## Phylogeny

• Orthologous proteins have been annotated in Mus musculus, Arabidopsis thaliana and multiple bacterial taxa, indicating conservation of the ACAD10 lineage across eukaryotes and prokaryotes (swigonova2009acylcoadehydrogenasesdynamic pages 1-3, he2011identificationandcharacterization pages 8-10, shen2009diversityanddispersal pages 5-6).  
• The human gene arose from a eukaryote-specific duplication that generated the paralog ACAD11; the two share ~46 % amino-acid identity (swigonova2009acylcoadehydrogenasesdynamic pages 1-3).  
• Sequence analysis places the N-terminal module in the aminoglycoside-phosphotransferase (APH)–like protein-kinase‐fold subgroup and aligns the full-length protein with bacterial LvaA/LvaC enzymes that catabolize 4-hydroxy acids (rashan2025acad10andacad11 pages 4-5).  
• ACAD10 is not classified within the canonical eukaryotic kinase groups described by Manning et al.

## Reaction Catalyzed

Kinase domain  
4-Hydroxyacyl-CoA + ATP → 4-Phosphoacyl-CoA + ADP (paquay2024acad10andacad11 pages 10-12).

ACAD domain  
4-Phosphoacyl-CoA → 2-Enoyl-CoA + Pi + 2 H⁺ (rashan2025acad10andacad11 pages 6-6).

Minor side activity  
R- or S-2-methyl-pentadecanoyl-CoA → 2-methyl-pentadecenoyl-CoA + 2 H⁺ (he2011identificationandcharacterization pages 10-11).

## Cofactor Requirements

• One tightly bound FAD is essential for the dehydrogenase reaction; substitution with 5-deazaFAD abolishes activity (rashan2025acad10andacad11 pages 5-6).

## Substrate Specificity

• Kinase activity requires CoA-conjugated 4-hydroxy fatty acids; highest turnover is observed with short- to medium-chain 4-hydroxyacyl-CoAs (paquay2024acad10andacad11 pages 10-12).  
• The ACAD domain oxidizes only the corresponding 4-phosphoacyl-CoAs and shows no activity toward standard C6–C22 acyl-CoAs (rashan2025acad10andacad11 pages 5-6).  
• Residual oxidation of branched substrates R/S-2-methyl-C15-CoA and 2-methyl-C16-CoA is ≤ 1.4 mU mg⁻¹ protein (he2011identificationandcharacterization pages 10-11).  
• No linear peptide consensus motif has been defined.

## Structure

Domain organisation  
N-terminal APH-like kinase domain (~1–300) – 4-hydroxyacyl-CoA phosphorylation (rashan2025acad10andacad11 pages 4-5).  
Central HAD-like segment (~300–450) – non-catalytic regulatory element (paquay2024acad10andacad11 pages 10-12).  
C-terminal ACAD domain (~450–1059) – FAD-dependent dehydrogenation (he2011identificationandcharacterization pages 7-8).

3-D information  
• Homology modelling predicts the canonical three-domain ACAD fold; the catalytic base is an aspartate that replaces the glutamate conserved in typical ACADs (he2011identificationandcharacterization pages 7-8).  
• Arg512 and His509 introduce unusual polarity into the substrate channel (he2011identificationandcharacterization pages 7-8).  
• Cryo-EM analysis of ACAD11 reveals a tetramer formed by back-to-back kinase dimers capped by an ACAD tetramer; sequence conservation suggests ACAD10 adopts a similar quaternary architecture (rashan2025acad10andacad11 pages 4-5).  
• No experimentally resolved ACAD10 structure is currently available.

## Regulation

• The full-length polypeptide undergoes proteolytic cleavage that separates the kinase/HAD module from the ACAD domain; the isolated HAD fragment exerts allosteric inhibition of the kinase activity (paquay2024acad10andacad11 pages 10-12).  
• N-terminal oxidative modification followed by arginylation has been reported, linking ACAD10 to pexophagy control pathways (rashan2025acad10andacad11 pages 9-10).  
• No additional phosphorylation, ubiquitination or acetylation sites have been experimentally defined.

## Function

• Transcript levels are highest in fetal brain, heart and kidney and lower in adult brain, indicating developmental regulation (he2011identificationandcharacterization pages 5-7).  
• Subcellular fractionation shows ~70 % of the protein in microsomal membranes and ~30 % in mitochondria in mouse tissues (he2011identificationandcharacterization pages 8-10).  
• The mitochondrial isoform executes the first two committed steps of 4-hydroxy fatty-acid catabolism, enabling entry into β-oxidation (paquay2024acad10andacad11 pages 10-12, rashan2025acad10andacad11 pages 6-6).  
• ACAD10-deficient mice accumulate 4-hydroxy acids and display altered lipid metabolism (rashan2025acad10andacad11 pages 9-10).  
• 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 (paquay2024acad10andacad11 pages 10-12).

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