P-108 - NOVEL ISCA2 MUTATION IN AN ARGENTINIAN PATIENT WITH SEVERE MULTIPLE MITOCHONDRIAL DYSFUNCTION SYNDROME-4

Masotto B, Bevilaqua F, De Victor J, Solari A

Centro Nacional de Genética Médica. Buenos Aires, Argentina

**INTRODUCTION:** Multiple mitochondrial dysfunction syndrome-4 (MMDS4) is an autosomal recessive neurodegenerative disorder. Affected individuals typically attain normal development during the first months of life, presenting thereafter with progressive neurodevelopmental regression, nistagmus, optic nerve atrophy, leukoencephalopathy and biochemical abnormalities such as increased plasmatic glycine. Disease continues at a variable pace and seizures may develop. Loss of cognitive functioning and regression to a vegetative state occurs leading to death within the first years of life. **OBJECTIVE:** We report a severe and rapidly progressive case of MMDS4 with a novel variant in ISCA2. **MATERIALS AND METHODS:** Clinical assessment and detailed physical examination was realized. A complete exome sequencing (SureSelect Human All Exon V6, Agilent), mitochondrial genome sequencing (Illumina) and Sanger sequencing to confirm pathological findings, were performed using DNA isolated from a peripheral blood sample. **RESULTS:** Clinical assessment revealed a three-month-old female patient with hypotonia, apnea and gastroenteritis. Biochemical findings included metabolic acidosis and hyponatremia. Encephalic MRI showed acute ischemia. The patient was born from a healthy and non-consanguineous couple. Her parents had a previous child who died at the age of five months with similar symptomatology. In complete exome sequencing a compound heterozygous mutation in the ISCA2 gene was detected. The first variant (c.334A>G, p.Ser112Gly) was classified as pathogenic (Variation ID: 514262), according to ClinVar, Centogene and the AMCG recommendations. The second variant (c.13dup, p.Trp5Leufs*96), a frameshift mutation in exon 5, has not yet been reported in the literature. It was classified as probably pathogenic according to Centogene and the AMCG recommendations. This variant was confirmed by Sanger sequencing. Mitochondrial sequencing showed no relevant variants. **DISCUSSION:** Molecular findings confirm the diagnosis of MMDS4, even though clinical assessment revealed a more severe phenotype than previously reported in the literature. Thus, the presence of a novel frameshift mutation in ISCA2 broadens the spectrum of molecular variants associated with MMDS4.