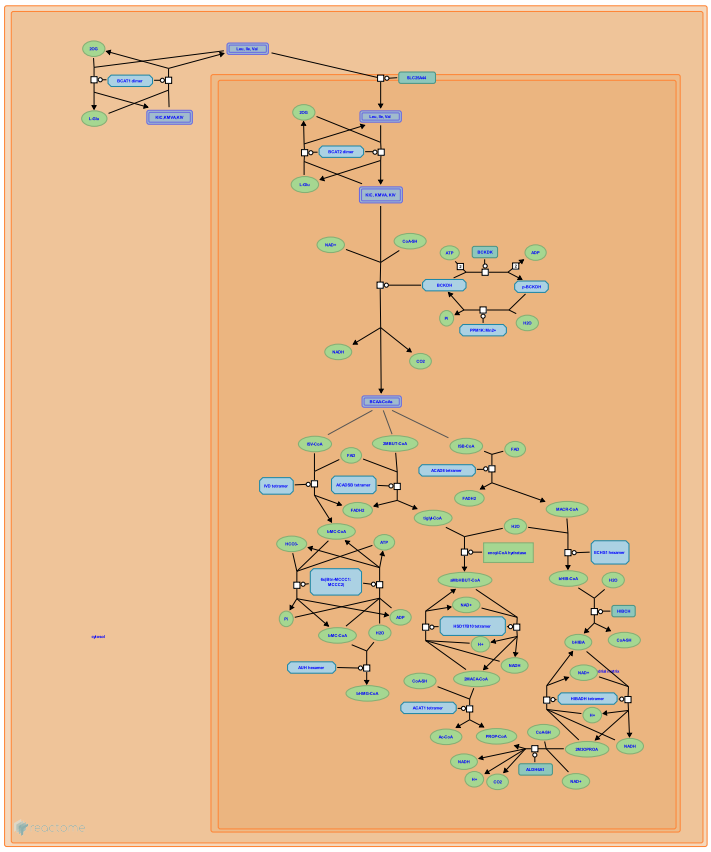
Branched-chain amino acid catabolism



D'Eustachio, P., Jassal, B., May, B.

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

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.

27/04/2024

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. ↗

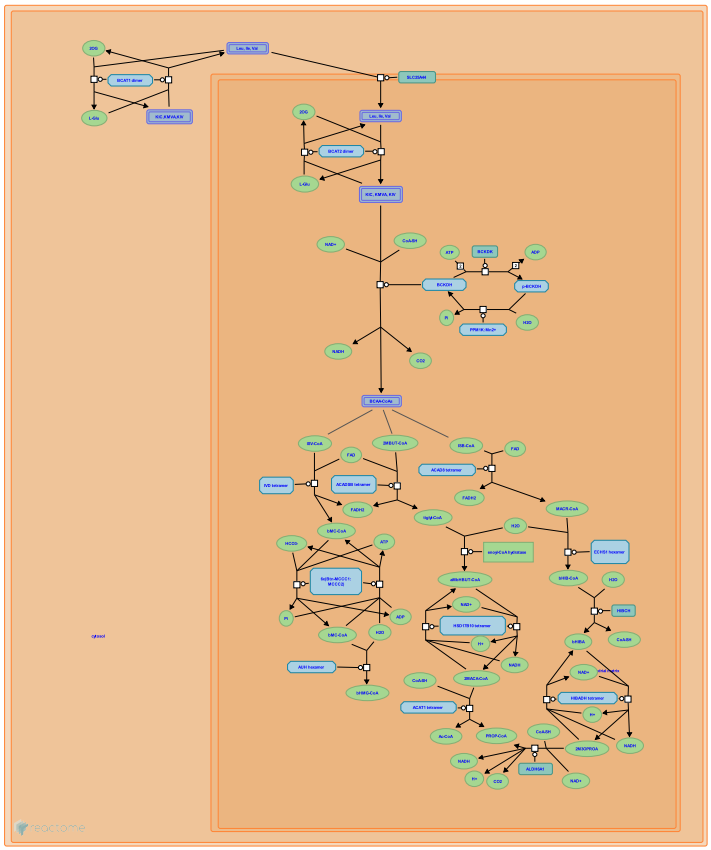
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Branched-chain amino acid catabolism ↗

Stable identifier: R-HSA-70895



The branched-chain amino acids, leucine, isoleucine, and valine, are all essential amino acids (i.e., ones required in the diet). They are major constituents of muscle protein. The breakdown of these amino acids starts with two common steps catalyzed by enzymes that act on all three amino acids: reversible transamination by branched-chain amino acid aminotransferase, and irreversible oxidative decarboxylation by the branched-chain ketoacid dehydrogenase complex. Isovaleryl-CoA is produced from leucine by these two reactions, alpha-methylbutyryl-CoA from isoleucine, and isobutyryl-CoA from valine. These acyl-CoA's undergo dehydrogenation, catalyzed by three different but related enzymes, and the breakdown pathways then diverge. Leucine is ultimately converted to acetyl-CoA and acetoacetate; isoleucine to acetyl-CoA and succinyl-CoA; and valine to succinyl-CoA. Under fasting conditions, substantial amounts of all three amino acids are generated by protein breakdown. In muscle, the final products of leucine, isoleucine, and valine catabolism can be fully oxidized via the citric acid cycle; in liver they can be directed toward the synthesis of ketone bodies (acetoacetate and acetyl-CoA) and glucose (succinyl-CoA) (Neinast et al. 2019).

Literature references

Arany, Z., Murashige, D., Neinast, M. (2019). Branched Chain Amino Acids. *Annu. Rev. Physiol., 81*, 139-164. ↗

Editions

2003-06-24	Authored	D'Eustachio, P.
2010-02-18	Revised	D'Eustachio, P.
2020-01-03	Revised	D'Eustachio, P.
2024-03-06	Edited	D'Eustachio, P.

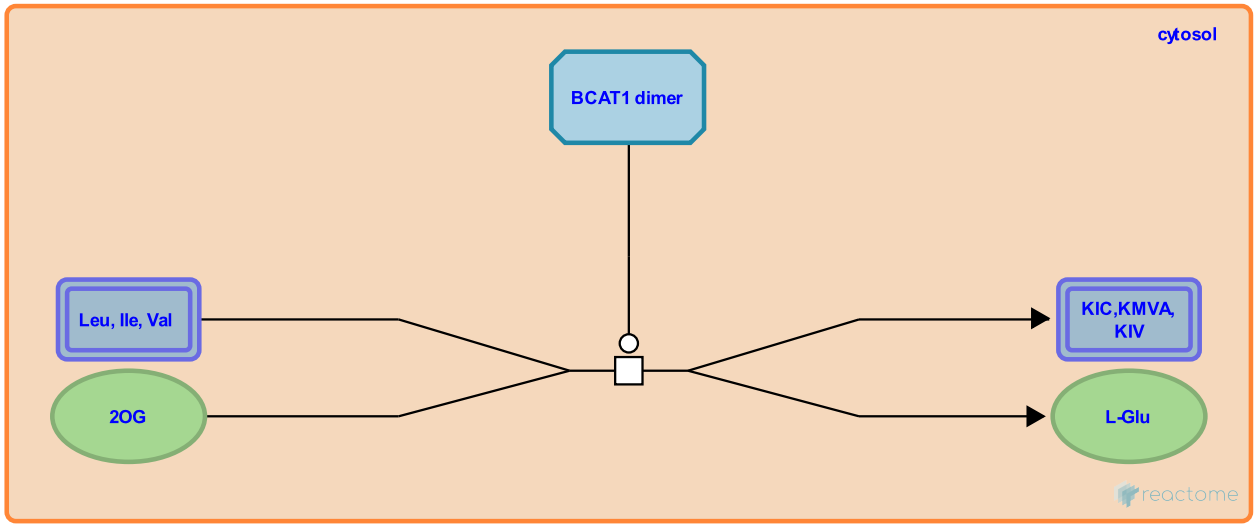
leu, ile, or val + alpha-ketoglutarate <=> a-ketoisocaproate, a-keto-b-methylvalerate, or a-ketoisovalerate + glutamate [BCAT1] ↗

Location: Branched-chain amino acid catabolism

Stable identifier: R-HSA-70723

Type: transition

Compartments: cytosol



Cytosolic branched-chain-amino-acid aminotransferase (BCAT1) catalyzes the reversible reactions of leucine, isoleucine, or valine with alpha-ketoglutarate (2-oxoglutarate) to form alpha-ketoisocaproate, alpha-keto-beta-methylvalerate, or a-ketoisovalerate, respectively, and glutamate. The active enzyme is a homodimer. Goto et al. (2005) have argued that cytosolic BCAT1 plays a major role in the generation of glutamate involved in synaptic transmission in neural tissue.

Literature references

Hirotsu, K., Goto, M., Islam, MM., Conway, ME., Hutson, SM., Yennawar, NH. et al. (2005). Structural determinants for branched-chain aminotransferase isozyme-specific inhibition by the anticonvulsant drug gabapentin. *J Biol Chem, 280*, 37246-56. ↗

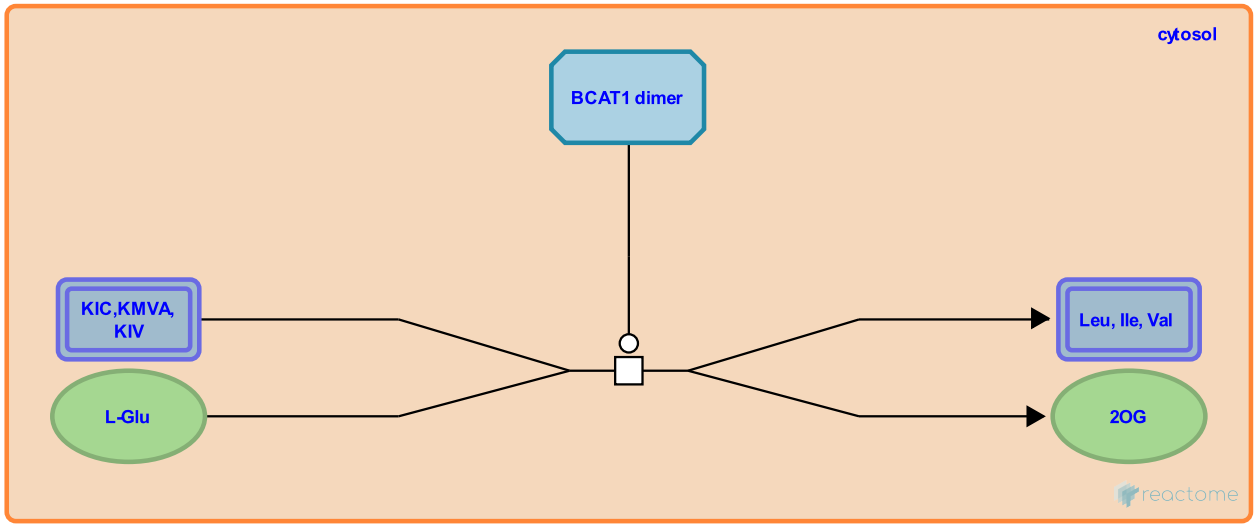
a-ketoisocaproate, a-keto-b-methylvalerate, or a-ketoisovalerate + glutamate <=> leu, ile, or val + alpha-ketoglutarate [BCAT1]

Location: Branched-chain amino acid catabolism

Stable identifier: R-HSA-508189

Type: transition

Compartments: cytosol



Cytosolic branched-chain-amino-acid aminotransferase (BCAT1) catalyzes the reversible reactions of alpha-ketoisocaproate, alpha-keto-beta-methylvalerate, or a-ketoisovalerate with glutamate to form leucine, isoleucine, or valine, respectively, and alpha-ketoglutarate (2-oxoglutarate). The active enzyme is a homodimer (Goto et al. 2005).

Literature references

Hirotsu, K., Goto, M., Islam, MM., Conway, ME., Hutson, SM., Yennawar, NH. et al. (2005). Structural determinants for branched-chain aminotransferase isozyme-specific inhibition by the anticonvulsant drug gabapentin. *J Biol Chem, 280*, 37246-56.

Editions

2010-02-18	Authored, Edited	D'Eustachio, P.
2010-02-27	Reviewed	Jassal, B.

SLC25A44 transports Leu, Ile and Val from cytosol to mitochondrial matrix ↗

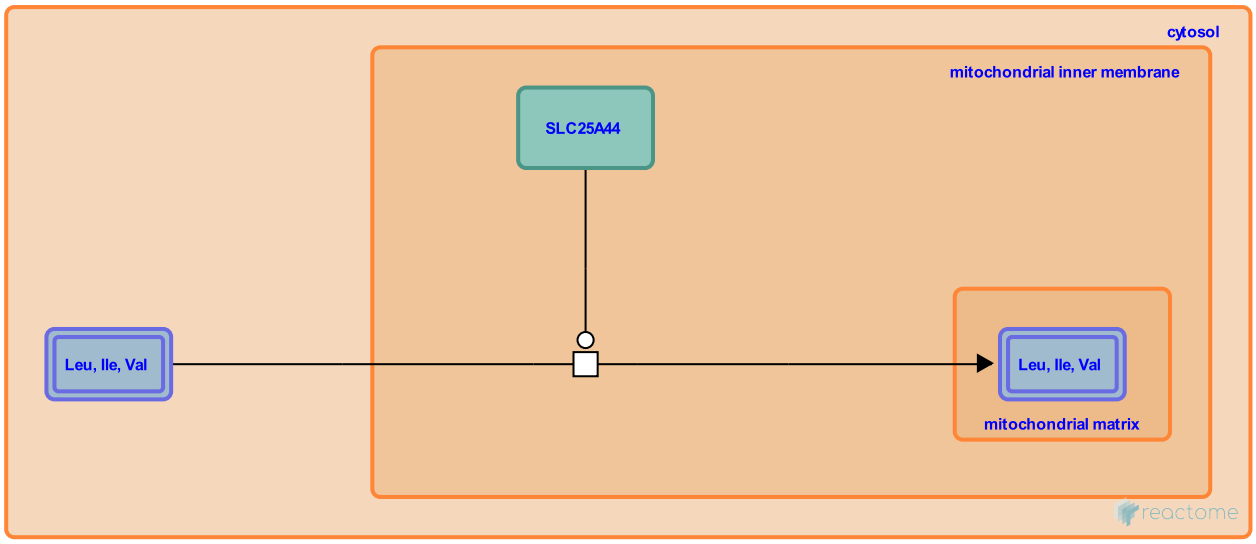
Location: Branched-chain amino acid catabolism

Stable identifier: R-HSA-9672770

Type: transition

Compartments: mitochondrial inner membrane

Inferred from: Slc25a44 transports Leu, Ile and Val from cytosol to mitochondrial matrix (Mus musculus)



Mitochondrial uptake of the three branched-chain amino acids leucine (Leu), isoleucine (Ile), and valine (Val) is mediated by solute carrier family 25 member 44 (SLC25A44), localized in the inner mitochondrial membrane. This human reaction is inferred from studies of the homologous mouse protein, Slc25a44 (Yoneshiro et al. 2019).

Followed by: leu, ile, or val + alpha-ketoglutarate <=> a-ketoisocaproate, a-keto-b-methylvalerate, or a-ketoisovalerate + glutamate [BCAT2]

Literature references

Oguri, Y., Saito, M., Pradhan, RN., Wang, Q., Brown, Z., Yoneshiro, T. et al. (2019). BCAA catabolism in brown fat controls energy homeostasis through SLC25A44. *Nature, 572*, 614-619. ↗

Editions

2020-01-02	Authored, Edited	D'Eustachio, P.
2020-01-03	Reviewed	Jassal, B.
2020-01-09	Reviewed	May, B.

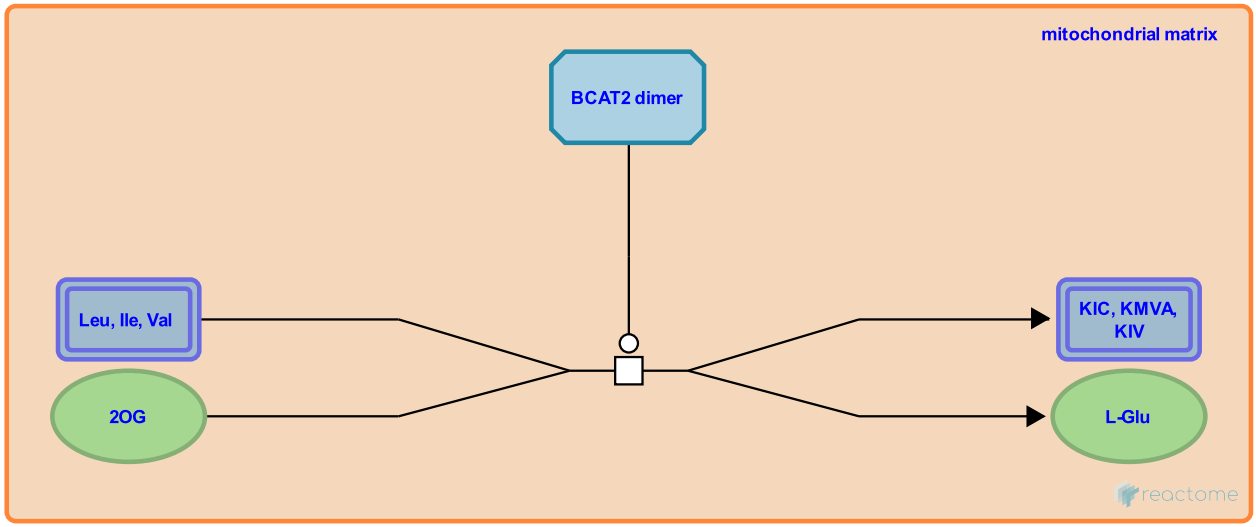
leu, ile, or val + alpha-ketoglutarate <=> a-ketoisocaproate, a-keto-b-methylvalerate, or a-ketoisovalerate + glutamate [BCAT2] ↗

Location: Branched-chain amino acid catabolism

Stable identifier: R-HSA-70724

Type: transition

Compartments: mitochondrial matrix



Mitochondrial branched-chain-amino-acid aminotransferase (BCAT2) catalyzes the reversible reactions of leucine, isoleucine, or valine with alpha-ketoglutarate (2-oxoglutarate) to form alpha-ketoisocaproate, alpha-keto-beta-methylvalerate, or a-ketoisovalerate, respectively, and glutamate (Bledsoe et al. 1997). The active enzyme is a homodimer (Yennawar et al. 2001, 2002). In the body, this enzyme is widely expressed but is especially abundant in muscle tissue.

Preceded by: SLC25A44 transports Leu, Ile and Val from cytosol to mitochondrial matrix

Followed by: BCKDH synthesizes BCAA-CoA from KIC, KMVA, KIV

Literature references

Hutson, SM., Dawson, PA., Bledsoe, RK. (1997). Cloning of the rat and human mitochondrial branched chain amino-transferases (BCATm). *Biochim Biophys Acta, 1339*, 9-13. ↗

Farber, GK., Yennawar, HP., Conway, ME., Hutson, SM., Yennawar, NH. (2002). Crystal structures of human mitochondrial branched chain aminotransferase reaction intermediates: ketimine and pyridoxamine phosphate forms. *Biochemistry, 41*, 11592-601. ↗

Farber, GK., Conway, ME., Hutson, SM., Yennawar, NH., Dunbar, J. (2001). The structure of human mitochondrial branched-chain aminotransferase. *Acta Crystallogr D Biol Crystallogr, 57*, 506-15. ↗

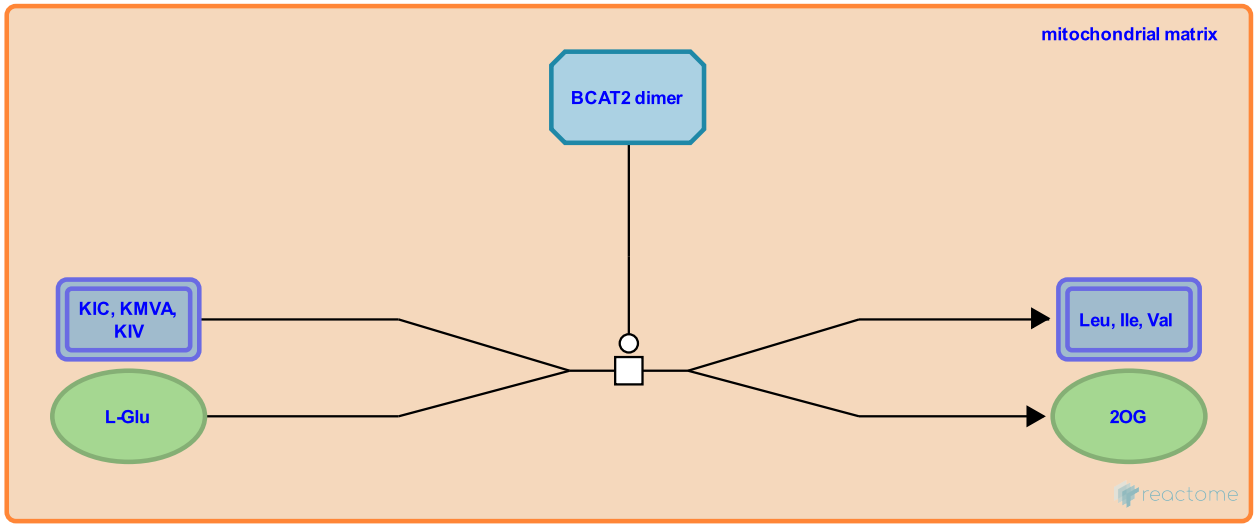
a-ketoisocaproate, a-keto-b-methylvalerate, or a-ketoisovalerate + glutamate <=> leu, ile, or val + alpha-ketoglutarate [BCAT2]

Location: Branched-chain amino acid catabolism

Stable identifier: R-HSA-508179

Type: transition

Compartments: mitochondrial matrix



Mitochondrial branched-chain-amino-acid aminotransferase (BCAT2) catalyzes the reversible reactions of alpha-ketoisocaproate, alpha-keto-beta-methylvalerate, or a-ketoisovalerate with glutamate to form leucine, isoleucine, or valine, respectively, and alpha-ketoglutarate (Bledsoe et al. 1997). The active enzyme is a homodimer (Yennawar et al. 2001, 2002). In the body, this enzyme is widely expressed but is especially abundant in muscle tissue.

Literature references

Hutson, SM., Dawson, PA., Bledsoe, RK. (1997). Cloning of the rat and human mitochondrial branched chain amino-transferases (BCATm). *Biochim Biophys Acta, 1339*, 9-13.

Farber, GK., Yennawar, HP., Conway, ME., Hutson, SM., Yennawar, NH. (2002). Crystal structures of human mitochondrial branched chain aminotransferase reaction intermediates: ketimine and pyridoxamine phosphate forms. *Biochemistry, 41*, 11592-601.

Farber, GK., Conway, ME., Hutson, SM., Yennawar, NH., Dunbar, J. (2001). The structure of human mitochondrial branched-chain aminotransferase. *Acta Crystallogr D Biol Crystallogr, 57*, 506-15.

Editions

2010-02-18	Authored, Edited	D'Eustachio, P.
2010-02-27	Reviewed	Jassal, B.

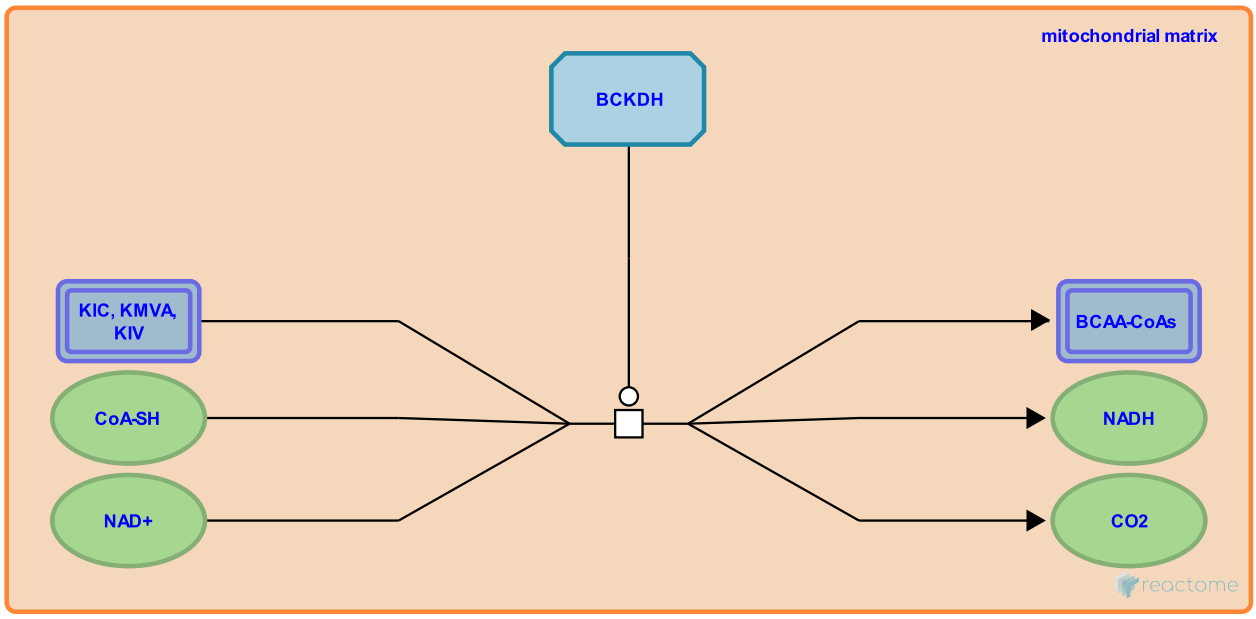
BCKDH synthesizes BCAA-CoA from KIC, KMVA, KIV ↗

Location: Branched-chain amino acid catabolism

Stable identifier: R-HSA-70713

Type: transition

Compartments: mitochondrial matrix



The mitochondrial branched-chain alpha-ketoacid dehydrogenase (BKCDH) complex catalyzes the reactions of alpha-ketoisocaproate, alpha-keto beta-methylvalerate, or alpha-ketoisovalerate with CoA and NAD+ to form isovaleryl-CoA, a-methylbutyryl-CoA, or isobutyryl-CoA, respectively, and CO2 and NADH (Chuang and Shih 2001). While bovine and microbial BCKD complexes have been characterized most extensively (Reed and Hackert 1990), structural studies of individual components and subcomplexes of human BKCD have confirmed their structures and roles in the overall oxidative carboxylation process, and have related these features to the disruptive effects of mutations on branched-chain amino acid metabolism in vivo: E1a and E1b components - AEvarsson et al. 2000; E2 - Chang et al. 2002; E3- Brautigam et al. 2005. In addition, structural studies have confirmed the lipoylation of lysine residue 44 in E2 protein (Chang et al. 2002) and the loss of an aminoterminal mitochondrial transport sequence from mature E3 protein (Brautigam et al. 2005). Loss of mitochondrial transport sequences from proteins E1a, E1b, and E2 has been demonstrated by sequence analysis (Wynn et al. 1994).

Preceded by: leu, ile, or val + alpha-ketoglutarate <=> a-ketoisocaproate, a-keto-b-methylvalerate, or a-ketoisovalerate + glutamate [BCAT2]

Followed by: isovaleryl-CoA + FAD => beta-methylcrotonyl-CoA + FADH2, alpha-methylbutyryl-CoA + FAD => tiglyl-CoA + FADH2, isobutyryl-CoA + FAD => methacrylyl-CoA + FADH2

Literature references

Reed, LJ., Hackert, ML. (1990). Structure-function relationships in dihydrolipoamide acyltransferases. *J Biol Chem, 265*, 8971-4. ↗

Beaudet, AL., Scriver, CR., Sly, WS., Valle, D. (2001). Maple syrup urine disease (branched-chain ketoaciduria), The Metabolic and Molecular Bases of Inherited Disease, 8th ed. *McGraw Hill*, 1971-2005.

Tomchick, DR., Machius, M., Chuang, DT., Chuang, JL., Brautigam, CA. (2005). Crystal structure of human dihydrolipoamide dehydrogenase: NAD+/NADH binding and the structural basis of disease-causing mutations. *J Mol Biol, 350*, 543-52. ↗

Hol, WG., Turley, S., Chuang, DT., Chuang, JL., Wynn, RM., Aevarsson, A. (2000). Crystal structure of human branched-chain alpha-ketoacid dehydrogenase and the molecular basis of multienzyme complex deficiency in maple syrup urine disease. *Structure Fold Des, 8*, 277-91. ↗

Chuang, DT., Chou, HT., Chuang, JL., Chang, CF., Huang, TH. (2002). Solution structure and dynamics of the lipoic acid-bearing domain of human mitochondrial branched-chain alpha-keto acid dehydrogenase complex. *J Biol Chem, 277*, 15865-73. ↗

Editions

2024-02-08	Reviewed	D'Eustachio, P.

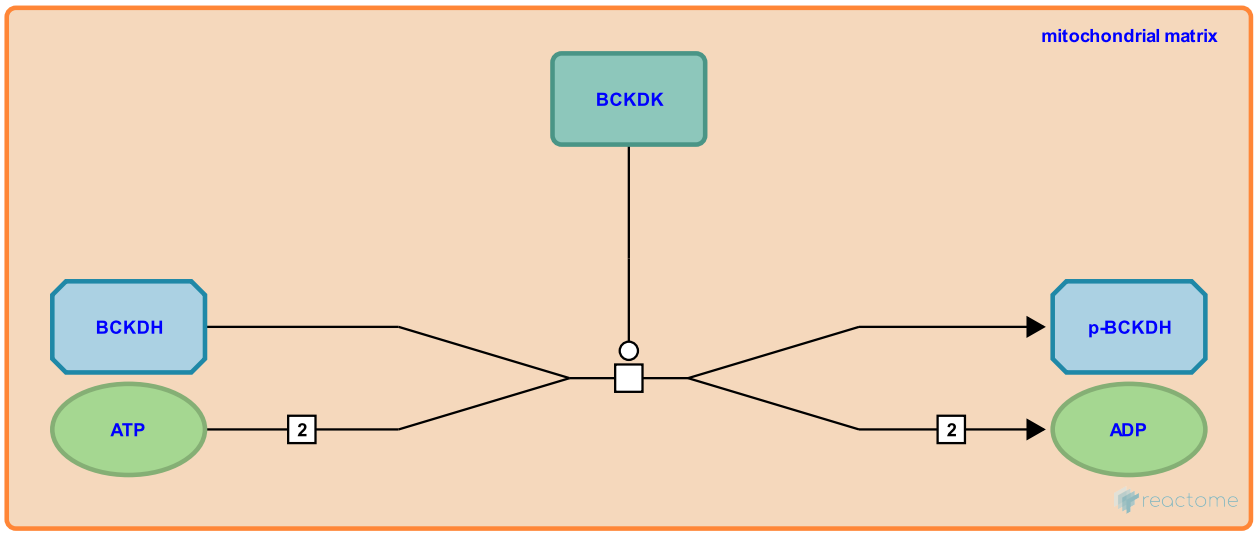
BCKDK phosphorylates BCKDH ↗

Location: Branched-chain amino acid catabolism

Stable identifier: R-HSA-5693148

Type: transition

Compartments: mitochondrial matrix



Mitochondrial 3-methyl-2-oxobutanoate dehydrogenase (lipoamide) kinase (BCKDK) catalyses the phosphorylation and inactivation of the branched-chain alpha-ketoacid dehydrogenase (BCKDH) complex, the key regulatory enzyme of the valine, leucine and isoleucine catabolic pathways (Li et al. 2004, Wynn et al. 2004). BCKDH occupies a strategic point in the branched-chain amino acid (BCAA) catabolic pathway, and careful regulation of its activity is essential for correct BCAA metabolism. The overall activity of the BCKDH complex is controlled by the phosphorylation (inactivation)/dephosphorylation (activation) cycle.
Defects in BCKDK can cause branched-chain ketoacid dehydrogenase kinase deficiency (BCKDKD; MIM:614923), a metabolic disorder characterised by autism, epilepsy, intellectual disability, and reduced BCAAs (Novarino et al. 2012, Garcia-Cazorla et al. 2014).

Literature references

Li, J., Tomchick, DR., Karthikeyan, S., Machius, M., Chuang, DT., Chuang, JL. et al. (2004). Cross-talk between thiamin diphosphate binding and phosphorylation loop conformation in human branched-chain alpha-keto acid decarboxylase/dehydrogenase. *J. Biol. Chem., 279*, 32968-78. ↗

Sanz, P., Castejón, E., Nunes, V., Ruiz-Sala, P., Agulló, SB., Palacin, M. et al. (2014). Two novel mutations in the BCKDK (branched-chain keto-acid dehydrogenase kinase) gene are responsible for a neurobehavioral deficit in two pediatric unrelated patients. *Hum. Mutat., 35*, 470-7. ↗

Li, J., Tomchick, DR., Machius, M., Chuang, DT., Chuang, JL., Wynn, RM. et al. (2004). Molecular mechanism for regulation of the human mitochondrial branched-chain alpha-ketoacid dehydrogenase complex by phosphorylation. *Structure, 12*, 2185-96. ↗

Khalil, RO., Harris, RA., Ben-Omran, T., State, MW., Gleeson, JG., Hashish, AF. et al. (2012). Mutations in BCKD-kinase lead to a potentially treatable form of autism with epilepsy. *Science, 338*, 394-7. ↗

Editions

2015-05-14	Authored, Edited	Jassal, B.
2015-06-26	Reviewed	D'Eustachio, P.

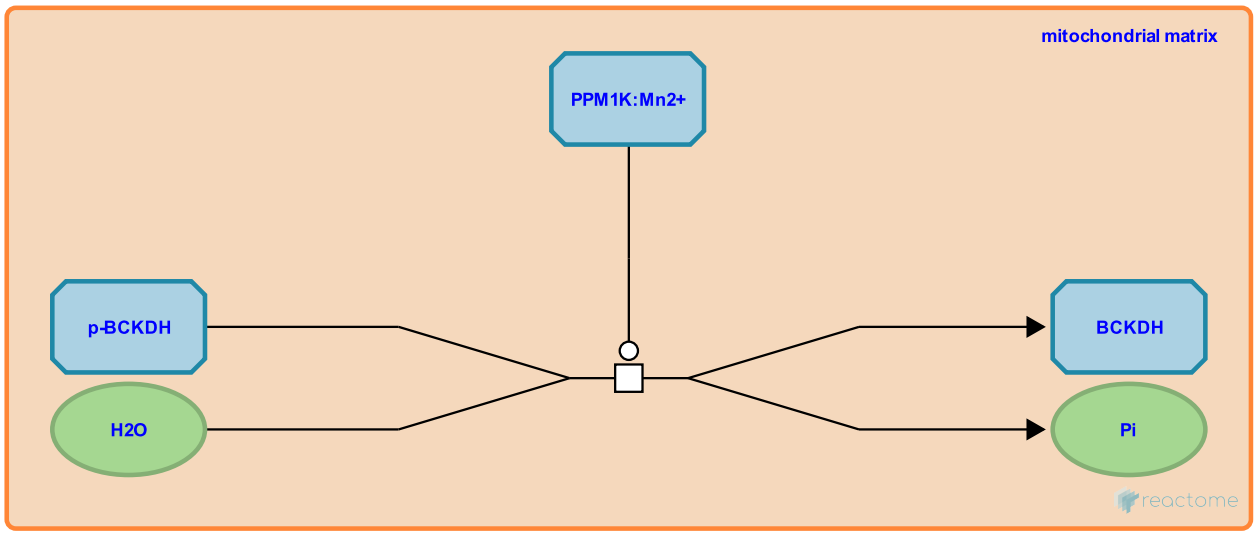
PPM1K dephosphorylates p-BCKDH ↗

Location: Branched-chain amino acid catabolism

Stable identifier: R-HSA-5693153

Type: transition

Compartments: mitochondrial matrix



The branched-chain alpha-ketoacid dehydrogenase (BCKDH) complex occupies a strategic point in the branched-chain amino acid (BCAA) catabolic pathway, and careful regulation of its activity is essential for correct BCAA metabolism. The overall activity of the BCKDH complex is controlled by the phosphorylation (inactivation)/dephosphorylation (activation) cycle. Mitochondrial protein phosphatase 1K (PPM1K) dephosphorylates the E1 beta subunit of BCKDH therby regaining its active state. PPM1K requires Mn2+ as a cofactor for phosphatase activity (Wynn et al. 2012).

Literature references

Li, J., Chuang, DT., Chuang, JL., Wynn, RM., Brautigam, CA. (2012). Structural and biochemical characterization of human mitochondrial branched-chain α-ketoacid dehydrogenase phosphatase. *J. Biol. Chem., 287*, 9178-92. ↗

Editions

2015-05-14	Authored, Edited	Jassal, B.
2015-06-26	Reviewed	D'Eustachio, P.

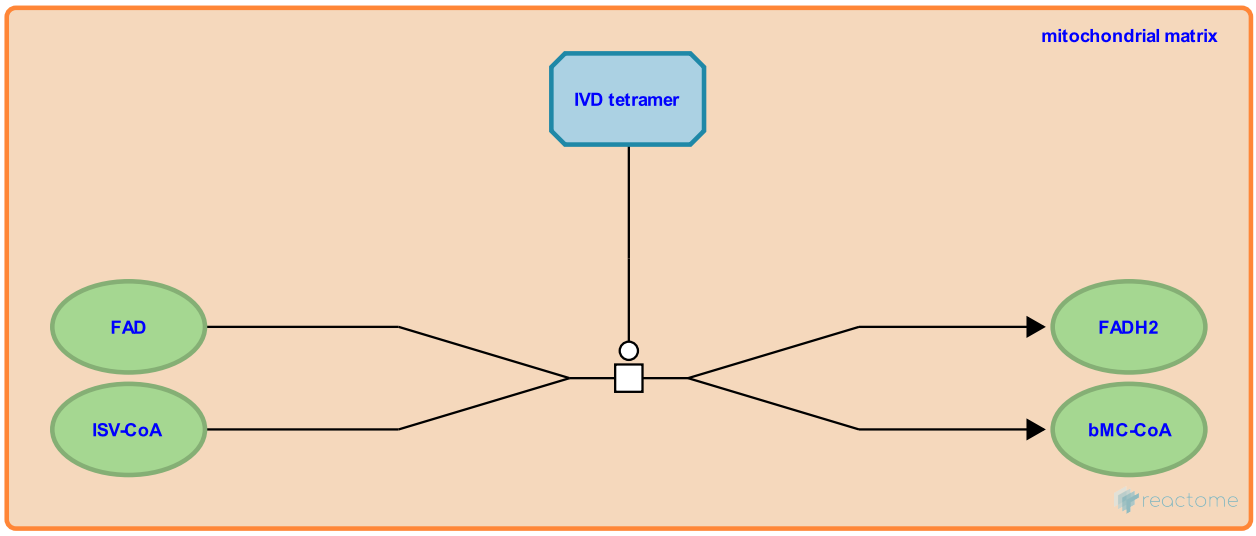
isovaleryl-CoA + FAD => beta-methylcrotonyl-CoA + FADH2 ↗

Location: Branched-chain amino acid catabolism

Stable identifier: R-HSA-70745

Type: transition

Compartments: mitochondrial matrix



Mitochondrial isovaleryl dehydrogenase (IVD) catalyzes the reaction of isovaleryl-CoA and FAD to form beta-methylcrotonyl-CoA and FADH2 (Finocchiaro et al. 1978; Rhead and Tanaka 1980). Crystallographic studies demonstrated the existene of a tetramer of IVD polypeptides lacking an aminoterminal mitochondrial targeting sequence (Tiffany et al. 1997).

Preceded by: BCKDH synthesizes BCAA-CoA from KIC, KMVA, KIV

Followed by: beta-methylcrotonyl-CoA + ATP + CO2 <=> beta-methylglutaconyl-CoA + ADP + orthophosphate + H2O [MCCA]

Literature references

Rhead, WJ., Tanaka, K. (1980). Demonstration of a specific mitochondrial isovaleryl-CoA dehydrogenase deficiency in fibroblasts from patients with isovaleric acidemia. *Proc Natl Acad Sci U S A, 77,* 580-3. ↗

Wang, M., Paschke, R., Tiffany, KA., Roberts, DL., Kim, JJ., Mohsen, AW. et al. (1997). Structure of human isovaleryl-CoA dehydrogenase at 2.6 A resolution: structural basis for substrate specificity. *Biochemistry, 36,* 8455-64. ↗

Tanaka, K., Finocchiaro, G., Ito, M. (1987). Purification and properties of short chain acyl-CoA, medium chain acyl-CoA, and isovaleryl-CoA dehydrogenases from human liver. *J Biol Chem, 262,* 7982-9. ↗

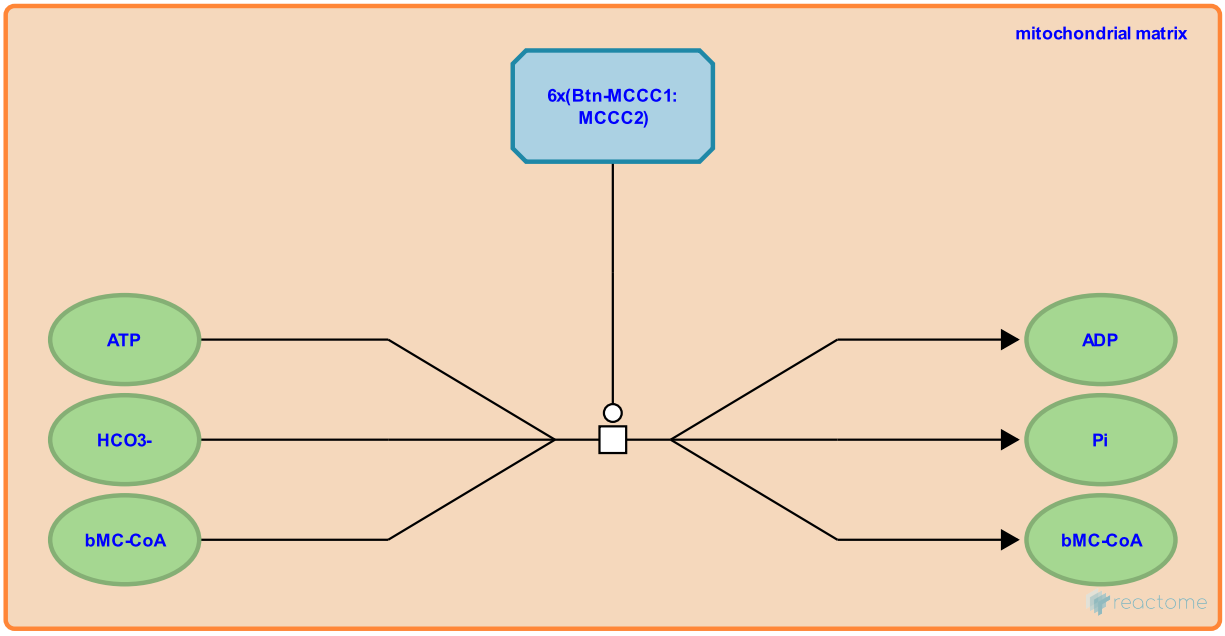
beta-methylcrotonyl-CoA + ATP + CO2 <=> beta-methylglutaconyl-CoA + ADP + ortho-phosphate + H2O [MCCA] ↗

Location: Branched-chain amino acid catabolism

Stable identifier: R-HSA-70773

Type: transition

Compartments: mitochondrial matrix



Methylcrotonyl CoA carboxylase (MCCA) catalyzes the reversible reaction of beta-methylcrotonyl-CoA, ATP, and CO2 to form beta-methylglutaconyl-CoA, ADP, orthophosphate, and H2O. Active MCCA is composed of two polypeptides, MCCA1 and MCCA2 (Baumgartner et al. 2001; Holzinger et al. 2001). The enzyme has been purified from fibroblast mitochondria. By analogy to the more thoroughly studied bovine homologue, MCCA is thought to be a hexamer of six MCCA1:MCCA2 dimers, and the MCCA1 polypeptide is thought to have a biotin moiety covalently bound to lysine residue 681. Localization of the complex to the mitochondrial inner membrane is inferred from studies of the bovine homologue (Hector et al. 1980). Mitochondrial import of MCCA1 and 2 is associated with removal of aminoterminal mitochondrial targeting sequences (Stadler et al. 2005).

Preceded by: isovaleryl-CoA + FAD => beta-methylcrotonyl-CoA + FADH2

Followed by: beta-methylglutaconyl-CoA + H2O <=> beta-hydroxy-beta-methylglutaryl-CoA

Literature references

Hector, ML., Logue, EA., Cochran, BC., Fall, RR. (1980). Subcellular localization of 3-methylcrotonyl-coenzyme A carboxylase in bovine kidney. *Arch Biochem Biophys, 199*, 28-36. ↗

Holzinger, A., Röschinger, W., Roscher, AA., Koch, HG., Muntau, AC., Thuy, LP. et al. (2001). Cloning of the human MCCA and MCCB genes and mutations therein reveal the molecular cause of 3-methylcrotonyl-CoA: carboxylase deficiency. *Hum Mol Genet, 10*, 1299-306. ↗

Baumgartner, ER., Cole, RN., Packman, S., Obie, C., Baumgartner, MR., Suormala, T. et al. (2001). The molecular basis of human 3-methylcrotonyl-CoA carboxylase deficiency. *J Clin Invest, 107*, 495-504. ↗

Holzinger, A., Anslinger, K., Röschinger, W., Roscher, AA., Herrmann, JM., Polanetz, R. et al. (2005). Mitochondrial targeting signals and mature peptides of 3-methylcrotonyl-CoA carboxylase. *Biochem Biophys Res Commun, 334*, 939-46. ↗

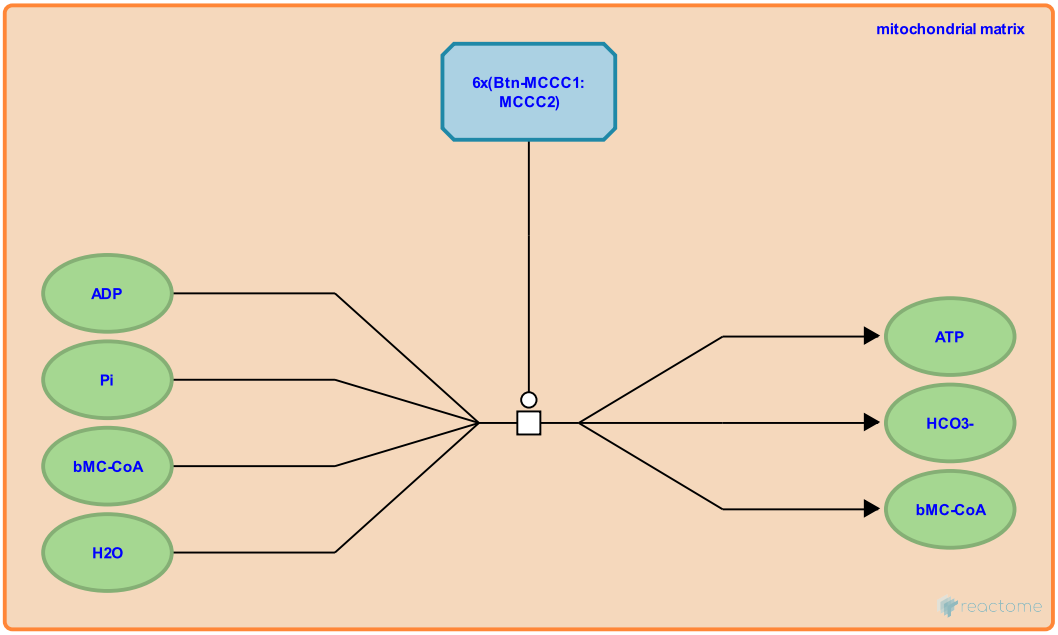
beta-methylglutaconyl-CoA + ADP + orthophosphate + H2O <=> beta-methylcrotonyl-CoA + ATP + CO2 [MCCA]

Location: Branched-chain amino acid catabolism

Stable identifier: R-HSA-508308

Type: transition

Compartments: mitochondrial matrix



Methylcrotonyl CoA carboxylase (MCCA) catalyzes the reversible reaction of beta-methylglutaconyl-CoA, ADP, orthophosphate, and H2O to form beta-methylcrotonyl-CoA, ATP, and CO2. Active MCCA is composed of two polypeptides, MCCA1 and MCCA2 (Baumgartner et al. 2001; Holzinger et al. 2001). The enzyme has been purified from fibroblast mitochondria. By analogy to the more thoroughly studied bovine homologue, MCCA is thought to be a hexamer of six MCCA1:MCCA2 dimers, and the MCCA1 polypeptides are thought to have biotin moieties covalently bound to a lysine residue at position 681 in the polypeptide chain. Mitochondrial import of MCCA1 and 2 is associated with removal of aminoterminal mitochondrial targeting sequences but the exact lengths of these sequences have not been determined.

Literature references

Holzinger, A., Röschinger, W., Roscher, AA., Koch, HG., Muntau, AC., Thuy, LP. et al. (2001). Cloning of the human MCCA and MCCB genes and mutations therein reveal the molecular cause of 3-methylcrotonyl-CoA: carboxylase deficiency. *Hum Mol Genet, 10*, 1299-306.

Baumgartner, ER., Cole, RN., Packman, S., Obie, C., Baumgartner, MR., Suormala, T. et al. (2001). The molecular basis of human 3-methylcrotonyl-CoA carboxylase deficiency. *J Clin Invest, 107*, 495-504.

Editions

2010-02-18	Authored	D'Eustachio, P.

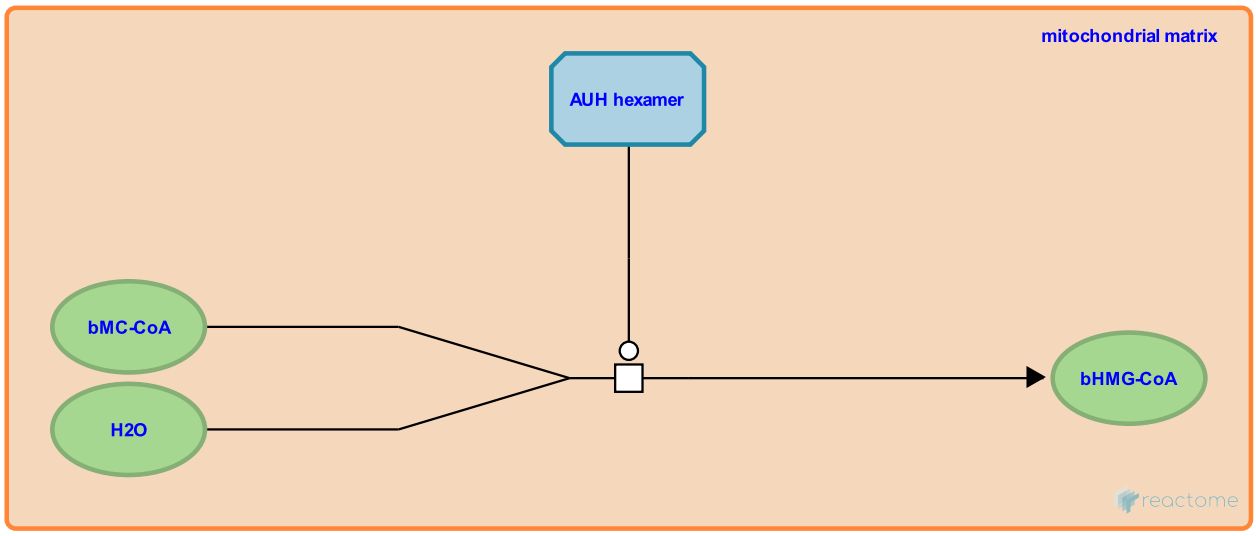
beta-methylglutaconyl-CoA + H2O <=> beta-hydroxy-beta-methylglutaryl-CoA ↗

Location: Branched-chain amino acid catabolism

Stable identifier: R-HSA-70785

Type: transition

Compartments: mitochondrial matrix



Mitochondrial ethylglutaconyl-CoA hydratase (AUH) catalyzes the hydrolysis of beta-methylglutaconyl-CoA to yield beta-hydroxy-beta-methylglutaryl-CoA (IJlst et al. 2002; Narisawa et al. 1986). Crystallographic studies have shown the active enzyme to be a hexamer of AUH polypeptides whose aminoterminal 67 residues, a mitochondrial targeting sequence, have been removed ((Kurimoto et al. 2001).

Preceded by: beta-methylcrotonyl-CoA + ATP + CO2 <=> beta-methylglutaconyl-CoA + ADP + orthophosphate + H2O [MCCA]

Literature references

Duran, M., Lehnert, W., IJlst, L., Loupatty, FJ., Ruiter, JP. (2002). 3-Methylglutaconic aciduria type I is caused by mutations in AUH. *Am J Hum Genet, 71*, 1463-6. ↗

Duran, M., Wadman, SK., Narisawa, K., Gibson, KM., Nyhan, WL., Sweetman, L. (1986). Deficiency of 3-methylglutaconyl-coenzyme A hydratase in two siblings with 3-methylglutaconic aciduria. *J Clin Invest, 77*, 1148-52. ↗

Kurimoto, K., Yokoyama, S., Muto, Y., Nureki, O., Fukai, S. (2001). Crystal structure of human AUH protein, a single-stranded RNA binding homolog of enoyl-CoA hydratase. *Structure, 9*, 1253-63. ↗

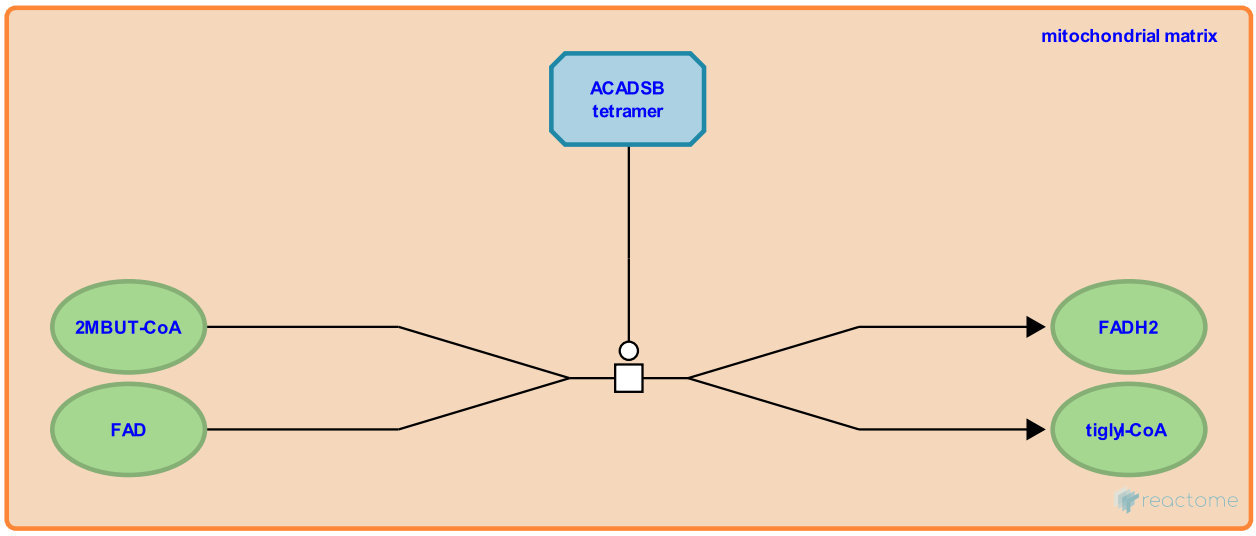
alpha-methylbutyryl-CoA + FAD => tiglyl-CoA + FADH2 ↗

Location: Branched-chain amino acid catabolism

Stable identifier: R-HSA-70800

Type: transition

Compartments: mitochondrial matrix



Mitochondrial 2-methyl branched chain acyl-CoA dehydrogenase (ACADSB) catalyzes the reaction of alpha-methylbutyryl-CoA and FAD to form 'tiglyl-CoA and FADH2 (Andresen et al. 2000; Gibson et al. 2000). Unpublished crystallographic data (PDB 2JIF) indicate that the enzyme is a tetramer of ACADSB polypeptides whose aminoterminal 51 residues, a mitochondrial targeting sequence, have been removed.

Preceded by: BCKDH synthesizes BCAA-CoA from KIC, KMVA, KIV

Followed by: tiglyl-CoA + H2O <=> alpha-methyl-beta-hydroxybutyryl-CoA

Literature references

Burlingame, TG., Hogema, B., Vockley, J., Rinaldo, P., Sacks, M., Kiss, D. et al. (2000). 2-Methylbutyryl-coenzyme A dehydrogenase deficiency: a new inborn error of L-isoleucine metabolism. *Pediatr Res, 47*, 830-3. ↗

Skovby, F., Schroeder, LD., Gregersen, N., Ruiter, JP., Winter, V., Knudsen, I. et al. (2000). Isolated 2-methylbutyrylglycinuria caused by short/branched-chain acyl-CoA dehydrogenase deficiency: identification of a new enzyme defect, resolution of its molecular basis, and evidence for distinct acyl-CoA dehydrogenases in isoleucine and valine metabolism. *Am J Hum Genet, 67*, 1095-103. ↗

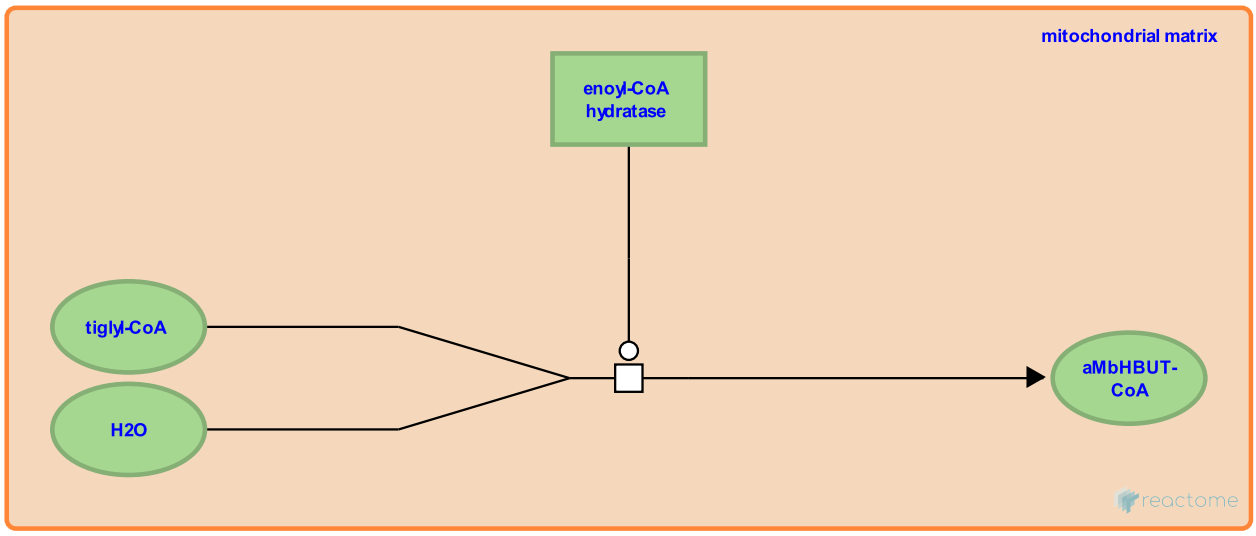
tiglyl-CoA + H2O <=> alpha-methyl-beta-hydroxybutyryl-CoA ↗

Location: Branched-chain amino acid catabolism

Stable identifier: R-HSA-70830

Type: transition

Compartments: mitochondrial matrix



Mitochondrial tiglyl-CoA is hydrolyzed to form alpha-methyl-beta-hydroxybutyryl-CoA. While crude extracts of human liver cells have been shown to catalyze the reaction, the specific enzyme responsible for it has not been identified (Sweetman and Williams 2001).

Preceded by: alpha-methylbutyryl-CoA + FAD => tiglyl-CoA + FADH2

Followed by: alpha-methyl-beta-hydroxybutyryl-CoA + NAD+ <=> alpha-methylacetoacetyl-CoA + NADH + H+

Literature references

Beaudet, AL., Scriver, CR., Sly, WS., Valle, D. (2001). Branched chain organic acidurias, The Metabolic and Molecular Bases of Inherited Disease, 8th ed. *McGraw Hill*, 2125-2163.

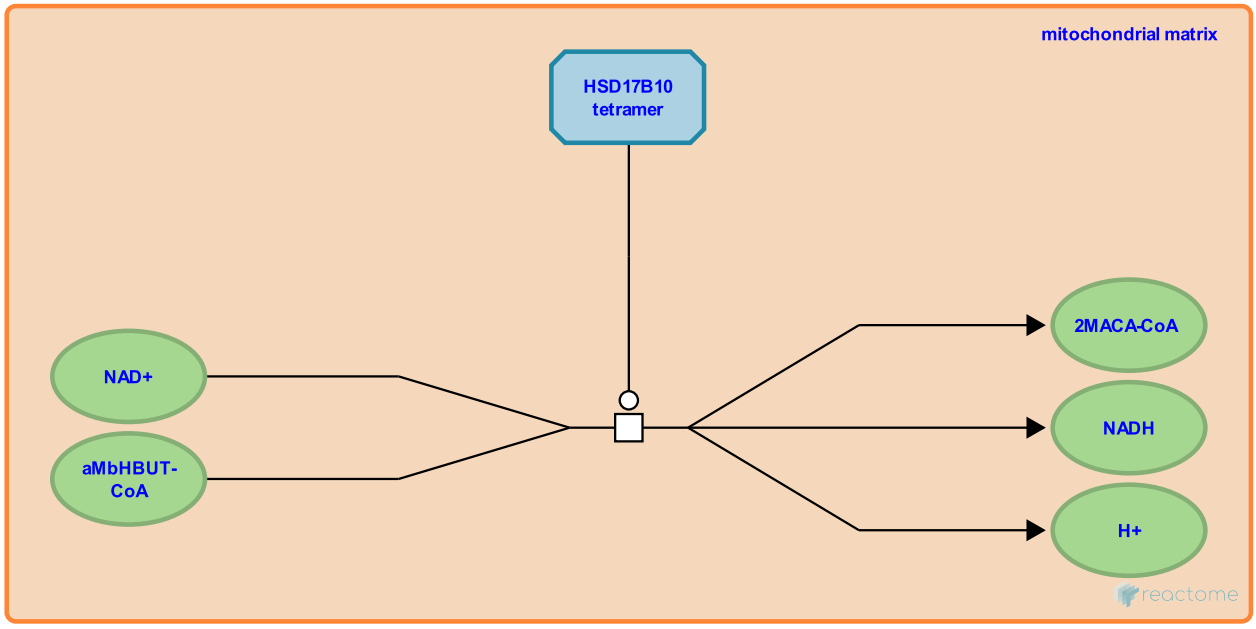
alpha-methyl-beta-hydroxybutyryl-CoA + NAD+ <=> alpha-methylacetoacetyl-CoA + NADH + H+ ↗

Location: Branched-chain amino acid catabolism

Stable identifier: R-HSA-70837

Type: transition

Compartments: mitochondrial matrix



Mitochondrial 3-hydroxyacyl-CoA dehydrogenase type-2 (HSD17B10; HADH2) catalyzes the reversible reaction of alpha-methyl-beta-hydroxybutyryl-CoA and NAD+ to form alpha-methylacetoacetyl-CoA and NADH + H+ (Ofman et al. 2003). Crystallographic data indicate that the enzyme is a homotetramer (Kissinger et al. 2004).

Preceded by: tiglyl-CoA + H2O <=> alpha-methyl-beta-hydroxybutyryl-CoA

Followed by: alpha-methyl-acetoacetyl-CoA + CoA => propionyl-CoA + acetyl-CoA

Literature references

Thomson, JA., Pelletier, LA., Abreo, MA., Vanderpool, D., Margosiak, S., Li, B. et al. (2004). Crystal structure of human ABAD/HSD10 with a bound inhibitor: implications for design of Alzheimer's disease therapeutics. *J Mol Biol, 342*, 943-52. ↗

Sass, JO., Duran, M., Sperl, W., Lehnert, W., Zschocke, J., Ensenauer, R. et al. (2003). 2-Methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency is caused by mutations in the HADH2 gene. *Am J Hum Genet, 72*, 1300-7. ↗

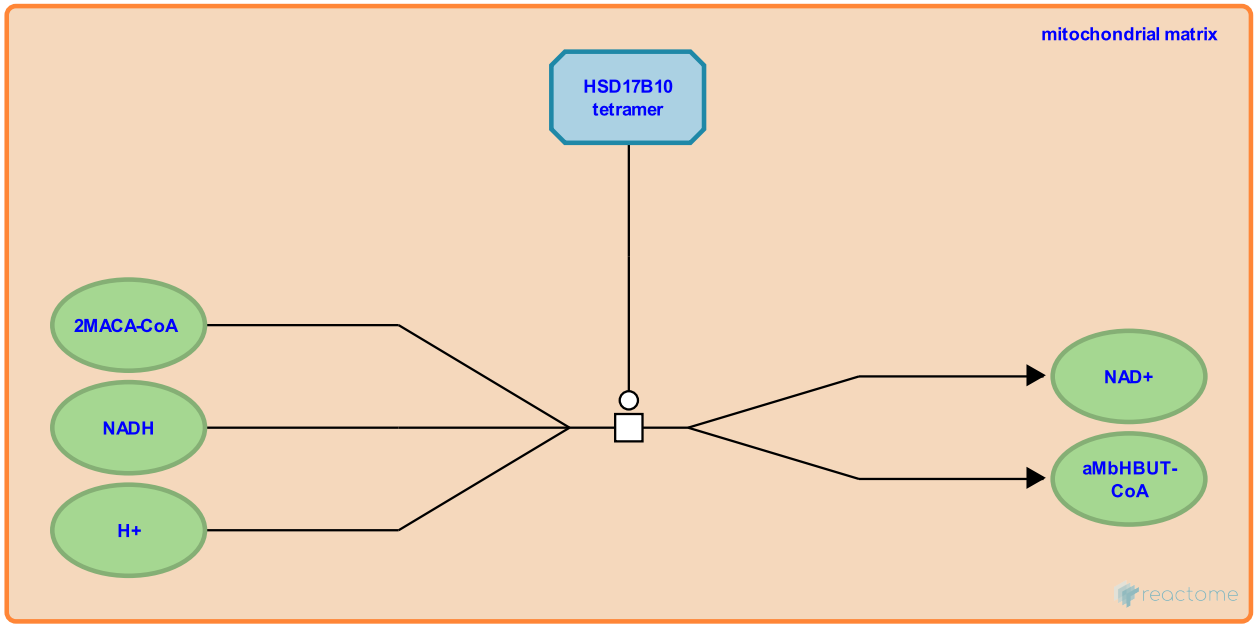
alpha-methylacetoacetyl-CoA + NADH + H+ <=> alpha-methyl-beta-hydroxybutyryl-CoA + NAD+ ↗

Location: Branched-chain amino acid catabolism

Stable identifier: R-HSA-508369

Type: transition

Compartments: mitochondrial matrix



Mitochondrial 3-hydroxyacyl-CoA dehydrogenase type-2 (HSD17B10; HADH2) catalyzes the reversible reaction of alpha-methylacetoacetyl-CoA and NADH + H+ to form alpha-methyl-beta-hydroxybutyryl-CoA and NAD+ (Ofman et al. 2003). Crystallographic data indicate that the enzyme is a homotetramer (Kissinger et al. 2004).

Literature references

Thomson, JA., Pelletier, LA., Abreo, MA., Vanderpool, D., Margosiak, S., Li, B. et al. (2004). Crystal structure of human ABAD/HSD10 with a bound inhibitor: implications for design of Alzheimer's disease therapeutics. *J Mol Biol, 342*, 943-52. ↗

Sass, JO., Duran, M., Sperl, W., Lehnert, W., Zschocke, J., Ensenauer, R. et al. (2003). 2-Methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency is caused by mutations in the HADH2 gene. *Am J Hum Genet, 72*, 1300-7. ↗

Editions

2010-02-18	Authored	D'Eustachio, P.

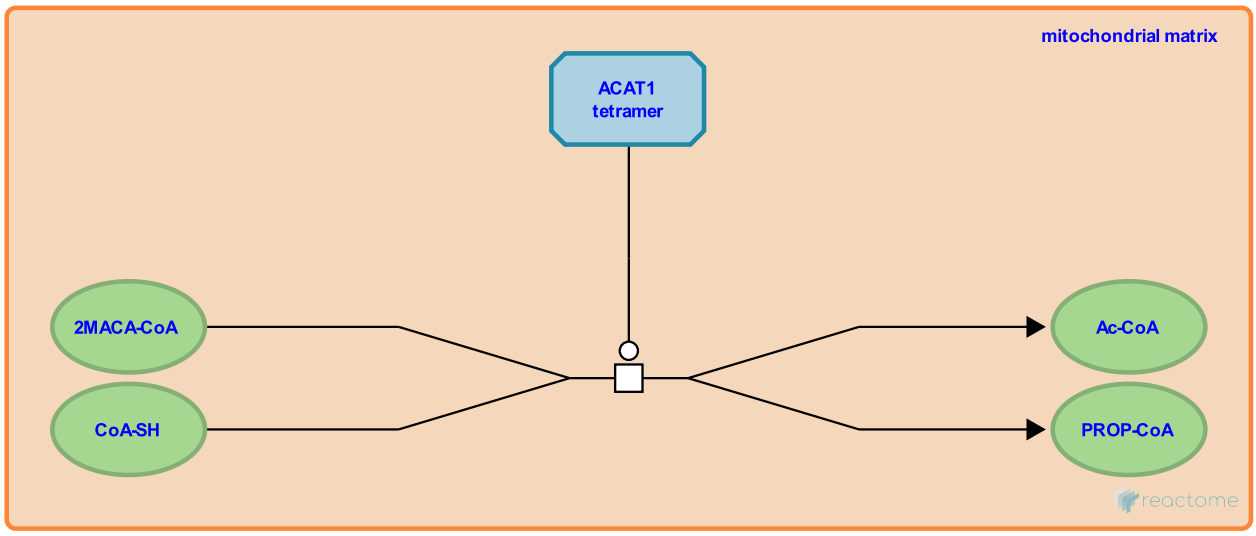
alpha-methyl-acetoacetyl-CoA + CoA => propionyl-CoA + acetyl-CoA ↗

Location: Branched-chain amino acid catabolism

Stable identifier: R-HSA-70844

Type: transition

Compartments: mitochondrial matrix



Mitochondrial acetyl-CoA acetyltransferase (ACAT1) catalyzes the reaction of alpha-methyl-acetoacetyl-CoA and CoA to form propionyl-CoA and acetyl-CoA. Structural studies have shown the active enzyme to be a tetramer of ACAT1 polypeptides whose aminoterminal 34 residues, a mitochondrial targeting sequence, have been removed (Haapalainen et al. 2007).

Preceded by: alpha-methyl-beta-hydroxybutyryl-CoA + NAD+ <=> alpha-methylacetoacetyl-CoA + NADH + H+

Literature references

Kondo, N., Haapalainen, AM., Fukao, T., Pirilä, PL., Wierenga, RK., Meriläinen, G. (2007). Crystallographic and kinetic studies of human mitochondrial acetoacetyl-CoA thiolase: the importance of potassium and chloride ions for its structure and function. *Biochemistry, 46*, 4305-21. ↗

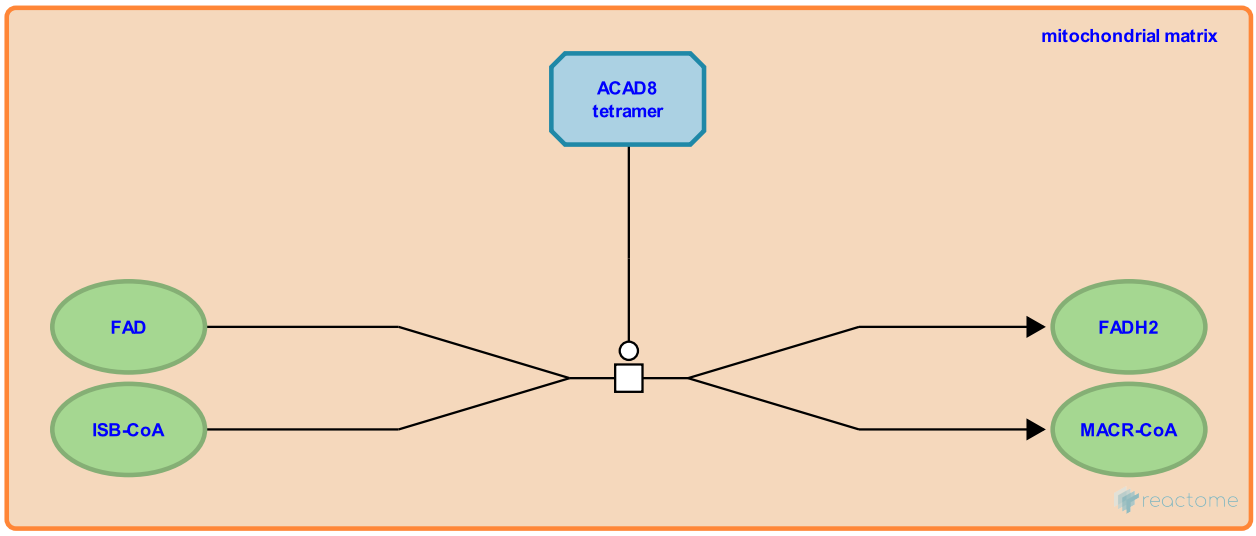
isobutyryl-CoA + FAD => methacrylyl-CoA + FADH2 ↗

Location: Branched-chain amino acid catabolism

Stable identifier: R-HSA-70859

Type: transition

Compartments: mitochondrial matrix



Mitochondrial isobutyryl-CoA dehydrogenase (ACAD8) catalyzes the reaction of isobutyryl-CoA and FAD to form methacrylyl-CoA and FADH2 (Roe et al. 1999; Nguyen et al. 2002). Crystallographic studies have shown the active enzyme to be a tetramer of ACAD8 polypeptides whose aminoterminal 23 residues, a mitochondrial targeting sequence, have been removed (Bataille et al. 2004).

Preceded by: BCKDH synthesizes BCAA-CoA from KIC, KMVA, KIV

Followed by: ECHS1 hydrates methacrylyl-CoA

Literature references

Mardach, R., Galindo, A., Cederbaum, SD., Roe, DS., Sweetman, L. (1999). Isolated isobutyryl-CoA dehydrogenase deficiency: an unrecognized defect in human valine metabolism. *Mol Genet Metab, 65*, 264-71. ↗

Cederbaum, SD., Lench, NJ., Roe, DS., Corydon, TJ., Ghisla, S., Andresen, BS. et al. (2002). Identification of isobutyryl-CoA dehydrogenase and its deficiency in humans. *Mol Genet Metab, 77*, 68-79. ↗

Kim, JJ., Battaile, KP., Vockley, J., Nguyen, TV. (2004). Structures of isobutyryl-CoA dehydrogenase and enzyme-product complex: comparison with isovaleryl- and short-chain acyl-CoA dehydrogenases. *J Biol Chem, 279*, 16526-34. ↗

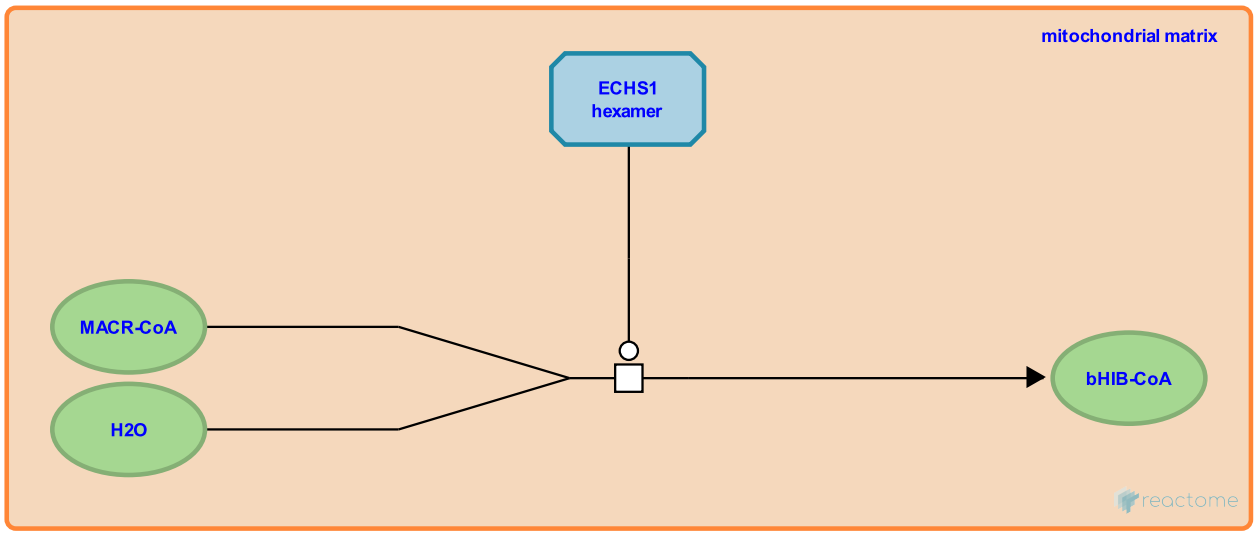
ECHS1 hydrates methacrylyl-CoA ↗

Location: Branched-chain amino acid catabolism

Stable identifier: R-HSA-70870

Type: transition

Compartments: mitochondrial matrix



Mitochondrial ECHS1 (enoyl-CoA hydratase) hexamer catalyzes the reversible addition of water to MACR-CoA (methacrylyl-CoA) to form bHIB-CoA (beta-hydroxybutyryl-CoA). Partially purified ECHS1 catalyzes this reaction with moderate efficiency in vitro, and patients deficient in the enzyme accumulate and excrete MACR-CoA (Yamada et al. 2015).

Preceded by: isobutyryl-CoA + FAD => methacrylyl-CoA + FADH2

Followed by: beta-hydroxyisobutyryl-CoA + H2O => beta-hydroxyisobutyrate + CoA

Literature references

Shimomura, Y., Yamaguchi, S., Nomura, N., Yamada, K., Kondo, Y., Pitt, J. et al. (2015). Clinical, biochemical and metabolic characterisation of a mild form of human short-chain enoyl-CoA hydratase deficiency: significance of increased N-acetyl-S-(2-carboxypropyl)cysteine excretion. *J. Med. Genet., 52*, 691-8. ↗

Editions

2020-01-02	Revised	D'Eustachio, P.
2020-01-03	Reviewed	Jassal, B.

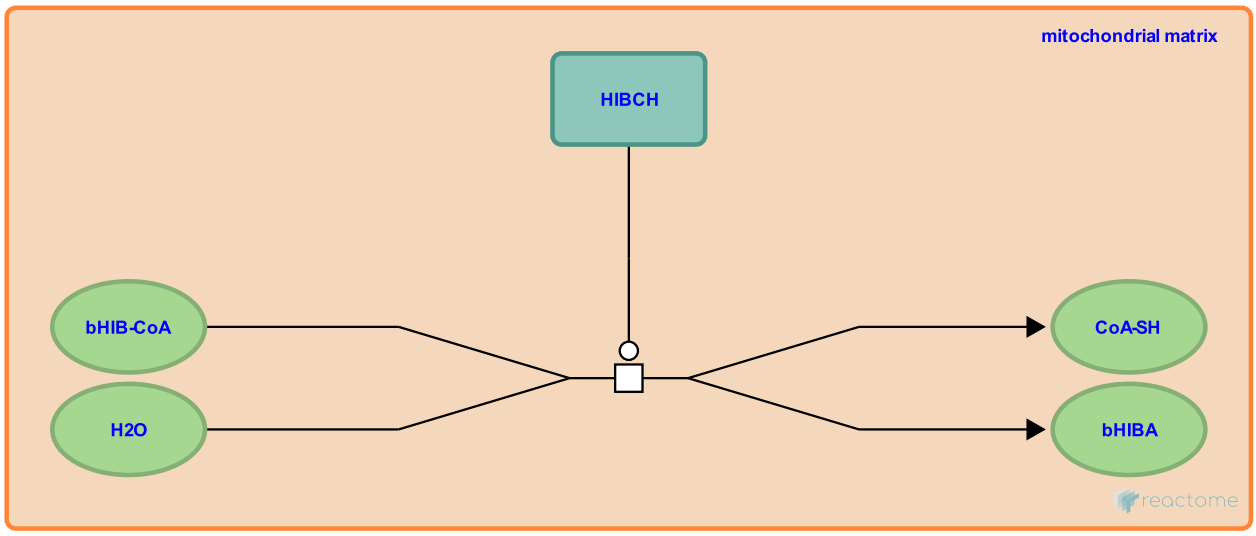
beta-hydroxyisobutyryl-CoA + H2O => beta-hydroxyisobutyrate + CoA ↗

Location: Branched-chain amino acid catabolism

Stable identifier: R-HSA-70881

Type: transition

Compartments: mitochondrial matrix



Mitochondrial 3-hydroxyisobutyryl-CoA hydrolase (HIBCH) catalyzes the hydrolysis of beta-hydroxyisobutyryl-CoA to form beta-hydroxyisobutyrate (3-hydroxy-2-methylpropanoate) and CoA (Hawes et al. 1996).

Preceded by: ECHS1 hydrates methacrylyl-CoA

Followed by: beta-hydroxyisobutyrate + NAD+ <=> methylmalonyl semialdehyde + NADH + H+

Literature references

Bunting, J., Harper, ET., Harris, RA., Shimomura, Y., Huang, B., Hawes, JW. et al. (1996). Primary structure and tissue-specific expression of human beta-hydroxyisobutyryl-coenzyme A hydrolase. *J Biol Chem, 271*, 26430-4. ↗

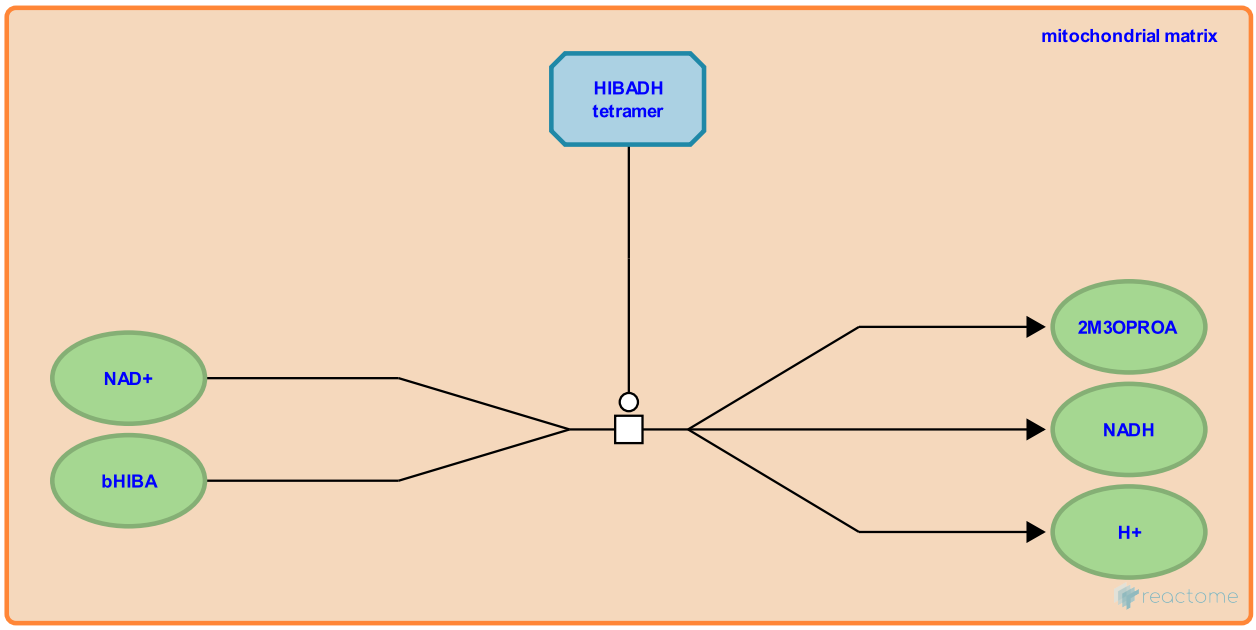
beta-hydroxyisobutyrate + NAD+ <=> methylmalonyl semialdehyde + NADH + H+ ↗

Location: Branched-chain amino acid catabolism

Stable identifier: R-HSA-70885

Type: transition

Compartments: mitochondrial matrix



Mitochondrial 3-hydroxyisobutyrate dehydrogenase (HIBADH) catalyzes the reversible reaction of beta-hydroxyisobutyrate and NAD+ to form methylmalonyl semialdehyde and NADH + H+. The biochemical properties of human HIBADH are inferred from those of its better-studied porcine homologue (Robinson and Coon 1957). Unpublished crystallographic studies (PDB 2GF2) have shown the active enzyme to be a tetramer of HIBADH polypeptides whose aminoterminal 40 residues, a mitochondrial targeting sequence, have been removed.

Preceded by: beta-hydroxyisobutyryl-CoA + H2O => beta-hydroxyisobutyrate + CoA

Followed by: methylmalonate semialdehyde + NAD+ + CoA => propionyl-CoA + CO2 + NADH + H+

Literature references

Coon, MJ., Robinson, WG. (1957). Purification and properties of beta-hydroxyisobutyric dehydrogenase. *J Biol Chem, 225*, 511-521. ↗

Editions

2010-02-27	Reviewed	Jassal, B.

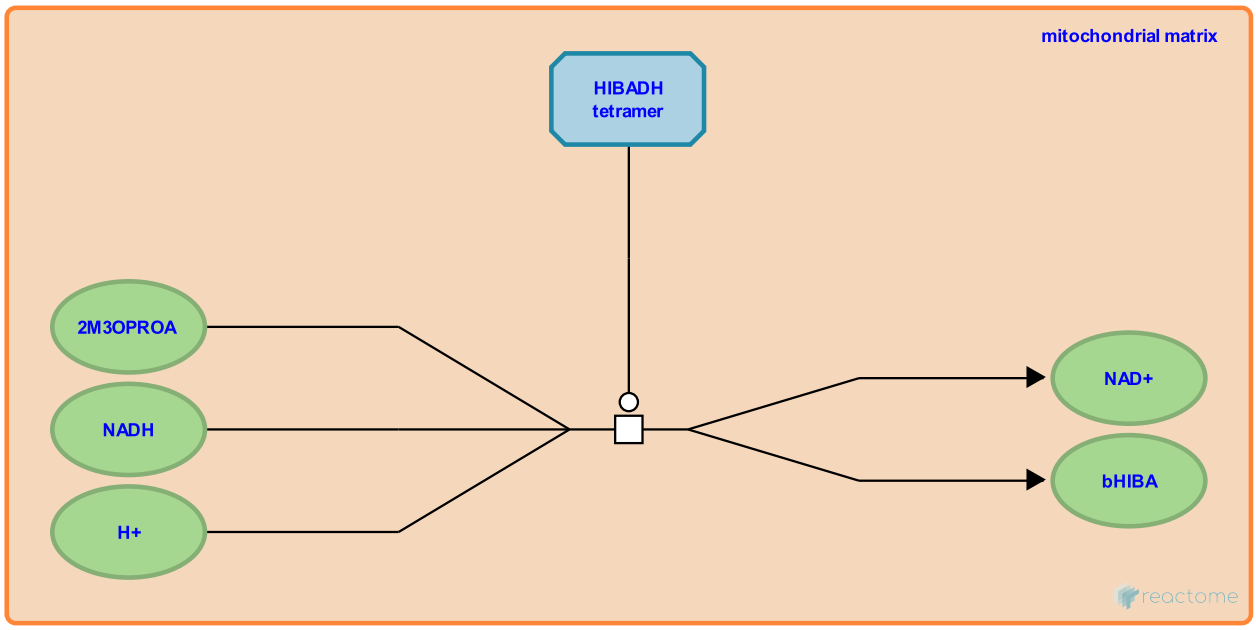
methylmalonyl semialdehyde + NADH + H+ <=> beta-hydroxyisobutyrate + NAD+ ↗

Location: Branched-chain amino acid catabolism

Stable identifier: R-HSA-508473

Type: transition

Compartments: mitochondrial matrix



Mitochondrial 3-hydroxyisobutyrate dehydrogenase (HIBADH) catalyzes the reversible reaction of methylmalonyl semialdehyde and NADH + H+ to form beta-hydroxyisobutyrate and NAD+. The biochemical properties of human HIBADH are inferred from those of its better-studied porcine homologue (Robinson and Coon 1957). Unpublished crystallographic studies (PDB 2GF2) have shown the active enzyme to be a tetramer of HIBADH polypeptides whose aminoterminal 40 residues, a mitochondrial targeting sequence, have been removed.

Literature references

Coon, MJ., Robinson, WG. (1957). Purification and properties of beta-hydroxyisobutyric dehydrogenase. *J Biol Chem, 225*, 511-521. ↗

Editions

2010-02-18	Authored, Edited	D'Eustachio, P.
2010-02-27	Reviewed	Jassal, B.

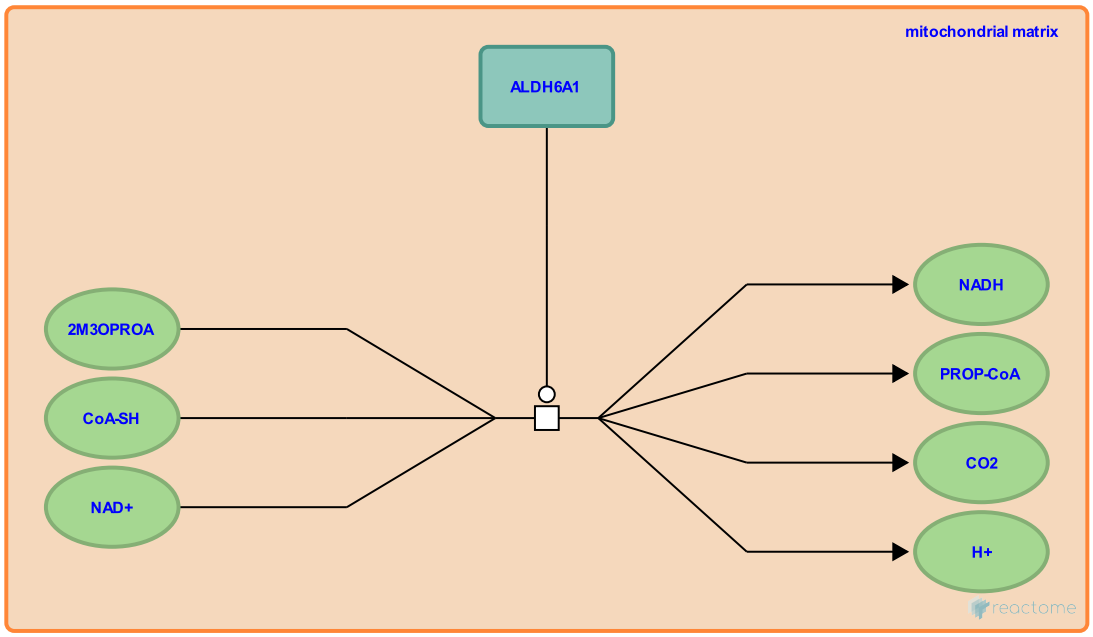
methylmalonate semialdehyde + NAD+ + CoA => propionyl-CoA + CO2 + NADH + H+ ↗

Location: Branched-chain amino acid catabolism

Stable identifier: R-HSA-70893

Type: transition

Compartments: mitochondrial matrix



Mitochondrial methylmalonate semialdehyde dehydrogenase (ALDH6A1) catalyzes the reaction of methylmalonate semialdehyde, NAD+, and CoA to form propionyl-CoA, CO2, and NADH + H+. A human ALDH6A1 gene has been cloned. Its sequence is closely homologous to that of the better-characterized rat enzyme (Kedishvili et al. 1992) and a missense mutation in a normally well-conserved codon has been found in the allele of the gene from a patient with a defect in methylmalonic semialdehyde dehydrogenase activity (Chambliss et al. 2000).

Preceded by: beta-hydroxyisobutyrate + NAD+ <=> methylmalonyl semialdehyde + NADH + H+

Literature references

Harris, RA., Rougraff, PM., Zhao, Y., Crabb, DW., Popov, KM., Kedishvili, NY. (1992). CoA-dependent methylmalonate-semialdehyde dehydrogenase, a unique member of the aldehyde dehydrogenase superfamily. cDNA cloning, evolutionary relationships, and tissue distribution. *J Biol Chem, 267*, 19724-9. ↗

Chambliss, KL., Gray, RG., Pollitt, RJ., Gibson, KM., Rylance, G. (2000). Molecular characterization of methylmalonate semialdehyde dehydrogenase deficiency. *J Inherit Metab Dis, 23*, 497-504. ↗

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