1. Phylogeny  
   ACAD11 (Acyl‐CoA dehydrogenase family member 11; gene symbol ACAD11; Uniprot Q709F0) is a member of the human acyl‐CoA dehydrogenase (ACAD) family that is evolutionarily related to other enzymes involved in mitochondrial fatty acid β‐oxidation. Its amino acid sequence shows only 20–30% identity to conventional ACAD enzymes such as medium‐chain acyl‐CoA dehydrogenase (MCAD), very long‐chain acyl‐CoA dehydrogenase (VLCAD) and ACAD9, yet modeling studies reveal that it retains the core structural fold common to these flavoenzymes (he2011identificationandcharacterization pages 7-8). Phylogenetic analyses place ACAD11 in a distinct subgroup together with ACAD10, suggesting that these enzymes have diverged to catalyze oxidation reactions in a substrate range that is not served by classical ACADs. ACAD11 is conserved across mammalian species and shows prominent expression in the central nervous system, particularly in the adult brain, which is consistent with its evolutionarily adapted role in regulating the composition of fatty acyl moieties within neuronal lipids (he2011identificationandcharacterization pages 1-2).
2. Reaction Catalyzed  
   ACAD11 catalyzes the α,β‐dehydrogenation of acyl‐CoA substrates, a reaction that constitutes the initial step in the mitochondrial β‐oxidation pathway. In this reaction, a saturated acyl‐CoA—most notably docosanoyl‐CoA (C22‐CoA)—is converted to its corresponding trans‐2‐enoyl‐CoA derivative. The reaction mechanism involves the abstraction of a proton from the α‐carbon and the concomitant hydride transfer from the β‐carbon to the bound flavin adenine dinucleotide (FAD) cofactor, thereby generating a double bond between the α and β carbons. The reduced FAD then transfers electrons further to the electron transfer flavoprotein (ETF), which in turn delivers reducing equivalents to the mitochondrial respiratory chain (he2011identificationandcharacterization pages 1-2, he2011identificationandcharacterization pages 7-8).
3. Cofactor Requirements  
   The dehydrogenation reaction catalyzed by ACAD11 is strictly dependent on the flavin adenine dinucleotide (FAD) cofactor, which is essential for accepting the hydride ion during the oxidation step. In addition, the enzyme requires an efficient electron acceptor in the form of electron transfer flavoprotein (ETF) to recover the oxidized state of FAD and maintain catalytic turnover. This cofactor requirement is characteristic of the ACAD family and supports the enzyme’s role in mitochondrial energy production by coupling fatty acid oxidation to the electron transport system (he2011identificationandcharacterization pages 1-2, he2011identificationandcharacterization pages 7-8).
4. Substrate Specificity  
   Biochemical assays have demonstrated that ACAD11 exhibits substrate specificity with a marked preference for very long‐chain fatty acyl‐CoA esters, showing maximal activity toward saturated C22‐CoA (docosanoyl‐CoA). In vitro, the enzyme displays appreciable dehydrogenation activity on acyl‐CoA substrates with carbon chain lengths ranging from 20 to 26 carbons, with an observed high C22/C20 activity ratio distinguishing it from related enzymes such as VLCAD and ACAD9 (he2011identificationandcharacterization pages 1-2). The substrate binding pocket of ACAD11 is uniquely configured, containing hydrophilic residues—including Arg512 and His509—which contrast with the predominantly hydrophobic pockets typical of many ACAD enzymes; these features likely contribute to its capacity to accommodate bulky acyl chains (he2011identificationandcharacterization pages 7-8).
5. Structure  
   Computational modeling and comparative sequence analyses indicate that ACAD11 adopts the classical ACAD fold, which comprises a central catalytic domain with an α/β‐sheet structure characteristic of FAD‐dependent oxidoreductases. One of the defining structural distinctions of ACAD11 is the substitution of the conserved catalytic glutamate—characteristically found in other members of the ACAD enzyme family—with an aspartate residue. This conservative amino acid change is thought to relate to the enzyme’s capacity to process longer and bulkier fatty acyl‐CoA substrates, as a shorter side chain in the catalytic base may reduce steric hindrance within the active site (he2011identificationandcharacterization pages 7-8). In addition, ACAD11 exhibits a substrate binding pocket of unusual composition; the presence of hydrophilic residues such as Arg512 and His509, which are conserved among species, likely supports the stabilization and proper orientation of the acyl‐CoA substrate. The overall domain organization of ACAD11 includes an N‐terminal region that directs mitochondrial import and a mature catalytic domain that integrates into multimeric complexes, most likely forming a tetramer analogous to other enzymes in the ACAD family. Immunofluorescence and biochemical fractionation studies have localized the mature ACAD11 protein predominantly to the mitochondrial membrane fraction of tissues such as human cerebellum and kidney (he2011identificationandcharacterization pages 1-2, he2011identificationandcharacterization pages 17-20).
6. Regulation  
   Data obtained from immunodetection studies demonstrate that ACAD11 is subject to regulation at the transcript level via alternative splicing, resulting in multiple mRNA variants that encode distinct protein isoforms. Such splicing events appear to determine the subcellular localization of the enzyme; for example, ACAD11 predominantly co-localizes with mitochondrial markers in neuroblastoma cells, whereas in skin fibroblasts its distribution is more cytoplasmic and even associated with vesicular structures. Despite extensive biochemical characterization, specific post-translational modifications—such as phosphorylation, ubiquitination, or acetylation—have not been consistently reported for ACAD11, and antibody inhibition studies have shown that targeting of specific peptide segments does not inhibit enzymatic activity. These observations suggest that the regulation of ACAD11 activity is more reliant on differential expression and subcellular localization than on direct covalent modification (he2011identificationandcharacterization pages 7-8, he2011identificationandcharacterization pages 8-10).
7. Function  
   Functionally, ACAD11 plays a critical role in the mitochondrial β‐oxidation of very long‐chain fatty acids, being primarily responsible for the oxidative dehydrogenation step that converts saturated acyl‐CoA substrates into their corresponding trans‐2‐enoyl‐CoA derivatives. Enzymatic assays have confirmed that ACAD11 exhibits maximal catalytic efficiency with docosanoyl‐CoA (C22‐CoA), a substrate representative of the very long‐chain fatty acids commonly found in neural tissues. The high level of ACAD11 transcript and protein detected in adult brain tissues—particularly in the white matter of the cerebellum—and in kidney supports its specialized role in regulating both energy metabolism and the composition of fatty acyl chains within cellular lipids. The enzyme’s activity is essential not only for ATP production via β‐oxidation but also for maintaining the balance of lipid species that are critical for membrane fluidity and myelin stability. In this capacity, ACAD11 is implicated in cellular processes related to metabolism and neurobiology by contributing to the regulated turnover of very long‐chain fatty acids (he2011identificationandcharacterization pages 1-2, he2011identificationandcharacterization pages 17-20).
8. Other Comments  
   At present, no specific chemical inhibitors or selective regulatory compounds have been identified for ACAD11. Although disease‐associated mutations in ACAD11 have not been explicitly documented in the published literature, its predominant expression in brain tissue and its pivotal role in mitochondrial β‐oxidation suggest that perturbations in ACAD11 function could potentially be linked to neurological or metabolic disorders involving dysregulated lipid homeostasis. The existence of multiple isoforms generated by alternative splicing further underscores the complexity of its regulation and possible tissue‐specific functions. Continued research into the enzymatic mechanisms, regulatory factors and potential disease mutations of ACAD11 may provide deeper insights into its biological importance in the context of energy production and lipid metabolism (he2011identificationandcharacterization pages 1-2, he2011identificationandcharacterization pages 7-8).
9. References
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