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Letter to the Editor

Are mtDNA Variants Actually Involved in the Pathophysiology of Bipolar Disorder and Schizophrenia?

[1] Josef Finsterer, [2] Sounira Mehri

[1] Department of Neurology, Neurology & Neurophysiology Center, Vienna, Austria
[2] Laboratory of "Nutrition - Functional Food & Health", Faculty of Medicine, University of Monastir, Tunisia

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Corresponding Author: **Josef Finsterer**

Letter to the Editor

We read with interest the article by Ohtani *et al*. on the presence of mtDNA variants in 163 autopsy brain samples from 54 patients with bipolar disorder (BD), 55 patients with schizophrenia (SZ) and 54 controls analysed by duplex molecular barcoding sequencing [1]. The authors found an enrichment of extremely rare heteroplasmic variants with allelic proportions of over 1% in BD [1]. Potentially pathogenic variants, such as m.3243A>G, loss-of-function variants and rRNA variants, were particularly enriched in BD [1]. Single-molecule analysis revealed no general trend towards an increase in low-grade heteroplasmic variants in BD in terms of mutation frequency per base and heteroplasmic fractions [1]. It was concluded that a subset of BD patients can be stratified according to the presence of ultra-rare mitochondrial variants [1]. The study is impressive, but some points should be discussed.

The first point is that mitochondrial disorders (MID) are usually multisystemic disorders, either at the onset of clinical manifestations or they become multisystemic during the course of the disease [2]. Therefore, we should know whether any of the 54 BD patients or the 55 SZ patients had phenotypic manifestations other than BD or SZ. In MID, not only the central nervous system but any organ can be affected. A multisystem disease could be an argument for the pathogenicity of the detected mtDNA variants.

The second point is that mtDNA variants are inherited through the maternal line in 75% of cases [3]. Therefore, it might be useful to know the family history of all patients in the BD and SZ cohort. Not only could first-degree family members have manifested with BD or SC, but also with abnormalities in organs other than the brain. Phenotypic heterogeneity between affected family members is a typical feature of MID, which is why abnormalities in organs other than the brain should also be considered as manifestations of a potentially causative variant.

The third point is that the pathogenicity of mtDNA variants should not only be assessed with in silico methods, but with more sophisticated methods. These include in particular the Yarham score and the modified Yarham score [4]. The modified Yarham score evaluates the number of publications on a particular variant, its heteroplasmy rate, disease segregation within a family, the presence of a biochemical defect of respiratory complexes I, III, and IV, segregation of the variant with the biochemical defect in single fiber studies, evidence of pathogenicity or normality in trans-mitochondrial cybrid studies, degree of evolutionary conservation of nucleotides, and evidence in histopathological studies [4]. Seven to 10 points on this score are classified as possibly pathogenic, 10-13 points without evidence from single fiber studies as probably pathogenic and >10 points with evidence from single fiber studies as definitely pathogenic [4].

In conclusion, it can be said that this interesting study has limitations that relativize the results and their interpretation. Removing these limitations could strengthen the conclusions and reinforce the message of the study. Unresolved issues need to be clarified before readers can uncritically accept the study's message. Before a causal relationship between rare mtDNA variants and BD or SC can be established, the pathogenicity of the discovered variants must be proven.

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