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Schizophrenia Patients carrying mtDNA Variants Require a Thorough Neurological Examination for the Presence of a Mitochondrial Disorder

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LETTER TO THE EDITOR

We read with interest the article by Bulduk *et al*. about a post-mortem study of brain samples from 40 patients with schizophrenia and 40 age- and sex-matched healthy controls (controls) for the presence of pathogenic mtDNA variants using mtDNA-targeted next generation sequencing and quantitative PCR [Bulduk, B. K. *et al*., 2024]. It was found that 35% of schizophrenia patients had mtDNA alterations, a significantly higher prevalence compared to 10% of healthy controls [Bulduk, B. K. *et al*., 2024]. In particular, schizophrenia patients had a significantly higher frequency of deletions (35 vs. 5 in controls), with an average number of deletions of 3.8 in schizophrenia vs. 1.0 in controls [Bulduk, B. K. *et al*., 2024]. Likely pathogenic missense variants were also significantly more common in schizophrenia patients than in controls (10 vs. 3 in controls), comprising 14 variants in patients and three in controls [Bulduk, B. K. *et al*., 2024]. The pathogenic tRNA variant m.3243A>*G* was identified in a schizophrenia patient with a heteroplasmy level of 32.2% [Bulduk, B. K. *et al*., 2024]. While no significant differences in mtDNA copy numbers were observed between schizophrenia patients and controls, antipsychotic drug users had significantly higher mtDNA copy numbers than non-users [Bulduk, B. K. *et al*., 2024]. The study is impressive, but some points require further discussion.

The first point is that it was not reported how many of the patients' organs other than the brain were affected. Since mitochondrial disorders (MIDs) are usually multisystem disorders [Finsterer, J, 2004], we should know how many of the patients included had organs other than the brain involved. Commonly affected organs or tissues other than the brain include the skeletal and smooth muscles, the peripheral and cranial nerves, the eyes, ears, endocrine system, the heart, the gastrointestinal tract, the kidneys, the immune system, the cartilage, and the skin.

A second point is that the patient with schizophrenia who carried the m.3243A>G variant with a heteroplasmy rate of 32.2% may have not only manifested with schizophrenia but also with other cerebral manifestations, including stroke-like lesions, epilepsy, ataxia, dystonia, spasticity, or visual dysfunction [Alves, C. A. P. F. *et al*., 2023]. Therefore, we should know whether this particular patient had classic MELAS features and how many of the schizophrenia patients had other central nervous system manifestations in addition to schizophrenia.

A third point is that forty healthy controls were included but had a brain autopsy performed. What is the reason why these healthy controls died and underwent brain autopsy? Knowing the cause of death and previous medical history is crucial because some of these patients may have had subclinical or mildly manifesting MID that also did not manifest in the brain. Patients undergoing autopsy should not be referred to as "healthy controls".

A fourth point is that whether patients with mtDNA deletions had single or multiple mtDNA deletions was not reported [Bulduk, B. K. *et al*., 2024]. Single deletions are often associated with primary adrenal insufficiency, chronic progressive external ophthalmoplegia (CPEO), Pearson syndrome (PS) or Kearns Sayre syndrome (KSS) [Siri, B. *et al*., 2023]. Multiple mtDNA deletions are usually due to mutations in mitochondrial genes that are encoded on nuclear DNA. These patients manifest with either CPEO, optic neuropathy, or myopathy [Carey, A. R. *et al*., 2024]. Therefore, we should know how many of the forty schizophrenia patients or any of the controls had single or multiple mtDNA deletions. Did any of the patients or controls have features of adrenal insufficiency, CPEO, PS, or KSS?

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A fifth point is that it was not reported how many of the mtDNA variants discovered were known pathogenic mutations associated with a previously descried MID phenotype. We should also know how many of the patients had a family history positive for MIDs.

In conclusion, the interesting study has limitations that put the results and their interpretation into perspective. Clarifying these weaknesses would strengthen the conclusions and could improve the study. Schizophrenia patients carrying mtDNA variants should undergo a thorough neurological examination for the presence of syndromic or non-syndromic MID.

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