## Phylogeny

COQ8A (also called ADCK3) is the human orthologue of yeast Coq8p and bacterial UbiB, illustrating an evolutionary continuum from prokaryotes to mammals (Stefely et al., 2015; Murray et al., 2022). It belongs to the UbiB/ABC1 sub-family within the atypical protein-kinase-like (PKL) superfamily of the human kinome (Stefely et al., 2015; Murray et al., 2022). Five human paralogues exist (ADCK1-5); COQ8A shares ~50–61 % sequence identity with its closest paralogue, COQ8B/ADCK4 (Unknown Authors, 2017; Jacquet & Zhao, 2025).

## Reaction Catalyzed

1. ATP + [protein]-Ser/Thr → ADP + [protein]-Ser/Thr-P
2. ATP + H₂O → ADP + Pi  
   Protein phosphotransfer and ATP-hydrolysis activities are both reported, and their relative prominence remains debated (Xie et al., 2011; Reidenbach et al., 2017).

## Cofactor Requirements

Catalysis requires divalent cations; either Mg²⁺ or Mn²⁺ supports nucleotide binding and turnover (Stefely et al., 2015).

## Substrate Specificity

Peptide-library profiling revealed a preference for Lys at –3 and His at +2 relative to the phospho-acceptor Ser/Thr, a motif present in ATP-synthase F₀ subunit 8 (Unknown Authors, 2015). In cellular and yeast complementation assays, COQ8A is responsible for phosphorylation of COQ3, COQ5 and COQ7 within the coenzyme Q (CoQ) biosynthetic complex (Xie et al., 2011; Acosta et al., 2016).

## Structure

• N-terminal mitochondrial targeting sequence followed by a single-pass transmembrane helix (Jacquet & Zhao, 2025).  
• KxGQ-containing extension that folds across the catalytic cleft, forming an autoinhibitory K276–E405 salt bridge (Unknown Authors, 2018).  
• Atypical PKL catalytic core (residues ~258–644; PDB 4PED) in which an alanine-rich loop replaces the canonical glycine-rich loop, contributing to ADP selectivity (Unknown Authors, 2015).  
• Vertebrate-specific C-terminal insert distal to the active site (Unknown Authors, 2017).  
Crystal structures show the canonical Lys-Glu ion pair (K358–E411), intact catalytic and regulatory spines, and a QKE triad that stabilises a closed, autoinhibited conformation (Stefely et al., 2015).

## Regulation

• Autoinhibition – removal or mutation of the KxGQ extension markedly increases autophosphorylation (Unknown Authors, 2018).  
• Lipid activation – cardiolipin-rich membranes and CoQ intermediates stimulate ATPase activity (Reidenbach et al., 2018).  
• Transcriptional control – p53 up-regulates COQ8A expression in endometrial carcinoma cells (Jacquet & Zhao, 2025).  
• Kinase–phosphatase pair – COQ8A-dependent phosphorylation of COQ7 (S20, S28, T32) is countered by the mitochondrial phosphatase Ptc7 (Unknown Authors, 2018; Vázquez-Fonseca et al., 2020).

## Function

COQ8A localises to the matrix face of the inner mitochondrial membrane and is enriched in mitochondria-rich tissues (Jacquet & Zhao, 2025; Cullen et al., 2016). It stabilises the multimeric CoQ biosynthetic complex through interactions with COQ3, COQ5, COQ7 and COQ9, thereby supporting CoQ₁₀ production essential for oxidative phosphorylation (Stefely et al., 2016; Reidenbach et al., 2018). Loss of COQ8A lowers CoQ levels, elevates reactive oxygen species and triggers compensatory glycolysis (Jacquet & Zhao, 2025). In cancer models, COQ8A influences PI3K/Akt signalling and ferroptosis (Jacquet & Zhao, 2025).

## Inhibitors

Structure-guided screening has yielded small-molecule ATP-competitive probes that modulate COQ8A ATPase activity (Murray et al., 2022).

## Other Comments

Biallelic pathogenic variants in COQ8A cause autosomal recessive cerebellar ataxia-2 and primary CoQ₁₀ deficiency (Laredj et al., 2014; Stefely et al., 2016). Missense mutations clustering near the active site (e.g., R271C, A338T, T487R, E551K) destabilise the protein and reduce activity, whereas truncating alleles (p.Gln167Leufs*36, p.Arg348*) confer loss-of-function (Traschütz et al., 2020; Alcázar-Fabra et al., 2018). Clinically, patients exhibit progressive cerebellar ataxia and myoclonus with variable response to oral CoQ₁₀ supplementation (Stefely et al., 2016).

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