LETTER TO THE EDITOR

Multisystem fatal infantile disease caused by a novel homozygous EARS2 mutation

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Sir, we read with great interest the report describing 12 patients presented with early onset severe neurological disease, characterized by unique MRI features of leukoencephalopathy involving the thalamus and brainstem with high lactate (LTBL; Steenweg et al., 2012). Clinically, the patients fell into two distinct groups. Four patients showed a severe progressive psychomotor regression soon after birth followed by complex irreversible neurological features, however, all patients were alive up to 7 years of age. Eight patients had mild spasticity, seizures and irritability between 6 and 12 months of life with improvement of both clinical and MRI signs in the second year. Stereotypical brain MRI appearances led to molecular diagnosis of mutations in the mitochondrial glutamyl-tRNA synthetase (EARS2) gene.

An increasing number of mutations have been identified recently in genes involved in mitochondrial protein synthesis (Smits et al., 2010; Chrzanowska-Lightowlers et al., 2011; Rotig, 2011). Most of these gene defects result in histological [cytochrome c oxidase (COX) deficient or ragged red fibres] and biochemical (multiple respiratory chain defect) abnormalities in affected organs. The clinical phenotypes are usually early-onset, severe, and often fatal diseases, implying the importance of mitochondrial translation from birth. Although some have distinguishing features (Chrzanowska-Lightowlers et al., 2011; Rotig, 2011), as a group they form an overlapping spectrum of disease. The MRI features described by Steenweg et al. (2012) in patients with EARS2 mutations add characteristic radiological features to the diagnostic armamentarium of these complex neurological disorders, allowing the clinician to target molecular genetic testing.

Here, we report a patient carrying a homozygous missense mutation in EARS2, who showed similarities to the index patient reported by Steenweg et al. (2012), but presented with a different phenotype. Unlike the patients described by Steenweg et al. (2012) presenting with isolated CNS features, the patient we describe here developed a severe infantile multisystem disease involving the brain and the liver. He was the third child of consanguineous Turkish parents and had two siblings. His mother had gestational diabetes and one sister had type I diabetes mellitus. He was born at term (4490 g), had hypospadias and incomplete cleft palate, and presented with hypotonia, failure to gain weight and lactic acidosis in the neonatal period. Cranial MRI performed in another centre at the age of 1 month revealed dysgenesis in the posterior part of corpus callosum. He did not have seizures and did not achieve any motor milestones. He developed mild elevation in liver enzymes, hepatomegaly and mild hypertrophy of cardiac interventricular septum. Peritoneal dialysis was done for lactic acidosis and he died of necrotizing bronchopneumonia at 3 months of age. Skeletal muscle biopsy showed ragged-red and ragged-blue fibres and COX deficiency (Fig. 1A). Post-mortem examination of the liver revealed hepatomegaly, severe macrovesicular steatosis with mild fibrosis and cholestasis and COX deficiency (Fig. 1A). The heart was unremarkable. Brain examination was not carried out.
A severe combined deficiency of respiratory chain complexes I and IV was detected in skeletal muscle (Fig. 1B). Genetic analysis excluded mitochondrial DNA depletion, deletions or point mutations in all three tissues. The POLG and DGUOK genes were normal. No pathogenic mutations were detected in nuclear genes encoding mitochondrial elongation factors or ribosomal proteins (EFTu, EFTs, GFM1, MRPS16) (Kemp et al., 2011).

Homozygosity mapping identified several homozygous genomic regions on several chromosomes including 1, 4, 5, 6, 8, 9, 12, 13, 16, 17, 19, 22. Exome sequencing identified two variants predicted to be pathogenic after exclusion of reported single nucleotide polymorphisms (Fig. 1C), but only the homozygous c.193A > G, p.Lys65Glu in EARS2 segregated with disease in the family (Fig. 1D). This mutation altered a conserved amino acid in a mitochondrial protein within the homozygous regions. It was absent in 126 British controls and 31 Turkish controls, and not present in the 1000 Genomes project supporting pathogenicity.

EARS2 is the newest member of an expanding group of nuclear mitochondrial disorders characterized by disturbed mitochondrial translation (Steenweg et al., 2012). Patients with mutations in translation elongation factors or mitochondrial ribosomal protein genes have a severe infantile multisystem disease (Chrzansowska-Lightowlers et al., 2011; Rotig, 2011). However, mutations in mitochondrial aminoacyl tRNA synthetases show strong tissue specificity and some gene defects affect most specifically the CNS, as exemplified by mutations in the mitochondrial aspartyl-tRNA synthetase 2 (DARS2), or arginyl tRNA synthetase 2 (RARS2) genes. Other mitochondrial tRNA synthetase gene mutations may affect different organs. The extreme variability and strict tissue specificity of the diseases caused by mutations in mitochondrial tRNA synthetase genes further illustrate the importance of understanding the factors influencing mitochondrial translation in different tissues (Chrzansowska-Lightowlers et al., 2011; Rotig, 2011).
Our case widens the clinical spectrum of EARS2 mutations by showing that in addition to CNS involvement, some patients can develop a rapidly progressive and fatal course in infancy with severe failure to thrive, intractable lactic acidosis, mitochondrial myopathy and hepatopathy, similar to mutations in mitochondrial translation elongation factors or mitochondrial ribosomal protein genes.

Although our patient had a progressive, fatal disease, most patients with EARS2 mutations showed clinical improvement with age (Steenweg et al., 2012) suggesting that an impaired function of mitochondrial tRNA{\text{Glu}}\text{C} may, similar to reversible COX deficiency myopathy (Horvath et al., 2009), may be a link with reversible disease.

We suggest that similar developmentally regulated tissue specific factors may contribute to the disease pathomechanism. Future work is needed to explore these mechanisms, which will provide a better understanding of the compensatory factors and may offer important clues towards molecular therapies.

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**References**


