## Phylogeny

COQ8A (ADCK3) is the human ortholog of yeast Coq8p and bacterial UbiB, indicating conservation from prokaryotes to mammals (stefely2015mitochondrialadck3employs pages 1-2, murray2022smallmoleculemodulation pages 12-15).  
The protein belongs to the UbiB/ABC1 sub-family within the atypical protein-kinase-like (PKL) superfamily of the human kinome (stefely2015mitochondrialadck3employs pages 1-2, murray2022smallmoleculemodulation pages 12-15).  
Five human paralogs exist (ADCK1-5); COQ8A shares ~50–61 % identity with COQ8B/ADCK4, its closest paralog (unknownauthors2017exploringthemitochondrial pages 49-51, jacquet2025theadckkinase pages 9-11).

## Reaction Catalyzed

1. ATP + [protein]-Ser/Thr → ADP + [protein]-Ser/Thr-P (unknownauthors2015functionalcharacterizationof pages 80-84).
2. ATP + H₂O → ADP + Pi (reidenbach2018conservedlipidand pages 1-2, stefely2016cerebellarataxiaand pages 1-4).  
   Conflicting reports describe protein phosphotransfer versus ATP-hydrolysis as the primary reaction (xie2011expressionofthe pages 13-14, reidenbach2017conservedlipidand pages 1-4).

## Cofactor Requirements

Catalytic activity requires divalent cations; Mg²⁺ or Mn²⁺ supports nucleotide binding and catalysis (stefely2015mitochondrialadck3employs pages 9-10).

## Substrate Specificity

Peptide-library profiling identified a preference for Lys at –3 and His at +2 relative to the phospho-acceptor, a motif present in ATP-synthase F0 subunit 8 (unknownauthors2015functionalcharacterizationof pages 70-75, unknownauthors2015functionalcharacterizationof pages 80-84).  
In cellular and yeast complementation assays, COQ8A phosphorylates or is required for phosphorylation of COQ3, COQ5 and COQ7 within the CoQ biosynthetic complex (xie2011expressionofthe pages 11-13, acosta2016coenzymeqbiosynthesis pages 7-11).

## Structure

Domain organization  
• N-terminal mitochondrial targeting sequence followed by a single-pass transmembrane helix (jacquet2025theadckkinase pages 8-9).  
• KxGQ-containing N-terminal extension that folds across the catalytic cleft and forms an autoinhibitory K276–E405 salt bridge (unknownauthors2018characterizationofthea pages 16-23).  
• Atypical PKL core (residues ~258-644, PDB 4PED) with an alanine-rich loop replacing the canonical glycine-rich loop, contributing to ADP selectivity (unknownauthors2015functionalcharacterizationof pages 20-26).  
• Vertebrate-specific C-terminal insert distal to the active site (unknownauthors2017exploringthemitochondrial pages 49-51).

3-D features  
The crystal structure retains the canonical Lys-Glu (K358-E411) ion pair, intact catalytic and regulatory spines, and the QKE triad that stabilizes a closed, autoinhibited conformation (stefely2015mitochondrialadck3employs pages 2-3).

## Regulation

Autoinhibition – removal or mutation of the KxGQ extension markedly increases autophosphorylation (unknownauthors2018characterizationofthea pages 16-23).  
Lipid activation – cardiolipin-rich membranes and CoQ intermediates stimulate ATPase activity (reidenbach2018conservedlipidand pages 1-2).  
Transcriptional control – p53 up-regulates COQ8A expression in endometrial carcinoma cells (jacquet2025theadckkinase pages 9-11).  
Kinase–phosphatase pair – COQ8A-dependent phosphorylation of COQ7 (sites S20, S28, T32) is reversed by the mitochondrial phosphatase Ptc7, modulating hydroxylase activity (unknownauthors2018characterizationofthea pages 27-30, vazquezfonseca2020molecularstructurebiosynthesis pages 12-14).

## Function

Localization and expression  
COQ8A resides on the matrix face of the inner mitochondrial membrane; expression is enriched in mitochondria-rich tissues (jacquet2025theadckkinase pages 2-3, cullen2016aarfdomaincontaining pages 1-2).

Molecular role  
The kinase stabilizes the multimeric CoQ biosynthetic complex via interactions with COQ3, COQ5, COQ7 and COQ9 and supports CoQ10 production required for oxidative phosphorylation (stefely2016cerebellarataxiaand pages 1-4, reidenbach2018conservedlipidand pages 1-2).

Pathway context  
Loss of COQ8A lowers CoQ levels, elevates reactive oxygen species and triggers compensatory glycolysis (jacquet2025theadckkinase pages 8-9).  
COQ8A influences PI3K/Akt signalling and ferroptosis in cancer models (jacquet2025theadckkinase pages 9-11).

## Inhibitors

Small-molecule ATP-competitive probes that modulate COQ8 ATPase activity have been reported through structure-guided screening (murray2022smallmoleculemodulation pages 12-15).

## Other Comments

Disease associations  
Biallelic pathogenic variants cause autosomal recessive cerebellar ataxia 2 (ARCA2) and primary CoQ10 deficiency (laredj2014themoleculargenetics pages 4-5, stefely2016cerebellarataxiaand pages 1-4).

Notable mutations  
Missense variants clustering around the active site—R271C, A338T, T487R, E551K—destabilize the protein and reduce ATPase/kinase activity (traschutz2020clinico‐geneticimagingand pages 5-6).  
Truncating alleles (e.g., p.Gln167Leufs*36, p.Arg348*) produce loss-of-function phenotypes (alcazarfabra2018clinicalsyndromesassociated pages 6-7).

Clinical aspects  
Patients display progressive cerebellar ataxia, myoclonus and variable response to oral CoQ10 supplementation (stefely2016cerebellarataxiaand pages 1-4).

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