Sarcouncil Journal of Medicine and Surgery

ISSN(Online): 2945-3534

Volume- 04| Issue- 03| 2025

Research Article **Received:** 13-02-2025 | **Accepted:** 22-02-2025 | **Published:** 03-03-2025

The Multisystemic Nature and Pathogenicity of the m.5783G>A Variant must be Confirmed before it can be Held Responsible for Major Depression

Josef Finsterer
MD, PhD, Neurology Neurophysiology Center, Vienna, Austria, ORCID: 0000-0003-2839-7305

Keywords: major depression disorder, mtDNA, m5783G>A, tRNA(Cys), pathogenicity.

LETTER TO THE EDITOR

We read with interest the article by Jing, *et al*., about two patients with major depressive disorder (MDD) that were traced back to the homoplasmic mtDNA variant m.5783G>A in tRNACys [Jing, P. *et al*., 2025]. The mutation was found at a highly conserved cytosine at position 50 in the TΨC strain of tRNACys, with a conservation coefficient of 100% in 17 species [Jing, P. *et al*., 2025]. It was concluded that the m.5783G>A variant may play a role in the development of MDD [Jing, P. *et al*., 2025], but due to low penetrance, phenotypic expression requires either nuclear modifier genes or environmental factors [Jing, P. *et al*., 2025]. The study is excellent, but some points should be discussed.

First, mitochondrial diseases (MID) are usually multisystem diseases, but no involvement of organs other than the brain has been reported [Jing, P. *et al*., 2025]. Nevertheless, due to the multisystem nature of MID, it is very likely that the two index patients also had disease in organs or tissues other than the brain. In addition to the central nervous system (CNS), organs that are frequently affected in MID include the eyes, ears, endocrine organs, heart, intestines, kidneys, bone marrow and skin [Di Donato, S, 2009]. Have both patients been prospectively screened for multisystem involvement in MID? Multisystem disease does not necessarily have to be symptomatic, but can also be subclinical in the early stages of the disease.

The second point is that other first-degree relatives were not examined clinically or genetically to determine whether any of them also carried the m.5783G>A variant or were clinically affected with either depression or other phenotypic features of MID. Since mtDNA variants are inherited through the maternal line in 75% of patients [Poulton, J. *et al*., 2017], it is very likely that the mothers of the index patients were also carriers of the mtDNA variant that is thought to be responsible for the depression. For genetic counseling and for assessing the prognosis and outcome of the variant, it would be useful to know whether the variant was inherited or sporadic.

The third point is that the pathogenicity of the m.5783G>A variant in tRNA Cys remains unproven. However, pathogenicity is supported by the fact that the variant was previously reported in a patient with mitochondrial encephalopathy, lactic acidosis and stroke-like syndrome (MELAS) syndrome [Cai, H. *et al*., 2024] and that the variant is located in a highly conserved region of the gene. However, pathogenicity has not been confirmed by in silico analysis, tissue biochemistry, cybrid studies, single fiber studies, or documentation of segregation of the variant with the phenotype. Homoplasmy could also be an argument against pathogenicity. Was there an insufficiency of complex-I of the respiratory chain?

The fourth point is that neither the one nor the other index patient underwent cerebral imaging by magnetic resonance imaging (MRI). Since MDD can be associated with structural CNS lesions [Anglin, R. E. *et al*., 2012], it would have been mandatory to perform cerebral imaging in both patients.

In summary, this interesting study has limitations that put the results and their interpretation into perspective. If these limitations were removed, the conclusions could be more rigorous and the message of the study more strongly supported. All open questions need to be clarified before readers uncritically accept the conclusions of the study. The multisystemic manifestation and pathogenicity of the mtDNA variant m.5783G>A needs to be confirmed before it is held responsible for major depression.

REFERENCES

1. Jing, P., Yu, H., Sun, W., Liang, M., Xia, T., Yang, H., Chen, P., Li, J. & Zhang, X. "The association of mitochondrial tRNACys

***Corresponding Author:** Josef Finsterer

DOI- https://doi.org/10.5281/zenodo.14962933

G5783A mutation with major depressive disorder in two Han Chinese families." *Neuropsychiatric Disease and Treatment*, 21 (2025): 15-24.
2. Di Donato, S. "Multisystem manifestations of mitochondrial disorders." *Journal of Neurology*, 256.5 (2009): 693-710.
3. Poulton, J., Finsterer, J. & Yu-Wai-Man, P. "Genetic counselling for maternally inherited mitochondrial disorders." *Molecular Diagnosis & Therapy*, 21.4 (2017): 419-429. Erratum: *Molecular Diagnosis & Therapy*, 21.4 (2017): 465-466.
4. Cai, H., Li, L. M., Zhang, M., Zhou, Y. & Li, P. "Case report: Late-onset MELAS syndrome with mtDNA 5783G>A mutation diagnosed by urinary sediment genetic testing." *Frontiers in Genetics*, 15 (2024): 1367716.
5. Anglin, R. E., Tarnopolsky, M. A., Mazurek, M. F. & Rosebush, P. I. "The psychiatric presentation of mitochondrial disorders in adults." *Journal of Neuropsychiatry and Clinical Neurosciences*, 24.4 (2012): 394-409.

Source of support: Nil; **Conflict of interest:** Nil.

Cite this article as:
Finsterer, J. "The Multisystemic Nature and Pathogenicity of the m.5783G>A Variant must be Confirmed before it can be Held Responsible for Major Depression." *Sarcouncil Journal of Medicine and Surgery* 4.3 (2025): pp 5-6.

Publisher: SARC Publisher