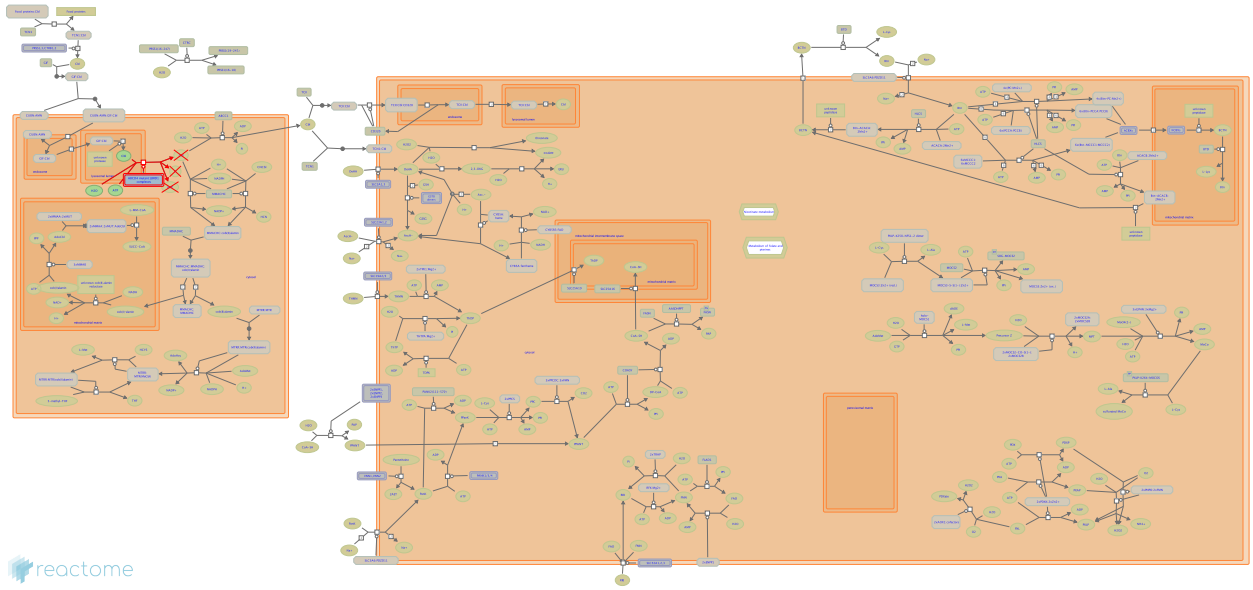
## Defective ABCD4 causes MAHCJ ↗

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

**Stable identifier:** R-HSA-5683329

**Diseases:** homocystinuria, methylmalonic acidemia




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

Coelho, D., Kim, JC., Miousse, IR., Fung, S., du Moulin, M., Buers, I. et al. (2012). Mutations in ABCD4 cause a new inborn error of vitamin B12 metabolism. *Nat. Genet., 44*, 1152-5. ↗

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