## Phylogeny

COQ8B (ADCK4) is classified within the protein-kinase-like (PKL) superfamily as an atypical kinase belonging to the ADCK/UbiB family (lagiertourenne2008adck3anancestral pages 6-8, asquith2019adck3coq8athechoice pages 1-3, stefely2016cerebellarataxiaand pages 9-10). According to kinome analyses such as those by Manning et al., ADCK proteins are separated from classical protein kinases due to their atypical domains and are classified in the atypical kinase group (lagiertourenne2008adck3anancestral pages 6-8, unknownauthors2018characterizationofthe pages 16-23, jacquet2025theadckkinase pages 15-17). The ADCK family is highly conserved across species including Drosophila, C. elegans, and mammals (jacquet2025theadckkinase pages 2-3).

COQ8B and its paralog ADCK3 (COQ8A) are co-orthologous to the yeast protein Coq8p and appear to have resulted from a gene duplication event in vertebrates (lagiertourenne2008adck3anancestral pages 6-8, unknownauthors2015functionalcharacterizationof pages 15-20). Bacterial homologs include UbiB from *E. coli* (lagiertourenne2008adck3anancestral pages 6-8, asquith2019adck3coq8athechoice pages 1-3). Functional conservation has been demonstrated by the rescue of yeast *coq8* mutants via expression of human ADCK3 (xie2011expressionofthe pages 1-2).

## Reaction Catalyzed

The enzymatic activity of COQ8B is debated. Experimental evidence supports a role as a serine/threonine protein kinase that catalyzes the transfer of a γ-phosphate from ATP to a protein substrate (unknownauthors2015functionalcharacterizationof pages 75-80, unknownauthors2015functionalcharacterizationof pages 80-84). The reaction is: ATP + a protein → ADP + a phosphoprotein

However, some reports propose that COQ8B may act as a small molecule or lipid kinase, or possess unorthodox ATPase activity that is not typical of a protein kinase (stefely2015mitochondrialadck3employs pages 9-10, asquith2019adck3coq8athechoice pages 1-3). COQ8B exhibits Mg²⁺-dependent, substrate-independent ATPase activity, hydrolyzing ATP to ADP and inorganic phosphate (Pi) (unknownauthors2015functionalcharacterizationof pages 20-26, unknownauthors2015functionalcharacterizationof pages 75-80). Structural analyses show that the active site is sterically occluded, which is inconsistent with the function of a typical protein kinase (asquith2019adck3coq8athechoice pages 1-3).

## Cofactor Requirements

The kinase activity of COQ8B requires divalent metal ions, such as Mg²⁺ or Mn²⁺, as cofactors (jacquet2025theadckkinase pages 9-11, stefely2015mitochondrialadck3employs pages 9-10). Mg²⁺-dependent ATPase and protein kinase activities have been demonstrated biochemically (unknownauthors2015functionalcharacterizationof pages 20-26, unknownauthors2015functionalcharacterizationof pages 75-80).

## Substrate Specificity

The provided context does not contain data from the priority publication *Johnson et al. (2023)* to define a comprehensive substrate motif atlas.

Based on the available context, COQ8B functions as an atypical serine/threonine protein kinase (unknownauthors2015functionalcharacterizationof pages 80-84). In assays using a truncated, active construct of ADCK4, the kinase showed a preference for phosphorylating serine residues that are preceded by basic residues and followed by hydrophobic residues (unknownauthors2015functionalcharacterizationof pages 64-70).

Putative protein substrates include components of the coenzyme Q biosynthetic complex, such as COQ3 (stefely2015mitochondrialadck3employs pages 9-10, unknownauthors2015functionalcharacterizationof pages 20-26). The yeast ortholog, Coq8, phosphorylates Coq3, Coq5, and Coq7 (acosta2016coenzymeqbiosynthesis pages 7-11, unknownauthors2015functionalcharacterizationof pages 75-80). A peptide sequence found within the ATP synthase F0 subunit 8 has also been identified as a plausible phosphorylation target (unknownauthors2015functionalcharacterizationof pages 80-84). The substrate specificity is debated, with some reports proposing that COQ8B is a small molecule kinase that acts on lipid intermediates in the CoQ pathway (stefely2015mitochondrialadck3employs pages 9-10).

## Structure

COQ8B is a mitochondrial protein that shares approximately 50% sequence identity with its paralog ADCK3, including nearly identical transmembrane domains (jacquet2025theadckkinase pages 9-11). It possesses a bilobal kinase domain that is characteristic of the ADCK/UbiB family (unknownauthors2015functionalcharacterizationof pages 15-20).

The kinase domain is atypical; it conserves some essential kinase motifs such as the AxK motif, the catalytic loop, and the DFG motif for Mg²⁺ coordination, but it lacks others, including the classical glycine-rich loop, C-terminal motifs like the APE motif, and subdomains VIII, X, and XI involved in peptide substrate recognition (unknownauthors2015functionalcharacterizationof pages 15-20, unknownauthors2018characterizationofthe pages 16-23). An alanine-rich loop is present in place of the canonical glycine-rich loop (unknownauthors2015functionalcharacterizationof pages 20-26, unknownauthors2018characterizationofthe pages 16-23).

A key structural feature is a large N-terminal extension containing a conserved KxGQ motif. This motif acts as an autoinhibitory domain by sterically occluding the active site and substrate-binding cleft (unknownauthors2015functionalcharacterizationof pages 20-26, unknownauthors2015functionalcharacterizationof pages 75-80, unknownauthors2018characterizationofthe pages 16-23).

## Regulation

The kinase activity of COQ8B is regulated by autoinhibition. An N-terminal extension containing a KxGQ motif blocks the substrate-binding cleft, preventing catalytic activity (unknownauthors2015functionalcharacterizationof pages 20-26, unknownauthors2015functionalcharacterizationof pages 75-80). Activation requires the removal or conformational displacement of this autoinhibitory domain, which exposes the catalytic site (unknownauthors2015functionalcharacterizationof pages 64-70, unknownauthors2015functionalcharacterizationof pages 75-80). This conformational change may be induced by post-translational modifications or interactions with regulatory partner proteins (unknownauthors2015functionalcharacterizationof pages 75-80). Specific post-translational modifications of ADCK4 have not been detailed (jacquet2025theadckkinase pages 2-3).

## Function

COQ8B is located in the inner mitochondrial membrane and cristae, with some presence also reported in the cytosol (jacquet2025theadckkinase pages 9-11, jacquet2025theadckkinase pages 3-5). It is essential for the biosynthesis of coenzyme Q (CoQ) and for maintaining mitochondrial homeostasis and function (jacquet2025theadckkinase pages 9-11). It stabilizes the CoQ biosynthetic complex (“complex Q”) through interactions with multiple CoQ proteins, primarily CoQ5 (jacquet2025theadckkinase pages 9-11, jacquet2025theadckkinase pages 11-12). Its other known interacting partners include COQ2, COQ3, COQ4, COQ6, COQ7, COQ9, COQ10A, PDSS1, and PDSS2 (jacquet2025theadckkinase pages 3-5).

Loss of COQ8B function impairs mitochondrial respiration, reduces levels of oxidative phosphorylation complex II proteins, and leads to cytoskeletal disorganization (jacquet2025theadckkinase pages 9-11, jacquet2025theadckkinase pages 11-12). COQ8B is also required for podocyte integrity and migration (jacquet2025theadckkinase pages 11-12, jacquet2025theadckkinase pages 2-3).

## Other Comments

Mutations in *COQ8B* cause a primary CoQ10 deficiency that leads to steroid-resistant nephrotic syndrome (SRNS), characterized by podocyte injury, focal segmental glomerulosclerosis, and renal impairment (jacquet2025theadckkinase pages 9-11, jacquet2025theadckkinase pages 11-12). In some cancers, *ADCK4* has been found in a fusion with the *NUMBL* gene, suggesting a potential role in oncogenesis (jacquet2025theadckkinase pages 11-12).

Treatment with 2,4-dihydroxybenzoate (2,4-diHB) has been shown to partially rescue mitochondrial defects and restore renal function in the context of ADCK4 deficiency (jacquet2025theadckkinase pages 9-11, jacquet2025theadckkinase pages 11-12).

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