Deciphering COASY-induced neurodegeneration: new variants, new phenotypes and insights into the transcriptomic profile of patient fibroblasts.

COASY, the gene encoding the bifunctional enzyme CoA synthase, which catalyses the last two reactions of cellular de novo coenzyme A (CoA) biosynthesis, has been associated with two extremely rare autosomal recessive disorders, namely COASY protein-associated neurodegeneration (CoPAN), a form of neurodegeneration with brain iron accumulation (NBIA), and pontocerebellar hypoplasia type 12 (PCH12).

We have identified five new individuals with new COASY variants. While one case had classic CoPAN features, the others showed atypical symptoms such as deafness, speech and autism spectrum disorders, brain atrophy, and microcephaly. All patients suffered from epilepsy, emphasising the potential prevalence of this condition in COASY-related disorders. Transcriptomic profiling of fibroblasts revealed impaired expression of genes associated with mitochondrial respiration, oxidative stress response, transmembrane transport, various cellular signalling pathways, and protein translation, modification and trafficking. Bioenergetic analysis revealed an impairment of mitochondrial oxygen consumption in COASY fibroblasts. Despite comparable total CoA levels to control cells, the levels of mitochondrial 4'-phosphopantetheinylated proteins were significantly reduced in COASY patients.

These results not only extend the clinical phenotype associated with COASY variants but also indicate a continuum between CoPAN and PCH12. The intricate interplay of altered cellular processes and signalling pathways provides valuable insights into the pathogenesis of COASY-associated diseases.