Dokumenttyp: journal article

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Titel des Beitrags: Novel (ovario) leukodystrophy related to AARS2 mutations.

Abstract: The study was focused on leukoencephalopathies of unknown cause in order to define a novel, homogeneous phenotype suggestive of a common genetic defect, based on clinical and MRI findings, and to identify the causal genetic defect shared by patients with this phenotype. Independent next-generation exome-sequencing studies were performed in 2 unrelated patients with a leukoencephalopathy. MRI findings in these patients were compared with available MRIs in a database of unclassified leukoencephalopathies; 11 patients with similar MRI abnormalities were selected. Clinical and MRI findings were investigated. Next-generation sequencing revealed compound heterozygous mutations in AARS2 encoding mitochondrial alanyl-tRNA synthetase in both patients. Functional studies in yeast confirmed the pathogenicity of the mutations in one patient. Sanger sequencing revealed AARS2 mutations in 4 of the 11 selected patients. The 6 patients with AARS2 mutations had childhood- to adulthood-onset signs of neurologic...
deterioration consisting of ataxia, spasticity, and cognitive decline with features of frontal lobe
dysfunction. MRIs showed a leukoencephalopathy with striking involvement of left-right connections,
descending tracts, and cerebellar atrophy. All female patients had ovarian failure. None of the patients
had signs of a cardiomyopathy. Mutations in AARS2 have been found in a severe form of infantile
cardiomyopathy in 2 families. We present 6 patients with a new phenotype caused by AARS2
mutations, characterized by leukoencephalopathy and, in female patients, ovarian failure, indicating
that the phenotypic spectrum associated with AARS2 variants is much wider than previously reported.