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Short communication

Progressive mitochondrial myopathy, deafness, and sporadic seizures associated with a novel mutation in the mitochondrial tRNASer$^{(AGY)}$ gene

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ABSTRACT

We sequenced the mitochondrial genome from a patient with progressive mitochondrial myopathy associated with deafness, sporadic seizures, and histological and biochemical features of mitochondrial respiratory chain dysfunction. Direct sequencing showed a heteroplasmic mutation at nucleotide 12262 in the tRNASer$^{(AGY)}$ gene. RFLP analysis confirmed that 63% of muscle mtDNA harboured the mutation, while it was absent in all the other tissues. The mutation is predicted to influence the functional behaviour of the aminoacyl acceptor stem of the tRNA. Several point mutations on mitochondrial tRNA genes have been reported in patients affected by encephalomyopathies, but between them only four were reported for tRNASer$^{(AGY)}$.

1. Introduction

Mitochondrial DNA (mtDNA) mutations are important causes of human genetic diseases and are associated with an impressive spectrum of different clinical presentations [1]. Tissues heavily reliant on oxidative metabolism, such as skeletal muscle, brain and heart, are the most affected. However, virtually any organ or tissue in the body may be affected and the disorders can be multisystemic (mitochondrial encephalomyopathies) or confined to a single tissue [2].

To date, more than 200 pathogenic mtDNA mutations have been identified, with mutations involving tRNA appearing to be the most common (http://www.mitomap.org). This can be explained by the essential role of tRNAs in the synthesis of proteins involved in energy metabolism. Interestingly, some tRNAs appear preferentially to be affected, for example, the tRNA for leucine(UUR), lysine, and isoleucine. Mutations in the other tRNA genes are more rarely reported in mitochondrial disorders [3]. In particular, the tRNA for serine(AGY) gene is one of the less affected, with only four mutations reported as pathogenic.

Here we report an adult patient with progressive mitochondrial myopathy associated with deafness, sporadic seizures, EEG changes and periventricular white matter abnormalities at MRI. Morphological, biochemical and molecular studies led us to identify a novel heteroplasmic mutation in the mitochondrial tRNA$^{Ser(AGY)}$ gene.

2. Case report

The patient, a 58-year-old woman was born from healthy unrelated parents. The medical family history was negative for genetic disorders. She was admitted to our hospital for weakness and elevation of serum creatine kinase (>1000 UI/l, n.v. <140). Previous clinical data suggested hypothyroidism, arterial hypertension, Q–T interval prolongation, and sporadic seizures from the age of 53. Neurological examination revealed bilateral muscle weakness and hypotrophy of upper limbs. Venous lactic acid was lightly increased (1.6 mmoli/l; normal value: 0.3–1.3 mmol/l); audiometric examination revealed mild neurosensorial deafness; EEG showed slow left temporal focal activity, with spike-waves abnormalities. EMG showed myopatic pattern. Brain Magnetic Resonance Imaging (MRI) revealed hyperintense T2 signal in the cerebral white matter bilaterally (Fig. 1a). Echocardiography evidenced mitral valve prolapse, resulting in moderate degree of valvular insufficiency. A muscle biopsy was performed showing cytochrome c oxidase (COX) deficiency and 6% of ragged-red fibres (Fig. 1b–d). Muscle biochemical analysis [4] revealed deficiency of complex I and IV of the respiratory chain (Fig. 2a). The muscle biopsy of the only patient's son was histochemically and biochemically normal.

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