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Letter to the Editor

POLG-Related Diseases Require Comprehensive Investigations of the Phenotype and Genotype

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Letter to the Editor

We read with interest the article by Mutairi *et al.* on a retrospective study of the clinical presentation and genetic background of 19 patients with POLG-associated disease from Saudi Arabia ^[1]. Two-thirds of the patients had developmental delay or encephalopathy, more than half had epilepsy, and 40% each had ataxia or dysphagia ^[1]. The most frequently detected variant was the c.3286C>T mutation ^[1]. It was concluded that understanding the molecular mechanism of POLG-associated disease could contribute to the development of future therapeutic strategies ^[1]. Although the study is noteworthy, some points require discussion.

First, the term "encephalopathy" is not sufficiently defined. "Encephalopathy" simply means "brain disease" without specifying what is meant by it. It should be clarified whether the author, by "encephalopathy," meant a clinical condition such as cognitive impairment, memory loss, personality changes, confusion or disorientation, behavioural changes, drowsiness, lethargy, or altered consciousness, or whether the term refers to an imaging finding such as white matter lesions, atrophy, hypoxia, or hydrocephalus. Encephalopathy can also be caused by intoxication, elevated ammonia levels, cerebral lactic acidosis, or traumatic brain injury. Since two-thirds of the patients were diagnosed with "encephalopathy," this term must be clearly defined.

Secondly, no distinction was made between non-syndromic and syndromic phenotypes. Like all mitochondrial diseases, POLG-related disorders can present as syndromes or non-syndromic. Known POLG-associated syndromes include Alpers-Huttenlocher syndrome, myoclonic epilepsy, myopathy and ataxia syndrome, progressive external ophthalmoplegia syndrome, ataxia and neuropathy spectrum, and childhood myo-cerebro-hepatopathy spectrum. How many of the patient met the criteria for a syndromic POLG-related disorder?

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

Fourth, mitochondrial DNA (mtDNA) was not analyzed in any of the included patients ^[1]. Because POLG mutations secondarily cause mtDNA rearrangements, particularly multiple mtDNA deletions or a reduction in mtDNA copy number, it would have been crucial to analyze the effects of the POLG mutation on mtDNA.

Fifth, it was not reported how the pathogenicity of the new variant c.1957G>A was confirmed ^[1]. The gold standard for demonstrating the pathogenicity of a DNA variant is splicing, protein expression, enzyme, and cell assays. Further criteria include that a new mutation must be extremely rare in the general population, that its de novo occurrence must be confirmed, that the variant segregates with the phenotype, or that computer-aided predictions are available. Were these criteria applied to the patient with the c.1957G>A mutation?

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References

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