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LETTER TO THE EDITOR

Sporadic PEO caused by a novel POLG variation and a Twinkle mutation: digenic inheritance?

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Abstract Progressive external ophthalmoplegia (PEO) with multiple deletions of mitochondrial DNA (mtDNA) is associated with several mutations in nuclear genes. They include *POLG*, *POLG2*, *ANT1*, *C10orf2/Twinkle*, and *OPA1*. However, digenic inheritance in mitochondrial disorders has been documented in a few cases over the years. Here we describe an 80-year-old man with sporadic PEO associated with mtDNA deletions. Sequencing of the *POLG* revealed a novel heterozygous mutation (c.2831A>G; p.Glu944Gly), predicted in silico as damaging, in the patient who also carried a heterozygous mutation in *C10orf2/Twinkle* (c.1142T>C; p.Leu381Pro). This case provides a second report of a PEO with different mutations in the *POLG* and *C10orf2/Twinkle* genes, supporting the hypothesis that the PEO phenotype can be determined by the co-existence of two abnormalities in separate genes, both involved in the maintenance and stability of mtDNA. Finally, this study expands the spectrum of POLG mutations and highlights the need to sequence the whole set of nuclear genes associated with PEO and multiple mtDNA deletions.

Keywords PEO · *POLG* gene · *C10orf2/Twinkle* gene · Digenic disorder

Progressive external ophthalmoplegia (PEO) with multiple mitochondrial DNA (mtDNA) deletions has been associated with mutations in nuclear genes as *POLG*, *POLG2, ANT1*, *C10orf2/Twinkle* and *OPA1* [1].

However, digenic inheritance in mitochondrial disorders has been documented in a few cases over the years.

Here, we report a patient with sporadic PEO, multiple mtDNA deletions and a novel *POLG* substitution co-occurring with a *C10orf2/Twinkle* mutation.

The patient, a 80-year-old male, was referred to us due to a bilateral ptosis appeared since the age of 70 years associated 2 years later with dysphagia. He was born from non-consanguineous parents with a family history negative for neurological diseases. He had a healthy son of 50 years of age.

Neurological examination showed short stature, severe bilateral ptosis with ophthalmoplegia and reduced deep tendon reflexes in all extremities. There was no evidence of muscle weakness. He had normal liver, renal, thyroid functions, electrolytes, sedimentation rate, and creatine kinase. Acetylcholine receptor antibodies and serum lactic acid were within normal limits. Electromyography (EMG) and peripheral nerves conduction velocities were in the normal range. Brain magnetic resonance imaging (MRI) showed diffuse white matter abnormalities, related to subcortical vascular changes. Echocardiogram revealed mild mitral and tricuspid insufficiency.

After obtaining the patient's informed consent, muscle biopsy and genetic analyses were performed.

Muscle biopsy showed mild variation in fiber size, and about 5 % cytochrome *c* oxidase (COX) negative fibers whereas modified trichrome staining did not reveal ragged red fibers (Fig. 1a). Ultrastructural examination showed lipofuscin deposits.

Long range PCR analysis of muscle DNA showed multiple mtDNA deletions (Fig. 1b).

We identified a heterozygous novel mutation in *POLG* (c.2831A>G in exon 18), corresponding with p.Glu944Gly

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