Pyruvate dehydrogenase complex deficiency disease is connected to regulatory loop disorder in the αV138M variant of human pyruvate dehydrogenase

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ABSTRACT

The pyruvate dehydrogenase multienzyme complex (PDHc) connects glycolysis to the tricarboxylic acid cycle by producing acetyl-coenzyme A via the decarboxylation of pyruvate. Because of its pivotal role in glucose metabolism, the complex is closely regulated in mammals by reversible phosphorylation, the modulation of which is of interest in treating cancer, diabetes, and obesity. Mutations such as αV138M in pyruvate dehydrogenase, the pyruvate-decarboxylating PDHc E1 component, can result in pyruvate dehydrogenase complex deficiency, an inborn error of metabolism that results in an array of symptoms such as lactic acidosis, progressive cognitive and neuromuscular deficits, and even death in infancy or childhood. Here we present an analysis of two X-ray crystal structures at 2.7 Å resolution, the first of the disease-associated human αV138M E1 variant, and the second of WT E1 bound to an adduct of its coenzyme thiamin diphosphate with the substrate analogue acetylphosphinate (ACP). The structures provide support for the role of regulatory loop disorder in E1 inactivation, and the αV138M variant structure also specifically demonstrates that altered coenzyme binding can result in such disorder even in the absence of phosphorylation. Combined with an analysis of αV138M activity, these results underscore the general connection between regulatory loop disorder and loss of E1 catalysis.