Heterozygous mutation in the X chromosomal NDUFA1 gene in a girl with complex I deficiency.

Abstract:
Respiratory chain enzymes consist of multiple subunits encoded either by the mitochondrial or by the nuclear genome. Recently the first X-chromosomal mutations in complex I deficient males have been described. Heterozygous female carriers did not seem to be affected. Here, we describe a girl initially presenting with mild muscular hypotonia, a moderate lactic acidosis and an increased beta-hydroxybutyrate/acetoacetate ratio. Biochemical investigations of a muscle biopsy revealed a deficiency in the amount and activity of complex I. Mutation screening of all structural subunits of complex I identified a heterozygous mutation c.94G>C, p.Gly32Arg in the X-chromosomal NDUFA1 gene. Analysis of the cDNA showed that 72% of the expressed mRNA was mutated in the muscle biopsy sample. Investigation of the X-inactivation pattern demonstrated that 74% of the paternally inherited allele was active in the muscle. This is the first report of an X-chromosomally inherited respiratory chain defect in a heterozygous female.