Titel des Beitrags:
Mutations in APOPT1, encoding a mitochondrial protein, cause cavitating leukoencephalopathy with cytochrome c oxidase deficiency.

Abstract:
Cytochrome c oxidase (COX) deficiency is a frequent biochemical abnormality in mitochondrial disorders, but a large fraction of cases remains genetically undetermined. Whole-exome sequencing led to the identification of APOPT1 mutations in two Italian sisters and in a third Turkish individual presenting severe COX deficiency. All three subjects presented a distinctive brain MRI pattern characterized by cavitating leukodystrophy, predominantly in the posterior region of the cerebral hemispheres. We then found APOPT1 mutations in three additional unrelated children, selected on the basis of these particular MRI features. All identified mutations predicted the synthesis of severely damaged protein variants. The clinical features of the six subjects varied widely from acute neurometabolic decompensation in late infancy to subtle neurological signs, which appeared in adolescence; all presented a chronic, long-surviving clinical course. We
showed that APOPT1 is targeted to and localized within mitochondria by an N-terminal mitochondrial targeting sequence that is eventually cleaved off from the mature protein. We then showed that APOPT1 is virtually absent in fibroblasts cultured in standard conditions, but its levels increase by inhibiting the proteasome or after oxidative challenge. Mutant fibroblasts showed reduced amount of COX holocomplex and higher levels of reactive oxygen species, which both shifted toward control values by expressing a recombinant, wild-type APOPT1 cDNA. The shRNA-mediated knockdown of APOPT1 in myoblasts and fibroblasts caused dramatic decrease in cell viability. APOPT1 mutations are responsible for infantile or childhood-onset mitochondrial disease, hallmarked by the combination of profound COX deficiency with a distinctive neuroimaging presentation.