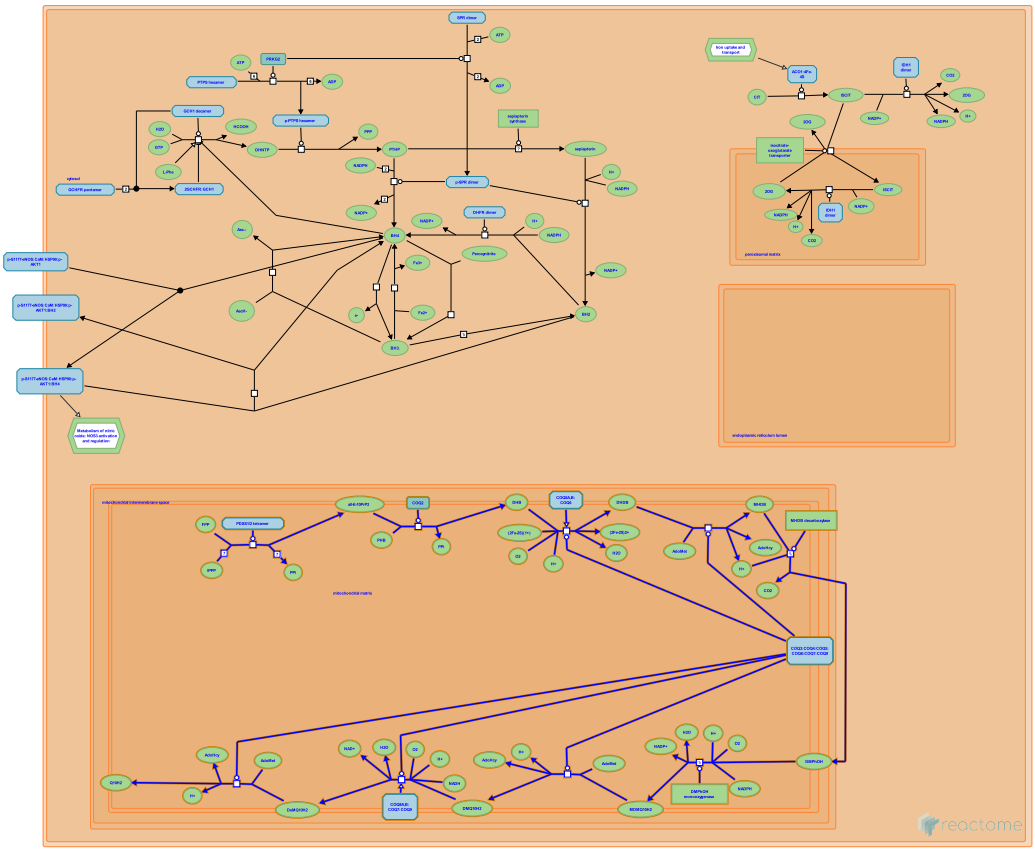
Ubiquinol biosynthesis



Kawamukai, M., Williams, MG.

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.

02/05/2024

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. ↗

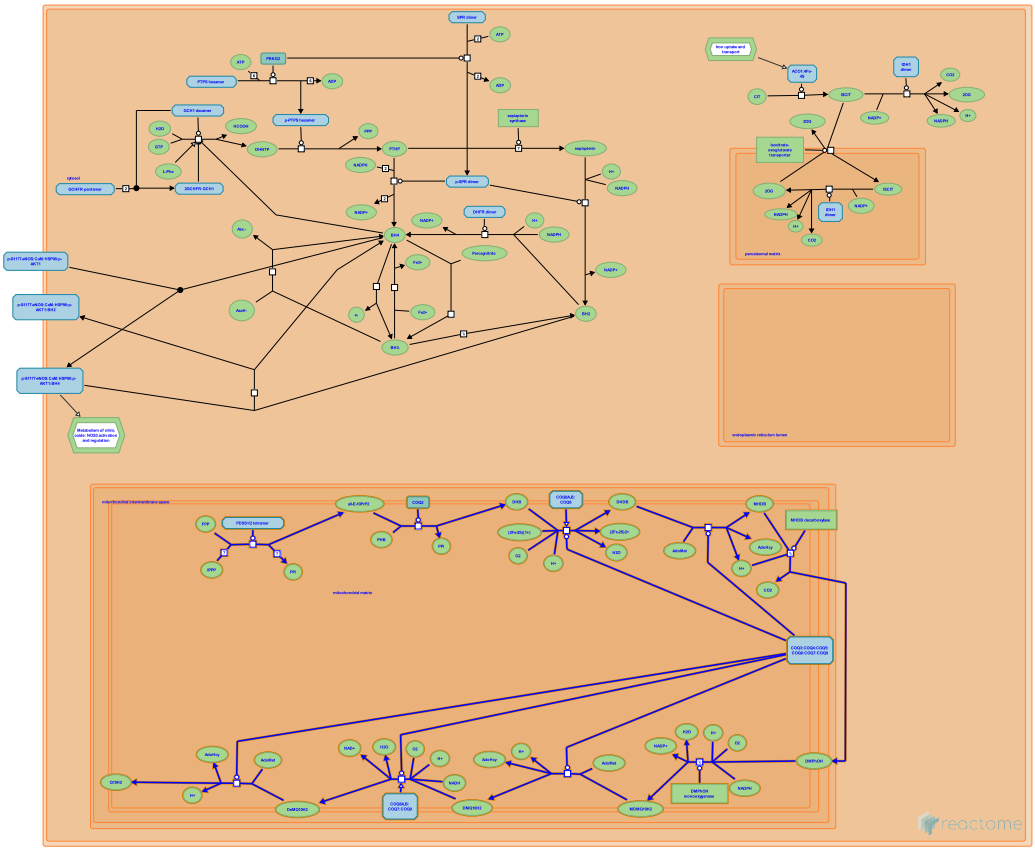
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 1 pathway and 9 reactions (see Table of Contents)

Ubiquinol biosynthesis ↗

Stable identifier: R-HSA-2142789



Mitochondrial 4-hydroxyphenylpyruvate dioxygenase-like protein (HPDL) processes 4-hydroxphenylpyruvate (HPP, HPPA) to (S)-4-hydroxymandelate (4-HMA). HPDL defects lead to CoQ10 deficiency. The HPDL product 4-hydroxymandelate apparently is a precursor for the synthesis of 4-hydroxybenzoate, which is a prerequisite for the assembly of the CoQ10 head group (Banh et al., 2021). Because HPDL is a mitochondrial protein, cytosolic HPP from tyrosine catabolism must either be imported by a yet unknown transport mechanism, or mitochondrial HPP could be the product of an unknown mitochondrial reaction (Husain et al., 2020; reviewed in Staiano et al., 2023).

Literature references

Kawamukai, M. (2009). Biosynthesis and bioproduction of coenzyme Q10 by yeasts and other organisms. *Biotechnol. Appl. Biochem., 53*, 217-26. ↗

Distelmaier, F., Wedell, A., Herebian, D., Freyer, C., Mayatepek, E., Seibt, A. et al. (2017). Detection of 6-demethoxy-ubiquinone in CoQ₁₀ deficiency disorders: Insights into enzyme interactions and identification of potential therapeutics. *Mol Genet Metab, 121*, 216-223. ↗

Quinn, PJ., Kagan, VE. (2000). Genetic Analysis of Coenzyme Q Biosynthesis, Coenzyme Q: Molecular Mechanisms in Health and Disease. *CRC Press*, 185-208.

Tran, UC., Clarke, CF. (2007). Endogenous synthesis of coenzyme Q in eukaryotes. *Mitochondrion, 7*, S62-71. ↗

Brea-Calvo, G., Staiano, C., Mantle, D., Millichap, LE., Hargreaves, I., García-Corzo, L. et al. (2023). Biosynthesis, Deficiency, and Supplementation of Coenzyme Q. *Antioxidants (Basel), 12*. ↗

Editions

2012-03-15	Edited	Williams, MG.
2012-03-19	Authored	Williams, MG.
2013-02-05	Reviewed	Kawamukai, M.

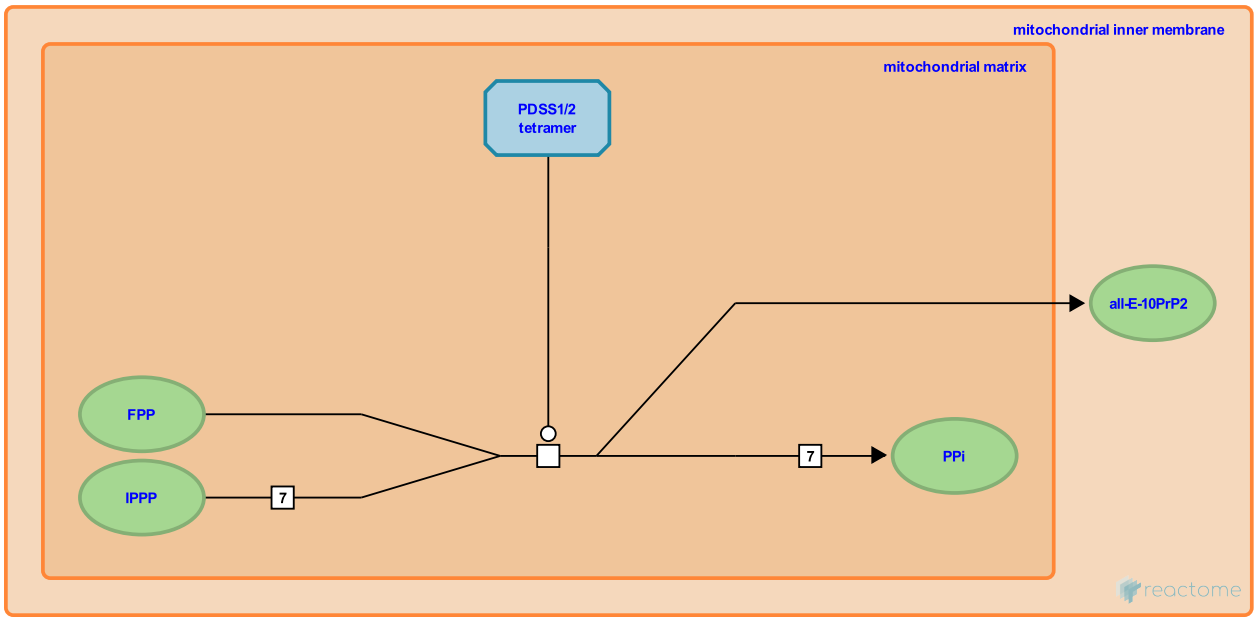
PDSS1,2 ligates FPP to IPPP ↗

Location: Ubiquinol biosynthesis

Stable identifier: R-HSA-2162253

Type: transition

Compartments: mitochondrial matrix



The polyprenyl diphosphate synthase consists of a tetramer comprising two units of decaprenyl-diphosphate synthase subunit 1 (PDSS1) and two units of decaprenyl-diphosphate synthase subunit 2 (PDSS2). One or several Mg(2+) ions per PDSS1 subunit act as cofactors, although the exact number is unknown. The complex catalyses the combination of 2-trans,6-trans-farnesyl diphosphate (FPP) with seven isopentenyl diphosphate (IPPP) molecules to form the polyisoprenoid tail, all-trans-decaprenyl diphosphate (all-E-10PrP2) (Saiki et al. 2005, Tekle et al. 2008). IPPP and FPP are provided by cytosolic cholesterol biosynthesis. However, the means of transport of FPP and IPPP into mitochondria is unknown.

Followed by: COQ2 ligates all-E-10PrP2 to PHB

Literature references

Dallner, G., Turunen, M., Swiezewska, E., Tekle, M., Chojnacki, T. (2008). Investigation of coenzyme Q biosynthesis in human fibroblast and HepG2 cells. *J Biochem Biophys Methods, 70*, 909-17. ↗

Kawamukai, M., Saiki, R., Kainou, T., Nagata, A., Matsuda, H. (2005). Characterization of solanesyl and decaprenyl diphosphate synthases in mice and humans. *FEBS J, 272*, 5606-22. ↗

Editions

2012-03-19	Authored	Williams, MG.
2012-03-23	Edited	Williams, MG.
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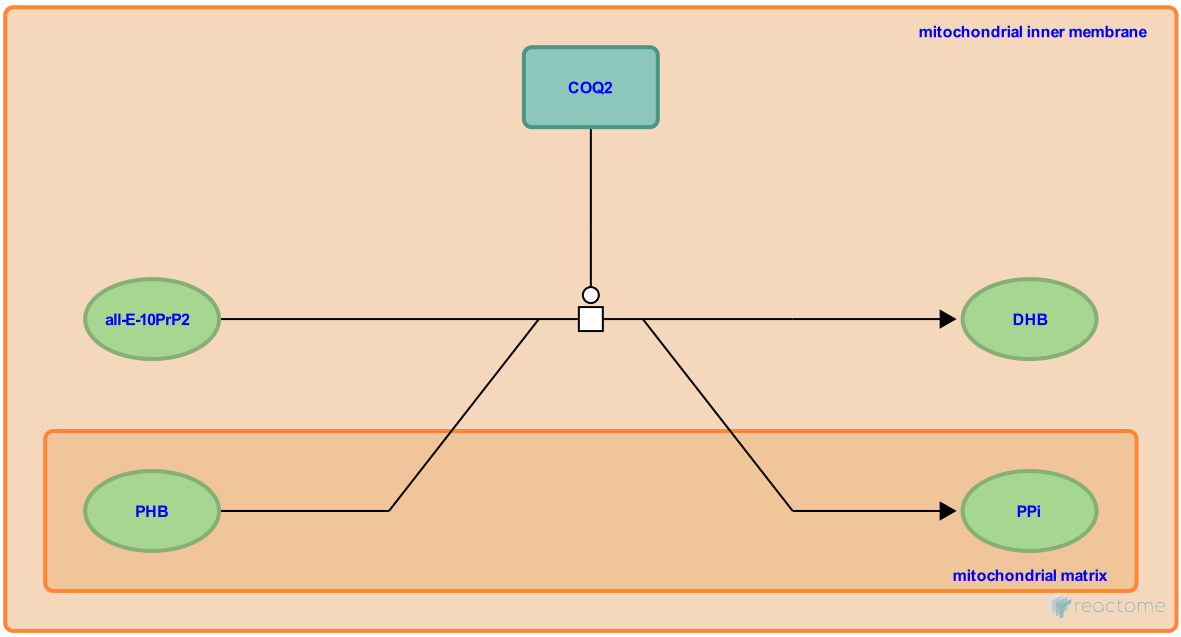
COQ2 ligates all-E-10PrP2 to PHB ↗

Location: Ubiquinol biosynthesis

Stable identifier: R-HSA-2162192

Type: transition

Compartments: mitochondrial inner membrane, mitochondrial matrix



4-Hydroxybenzoate polyprenyltransferase (COQ2) catalyses the combination of 4-hydroxybenzoic acid, aka para-hydroxybenzoic acid (PHB), with the polyisoprenoid tail all-trans-decaprenyl diphosphate (all-E-10PrP2) to form 3-decaprenyl-4-hydroxybenzoate (DHB) (Forsgren et al., 2004; Lopez-Martin ef al., 2007; Tekle et al., 2008).

Preceded by: PDSS1,2 ligates FPP to IPPP

Followed by: COQ6 hydroxylates DHB

Literature references

Dallner, G., Turunen, M., Swiezewska, E., Tekle, M., Chojnacki, T. (2008). Investigation of coenzyme Q biosynthesis in human fibroblast and HepG2 cells. *J Biochem Biophys Methods, 70*, 909-17. ↗

Salviati, L., Trevisson, E., Sánchez-Alcázar, JA., DiMauro, S., Rodriguez-Hernandez, A., Hirano, M. et al. (2007). Missense mutation of the COQ2 gene causes defects of bioenergetics and de novo pyrimidine synthesis. *Hum Mol Genet, 16*, 1091-7. ↗

Dallner, G., Climent, I., Grünler, J., Attersand, A., Swiezewska, E., Forsgren, M. et al. (2004). Isolation and functional expression of human COQ2, a gene encoding a polyprenyl transferase involved in the synthesis of CoQ. *Biochem J , 382*, 519-26. ↗

Editions

2012-03-19	Authored	Williams, MG.
2012-03-23	Edited	Williams, MG.
2013-02-05	Reviewed	Kawamukai, M.

COQ6 hydroxylates DHB ↗

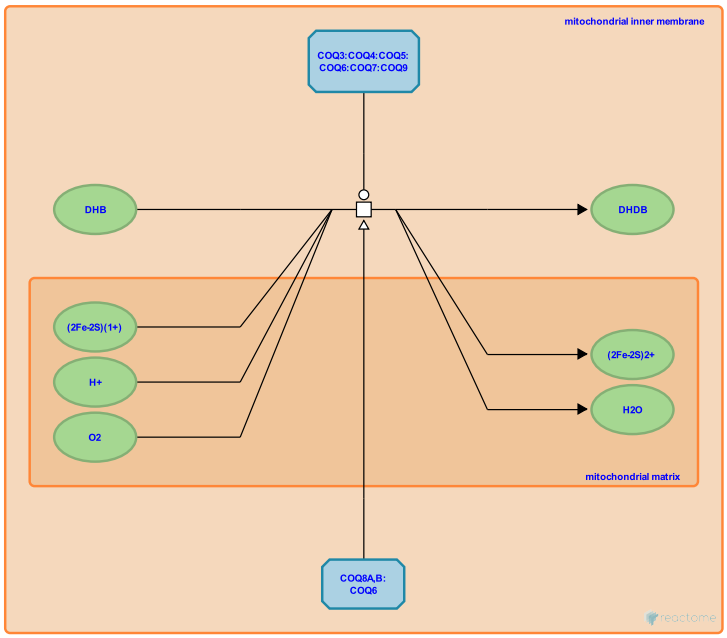
Location: Ubiquinol biosynthesis

Stable identifier: R-HSA-2162187

Type: transition

Compartments: mitochondrial inner membrane, mitochondrial matrix

Inferred from: HHB is hydroxylated to DHHB by Coq6 (Saccharomyces cerevisiae)



Flavin-dependent monooxygenase COQ6 (Heeringa et al. 2011) catalyses the C5-hydroxylation of 3-decaprenyl-4-hydroxybenzoic acid (DHB) to 3,4-dihydroxy-5-decaprenylbenzoic acid (DHDB). The electrons needed likely come from the iron-sulfur cluster on a ferredoxin that is recycled with NADPH. COQ6 is a peripheral membrane protein that localizes to the matrix side of the inner mitochondrial membrane (Gin et al. 2003). This reaction involving COQ6 is inferred from the equivalent reaction in yeast, where hexaprenyl sidechains occur instead of decaprenyl moieties in human (Ozeir et al. 2011, Gin et al. 2003). Both COQ8A and COQ8B bind to COQ6, presumably during formation of a hypothetical multienzyme COQ complex. Both COQ8A,B are required for Q10 biosynthesis (Ashraf et al., 2013; Floyd et al., 2016; reviewed in Hojabri et al., 2023; Liang et al., 2023).

Preceded by: COQ2 ligates all-E-10PrP2 to PHB

Followed by: COQ3 methylates DHDB

Literature references

Stefely, JA., Taylor, RW., Dolan, BK., Westphall, MS., Wilkerson, EM., Veling, MT. et al. (2016). Mitochondrial Protein Interaction Mapping Identifies Regulators of Respiratory Chain Function. *Mol Cell, 63*, 621-632. ↗

Tzagoloff, A., Rothman, SC., Jonassen, T., Hsu, AY., Gin, P., Lee, PT. et al. (2003). The Saccharomyces cerevisiae COQ6 gene encodes a mitochondrial flavin-dependent monooxygenase required for coenzyme Q biosynthesis. *J Biol Chem, 278*, 25308-16. ↗

Yang, Q., Zhang, Y., Liang, R., Chen, H., Yang, H., Wu, D. et al. (2022). Clinical features and gene variation analysis of COQ8B nephropathy: Report of seven cases. *Front Pediatr, 10*, 1030191. ↗

Salviati, L., Washburn, J., Choi, M., Barua, M., Gee, HY., Han, Z. et al. (2013). ADCK4 mutations promote steroid-resistant nephrotic syndrome through CoQ10 biosynthesis disruption. *J Clin Invest, 123*, 5179-89. ↗

Nejad Biglari, H., Irilouzadian, R., Sarmadian, R., Hojabri, M., Gilani, A. (2023). Adolescence Onset Primary Coenzyme Q10 Deficiency With Rare CoQ8A Gene Mutation: A Case Report and Review of Literature. *Clin Med Insights Case Rep, 16*, 11795476231188061. ↗

Editions

2012-03-19	Authored	Williams, MG.
2012-03-23	Edited	Williams, MG.
2013-02-05	Reviewed	Kawamukai, M.

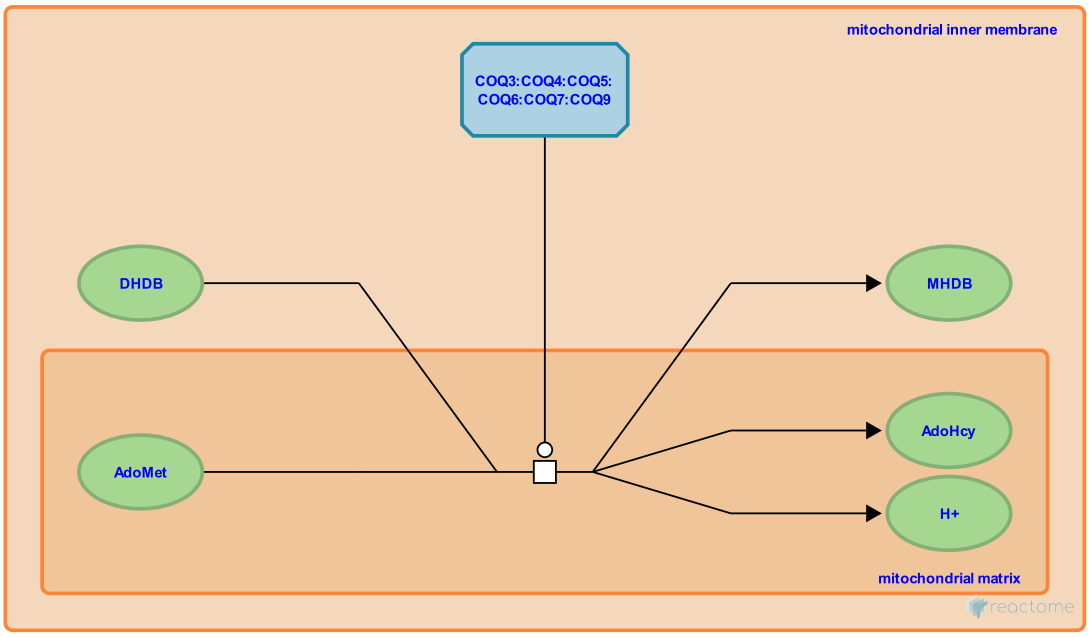
COQ3 methylates DHDB ↗

Location: Ubiquinol biosynthesis

Stable identifier: R-HSA-2162193

Type: transition

Compartments: mitochondrial matrix



Mitochondrial O-methyltransferase COQ3 converts 3,4-dihydroxy-5-decaprenylbenzoic acid (DHDB) to 3-methoxy-4-hydroxy-5-decaprenylbenzoic acid (MHDB) (Jonassen & Clarke 2000). COQ3 is a membrane protein (Zhu et al., 2015).

Preceded by: COQ6 hydroxylates DHB

Followed by: Unknown enzyme decarboxylates MHDB

Literature references

Zhang, X., Zhu, Y., Niu, L., Wu, B., Wang, J., Li, X. et al. (2015). Structural and biochemical studies reveal UbiG/Coq3 as a class of novel membrane-binding proteins. *Biochem J, 470*, 105-14. ↗

Jonassen, T., Clarke, CF. (2000). Isolation and functional expression of human COQ3, a gene encoding a methyltransferase required for ubiquinone biosynthesis. *J Biol Chem, 275*, 12381-7. ↗

Editions

2012-03-19	Authored	Williams, MG.
2012-03-23	Edited	Williams, MG.
2013-02-05	Reviewed	Kawamukai, M.

Unknown enzyme decarboxylates MHDB ↗

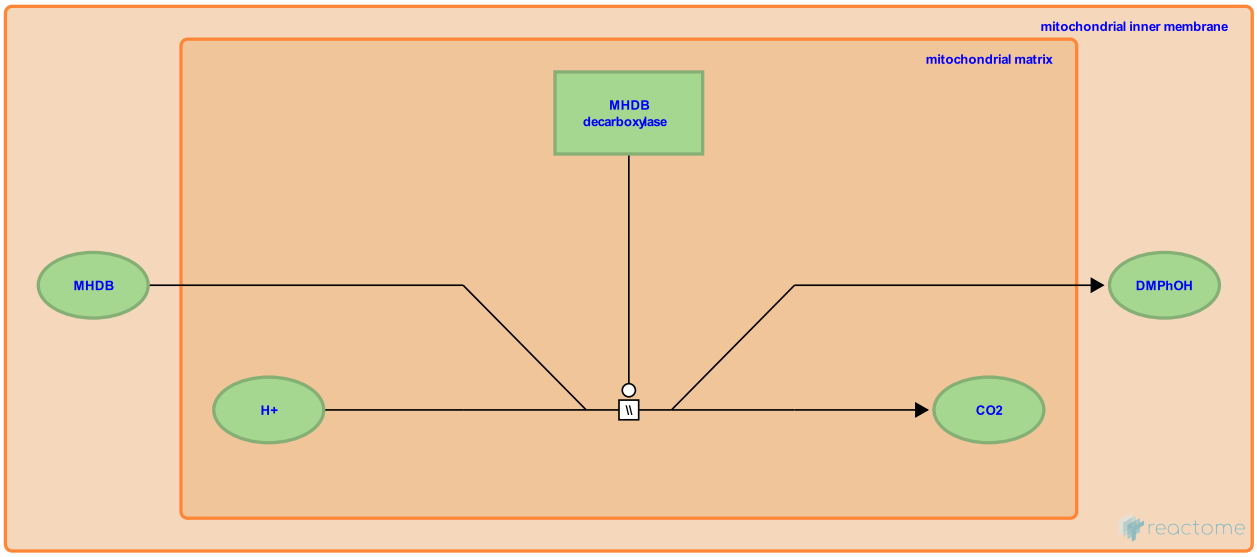
Location: Ubiquinol biosynthesis

Stable identifier: R-HSA-2162195

Type: omitted

Compartments: mitochondrial matrix

Inferred from: MHHB is decarboxylated to HMPhOH by MHHB decarboxylase (Saccharomyces cerevisiae)



3-methoxy-4-hydroxy-5-decaprenylbenzoic acid (MHDB) is enzymatically decarboxylated to form 2-methoxy-6-decaprenylphenol (DMPhOH). At the present time the enzyme identity is unknown but is thought to be a member of the COQ family. This reaction is inferred from the equivalent reaction in yeast (Casey & Threlfall 1978, Goewert et al. 1981).

Preceded by: COQ3 methylates DHDB

Followed by: Unknown enzyme hydroxylates DMPhOH

Literature references

Threlfall, DR., Casey, J. (1978). Synthesis of 5-demethoxyubiquinone-6 and ubiquinone-6 from 3-hexaprenyl-4-hydroxybenzoate in yeast mitochondria. *FEBS Lett, 85*, 249-53. ↗

Olson, RE., Sippel, CJ., Goewert, RR., Grimm, MF. (1981). Identification of 3-methoxy-4-hydroxy-5-hexaprenylbenzoic acid as a new intermediate in ubiquinone biosynthesis by Saccharomyces cerevisiae. *Biochemistry, 20*, 5611-6. ↗

Editions

2012-03-19	Authored	Williams, MG.
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2013-02-05	Reviewed	Kawamukai, M.

Unknown enzyme hydroxylates DMPhOH ↗

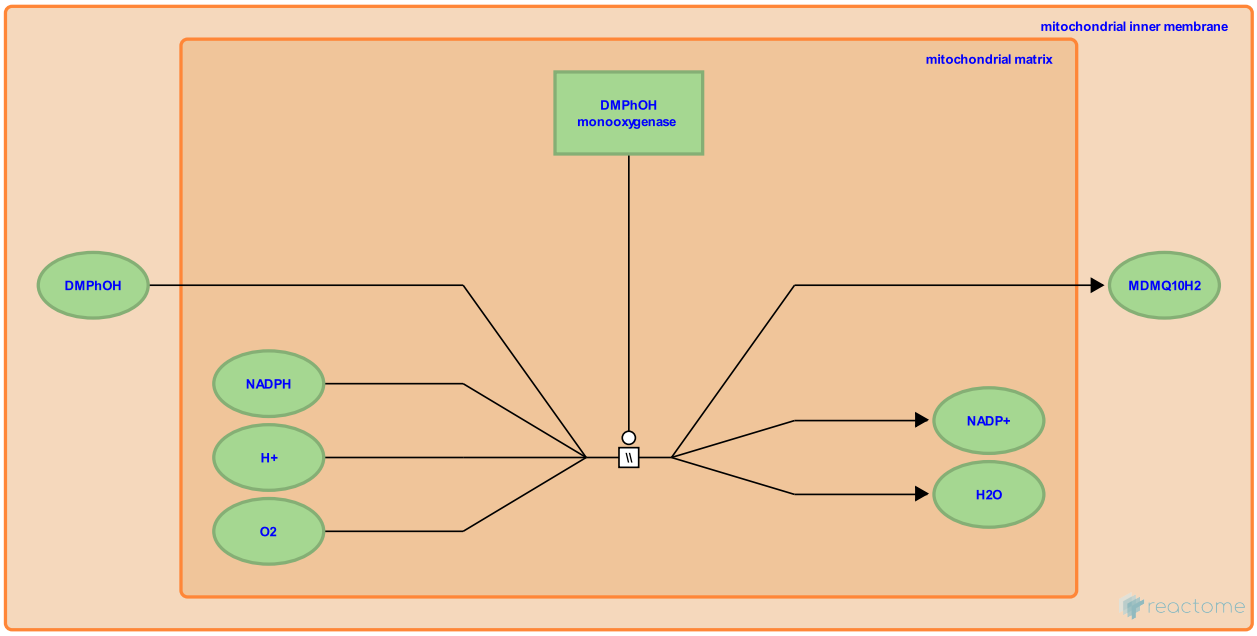
Location: Ubiquinol biosynthesis

Stable identifier: R-HSA-2162191

Type: omitted

Compartments: mitochondrial matrix

Inferred from: HMPhOH is hydroxylated to MDMQ6H2 by HMPhOH monooxygenase (Saccharomyces cerevisiae)



2-methoxy-6-decaprenylphenol (DMPhOH) is enzymatically converted to 2-methoxy-6-decaprenyl-1,4-benzoquinol (MDMQ10H2). It was thought at one time that the flavin-dependent monooxygenase, COQ6, was the enzyme that catalysed this reaction, however, it has been subsequently shown that COQ6 is not essential for this reaction (Ozeir et al. 2011). However, it is still believed that another member of the COQ family catalyses this event. This reaction is inferred from the equivalent reaction in yeast (Gin et al. 2003, Ozeir et al. 2011).

Preceded by: Unknown enzyme decarboxylates MHDB

Followed by: COQ5 methylates MDMQ10H2

Literature references

Tzagoloff, A., Rothman, SC., Jonassen, T., Hsu, AY., Gin, P., Lee, PT. et al. (2003). The Saccharomyces cerevisiae COQ6 gene encodes a mitochondrial flavin-dependent monooxygenase required for coenzyme Q biosynthesis. *J Biol Chem, 278*, 25308-16. ↗

Ozeir, M., Fontecave, M., Lill, R., Pierrel, F., Webert, H., Mühlenhoff, U. (2011). Coenzyme Q biosynthesis: Coq6 is required for the C5-hydroxylation reaction and substrate analogs rescue Coq6 deficiency. *Chem Biol, 18*, 1134-42. ↗

Editions

2012-03-19	Authored	Williams, MG.
2012-03-23	Edited	Williams, MG.
2013-02-05	Reviewed	Kawamukai, M.

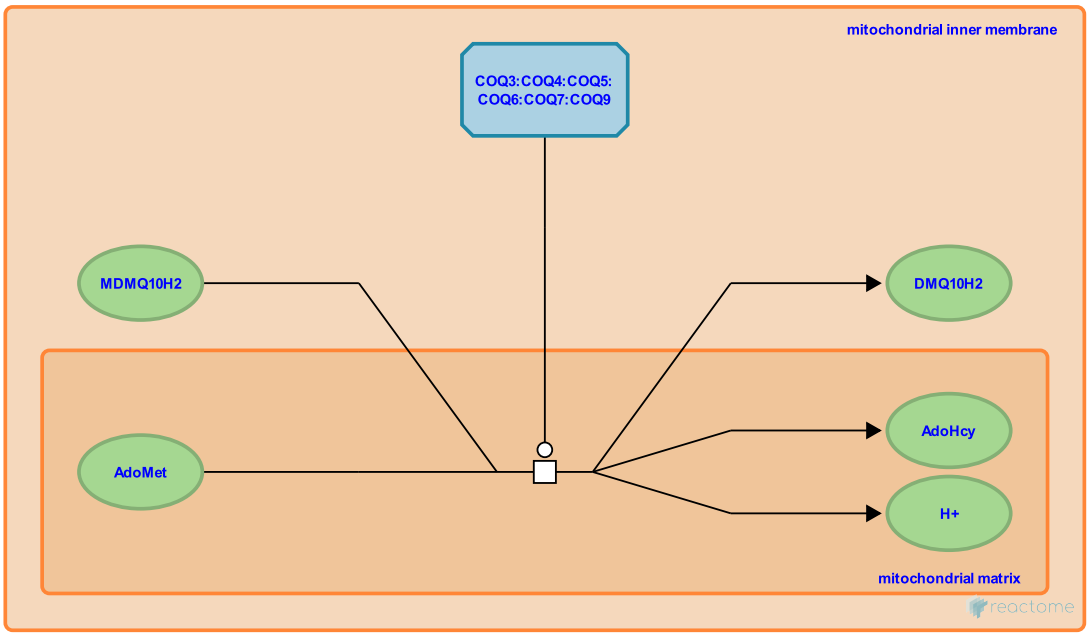
COQ5 methylates MDMQ10H2 ↗

Location: Ubiquinol biosynthesis

Stable identifier: R-HSA-2162188

Type: transition

Compartments: mitochondrial matrix



2-methoxy-6-polyprenyl-1,4-benzoquinol methylase (COQ5) catalyses the C-methyltransferase conversion of 2-methoxy-6-decaprenyl-1,4-benzoquinol (MDMQ10H2) to 6-methoxy-3-methyl-2-decaprenyl-1,4-benzoquinol (DMQ10H2). The monomer, while localized in the mitochondrial matrix, is part of a multimeric complex residing in the mitochondrial inner membrane (Chen et al., 2013; Nguyen et al., 2015; Yen et al., 2016). This reaction was first studied in yeast (Barkovich et al. 1997).

Preceded by: Unknown enzyme hydroxylates DMPhOH

Followed by: COQ7:COQ9 octamer hydroxylates DMQ10H2

Literature references

Feng, YH., Yen, HC., Wei, YH., Lee, SH., Kan, CC., Chen, CW. et al. (2016). Disruption of the human COQ5-containing protein complex is associated with diminished coenzyme Q10 levels under two different conditions of mitochondrial energy deficiency. *Biochim Biophys Acta, 1860*, 1864-76. ↗

Salviati, L., Trevisson, E., Desbats, MA., Casarin, A., Nguyen, TP., Navas, P. et al. (2014). Molecular characterization of the human COQ5 C-methyltransferase in coenzyme Q10 biosynthesis. *Biochim Biophys Acta, 1841*, 1628-38. ↗

Tzagoloff, A., Shepherd, JA., Shtanko, A., Barkovich, RJ., Lee, PT., Myles, DC. et al. (1997). Characterization of the COQ5 gene from Saccharomyces cerevisiae. Evidence for a C-methyltransferase in ubiquinone biosynthesis. *J Biol Chem, 272*, 9182-8. ↗

Yen, HC., Chen, SW., Liu, CC. (2013). Detection of suppressed maturation of the human COQ5 protein in the mitochondria following mitochondrial uncoupling by an antibody recognizing both precursor and mature forms of COQ5. *Mitochondrion, 13*, 143-52. ↗

Editions

2012-03-19	Authored	Williams, MG.
2012-03-23	Edited	Williams, MG.
2013-02-05	Reviewed	Kawamukai, M.

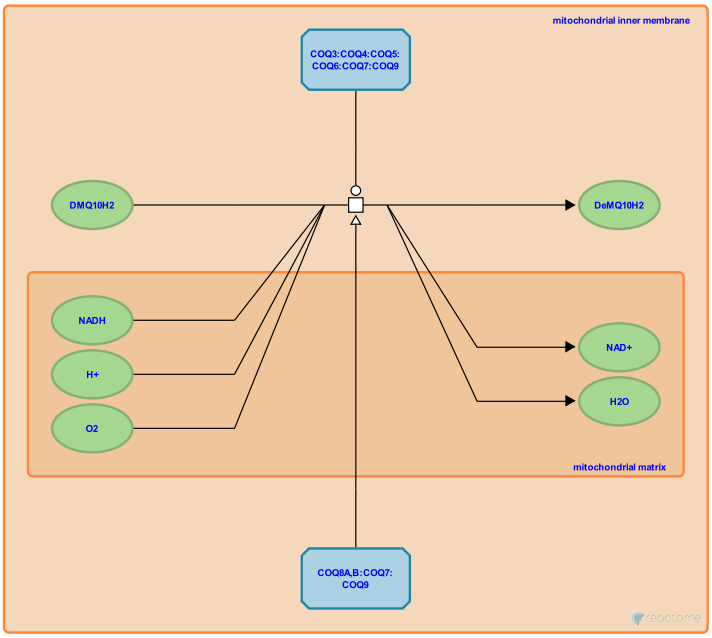
COQ7:COQ9 octamer hydroxylates DMQ10H2 ↗

Location: Ubiquinol biosynthesis

Stable identifier: R-HSA-2162194

Type: transition

Compartments: mitochondrial inner membrane, mitochondrial matrix



5-Demethoxyubiquinone hydroxylase COQ7 catalyzes the hydroxylation of 6-methoxy-3-methyl-2-decaprenyl-1,4-benzoquinol (DMQ10H2, DMQ) to 3-demethylubiquinol-10 (DeMQ10H2, DeMQ), using NADH and oxygen. COQ7 forms a heterooctameric complex with ubiquinone biosynthesis protein COQ9, a lipid-binding protein presenting the substrate to COQ7 activity. In this complex, COQ7 binds two iron ions and forms a heterodimer with COQ9, with four of these dimers forming an octameric cage (Vajo et al., 1999; Lohman et al., 2014; Manicki et al., 2022). This reaction was first studied in yeast (Marbois & Clarke, 1996; Tran et al., 2006). Both COQ8A and COQ8B bind to COQ7, presumably during formation of a hypothetical multienzyme COQ complex. COQ8A,B are required for the assembly of the complex but may not be stably incorporated into it, so only the components identified by Floyd et al. are annotated (Ashraf et al., 2013; Floyd et al., 2016; reviewed in Hojabri et al., 2023; Liang et al., 2023).

Preceded by: COQ5 methylates MDMQ10H2

Followed by: COQ3 methylates DeMQ10H2

Literature references

Stefely, JA., Taylor, RW., Dolan, BK., Westphall, MS., Wilkerson, EM., Veling, MT. et al. (2016). Mitochondrial Protein Interaction Mapping Identifies Regulators of Respiratory Chain Function. *Mol Cell, 63*, 621-632. ↗

Yang, Q., Zhang, Y., Liang, R., Chen, H., Yang, H., Wu, D. et al. (2022). Clinical features and gene variation analysis of COQ8B nephropathy: Report of seven cases. *Front Pediatr, 10*, 1030191. ↗

Ho, N., Francomano, CA., Jonassen, T., King, LM., Wilkin, DJ., Munnich, A. et al. (1999). Conservation of the Caenorhabditis elegans timing gene clk-1 from yeast to human: a gene required for ubiquinone biosynthesis with potential implications for aging. *Mamm Genome, 10*, 1000-4. ↗

Salviati, L., Washburn, J., Choi, M., Barua, M., Gee, HY., Han, Z. et al. (2013). ADCK4 mutations promote steroid-resistant nephrotic syndrome through CoQ10 biosynthesis disruption. *J Clin Invest, 123*, 5179-89. ↗

Frost, A., Pagliarini, DJ., Guerra, RM., Dal Peraro, M., Aydin, H., Abriata, LA. et al. (2022). Structure and functionality of a multimeric human COQ7:COQ9 complex. *Mol Cell, 82*, 4307-4323.e10. ↗

Editions

2012-03-19	Authored	Williams, MG.
2012-03-23	Edited	Williams, MG.
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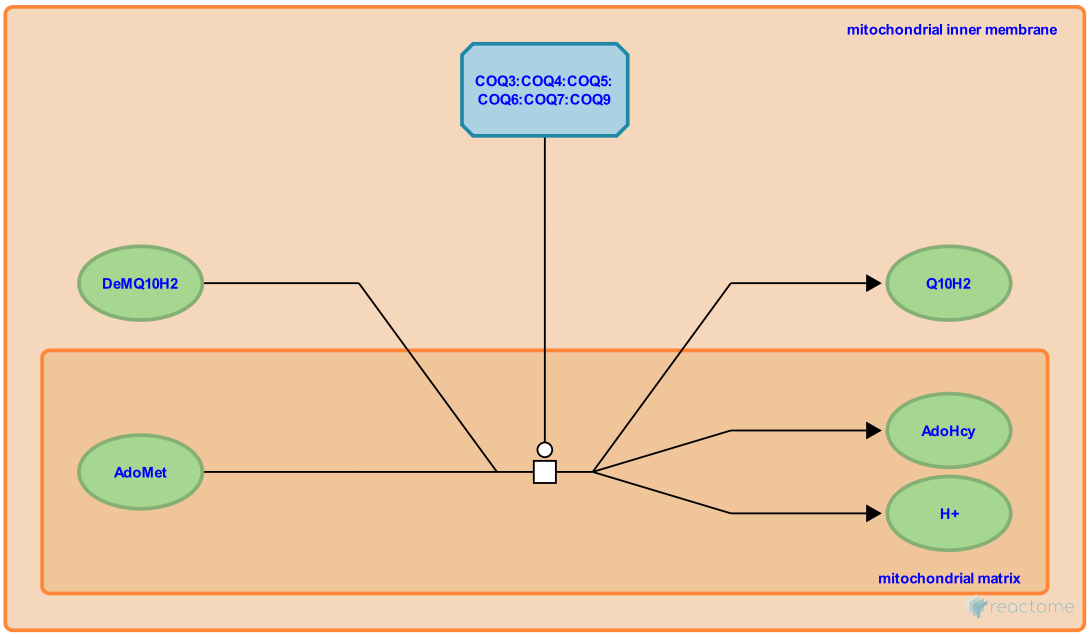
COQ3 methylates DeMQ10H2 ↗

Location: Ubiquinol biosynthesis

Stable identifier: R-HSA-2162186

Type: transition

Compartments: mitochondrial matrix



Mitochondrial COQ3 is an O-methyltransferase required in the reaction to convert 3-demethylubiquinol-10 (DeMQ10H2) to ubiquinol-10 (Q10H2) (Jonassen & Clarke 2000).

Preceded by: COQ7:COQ9 octamer hydroxylates DMQ10H2

Literature references

Zhang, X., Zhu, Y., Niu, L., Wu, B., Wang, J., Li, X. et al. (2015). Structural and biochemical studies reveal UbiG/Coq3 as a class of novel membrane-binding proteins. *Biochem J, 470,* 105-14. ↗

Jonassen, T., Clarke, CF. (2000). Isolation and functional expression of human COQ3, a gene encoding a methyltransferase required for ubiquinone biosynthesis. *J Biol Chem, 275,* 12381-7. ↗

Editions

2012-03-19	Authored	Williams, MG.
2012-03-23	Edited	Williams, MG.
2013-02-05	Reviewed	Kawamukai, M.

Table of Contents