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Titel des Beitrags: DHTKD1 mutations cause 2-aminoadipic and 2-oxoadipic aciduria.

Abstract: Abnormalities in metabolite profiles are valuable indicators of underlying pathologic conditions at the molecular level. However, their interpretation relies on detailed knowledge of the pathways, enzymes, and genes involved. Identification and characterization of their physiological function are therefore crucial for our understanding of human disease: they can provide guidance for therapeutic intervention and help us to identify suitable biomarkers for monitoring associated disorders. We studied two individuals with 2-aminoadipic and 2-oxoadipic aciduria, a metabolic condition that is still unresolved at the molecular level. This disorder has been associated with varying neurological symptoms. Exome sequencing of a single affected individual revealed compound heterozygosity for an initiating methionine mutation (c.1A>G) and a missense mutation (c.2185G>A [p.Gly729Arg]) in DHTKD1. This gene codes for dehydrogenase E1 and transketolase domain-containing protein 1, which is part of a 2-oxoglutarate-dehydrogenase-complex-like protein. Sequence analysis of a second individual identified the same missense mutation together with a nonsense mutation (c.1228C>T [p.Arg410(*)]) in DHTKD1. Increased levels of 2-oxoadipate in individual-derived fibroblasts normalized upon lentiviral expression
of the wild-type DHTKD1 mRNA. Moreover, investigation of L-lysine metabolism showed an accumulation of deuterium-labeled 2-oxoadipate only in noncomplemented cells, demonstrating that DHTKD1 codes for the enzyme mediating the last unresolved step in the L-lysine-degradation pathway. All together, our results establish mutations in DHTKD1 as a cause of human 2-aminoadipic and 2-oxoadipic aciduria via impaired turnover of decarboxylation 2-oxoadipate to glutaryl-CoA.