Leukoencephalopathy with thalamus and brainstem involvement and high lactate(LTBL) caused by EARS2 mutations.

In the large group of genetically undetermined infantile-onset mitochondrial encephalopathies, multiple defects of mitochondrial DNA-related respiratory-chain complexes constitute a frequent biochemical signature. In order to identify responsible genes, we used exome-next-generation sequencing in a selected cohort of patients with this biochemical signature. In an isolated patient, we found two mutant alleles for EARS2, the gene encoding mitochondrial glutamyl-tRNA synthetase. The brain magnetic resonance imaging of this patient was hallmarked by extensive symmetrical cerebral white matter abnormalities sparing the periventricular rim and symmetrical signal abnormalities of the thalami, midbrain, pons, medulla oblongata and cerebellar white matter. Proton magnetic resonance spectroscopy showed increased lactate. We matched this magnetic resonance imaging pattern with that of a cohort of 11 previously selected unrelated cases. We found mutations in the EARS2 gene in all. Subsequent detailed clinical and magnetic resonance imaging based phenotyping revealed two distinct groups: mild and severe. All 12 patients shared an infantile onset and rapidly progressive disease with severe magnetic resonance imaging
abnormalities and increased lactate in body fluids and proton magnetic resonance spectroscopy. Patients in the 'mild' group partially recovered and regained milestones in the following years with striking magnetic resonance imaging improvement and declining lactate levels, whereas those of the 'severe' group were characterized by clinical stagnation, brain atrophy on magnetic resonance imaging and persistent lactate increases. This new neurological disease, early-onset leukoencephalopathy with thalamus and brainstem involvement and high lactate, is hallmarked by unique magnetic resonance imaging features, defined by a peculiar biphasic clinical course and caused by mutations in a single gene, EARS2, expanding the list of medically relevant defects of mitochondrial DNA translation.