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Observation

September 2010

**Isolated Distal Myopathy of the Upper Limbs Associated With Mitochondrial DNA Depletion and Polymerase γ Mutations**

[Carla Giordano, MD, PhD](https://jamanetwork.com/searchresults?author=Carla+Giordano&q=Carla+Giordano); [Floriana Pichiorri, MD](https://jamanetwork.com/searchresults?author=Floriana+Pichiorri&q=Floriana+Pichiorri); [Emma L. Blakely, PhD](https://jamanetwork.com/searchresults?author=Emma+L.+Blakely&q=Emma+L.+Blakely); et al [Elena Perli, BSc](https://jamanetwork.com/searchresults?author=Elena+Perli&q=Elena+Perli); [Maurizia Orlandi, BSc](https://jamanetwork.com/searchresults?author=Maurizia+Orlandi&q=Maurizia+Orlandi); [Pietro Gallo, MD](https://jamanetwork.com/searchresults?author=Pietro+Gallo&q=Pietro+Gallo); [Robert W. Taylor, PhD, FRCPath](https://jamanetwork.com/searchresults?author=Robert+W.+Taylor&q=Robert+W.+Taylor); [Maurizio Inghilleri, MD](https://jamanetwork.com/searchresults?author=Maurizio+Inghilleri&q=Maurizio+Inghilleri); [Giulia d’Amati, MD, PhD](https://jamanetwork.com/searchresults?author=Giulia+d%e2%80%99Amati&q=Giulia+d%e2%80%99Amati)

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Abstract

**Objective**  To describe an unusual clinical phenotype in an adult harboring 2 compound heterozygous polymerase γ (*POLG*) mutations.

**Design**  Case report.

**Setting**  University-based outpatient neurology clinic and pathology and genetics laboratory.

**Patient**  A 27-year-old man presenting with isolated distal myopathy of the upper extremities in the absence of sensory disturbances.

**Results**  Histochemical analysis of a muscle biopsy specimen showed numerous cytochrome c oxidase–deficient fibers. Molecular analysis revealed marked depletion of muscle mitochondrial DNA in the absence of multiple mitochondrial DNA deletions. Sequence analysis of the *POLG* gene revealed heterozygous sequence variants in compound c.1156C>T (p.R386C) and c.2794C>T (p.H932Y) segregating with clinical disease in the family. The p.R386C change appears to be a novel mutation.

**Conclusion**  Our case broadens the phenotypic spectrum of disorders associated with *POLG* mutations and highlights the complex relationship between genotype and phenotype in *POLG*-related disease.

Mutations in the catalytic subunit of the mitochondrial DNA (mtDNA) polymerase γ gene (*POLG*) are associated with a variety of disorders characterized by secondary defects of the mitochondrial genome and respiratory chain dysfunction.[1](https://jamanetwork.com/journals/jamaneurology/fullarticle/801106#ref-nob90025-1) The phenotypic spectrum of *POLG*-related disease is extremely heterogeneous, ranging from late-onset progressive external ophthalmoplegia with multiple mtDNA deletions (OMIM [157640](https://omim.org/entry/157640)) to fatal infantile disorders, such as the Alpers-Huttenlocher syndrome, usually associated with profound mtDNA depletion in affected tissues.[2](https://jamanetwork.com/journals/jamaneurology/fullarticle/801106#ref-nob90025-2),[3](https://jamanetwork.com/journals/jamaneurology/fullarticle/801106#ref-nob90025-3) Herein, we describe the unusual association of distal myopathy of the upper limbs and marked mtDNA depletion in skeletal muscle of an adult patient due to compound heterozygous mutations in *POLG*.

Report of a case

Case

A 27-year-old man born to nonconsanguineous parents presented with a 3-year history of progressive weakness of the distal upper limbs in the absence of sensory disturbances. He used to be an amateur tennis player but had to stop this activity on account of his reduced muscle strength. He reported normal motor development and there was no family history suggestive of neuromuscular disease. Clinical examination showed asymmetric, moderate weakness of wrist extension (Medical Research Council Scale score 3/5 on the right side and 4/5 on the left) and elbow flexion and finger extension (Medical Research Council Scale score 4/5). There was no muscle atrophy. Deep tendon reflexes were reduced in the upper extremities, corresponding with strength reduction. Muscle strength of the lower extremities was normal, and he had no evidence of ptosis or external ophthalmoplegia. His creatine kinase level was mildly increased (396 U/L; reference range, 22-269 U/L [to convert to microkatals per liter, multiply by 0.0167]), whereas his serum lactate level was normal (17.02 mg/dL; reference range, 4.5-20 mg/dL [to convert to millimoles per liter, multiply by 0.111]). Radial, ulnar, and posterior tibialis nerve conduction studies were performed to rule out motor neuropathies and results were repeatedly normal. Electromyography consistently showed myopathic features characterized by early interference pattern and small polyphasic motor unit potentials in the biceps brachii, wrist extensors, and finger extensors bilaterally, although no electromyography abnormalities were observed in the trunk or lower limb muscles. Renal and hepatic profiles and thyroid, pancreatic, and cardiac function were all unremarkable. He subsequently underwent an open biopsy of the deltoid muscle for diagnostic purposes.

Analysis

Standard histological and histochemical analyses were performed on fresh frozen muscle sections (10 μm). Total DNA was extracted from blood and whole-muscle homogenates by standard procedures. Single cytochrome c oxidase (COX)–positive and COX-deficient skeletal muscle cells were separately obtained by laser-capturing microdissection with the MMI UV-CUT System (Nikon Instruments, Kingston, England).[4](https://jamanetwork.com/journals/jamaneurology/fullarticle/801106#ref-nob90025-4) The total amount of mtDNA was measured by quantitative real-time polymerase chain reaction, as previously described.[5](https://jamanetwork.com/journals/jamaneurology/fullarticle/801106#ref-nob90025-5) Briefly, an mtDNA fragment (nucleotide 4625-4714) and a nuclear DNA fragment (*FasL* gene) were coamplified using a multiplex TaqMan polymerase chain reaction assay (Invitrogen, Life Technologies, Parsley, England). For each assay, a standard curve for mtDNA and nuclear DNA was generated using serial dilutions of a vector (kind gift from Andrea Cossarizza, MD, PhD) in which the regions used as the template for the 2 amplifications were cloned tail to tail to have a ratio of 1:1 of the reference molecules. The absolute mtDNA copy number per nucleus was obtained by multiplying the ratio of mtDNA to nuclear DNA values by 2 (because 2 copies of the nuclear gene are present in a cell). Screening for mtDNA large-scale rearrangements was carried out by real-time polymerase chain reaction[6](https://jamanetwork.com/journals/jamaneurology/fullarticle/801106#ref-nob90025-6) and conventional polymerase chain reaction using shifted primer sets within the major arc of human mtDNA[7](https://jamanetwork.com/journals/jamaneurology/fullarticle/801106#ref-nob90025-7) both on muscle homogenate DNA and on microdissected cells. The entire coding region and intron-exon boundaries of *POLG* were amplified and directly sequenced as previously reported.[1](https://jamanetwork.com/journals/jamaneurology/fullarticle/801106#ref-nob90025-1)

Results

Histological analysis of the muscle biopsy specimen revealed a mild variation in fiber size with scattered, isolated atrophic fibers ([Figure](https://jamanetwork.com/journals/jamaneurology/fullarticle/801106#nob90025f1), A). Oxidative enzyme histochemical analysis showed numerous COX-deficient muscle fibers, many showing subsarcolemmal accumulation of mitochondria, consistent with a mitochondrial myopathy ([Figure](https://jamanetwork.com/journals/jamaneurology/fullarticle/801106#nob90025f1), B). Molecular analysis of muscle homogenate mtDNA revealed marked mtDNA depletion (up to 93% decreased compared with age-matched controls) ([Figure](https://jamanetwork.com/journals/jamaneurology/fullarticle/801106#nob90025f1), C) while a screen for mtDNA rearrangements both on muscle homogenate and within-individual COX-positive and COX-deficient muscle fibers excluded large-scale mtDNA deletions (data not shown). Sequence analysis of *POLG* revealed heterozygous missense mutations in compound c.1156C>T in exon 5 predicting p.R386C and c.2794C>T in exon 18 predicting p.H932Y, a recognized pathogenic mutation (<http://tools.niehs.nih.gov/polg/>) ([Figure](https://jamanetwork.com/journals/jamaneurology/fullarticle/801106#nob90025f1), D). The p.R386C mutation is a novel mutation affecting a highly conserved arginine residue within the linker region of the POLG protein. Sequencing of parental samples confirmed recessive inheritance of both mutated alleles, while analysis of the patient's clinically unaffected sister (23 years of age) revealed she was a heterozygous carrier of the p.H932Y mutation, which had been inherited from the mother (data not shown).

Figure.

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Morphologic and molecular analysis. A, Histologic analysis of the muscle biopsy specimen showing variation in fiber size with evidence of hypotrophic fibers (arrows) (hematoxylin-eosin, original magnification ×10). B, Sequential cytochrome c oxidase/succinate dehydrogenase histochemical analysis of the skeletal muscle biopsy specimen showing numerous cytochrome c oxidase–deficient (blue-stained) muscle fibers with evidence of mitochondrial proliferation. C, Quantitative real-time polymerase chain reaction evaluation of the total mitochondrial DNA (mtDNA) amount in muscle homogenate DNA from the patient and age-matched controls (n = 5). As a positive control for this assay, we also show the loss of muscle mtDNA copy number in a patient with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) syndrome. D, Sequencing electropherograms demonstrating the 2 heterozygous *POLG* mutations identified in compound in the patient.

Comment

We describe an unusual phenotype characterized by the association of isolated distal myopathy of the upper limbs and profound muscle mtDNA depletion in an adult patient harboring compound heterozygous *POLG* mutations. The p.H932Y mutation resides within the polymerase domain of the POLG protein and has been reported as a pathogenic recessive mutation in patients with progressive external ophthalmoplegia and the sensory ataxic neuropathy, dysarthria, and ophthalmoparesis phenotype (in compound with another mutation).[8](https://jamanetwork.com/journals/jamaneurology/fullarticle/801106#ref-nob90025-8),[9](https://jamanetwork.com/journals/jamaneurology/fullarticle/801106#ref-nob90025-9) The p.R386C change is predicted to alter the highly conserved arginine 386 to cysteine in the linker region of the POLG protein and appears to be novel. Neither mutation caused disease in heterozygous relatives, while in compound they were associated with marked mtDNA depletion in muscle without evidence of multiple mtDNA deletions. In spite of this profound mtDNA depletion, several muscle fibers retained COX activity on muscle biopsy specimen and the clinical presentation was in adulthood with a very mild clinical phenotype. Additionally, the distribution of affected muscles in our patient is very different from the typical pattern of muscle involvement in mitochondrial myopathies, where many patients have a proximal muscle weakness eventually associated with exercise intolerance or present with progressive external ophthalmoplegia and ptosis due to involvement of the extraocular muscles.

The occurrence of marked mtDNA depletion is well described in patients harboring *POLG* mutations; however, this usually occurs in the context of severe early-onset disorders such as Alpers-Huttenlocher syndrome or multisystem disorders without liver failure.[3](https://jamanetwork.com/journals/jamaneurology/fullarticle/801106#ref-nob90025-3) Patients with milder *POLG*-associated phenotypes, such as the autosomal dominant or recessive progressive external ophthalmoplegia, more often present with multiple mtDNA deletions in skeletal muscle,[3](https://jamanetwork.com/journals/jamaneurology/fullarticle/801106#ref-nob90025-3) although the occurrence of both deletions and depletion in skeletal muscle has been reported.[10](https://jamanetwork.com/journals/jamaneurology/fullarticle/801106#ref-nob90025-10) In this context, our case is peculiar as it broadens the phenotypic spectrum of *POLG*-related disease yet further and highlights the very complex relationship between genotype and phenotype in mitochondrial genetic disorders.

**Correspondence:** Giulia d’Amati, MD, PhD, Department of Experimental Pathology, Section of Pathology, Sapienza University, Policlinico Umberto I, Viale Regina Elena 324, 00161 Roma, Italy ([giulia.damati@uniroma1.it](mailto:giulia.damati@uniroma1.it)).

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**Author Contributions:***Study concept and design*: Giordano, Taylor, and d’Amati. *Acquisition of data*: Pichiorri, Blakely, Orlandi, Perli, and Inghilleri. *Analysis and interpretation of data*: Giordano, Pichiorri, Blakely, Orlandi, Gallo, Perli, Taylor, Inghilleri, and d’Amati. *Drafting of the manuscript*: Giordano, Pichiorri, Blakely, Orlandi, Gallo, Perli, Taylor, Inghilleri, and d’Amati. *Critical revision of the manuscript for important intellectual content*: Giordano, Pichiorri, Taylor, Inghilleri, and d’Amati. *Administrative, technical, and material support*: Gallo. *Study supervision*: Giordano and d’Amati.

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