Exome sequence reveals mutations in CoA synthase as a cause of neurodegeneration with brain iron accumulation.

Neurodegeneration with brain iron accumulation (NBIA) comprises a clinically and genetically heterogeneous group of disorders with progressive extrapyramidal signs and neurological deterioration, characterized by iron accumulation in the basal ganglia. Exome sequencing revealed the presence of recessive missense mutations in COASY, encoding coenzyme A (CoA) synthase in one NBIA-affected subject. A second unrelated individual carrying mutations in COASY was identified by Sanger sequence analysis. CoA synthase is a bifunctional enzyme catalyzing the final steps of CoA biosynthesis by coupling phosphopantetheine with ATP to form dephospho-CoA and its subsequent phosphorylation to generate CoA. We demonstrate alterations in RNA and protein expression levels of CoA synthase, as well as CoA amount, in fibroblasts derived from the two clinical cases and in yeast. This is the second inborn error of coenzyme A biosynthesis to be implicated in NBIA.