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Short communication

# *POLG* mutation in a patient with cataracts, early-onset distal muscle weakness and atrophy, ovarian dysgenesis and 3-methylglutaconic aciduria

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ABSTRACT

Mutations in *POLG* account for one of the most frequent nuclear encoded causes of mitochondrial disorders to date. Individuals harboring *POLG* mutations exhibit fairly heterogeneous clinical presentations leading to increasing difficulties in classifying these patients into defined clinical phenotypes. This study aims to investigate the molecular basis of a mitochondrial cytopathy in a patient with 3-methylglutaconic aciduria and to expand the clinical phenotype associated with *POLG* mutations.

Clinical, molecular and genetic analyses as well as neurophysiological examinations were carried out for a 23-year-old woman of mixed Caucasian and Latin American ancestry with a history of cataracts diagnosed at age 1year, she had onset of distal muscle weakness at age 2years progressing to atrophy and ovarian dysgenesis at puberty. The patient was found to have 3-methylglutaconic acid with normal 3 hydroxyisovaleric acid on urine organic acid analysis. *POLG* sequencing was done and a heterozygous variant, c.2851T>A (p.Y951N) was found which is predicted to be deleterious. There are limited reports of *POLG* mutations in individuals with 3-methylglutaconic aciduria. This case report of a young woman with a heterozygous mutation in *POLG*, presenting with muscle weakness and atrophy at a young age aims to aid clinicians in similar challenging diagnostic situations as well as enhances our understanding of *POLG*-related disease phenotypes.

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## 1. Introduction

Human mitochondrial DNA (mtDNA) is continuously replicated in dividing cells and postmitotic tissues by the nuclear-encoded DNA polymerase gamma (POLG). POLG is the sole mtDNA polymerase and plays a major role in maintaining mtDNA integrity (Milone and Massie, 2010). POLG is a heterotrimer and consists of a catalytic subunit (p140) and 2 smaller identical accessory subunits (p55). The catalytic subunit is encoded by *POLG*, whereas the accessory subunits are encoded by *POLG2*. *POLG* maps to 15q25 and *POLG2* maps to 17q21. The catalytic subunit plays a critical role since it contains both polymerase and proofreading exonuclease activities (Longley et al., 2001). Mutations in *POLG* represent the most common causes of autosomally inherited mitochondrial diseases in children and adults (Wong et al., 2008). The first mutation in *POLG* was discovered in 2001 in a Belgian family with Progressive External Ophthalmoplegia (PEO) (Van Goethem et al., 2001). The phenotype of patients with *POLG* mutations is often heterogeneous and, as observed in other mitochondrial disorders, may lead to involvement of several organ systems. The reported *POLG* mutations are inherited either in an autosomal recessive or autosomal dominant manner (DiMauro et al., 2006; Horvath et al., 2006). Diagnosis in a clinical setting may pose a challenge to clinicians and molecular testing including sequencing of *POLG* in suspected cases can help to reach a diagnosis and institute proper counseling. In this report we present an adult patient with a complicated medical history where multiple evaluations had failed to arrive at a diagnosis until a novel *POLG* mutation, briefly described in an earlier paper by Tang et al. (2011) was found. The clinical presentation of this patient and its association with a *POLG* mutation will add to our current knowledge and understanding of *POLG*-related disease phenotypes.

*Abbreviations:* POLG, Polymerase gamma; MRI, Magnetic resonance imaging; EKG, Electrocardiogram; EEG, Electroencephalogram; GALT, Galactose-1-phosphate uridyltransferase; ***GJB1***, Gap junction beta-1; ***MPZ***, Myelin protein zero; DNA, Deoxyribose nucleic acid; STR, Short tandem repeat; SIFT, Sort Intolerant from Tolerant.

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## 2. Subject and methods

### 2.1. Study subject

A 23-year-old woman of mixed Caucasian and Mexican descent was evaluated in the Adult Genetics clinic for a history of bilateral cataracts, ovarian dysgenesis and distal muscle weakness and atrophy. Several studies including genetic testing were undertaken over a period of several years to determine a diagnosis, until a final diagnosis was reached that explained her presentation.

### 2.2. Non-genetic investigations

At age 18years, she had a syncopal episode at school and underwent a diagnostic work-up that included an echocardiogram, EKG, cardiac MRI, brain MRI without contrast and EEG. At age 19years, due to progressive muscle weakness, electromyogram (EMG) and nerve conduction velocities (NCV) were carried out. Based on those results, a skeletal muscle biopsy was undertaken to understand the muscular atrophy. In the Genetics clinic, biochemical testing was sent for acylcarnitine analysis, plasma amino acids, urine organic acids, lactic acid levels, liver function tests and basic metabolic panel. An echocardiogram to determine structural anomalies of the heart was also ordered. A galactose 1-phosphate level was also obtained to rule out GALT deficiency due to the history of bilateral cataracts, ovarian dysgenesis and neurological compromise.

### 2.3. Genetic testing

DNA tests for spinal muscular atrophy and myotonic dystrophy were sent. Sequencing of *GJB1* and *MPZ* was also performed as part of the evaluation for Charcot–Marie Tooth disease. An oligonucleotide-based chromosomal microarray analysis to rule out genomic copy number variants was sent. Based on her overall clinical picture at age 23years, it was decided to pursue a work-up for mitochondrial disease. Since mutations in *POLG* are associated with variable presentations that include but are not limited to encephalopathy, parkinsonism, stroke-like episodes, exercise intolerance, ataxia–neuropathy and PEO (progressive external ophthalmoplegia) and limb myopathy, *POLG* sequencing was pursued. Subsequently, MitoMet array (copy number analysis of metabolic and mitochondrial related genes) was also performed to evaluate for deletions in the *POLG* gene.

## 3. Results

### 3.1. Clinical history of the subject

The subject was healthy at birth with no significant problems during the first year of life. At the age of 1year, she developed vision problems and was found to have bilateral cataracts which were removed. At the age of 2years, she manifested increasing difficulties with motor movements of both hands that led to delayed fine motor skills which continued to progress, leading to the inability to use both of her hands, with consequent atrophy of arm and hand muscles. At the age of 16years she had a gynecological evaluation due to absent menarche which resulted in the diagnosis of ovarian dysgenesis. Hormone replacement therapy was initiated with appropriate response. At the age of 18years, she had a syncopal episode at school. At the age of 23years, she presented with a seizure like episode of unknown etiology. The episode consisted of generalized tonic–clonic convulsions without loss of bowel or bladder continence or tongue bite; however, she developed post-ictal confusion. Two months later, she was evaluated at the Adult Genetics clinic. At that time, she was attending college and exhibited an intact cognitive function. Family history was non-contributory for any history of similar conditions. The patient has one sibling, a 24year old brother, who was diagnosed with depression.

### 3.2. Clinical findings in the subject on physical examination (see Supplemental figure online)

The patient was a thin young woman with a height of 170.2cm (75th–90th percentile) and a weight of 53.9kg (25th percentile). She had remarkable atrophy of arm and hand muscles but no facial dysmorphic features. Pupils were irregular and sluggish bilaterally. On neurological examination she was alert and oriented. There were no cranial nerve deficits and her coordination was normal. There was severe atrophy of arm and hand muscles including biceps, triceps, forearm and hands with claw hand deformity and digitalization of the thumbs. However, deltoid muscles had normal bulk and tone. Lower extremities were diffusely thin and feet arches were normal. Motor examination in upper extremities revealed her power to be 0/5 at wrist flexors and extensors, hand and forearm and 0/5 at biceps; however, it was 5/5 at deltoid muscles and 3/5 at triceps. At the lower extremities, her power was 5/5 in proximal muscles including hip flexors, quadriceps and hamstrings and 4/5 at tibialis anterior. She displayed absent reflexes in upper extremities, whereas her lower extremities had normal symmetric reflexes at knees and ankles. The rest of the examination was unremarkable.

### 3.3. Results of non-genetic investigations

Echocardiogram, EKG, cardiac MRI, brain MRI without contrast and EEG done at the age of 18years did not detect any abnormalities. NCV revealed diffusely decreased amplitude of compound motor action potentials with otherwise normal motor and sensory responses including sural responses. EMG revealed mixed short and long duration motor unit potentials with normal firing frequency suggestive of a chronic myopathic process affecting the distal muscles although the pattern could also be seen in patients with chronic neurogenic conditions. Skeletal muscle biopsy revealed severe myofiber degeneration and on electron microscopy there was evidence of end stage muscle disease that precluded interpretation.

Urine organic acid analysis showed presence of 3-methylglutaconic acid with normal 3 hydroxyisovaleric acid excluding the possibility of 3-methylglutaconic aciduria type I. All other biochemical tests were normal.

### 3.4. Results of genetic testing

*POLG* sequencing revealed a heterozygous variant, c.2851T>A (p.Y951N). Mitomet array was normal excluding a deletion on the other *POLG* allele. Neither parent carried the c.2851T>A (p.Y951N) *POLG* variant. As there are reports of multiple mtDNA deletions in both dominant and recessive forms of *POLG1*[1], a repeat muscle biopsy was considered to look for deletions and to characterize the muscle involvement better. However, the patient declined a repeat biopsy.

All other genetic tests were normal.

## 4. Discussion

The clinical presentation associated with *POLG* mutations is very heterogeneous. The different clinical phenotypes include: 1) Alpers syndrome 2) PEO with or without Limb Myopathy 3) PEO, Parkinsonism, and Early Menopause 4) Ataxia Neuropathy Spectrum (ANS) disorders 5) Myocerebrohepatopathy Spectrum disorders (MCHS) and 6) Myoclonus Epilepsy Myopathy Sensory Ataxia (MEMSA) (Wong et al., 2008). In this report we describe a 23-year-old woman with cataracts, ovarian dysgenesis and early-onset distal muscle weakness. This patient does not fit into any of the prior classifications although there are some similarities with the phenotypes reported previously.