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Case report

# A novel de novo mutation of the mitochondrial tRNA$^{lys}$ gene mt.8340G>A associated with pure myopathy

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**Abstract**

Most patients with mutations in the tRNA$^{lys}$ gene (*MTTK*) present with symptoms from the central nervous system (CNS). We describe a 41-year-old woman with pure myopathy associated with a novel de novo mtDNA mutation, mt.8340G>A, which was heteroplasmic in muscle (53%), blood, urine and mouth epithelial cells (<7%). No other family members, including her mother, carried the mutation. She presented with exercise intolerance from age 9, and since age 20 she experienced ptosis and reduced ocular motility. A muscle biopsy revealed ragged red fibres (10%), no COX negative fibres, and many fibres with central nuclei (30%), indicating ongoing damage and repair. The present case expands the mutational and phenotypic spectrum of diseases associated with mutations in *MTTK*.
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*Keywords:* Novel mutation; Mitochondrial DNA; *MTTK* gene; tRNA$^{lys}$

## 1. Introduction

Almost 75% of the known disease-causing mtDNA mutations are located in the mitochondrial transfer RNA (tRNA) genes [1]. Mutations in mtDNA are generally associated with a high variability in phenotype, even among patients harbouring the same genotype [2]. Especially the common mt.3243A>G point mutation in the tRNA leucine (leu) gene can cause a highly variable phenotype, ranging from pure myopathy to the multisystemic mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) [3]. However, another common mutation in mtDNA, the mt.8344A>G point mutation in the tRNA lysine (lys) gene (*MTTK*) has generally been associated with mainly two different phenotypes; one leading to myoclonic epilepsy and ragged red fibres (MERRF), and second rare form leading to lipomas with or without CNS involvement [4]. At present, 17 different mtDNA mutations in the *MTTK* have been reported [1]. Most of these patients presented with CNS symptoms (ataxia, myoclonus and/or epilepsy). Only three patients with sporadic mutations of *MTTK* have been reported to have pure myopathic symptoms [5–7]. In this study, we present a patient with a novel de novo mtDNA mutation located at position mt.8340A>G, who presented with pure myopathic symptoms of exercise intolerance, limb weakness and chronic progressive external ophthalmoplegia (CPEO).

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## 2. Methods

### 2.1. Subjects

The patient, a 41 year-old woman, had a history of CPEO since age 20, limb weakness for approximately 10 years and exercise intolerance since age 9. She could not participate in gym classes during childhood, she had not been able to ride a bicycle since her 20ties and at the time of examination she had problems walking more than 500 m, walking stairs, and doing household keeping. She was trained as a dental assistant, but had to stop any kind of employment at age 20 because of physical exhaustion, and received early retirement benefits from that age. She had no cognitive dysfunction and had never experienced other symptoms, including CNS symptoms such as ataxia and epilepsy and she had never experience problems with hearing or vision. None of the proband's closest family members had any neurological symptoms.

### 2.2. Genetic investigations and health status of family members

The proband had a full neurological examination, including ophthalmoscopy. Muscle strength was assessed manually, using the MRC scale from 0 to 5.

Tissue samples were taken from blood, muscle, buccal swap and urine and DNA was isolated from sediments using the QIAamp system according to the manufacture's description (Qiagen). When the mtDNA mutation was found in the patient, she contacted the closest family members. Her mother, brother, a maternal aunt, two children of a deceased maternal aunt subsequently contacted us for genetic counselling. After this, everybody except the proband's sibling, requested further diagnostic work-up and like the proband, they had a full neurological examination and ophthalmoscopy performed (Pedigree Fig. 1A). Furthermore, they had a needle biopsy performed in the vastus lateralis muscle for genetic and muscle morphology investigations, and had tissue samples taken from blood, buccal and urine mucosa for mtDNA mutation analysis. The proband's brother reported no symptoms indicating mitochondrial dysfunction. One of the mother's two sisters had died from a melanoma 20 years earlier, but she was described as healthy otherwise.

In the proband, single muscle fibres were isolated from 10 μm thick sections after staining with COX and SDH in adjacent serially cut sections. The patient did not have any COX negative fibres, but multiple ragged blue fibres (RBF) indicating accumulation of mitochondria (Fig. 2B). From a SDH stained muscle section, four normally appearing muscle cells and four with RBF were cut out using a laser capture, microdissection system (Olympus CellCut IX71, Japan). Each fibre was analysed separately. DNA was extracted by the Arcturus PicoPure DNA extraction kit according to the instruction given by the manufacture (Applied Biosystems, Denmark). mtDNA mutation load was determined in each fibre from sequencing traces with Mutation Surveyor Quantify Software (SoftGenetics, PA).

### 2.3. Muscle morphology, mitochondrial enzyme activity, cycle ergometry, neurophysiological examination and echocardiography

The number of RBF, COX-negative fibres, fibres containing excessive amounts of lipid droplets in the cytoplasm, centrally nucleated fibres (CNF), and apoptotic nuclei were assessed in full muscle sections (~700 fibres). Mitochondrial enzyme activities in muscle of complexes I–IV and citrate synthase (CS) were measured as described previously [8]. Maximal oxidative capacity ($VO_{2max}$) and peak exercise-induced plasma lactate levels were determined by an incremental cycle test to exhaustion in the patient and family members [8]. Electroneurography of the lower legs and echocardiography were performed in the patient, using standard methods. Since the patient had no neurological symptoms, besides the myopathic ones, no auditory-, VEP- or EEG tests were performed.

### 2.4. Blood samples and glucose tolerance test

Plasma levels of electrolytes, creatinine, creatine kinase, thyroid gland hormones, and liver enzymes were assessed in the proband.

Potential glucose intolerance or diabetes mellitus in the proband and family members were assessed by measuring plasma glucose levels before and two hours after ingesting a standardised load of glucose following an overnight fast.

## 3. Results

### 3.1. Clinical findings

The proband presented with a slim figure (51 kg and 165 cm), but no overt muscle wasting. The muscle strength was 4 in all limb muscle, except shoulder and hip muscles (strength 3), and finger, wrist, ankle and toe (strength 4+). She also had facial weakness (strength 3+ to 4). The patient had ophthalmoplegia with moderate affection of the eye muscles and ptosis with eyelids covering 1/3 of the pupils. The rest of her neurological examination was normal; in particular there was normotonia, no signs of limb or facial fasciculations and normal tendon reflexes. All family members had a normal neurological examination.

### 3.2. Genetic investigations

Genetic investigation of the mtDNA revealed a novel mt.8340G>A mtDNA point mutation in the *MTTK* in the muscle of the proband (Fig. 2A and 2C). The average mtDNA mutation load in muscle was 53% (Fig. 1A). The

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