Complex I assembly function and fatty acid oxidation enzyme activity of ACAD9 both contribute to disease severity in ACAD9 deficiency.

Abstract:
Acyl-CoA dehydrogenase 9 (ACAD9) is an assembly factor for mitochondrial respiratory chain Complex I (CI), and ACAD9 mutations are recognized as a frequent cause of CI deficiency. ACAD9 also retains enzyme ACAD activity for long-chain fatty acids in vitro, but the biological relevance of this function remains controversial partly because of the tissue specificity of ACAD9 expression: high in liver and neurons and minimal in skin fibroblasts. In this study, we hypothesized that this enzymatic ACAD activity is required for full fatty acid oxidation capacity in cells expressing high levels of ACAD9 and that loss of this function is important in determining phenotype in ACAD9-deficient patients. First, we confirmed that HEK293 cells express ACAD9 abundantly. Then, we showed that ACAD9 knockout in HEK293 cells affected long-chain fatty acid oxidation along with CI, both of which were rescued by wild type ACAD9. Further, we evaluated whether the loss of ACAD9 enzymatic fatty acid oxidation affects clinical severity in patients with ACAD9 mutations. The effects on ACAD activity of 16 ACAD9 mutations...
identified in 24 patients were evaluated using a prokaryotic expression system. We showed that there was a significant inverse correlation between residual enzyme ACAD activity and phenotypic severity of ACAD9-deficient patients. These results provide evidence that in cells where it is strongly expressed, ACAD9 plays a physiological role in fatty acid oxidation, which contributes to the severity of the phenotype in ACAD9-deficient patients. Accordingly, treatment of ACAD9 patients should aim at counteracting both CI and fatty acid oxidation dysfunctions.