



Received: 23-09-2026
Accepted: 03-10-2026

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

Letter to the Editor

Carriers of POLG1 Variants Require a Comprehensive Genetic and Clinical Examination

Josef Finsterer

Neurology & Neurophysiology Center, Vienna, Austria

Corresponding Author: **Josef Finsterer**

Letter to the Editor

We read with interest the article by Melo *et al.* about a 41-year-old man of African descent with an ataxia-neuropathy spectrum disorder due to the known homozygous variant c.2243G>C in the POLG1 gene ^[1]. The variant manifested phenotypically with ophthalmoparesis, cerebellar ataxia, and axonal neuropathy, with only a slight worsening of symptoms during a two-year follow-up ^[1]. The patient was identified as the first person of African descent with a mutation known as a European founder mutation ^[1]. The study is noteworthy, but some points require discussion.

First, an mtDNA depletion syndrome cannot be diagnosed solely by detecting a POLG1 variant. Since mtDNA depletion is characterized by a reduction in the number of mtDNA copies in the mitochondria, this reduction must be demonstrated. The method of choice for detecting a reduced mtDNA copy number is quantitative PCR ^[2]. Was quantitative PCR performed on the index patient, and was the mtDNA copy number indeed reduced?

Secondly, the mitochondrial DNA (mtDNA) of the index patient was not sequenced ^[1]. Since POLG1 mutations cause secondary mtDNA rearrangements, particularly multiple mtDNA deletions ^[3], long-range PCR or real-time quantitative PCR would have been essential.

Thirdly, none of the first-degree relatives were tested for the index patient's mutation ^[1]. To determine whether the variant was inherited or arose *de novo*, it would have been essential to test the father and mother, as well as the six siblings and their children, for the POLG1 variant. Knowledge of the segregation pattern is crucial not only for genetic counseling but also for assessing potential phenotypic heterogeneity within the family. Furthermore, it should be reported whether any of the six living siblings exhibit clinical features of a mitochondrial disease.

The fourth point concerns the discrepancy between the statement in the case description that the patient's grandfather was of European descent and the statement in the discussion that the index patient had no documented European ancestry ^[1]. This discrepancy should be clarified.

Fifth, the patient was not systematically screened for multi-organ involvement. Since POLG-related disorders can affect not only the brain but also other organs, it is crucial to systematically screen these patients for mild or subclinical manifestations of the gene defect.

Sixth, the oculomotor disturbances were not adequately analyzed ^[1]. Was the patient examined by an ophthalmologist or neuro-ophthalmologist? Were visually-evoked potentials, retinography, optical coherence tomography, fluorescein angiography, and oculography performed? Was there evidence of visual disturbances, optic atrophy, thinning of the retinal nerve fiber layer, ophthalmoparesis, nystagmus, or abnormal saccades?

Seventh, no EEG was recorded. Since POLG1 variants are frequently associated with seizures ^[4], it would be important to know if the patient has ever experienced syncope or focal or generalized seizures, and whether paroxysmal activity has been documented on EEG.

Finally, neither magnetic resonance spectroscopy (MRS) nor cerebrospinal fluid (CSF) analysis was performed. MRS could detect single or double lactate spikes as well as a reduced N-acetylaspartate spike, and a CSF analysis could directly show elevated lactate levels in the CSF. Elevated CSF lactate levels are possible even with normal serum lactate levels ^[5].

Declarations

Funding: No funding was received.

Availability of Data and Material: All data are available from the corresponding author.

Ethics Approval and Consent to Participate: Not applicable.

Consent for Publication: Not applicable.

Author Contribution: JF: design, literature search, discussion, first draft, critical comments, final approval.

Disclosures: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Compliance with Ethics Guidelines: This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Acknowledgements: None.

Keywords: POLG1, Mitochondrial Disorder, ANS Spectrum Disorder, SANDO, Axonal Neuropathy

References

1. Melo CF, De Vasconcelos LT, Evangelista LAB. Progressive Axonal Neuropathy and Cerebellar Ataxia Associated with Homozygous Pathogenic *POLG* Mutation in a Patient of African Descent from Northern Minas Gerais/Jequitinhonha Valley, Brazil: A Case Report and Epidemiological Implications. Tremor Other Hyperkinet Mov (N Y), Sep 4, 2026; 16:52. Doi: 10.5334/tohm.1238
2. Parikh S, Goldstein A, Koenig MK, Scaglia F, Enns GM, Saneto R, *et al.* Diagnosis and management of mitochondrial disease: A consensus statement from the Mitochondrial Medicine Society. Genet Med, Sep 2015; 17(9):689-701. Doi: 10.1038/gim.2014.177
3. Finsterer J, Zarrouk S. Carriers of POLG1 variants require investigations for multisystem disease and for mtDNA variations. Neurol Res Pract, Jul 11, 2022; 4(1):33. Doi: 10.1186/s42466-022-00195-8
4. Specchio N, Pietrafusa N, Calabrese C, Trivisano M, Pepi C, De Palma L, *et al.* POLG1-Related Epilepsy: Review of Diagnostic and Therapeutic Findings. Brain Sci, Oct 23, 2020; 10(11):768. Doi: 10.3390/brainsci10110768
5. Pia S, Lui F. Melas Syndrome. [Updated 2024 Jan 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, Jan 2026. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK532959/>