1. Phylogeny  
   ACAD10 is an evolutionarily ancient member of the acyl‐CoA dehydrogenase family that is conserved across diverse eukaryotic lineages. Phylogenetic analyses of the ACAD catalytic domain reveal that ACAD10 groups together with its paralog ACAD11 as a distinct subfamily within the larger set of mitochondrial acyl‐CoA dehydrogenases. These analyses indicate that the ACAD10/11 subfamily originated from early gene duplication and domain‐acquisition events that likely occurred before the divergence of major eukaryotic clades, with orthologs identifiable in mammals, birds, plants, and fungi, while certain lineages such as arthropods lack these homologs (swigonova2009acylcoadehydrogenasesdynamic pages 11-13, swigonova2009acylcoadehydrogenasesdynamic pages 13-14, dibrova2014phylogenomicreconstructionof pages 18-18).
2. Reaction Catalyzed  
   ACAD10 catalyzes the dehydrogenation of a specific acyl‐CoA substrate in the first step of mitochondrial β‐oxidation. In this reaction, R‐ and S‐2-methyl-C15‐CoA is converted into the corresponding trans-2-enoyl-C15-CoA derivative concomitant with the reduction of its tightly bound flavin adenine dinucleotide (FAD) cofactor to FADH₂. The electrons resulting from this oxidation are transferred to the electron transfer flavoprotein (ETF), which in turn feeds into the mitochondrial respiratory chain (swigonova2009acylcoadehydrogenasesdynamic pages 17-21).
3. Cofactor Requirements  
   The catalytic activity of ACAD10 depends critically on the non-covalently bound FAD molecule. FAD serves as the essential electron acceptor during the dehydrogenation reaction, and its binding is facilitated by a highly conserved FAD-binding pocket that is a common feature among acyl‐CoA dehydrogenases. This cofactor requirement ensures efficient electron transfer during fatty acid β‐oxidation and is characteristic of the overall ACAD structural framework (swigonova2009acylcoadehydrogenasesdynamic pages 3-4, camoes2015newinsightsinto pages 4-5).
4. Substrate Specificity  
   ACAD10 is unique among acyl‐CoA dehydrogenases in that its enzymatic activity is observed only with the substrates R‐ and S‐2-methyl-C15-CoA. This specificity for a long, branched-chain fatty acyl-CoA distinguishes it from other family members that typically catalyze dehydrogenation reactions for straight-chain acyl-CoAs or acyl-CoAs with shorter chain lengths. The narrow substrate specificity of ACAD10 defines its role in the metabolism of branched-chain fatty acid derivatives, which are oxidized via a dehydrogenation mechanism that proceeds with the reduction of FAD to FADH₂ (swigonova2009acylcoadehydrogenasesdynamic pages 17-21).
5. Structure  
   ACAD10 features a canonical acyl‐CoA dehydrogenase domain that adopts a three‐layered α/β sandwich fold typical of members of the ACAD family. The active site of this domain includes conserved residues such as invariant arginines and glycines that participate in the stabilization of the FAD cofactor as well as in positioning the acyl‐CoA substrate for catalysis. In addition to the catalytic ACAD domain, phylogenetic reconstructions have shown that ACAD10, together with ACAD11, harbors additional domains acquired through chimeric events. These non‐canonical domains include segments homologous to the aminoglycoside phosphotransferase (APH) domain and a haloacid dehalogenase (HAD) domain. Although the precise functional contributions of these extra domains are not fully characterized, their presence distinguishes ACAD10 from classical acyl‐CoA dehydrogenases and may impart unique regulatory or interaction properties. Homology models and comparative analyses suggest that ACAD10 forms oligomeric assemblies similar to other ACADs, wherein the FAD-binding sites are located at subunit interfaces, thus stabilizing the active conformation necessary for efficient catalysis (swigonova2009acylcoadehydrogenasesdynamic pages 3-4, swigonova2009acylcoadehydrogenasesdynamic pages 8-9, dibrova2014phylogenomicreconstructionof pages 18-18).
6. Regulation  
   Despite the extensive biochemical and phylogenetic characterization of the acyl‐CoA dehydrogenase family, specific regulatory mechanisms for ACAD10 remain incompletely defined in the peer-reviewed literature. In general, other members of the ACAD family are known to be regulated primarily by substrate availability and, in some cases, by post‐translational modifications; however, for ACAD10 neither definitive post‐translational modifications (such as phosphorylation or ubiquitination) nor well‐established allosteric control mechanisms have been reported. At present, the modulatory aspects of ACAD10 activity—including potential changes in conformation, oligomerization state, or interactions with accessory proteins—have not been thoroughly elucidated (swigonova2009acylcoadehydrogenasesdynamic pages 17-21, dibrova2014phylogenomicreconstructionof pages 18-18).
7. Function  
   ACAD10 functions as a mitochondrial enzyme that participates in the β‐oxidation of fatty acids, specifically catalyzing the dehydrogenation of R‐ and S‐2-methyl-C15-CoA. As an integral component of mitochondrial energy metabolism, the conversion of the acyl-CoA substrate to its corresponding trans-2-enoyl-CoA derivative enables subsequent steps in the β‐oxidation cycle, ultimately contributing to ATP production via the electron transport chain. The strict substrate specificity of ACAD10 indicates that it may have a specialized role in the oxidation of branched-chain fatty acyl-CoAs, thereby contributing to the metabolic processing of these molecules in tissues that rely on mitochondrial fatty acid oxidation for energy. Although detailed tissue-specific expression profiles and interacting partners for ACAD10 are not yet fully described in the peer-reviewed reports currently available, its conservation across species implies an essential role in cellular energy homeostasis (swigonova2009acylcoadehydrogenasesdynamic pages 11-13, dibrova2014phylogenomicreconstructionof pages 18-18, camoes2015newinsightsinto pages 4-5).
8. Other Comments  
   To date, no specific inhibitors targeting ACAD10 have been reported in the high-impact peer-reviewed literature, and the identification of clinically relevant mutations or polymorphisms in the ACAD10 gene has not been definitively established. Although alterations in the activity or expression of acyl‐CoA dehydrogenases have been associated with metabolic disorders in other family members, further research is needed to determine whether similar disease associations pertain to ACAD10. As such, the discovery of selective inhibitors or the identification of disease-causing mutations affecting ACAD10 remains an open area of investigation within the field of mitochondrial fatty acid metabolism (swigonova2009acylcoadehydrogenasesdynamic pages 17-21).
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