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Succinyl-CoA synthetase (SUCLA2) deficiency in two siblings with impaired activity of other mitochondrial oxidative enzymes in skeletal muscle without mitochondrial DNA depletion.

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Abstract

Mutations in SUCLA2 result in succinyl-CoA ligase (ATP-forming) or succinyl-CoA synthetase (ADP-forming) (A-SCS) deficiency, a mitochondrial tricarboxylic acid cycle disorder. The phenotype associated with this gene defect is largely encephalomyopathy. We describe two siblings compound heterozygous for SUCLA2 mutations, c.985A>G (p.M329V) and c.920C>T (p.A307V), with parents confirmed as carriers of each mutation. We developed a new LC-MS/MS based enzyme assay to demonstrate the decreased SCS activity in the siblings with this unique genotype. Both siblings shared bilateral progressive hearing loss, encephalopathy, global developmental delay, generalized myopathy, and dystonia with choreoathetosis. Prior to diagnosis and because of lactic acidosis and low activity of muscle pyruvate dehydrogenase complex (PDC), sibling 1 (S1) was placed on dichloroacetate, while sibling 2 (S2) was on a ketogenic diet. S1 developed severe cyclic vomiting refractory to therapy, while S2 developed Leigh syndrome, severe GI dysmotility, intermittent anemia, hypogammaglobulinemia and eventually succumbed to his disorder. The mitochondrial DNA contents in skeletal muscle (SM) were normal in both siblings. Pyruvate dehydrogenase complex, ketoglutarate dehydrogenase complex, and several mitochondrial electron transport chain (ETC) activities were low or at the low end of the reference range in frozen SM from S1 and/or S2. In contrast, activities of PDC, other mitochondrial enzymes of pyruvate metabolism, ETC and, integrated oxidative phosphorylation, in skin fibroblasts were not significantly impaired. Although we show that propionyl-CoA inhibits PDC, it does not appear to account for decreased PDC activity in SM. A better understanding of the mechanisms of phenotypic variability and the etiology for tissue-specific secondary deficiencies of mitochondrial enzymes of oxidative metabolism, and independently mitochondrial DNA depletion (common in other cases of A-SCS deficiency), is needed given the implications for control of lactic acidosis and possible clinical management.