By way of whole-exome sequencing, we identified a homozygous missense mutation in VARS2 in one subject with microcephaly and epilepsy associated with isolated deficiency of the mitochondrial respiratory chain (MRC) complex I and compound heterozygous mutations in TARS2 in two siblings presenting with axial hypotonia and severe psychomotor delay associated with multiple MRC defects. The nucleotide variants segregated within the families, were absent in Single Nucleotide Polymorphism (SNP) databases and are predicted to be deleterious. The amount of VARS2 and TARS2 proteins and valyl-tRNA and threonyl-tRNA levels were decreased in samples of afflicted patients according to the genetic defect. Expression of the corresponding wild-type transcripts in immortalized mutant fibroblasts rescued the biochemical impairment of mitochondrial respiration and yeast modeling of the VARS2 mutation confirmed its pathogenic role. Taken together, these data demonstrate the role of the identified mutations for these mitochondriopathies. Our study reports the first mutations in the
VARS2 and TARS2 genes, which encode two mitochondrial aminoacyl-tRNA synthetases, as causes of clinically distinct, early-onset mitochondrial encephalopathies.