MCAD
Medium Chain Acyl-CoA Dehydrogenase: The Answer to Some SIDS Cases

Jessica Benson, Amy Ramirez and Nerissa Seward
Faculty Advisor: Colleen Conway
Mount Mary College, 2900 North Menomonee River Parkway, Milwaukee, WI 53222
Research Mentor: Jung-Ja Kim, Medical College of Wisconsin, Milwaukee, WI 53222

Abstract:
Sudden Infant Death Syndrome (SIDS) is a common "cause" of non-accidental infant deaths. Some SIDS mortality may be due to defects in the medium chain acyl-CoA dehydrogenase (MCAD) enzyme. This is a common genetic defect in people of northern European descent. Prenatal screening has prevented deaths.

MCAD is the first enzyme in the mitochondrial beta oxidation spiral for fatty acyl-CoA substrates of four to twelve carbons. This enzyme removes two hydrogen atoms and creates a carbon-carbon double bond in the substrate. Related enzymes include short chain acyl-CoA dehydrogenase (SCAD), long chain acyl-CoA dehydrogenase (LCAD), and very long chain acyl-CoA dehydrogenase (VLCAD). The remaining steps of the beta oxidation of fatty acids each have their own family of enzymes that work on different chain lengths of substrate. MCAD is often used as the model for enzymes in its family.

MCAD is a homotetramer with an electron transport flavoprotein (ETF) attached to one subunit. Each subunit has a flavin adenine dinucleotide (FAD) molecule that is the electron transporter for electrons from the substrate (acyl-CoA) to ETF and eventually to the electron transport chain (ETC).

In our model, each of the four subunits is displaying a different feature of MCAD. Subunit A shows the amino acids of the active site, the amino acids that are affected by mutations, and the secondary protein structure (alpha helices and beta sheets). Subunit B shows FAD and the interactions between FAD and MCAD. Subunit C shows the active site and the substrate binding interactions. Subunit D shows interactions between ETF and MCAD.

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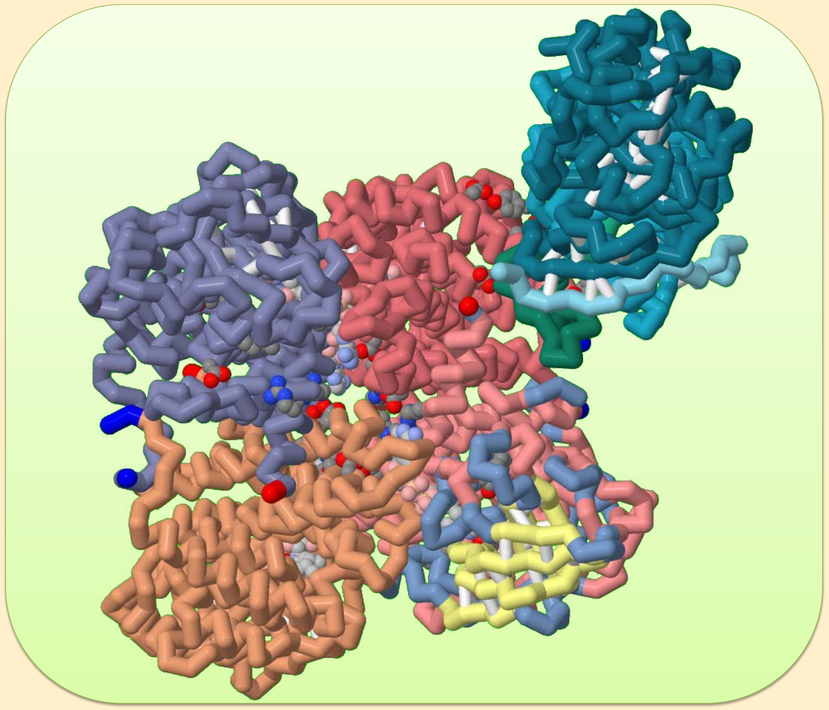
Introduction:
MCAD (medium chain acyl Co-A dehydrogenase) is the first enzyme in the fatty acid beta oxidation spiral that degrades fatty acids into acetyl-CoA. A point mutation in the DNA leads to an MCAD deficiency that can result in infant mortality due to lack of cellular energy. One percent of the infants that die from Sudden Infant Death Syndrome (SIDS) actually have the MCAD deficiency. The deficiency presents itself when the infant has a viral infection or is not eating. Up to twenty-five percent of patients with MCAD deficiency die during their first episode of illness. The treatment is merely making sure that if infants are sick that they are getting sufficient food to make up for the loss of energy, either by mouth or intravenously with glucose. The deficiency can present itself at any time during the affected individual's lifetime, but commonly occurs in infants. Prenatal testing has decreased the deaths associated with this deficiency.



Supporting Information:
Researchers were able to obtain structural information by using X-ray crystallography and functional information by mutation studies. X-ray crystallography confirmed the structure of wild type and mutated enzymes. The mutated enzyme folds differently, inhibiting its function. By creating point mutations, researchers found that glutamate-376 was the catalytic site. Similar procedures were done for other suspected important residues.

Future Research:
MCAD is the most well-studied of this family of dehydrogenases. Information about the amino acid residues necessary for catalysis by MCAD has been used to compare to other members of the family. Some researchers have found similarities throughout the family, but there are also some differences.

Active Site:
The active site cavity is deep enough to accommodate substrates up to twelve carbons long. When the fatty acid enters the active site, it binds the resident FAD at the 2'-OH of the ribityl chain of the flavin ring. Glutamate-376 is the catalytic base of the enzyme, and the substrate binds to it at the amide nitrogen. These interactions position and align the flavin, substrate, and glutamate-376 to allow hydrogen atom removal and the formation of the double bond.

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FAD:
FAD is embedded in both MCAD and ETF and functions to transfer electrons. The exact mechanism is not known, but the isoalloxazine ring has been identified as vital in this process.

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ETF:
ETF attaches to the D chain of MCAD. The two components interact by noncovalent means at the hydrophobic patch of MCAD. The recognition loop of ETF locates this patch and allows the two to bind.

The FAD on ETF is in close proximity to the FAD on MCAD to allow transfer of electrons from MCAD to ETF. The ETF then carries those electrons to the ETC and the metabolic cycle continues.

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The CREST Program is funded by grant #1022793 from NSF-CCLI.