Int. j. adv. multidisc. res. stud. 2026; 6(3):482-483

Received: 26-04-2026
Accepted: 06-05-2026

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

Letter to the Editor

To Assess Whether Imeglimin is Beneficial in Mitochondrial Nephropathy, Appropriately Designed Studies are Needed

Josef Finsterer
Department of Neurology, Neurology & Neurophysiology Center, Vienna, Austria

Corresponding Author: **Josef Finsterer**

Letter to the Editor

We read with interest the article by Ikeda *et al*. about a 25-year-old man with mitochondrial nephropathy due to the mtDNA variant m.5538G>A with 53% heteroplasmy in the kidneys who was treated with imeglimin [1]. One year after starting imeglimin therapy, kidney function deteriorated rapidly, but proteinuria decreased [1]. A nephroprotective effect of imeglimin was suggested [1]. The study is promising, but some points require discussion.

First, the effect of a drug cannot be assessed by examining a single patient. To determine whether imeglimin is actually beneficial in mitochondrial nephropathy, adequately designed studies (randomized, placebo-controlled crossover trials) are essential. The results of a single case can be misleading and lead to misinterpretations and inappropriate recommendations.

Secondly, mtDNA copy number has not been identified and discussed as a modifier of the phenotype [1]. mtDNA copy number influences the effect of an mtDNA variant by acting as a buffer or amplifier of the m.5538G>A mutation [2]. Higher copy numbers can compensate for a pathogenic mutation and lead to milder symptoms, while lower numbers exacerbate dysfunction and cause a more severe disease course [2]. This occurs through altered efficiency of oxidative phosphorylation and mitochondrial translation and serves as a compensatory mechanism or biomarker for disease severity [2].

Third, the mtDNA haplotype has not been described as a modifier of the phenotype [3]. The mtDNA haplotype alters mitochondrial function through interaction with nuclear DNA (nDNA), thereby influencing cellular properties such as energy metabolism, differentiation, fusion, fission, and disease risk. These alterations lead to complex traits such as aging, metabolic health, and muscle development [3]. Different haplotypes establish different mitochondrial set points for energy production, thus influencing the cellular stress response. This leads to different gene expression patterns and even alterations in DNA methylation in nDNA, ultimately shaping the phenotype [3].

Fourth, no information on family history was provided. In order to assess whether the m.5538G>A variant was inherited from the mother or whether it arose de novo, it is crucial to know whether the mother or another first-degree relative carried the pathogenic variant and was clinically affected either by renal insufficiency or by another typical mitochondrial organ involvement.

The fifth point is that the index patient was not systematically screened for involvement of organs other than the kidneys. Since mitochondrial diseases are usually multisystemic - either at the onset of the disease or during its progression - it is crucial to screen these patients for involvement of organs other than the kidneys. The m.5538G>A variant is known to also manifest as myoclonic epilepsy, diabetes, and hypothyroidism [4].

In summary, interpreting the phenotype of the m.5538G>A variant requires determining the haplotype and mtDNA copy number. Appropriately designed studies are needed to assess whether imeglimin is indeed beneficial in mitochondrial nephropathy.

Declarations

Ethical Approval: Not applicable.

Consent to Participation: Not applicable.

Consent for Publication: Not applicable.

Funding: None received.

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

Completing Interests: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contribution: JF was responsible for the design and conception, discussed available data with coauthors, wrote the first draft, and gave final approval.

Keywords: mtDNA, m.5538G>A, Mitochondrial Nephropathy, Imeglimine, Heteroplasmy

References

1. Ikeda M, Imasawa T, Akanuma T, Goto YI, Okazaki Y, Murayama K, *et al*. Mitochondrial Nephropathy with m.5538G>A Mutation Within the tRNA-Trp Region Assessed by Mitochondrial Function Analysis: A Case Report. Nephrology (Carlton), Nov 2025; 30(11):e70153. Doi: 10.1111/nep.70153
2. Zaidi AA, Verma A, Morse C; Penn Medicine BioBank; Ritchie MD, Mathieson I. The genetic and phenotypic correlates of mtDNA copy number in a multi-ancestry cohort. HGG Adv, May 9, 2023; 4(3):100202. Doi: 10.1016/j.xhgg.2023.100202
3. St John JC, Tsai TS. The association of mitochondrial DNA haplotypes and phenotypic traits in pigs. BMC Genet, Jul 6, 2018; 19(1):41. Doi: 10.1186/s12863-018-0629-4
4. Malfatti E, Cardaioli E, Battisti C, Da Pozzo P, Malandrini A, Rufa A, *et al*. A novel point mutation in the mitochondrial tRNA (Trp) gene produces late-onset encephalomyopathy, plus additional features. J Neurol Sci, Oct 15, 2010; 297(1-2):105-108. Doi: 10.1016/j.jns.2010.06.009