## Phylogeny

ADCK2 (UniProt Q7Z695) is a member of the AarF domain-containing kinase (ADCK) family, also known as the UbiB kinase family (jacquet2025theadckkinase pages 15-17). Based on the classification by Manning et al. (2002), ADCK2 is categorized within the atypical kinase (aPK) group, which is distinct from the conventional eukaryotic protein kinase (ePK) groups such as AGC, CAMK, and CMGC (jacquet2025theadckkinase pages 15-17, manning2002theproteinkinase pages 1-2). This family represents an ancestral branch of the kinase superfamily (jacquet2025theadckkinase pages 15-17). The five vertebrate ADCK paralogs (ADCK1-5) are divided into subgroups, with ADCK2 belonging to the first subgroup along with ADCK1 and ADCK5 (unknownauthors2017exploringthemitochondrial pages 49-51). ADCK family proteins are evolutionarily conserved across species (jacquet2025theadckkinase pages 1-2, jacquet2025theadckkinase pages 2-3). Known orthologs of ADCK2 include the yeast proteins Coq8 and YPL109c, bacterial UbiB proteins, and *Drosophila* ADCK1 (jacquet2025theadckkinase pages 15-17, unknownauthors2017exploringthemitochondrial pages 49-51, vazquezfonseca2019adck2haploinsufficiencyreduces pages 10-11). Human paralogs include ADCK1, ADCK3 (COQ8A), and ADCK4 (jacquet2025theadckkinase pages 15-17).

## Reaction Catalyzed

The specific chemical reaction catalyzed by ADCK2 is not detailed in the available literature (jacquet2025theadckkinase pages 15-17). The ADCK family includes kinases capable of phosphorylating lipids such as phosphatidylinositol and phosphoinositides (unknownauthors2017exploringthemitochondrial pages 49-51).

## Cofactor Requirements

Members of the ADCK family, including ADCK2, contain conserved kinase motifs VIB and VII, which possess two conserved aspartate residues that bind magnesium ions chelated by ATP (unknownauthors2017exploringthemitochondrial pages 49-51).

## Substrate Specificity

Specific substrate motifs for ADCK2 are not identified in the provided literature (jacquet2025theadckkinase pages 15-17).

## Structure

The ADCK2 gene is located on chromosome 7q34, spanning approximately 22,165 base pairs with eight exons (jacquet2025theadckkinase pages 5-6, jacquet2025theadckkinase pages 6-8). Detailed 3D structural features for ADCK2 have not been described (jacquet2025theadckkinase pages 3-5, jacquet2025theadckkinase pages 5-6, jacquet2025theadckkinase pages 8-9). ADCK2 and other family members possess an N-terminal KxGQ domain, which contains a highly conserved lysine residue and is implicated in coenzyme Q metabolism (unknownauthors2017exploringthemitochondrial pages 49-51). The protein retains four “universal core” kinase motifs (I, II, VIB, and VII) and protein kinase motif III, which are associated with ATP binding and phosphotransfer activity (unknownauthors2017exploringthemitochondrial pages 49-51). Mutations resulting in truncated protein forms fail to restore CoQ biosynthesis, indicating the essentiality of its structural domains for function (vazquezfonseca2019adck2haploinsufficiencyreducesa pages 10-11).

## Regulation

Information regarding the regulation of ADCK2 by post-translational modifications (PTMs), including specific modification sites or the responsible enzymes, is not reported in the provided literature (jacquet2025theadckkinase pages 3-5, jacquet2025theadckkinase pages 5-6, jacquet2025theadckkinase pages 8-9, vazquezfonseca2019adck2haploinsufficiencyreduces pages 10-11).

## Function

ADCK2 is a mitochondrial protein that localizes to the mitochondrial matrix and may also associate with the inner mitochondrial membrane (jacquet2025theadckkinase pages 5-6, jacquet2025theadckkinase pages 6-8, vazquezfonseca2019adck2haploinsufficiencyreduces pages 10-11). It is absent from the endoplasmic reticulum and cytosolic fractions (vazquezfonseca2019adck2haploinsufficiencyreducesa pages 10-11). ADCK2 is centrally involved in the biosynthesis of coenzyme Q (CoQ), a process critical for mitochondrial oxidative phosphorylation and antioxidant defense (jacquet2025theadckkinase pages 3-5, jacquet2025theadckkinase pages 6-8). It also participates in mitochondrial lipid metabolism and fatty acid β-oxidation (jacquet2025theadckkinase pages 6-8, vazquezfonseca2019adck2haploinsufficiencyreduces pages 10-11). ADCK2 interacts directly or indirectly with CoQ biosynthesis proteins such as COQ2 and COQ3 (jacquet2025theadckkinase pages 3-5).

In cancer biology, ADCK2 modulates multiple signaling pathways. In non-small cell lung cancer (NSCLC), ADCK2 activates the Akt-mTOR signaling pathway via phosphorylation of Akt and S6K1 (jacquet2025theadckkinase pages 6-8). In prostate and osteosarcoma cells, it modulates the RELB-dependent NF-κB pathway and TNFα-induced HIF-1α accumulation (jacquet2025theadckkinase pages 6-8). In melanoma, ADCK2 regulates cell motility through MYL6 and cytoskeletal proteins (jacquet2025theadckkinase pages 6-8, jacquet2025theadckkinase pages 15-17).

## Other Comments

ADCK2 deficiency, often resulting from haploinsufficiency, is classified as a mitochondrial disorder characterized by impaired mitochondrial lipid metabolism, reduced mitochondrial CoQ levels, decreased fatty acid β-oxidation, and myopathy (jacquet2025theadckkinase pages 6-8, vazquezfonseca2019adck2haploinsufficiencyreduces pages 10-11, vazquezfonseca2019adck2haploinsufficiencyreducesa pages 10-11). Mitochondrial dysfunction associated with ADCK2 insufficiency can be partially rescued by CoQ supplementation (jacquet2025theadckkinase pages 6-8).

In oncology, ADCK2 expression levels have prognostic and functional implications. Elevated ADCK2 expression correlates with tumor size in estrogen receptor-positive luminal A breast cancer, and mutations in ADCK2 are found in a subset of breast cancers (jacquet2025theadckkinase pages 6-8). In NSCLC, ADCK2 expression is inversely related to patient survival, and its knockout inhibits tumor growth (jacquet2025theadckkinase pages 6-8). It also contributes to hypoxia-driven tumor progression in prostate cancer and osteosarcoma and affects metastasis in melanoma (jacquet2025theadckkinase pages 6-8).

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