## Phylogeny

Orthologues are found in Mus musculus, Arabidopsis thaliana and several bacterial phyla, indicating that the ACAD10 lineage is conserved across eukaryotes and prokaryotes (Swigoňová et al., 2009; He et al., 2011; Shen et al., 2009). Within eukaryotes, a duplication produced the paralog ACAD11; ACAD10 and ACAD11 share ~46 % amino-acid identity (Swigoňová et al., 2009). The N-terminal region groups with aminoglycoside-phosphotransferase-like protein-kinase folds and aligns with bacterial LvaA/LvaC 4-hydroxy-acid catabolic enzymes (Rashan et al., 2025). ACAD10 is not assigned to any of the canonical eukaryotic kinase families described by Manning and colleagues.

## Reaction Catalyzed

4-Hydroxyacyl-CoA + ATP → 4-Phosphoacyl-CoA + ADP (Paquay et al., 2024).

## Cofactor Requirements

One tightly bound FAD is essential for the dehydrogenase activity; replacement with 5-deazaFAD abolishes function (Rashan et al., 2025).

## Substrate Specificity

• Kinase activity requires CoA-conjugated 4-hydroxy fatty acids, with highest turnover for short- to medium-chain substrates (Paquay et al., 2024).  
• The ACAD domain oxidises only the corresponding 4-phosphoacyl-CoAs; no activity is detected with standard C6–C22 acyl-CoAs (Rashan et al., 2025).  
• Minor oxidation of branched R/S-2-methyl-C15-CoA and 2-methyl-C16-CoA is ≤ 1.4 mU mg⁻¹ protein (He et al., 2011).  
• No linear peptide consensus motif has been identified.

## Structure

Domain organisation: N-terminal APH-like kinase (~1–300) → central non-catalytic HAD-like segment (~300–450) → C-terminal FAD-dependent ACAD domain (~450–1059) (Rashan et al., 2025; Paquay et al., 2024; He et al., 2011).  
3-D information: Homology models predict the canonical ACAD fold with an aspartate-based catalytic base replacing the usual glutamate; Arg512 and His509 create an unusually polar substrate channel (He et al., 2011). Cryo-EM of ACAD11 shows a tetramer composed of back-to-back kinase dimers capped by an ACAD tetramer; sequence conservation suggests that ACAD10 adopts the same quaternary architecture (Rashan et al., 2025). No experimentally determined ACAD10 structure is yet available.

## Regulation

Full-length ACAD10 undergoes proteolytic cleavage that separates the kinase/HAD module from the ACAD domain; the liberated HAD fragment allosterically inhibits kinase activity (Paquay et al., 2024). Oxidative N-terminal modification followed by arginylation has been reported and links ACAD10 to pexophagy control pathways (Rashan et al., 2025). No other phosphorylation, ubiquitination or acetylation sites have been characterised.

## Function

Transcript abundance peaks in fetal brain, heart and kidney and is lower in adult brain, indicating developmental regulation (He et al., 2011). Subcellular fractionation places ~70 % of the protein in microsomal membranes and ~30 % in mitochondria in mouse tissues (He et al., 2011). The mitochondrial isoform performs the first two committed steps of 4-hydroxy fatty-acid catabolism, permitting entry into β-oxidation (Paquay et al., 2024; Rashan et al., 2025). ACAD10-deficient mice accumulate 4-hydroxy acids and display altered lipid metabolism (Rashan et al., 2025). Upstream regulators and stable protein partners have not yet been identified.

## Other Comments

Genome-wide association studies link ACAD10 variants to hypertension, type 2 diabetes, weight gain and glaucoma (Paquay et al., 2024).

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