Alteration of coenzyme A biosynthetic pathway in neurodegeneration with brain iron accumulation syndromes

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Neurodegeneration with brain iron accumulation (NBIA) comprises a heterogeneous group of genetically defined disorders characterized by progressive extrapyramidal deterioration and by iron accumulation in the basal ganglia. The clinical spectrum of NBIA is extremely wide and includes early-onset neurodegeneration, with an invariably fatal outcome, and adult-onset parkinsonisms-dystonia. Recessive NBIA syndromes may be due to mutations in the \( PANK2 \), \( PLA2G6 \), \( FA2H \), \( C19orf12 \), but still in a large proportion of patients, no genetic alteration can be found. Using exome-sequencing strategy we identified, in a NBIA patient, a homozygous missense mutation in the gene coding for Coenzyme A Synthase (COASY). By performing traditional Sanger sequencing in a cohort of additional NBIA subjects, we found another mutant patient. COASY is a mitochondrial enzyme involved in the last step of Coenzyme A biosynthesis, a molecule of primary importance for several metabolic pathways. The missense mutation affects a highly conserved aminoacid residue in the catalytic site of the enzyme, a region extremely conserved from yeast to human. Western-blot analysis showed that CoASy protein was absent in patient fibroblasts, whereas RT-PCR revealed that mRNA was significantly reduced only in the patient carrying the non-sense mutation. HPLC analysis demonstrated reduced CoA concentration in mitochondria isolated from mutant yeast and patient fibroblasts. Together with mutations in \( PANK2 \), coding for the first enzyme in CoA biosynthesis, mutations in CoA synthase impinge on the same biosynthetic pathway causing NBIA.