Computational analysis of pathogenic mutation effects on human acyl-CoA dehydrogenase structure and stability

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Abstract: Acyl-CoA dehydrogenases (ACADs) are mitochondrial flavoproteins that catalyze the initial reaction in fatty acid β-oxidation with the same basic chemical mechanism [1]. Clinical symptoms of ACAD deficiency are variable and include hypoglycemic coma, hepatic dysfunction, and may even lead to sudden death [2, 3] . This study focuses on short chain acyl-CoA dehydrogenase (SCAD) pathogenic missense mutations. We constructed native and 15 mutant models of ACAD by homology modeling using YASARA [4, 5] and chose the best models after quality evaluation [6, 7]. Secondary structure, radius of gyration, potential energy and Root Mean Square Deviation (RMSD) of residues were evaluated in each model. Important contacts between substrate and protein including H-bonds, hydrophobic, and electrostatic interactions were investigated as well. To compare the structural stability, 75 ns molecular dynamics simulations were performed on native and two mutants (G209S and R171W) with temperatures of 299 K, 310 K, and 314 K. The energy levels of the mutant models (G209S and R171W) were lower than native model at all used simulation temperatures. There was no significant difference between the RMSD of simulated models (< 1 Å). Except at 310 K temperature, the distances of two important H-bonds between enzyme and substrate remained shorter than 5 Å in native model while in mutant models, these H-bonds were affected. In conclusion, SCAD pathogenic point mutations were detected on structural parameters of this enzyme by using in silico methods.

Keywords: beta oxidation; missense mutation; acyl-CoA dehydrogenase; ACADD; SCAD

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