## Phylogeny

ADCK1 is a member of the AarF domain-containing kinase (ADCK) family, which in humans and mice includes five proteins: ADCK1, ADCK2, ADCK3, ADCK4, and ADCK5 (unknownauthors2013pathophysiologicalandmolecular pages 89-92, jacquet2025theadckkinase pages 1-2). According to Manning et al., ADCK1 is classified as an atypical kinase (AK) within the eukaryotic protein kinase-like superfamily and belongs to the AGC-related kinases subfamily (unknownauthors2013pathophysiologicalandmolecular pages 89-92). The ADCK family is highly conserved across species such as Drosophila, C. elegans, and mammals (jacquet2025theadckkinase pages 2-3). Within the family, ADCK1, ADCK2, and ADCK5 belong to a subgroup that diverged earlier than the subgroup containing ADCK3 (COQ8A) and ADCK4 (COQ8B) (unknownauthors2013pathophysiologicalandmolecular pages 89-92, unknownauthors2017exploringthemitochondrial pages 49-51). ADCK family proteins are homologous to the bacterial UbiB and yeast Coq8 proteins involved in Coenzyme Q biosynthesis (unknownauthors2013pathophysiologicalandmolecular pages 89-92).

## Reaction Catalyzed

The specific kinase activity and reaction catalyzed by ADCK1 have not been experimentally demonstrated and remain unknown (jacquet2025theadckkinase pages 1-2, acosta2016coenzymeqbiosynthesis pages 7-11).

## Cofactor Requirements

Specific cofactors for ADCK1 are not well characterized (jacquet2025theadckkinase pages 5-6, unknownauthors2013pathophysiologicalandmolecular pages 89-92). The closely related family members ADCK3 and ADCK4 exhibit Mg2+-dependent ATPase activity, and disease-causing mutations in ADCK3 can affect Mg2+ coordination near the DFG motif (unknownauthors2015functionalcharacterizationof pages 59-64, unknownauthors2015functionalcharacterizationof pages 64-70).

## Substrate Specificity

ADCK1 has not been profiled in the comprehensive kinase substrate specificity studies by Johnson et al. (Nature), and its specific substrates remain unclarified (jacquet2025theadckkinase pages 2-3, jacquet2025theadckkinase pages 5-6, unknownauthors2013pathophysiologicalandmolecular pages 89-92). The closely related homologs ADCK3 and ADCK4 are active atypical serine/threonine kinases that phosphorylate specific peptide substrates when their N-terminal autoinhibitory domain is removed (unknownauthors2015functionalcharacterizationof pages 80-84, unknownauthors2015functionalcharacterizationof pages 64-70). Peptide substitution analysis of ADCK3 showed a preference for serine residues with a basic residue at the -3 position and hydrophobic residues at the +1 and -1 positions; acidic residues near the phosphorylation site reduce recognition (unknownauthors2015functionalcharacterizationof pages 64-70). A potential substrate identified for ADCK3 is a sequence within the mitochondrial ATP synthase F0 subunit 8 (unknownauthors2015functionalcharacterizationof pages 80-84, unknownauthors2015functionalcharacterizationof pages 75-80).

## Structure

ADCK proteins adopt an atypical protein kinase-like (PKL) fold (stefely2015mitochondrialadck3employs pages 1-2, jacquet2025theadckkinase pages 14-15). A detailed 3D structure for ADCK1 is not available (jacquet2025theadckkinase pages 15-17). The ADCK family possesses a kinase domain and a conserved AarF domain (jacquet2025theadckkinase pages 15-17). The kinase domain retains some canonical motifs, including AxK and DFG, but lacks others like the glycine-rich loop and the C-terminal APE motif (unknownauthors2015functionalcharacterizationof pages 15-20). A unique feature is a conserved N-terminal KxGQ motif that, in the ADCK3 crystal structure, forms a salt bridge that occludes the substrate-binding cleft, resulting in autoinhibition (unknownauthors2015functionalcharacterizationof pages 80-84, unknownauthors2015functionalcharacterizationof pages 64-70, unknownauthors2017exploringthemitochondrial pages 49-51). Instead of a glycine-rich loop, ADCK3 has an alanine-rich loop that preferentially binds ADP over ATP (stefely2015mitochondrialadck3employs pages 1-2, unknownauthors2015functionalcharacterizationof pages 59-64).

## Regulation

Regulation of ADCK1 may involve phosphorylation and interactions with mitochondrial proteins, but specific mechanisms are not fully clarified (jacquet2025theadckkinase pages 14-15, jacquet2025theadckkinase pages 2-3). Genetic polymorphisms and somatic mutations also regulate its function (jacquet2025theadckkinase pages 5-6). In the homologs ADCK3 and ADCK4, activity is regulated by an autoinhibitory N-terminal extension containing the KxGQ motif (unknownauthors2015functionalcharacterizationof pages 75-80). Activation requires displacement of this domain, which may occur through post-translational modifications or interaction with regulatory partners (unknownauthors2015functionalcharacterizationof pages 75-80). Dimerization may also facilitate trans-autophosphorylation and activation (unknownauthors2015functionalcharacterizationof pages 75-80).

## Function

ADCK1 is localized to the mitochondrial membrane and is involved in Coenzyme Q (CoQ) biosynthesis, mitochondrial homeostasis, and mitochondrial lipid metabolism (jacquet2025theadckkinase pages 2-3, jacquet2025theadckkinase pages 14-15, jacquet2025theadckkinase pages 5-6). It modulates the ER-mitochondria encounter structure (ERMES) complex, which is essential for lipid homeostasis and mitochondrial membrane integrity (jacquet2025theadckkinase pages 5-6, jacquet2025theadckkinase pages 3-5). ADCK1 interacts directly with CoQ biosynthesis enzymes (COQ3, COQ4, COQ5, COQ6, COQ9), mitochondrial complex subunits (NDUFS3, NDUFV2), MT-CO1, and the mitochondrial protease YME1L1 (jacquet2025theadckkinase pages 2-3). Indirect interactors include OPA1, IMMT (mitofilin), TCF4, and β-catenin (jacquet2025theadckkinase pages 2-3). In colon cancer, ADCK1 enhances β-catenin/TCF4-dependent Wnt signaling (jacquet2025theadckkinase pages 5-6). It promotes tumor growth, cell proliferation, invasion, and migration in various cancers; its knockout in osteosarcoma cells leads to apoptosis, decreased mitochondrial membrane potential, and increased reactive oxygen species (ROS) (jacquet2025theadckkinase pages 2-3, jacquet2025theadckkinase pages 5-6).

## Other Comments

Dysregulation and mutations in ADCK1 are associated with human diseases (jacquet2025theadckkinase pages 14-15, jacquet2025theadckkinase pages 2-3). Overexpression of ADCK1 functions oncogenically in osteosarcoma and colon cancer, and recurrent dominant-negative somatic mutations are found in parathyroid cancer (jacquet2025theadckkinase pages 5-6). Genetic polymorphisms in ADCK1 have been shown to affect the efficacy of paliperidone palmitate treatment in schizophrenia (jacquet2025theadckkinase pages 5-6). Mutations in other family members are linked to distinct disorders: ADCK3 mutations cause primary CoQ10 deficiency and Autosomal Recessive Cerebellar Ataxia Type-2 (ARCA-2), and ADCK4 mutations are linked to steroid-resistant nephrotic syndrome (jacquet2025theadckkinase pages 14-15, cullen2016aarfdomaincontaining pages 1-2).

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