Int. j. adv. multidisc. res. stud. 2026; 6(3):466-467

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

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

Letter to the Editor

Don't Forget Haplotype, mtDNA Copy Number, and nDNA as Modifiers of the m.3243A>G Mutation's Phenotypic Expression

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

Corresponding Author: **Josef Finsterer**

Letter to the Editor

We read with interest the review article by Chu *et al*. on the current state of knowledge regarding the mitochondrial DNA (mtDNA) variant m.3243A>G, with a particular focus on the two most important associated syndromes - MELAS syndrome (mitochondrial encephalopathy, lactic acidosis, and stroke-like episode) and MIDD syndrome (maternally inherited diabetes and deafness) [1]. The article is engaging, but some points warrant further discussion.

First, the mtDNA haplotype has not been considered a modifier of the m.3243A>G phenotype [2]. The mtDNA haplotype alters mitochondrial function through interaction with 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, often involving trade-offs [2]. Different haplotypes establish different mitochondrial setpoints for energy production, thus influencing the cellular response to stress. This results in different gene expression patterns and even alterations in DNA methylation in nuclear DNA, ultimately shaping the phenotype) [2].

Secondly, mtDNA copy number has not been discussed as a modifier of the phenotype [1]. The mtDNA copy number influences the severity of the effects of an mtDNA variant on the phenotype [3]. It fulfills this function by acting as a buffer or amplifier of the m.3243A>G mutation [3]. Higher copy numbers can compensate for pathogenic mutations and lead to milder symptoms, while lower numbers exacerbate dysfunction and cause more severe disease [3]. This is achieved through altered efficiency of oxidative phosphorylation and mitochondrial translation and serves as a compensatory mechanism or biomarker for disease severity [3].

Third, there is currently no evidence that vascular pathologies play a pathophysiological role in the development of stroke-like episodes (SLEs) in MELAS [1]. The correlate of SLE on cerebral magnetic resonance imaging (MRI) is the so-called stroke-like lesion (SLL), which is characterized by typical changes in different MRI modalities and dynamic changes over time, and which are not restricted to a specific vascular territory [4]. Therefore, the vascular hypothesis of SLEs has been rejected. More likely than caused by vasculopathy or epileptic seizures, SLLs are triggered by metabolic stress in the cortex or subcortical areas, which tends to spread focally. We therefore disagree that the vascular hypothesis explains the predominant occurrence of SLLs in the occipital lobe [1].

The fourth point is that molecular genetic tests can be performed not only on muscle, blood, or urinary tract epithelial cells, but also on oral mucosal cells, skin fibroblasts, or hair follicles. If available, brain, liver, kidney, and myocardium can also be examined for mtDNA mutations.

The fifth point is that MIDs not only impair oxidative phosphorylation, as mentioned in the introduction, but also various other enzymatic or signaling pathways (e.g., beta-oxidation, amino acid metabolism, heme biosynthesis, steroid and phospholipid synthesis), mitochondrial reproduction, repair, apoptosis, antioxidant capacity, mitochondrial dynamics, and pore function.

In summary, the phenotypic expression of the m.3243A>G variant depends not only on heteroplasmy, but also on haplotype, mtDNA copy number, and the interaction between mtDNA and nDNA. SLEs cannot be explained by mitochondrial vasculopathy.

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. FS and CS: contributed to literature search, discussion, correction, and final approval.

Keywords: mtDNA, m.3243A>G, MELAS, MIDD, Heteroplasmy

References

1. Chu KY. Mitochondrial DNA A3243G variant: Current perspectives and clinical implications. Intractable Rare Dis Res, Nov 30, 2025; 14(4):249-257. Doi: 10.5582/irdr.2025.01051
2. 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
3. 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
4. Finsterer J. Characteristics of stroke-like lesions on cerebral imaging. Ideggyogy Sz, Jan 30, 2023; 76(1-2):5-10. Doi: 10.18071/isz.76.0005