Zebrafish models of PKAN and COPAN.

Coenzyme A (CoA) is an essential cofactor in all living organisms, functioning either as an activator of molecules with carbonyl groups or as a carrier of acyl moieties. CoA biosynthesis involves five highly conserved enzymatic steps. In humans, defects in genes encoding the CoA biosynthesis enzymes cause ultrarare inherited disorders. While mutations in phosphopantothenoylcysteine synthetase (PPCS), catalyzing the second enzymatic step, are associated with an autosomal-recessive form of dilated cardiomyopathy, sequence variations in pantothenate kinase 2 (PANK2) and coenzyme A synthase (COASY), the first and last enzymes of the biosynthetic pathway, are found in patients affected by rare forms of neurodegeneration with brain iron accumulation (NBIA), PKAN and CoPAN, respectively. These disorders share similar clinical features, including dystonia, parkinsonian traits, and cognitive impairment. In the most recent years, we explored the potential of the zebrafish (Danio rerio) animal model to investigate the role of these genes in neurodevelopment and elucidate the biological mechanisms leading to neurodegeneration. We generated zebrafish lines with partial or complete abrogation of pank2 and coasy function. The phenotypic characterization of pank2 morphants and mutants revealed anomalies in the development of venous vascular structures and of germinal cells. Adult fish showed testicular atrophy and altered behavioural response in an anxiety test, but no evident signs of neurodegeneration. The down-regulation of coasy expression perturbed the dorso-ventral patterning and severely altered neuronal development in zebrafish embryos; the complete disruption of coasy gene lead to larval lethality, with death occurring around 15 dpf. Mutant embryos showed a dilated heart and significant changes in lipid content, but apparently no evident signs of neurodegeneration.