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The Outcome of Primary Brain Tumors does not Only Depend on the Presence of mtDNA Variants in the Tumour

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LETTER TO THE EDITOR

We read with interest the article by Khair, *et al*., about a post-mortem study on 54 patients with primary brain tumors (glial tumors (n=25), non-glial tumors (n=29)) in which tumor specimens and blood samples underwent Sanger sequencing for the presence of mitochondrial DNA (mtDNA) sequence variants *[Khair, S. Z. N. M. et al., 2024]*. The study is compelling, but some points require discussion.

The first point is that the outcome of primary brain tumours depends not only on the prevalence of mtDNA variants in the tumour, but on several other factors, such as the type of tumor, age, gender, immunological fitness, response to surgery, chemotherapy or radiation therapy, and comorbidities. Furthermore, the design of the study (single-centre and low power (n=54)) is not suitable for drawing such general conclusions as in the article.

The second point is that the pathogenicity of the mtDNA variants was only analysed using mitimpact2 *[Khair, S. Z. N. M. et al., 2024]*. To assess the pathogenicity of an mtDNA variant, biochemical studies, segregation analysis, and cybrid studies are required. Until such studies have been carried out, the four mtDNA variants classified as deleterious (8894delA, (ATP6), T4705C (ND2), C8897G (ATP6), and C8914A (ATP6)) can only be classified as variants of unknown significance (VUS).

The third point is that the results of the blood test for mtDNA variants found in the tumor were not reported. Since the variant m.4705T>C in *ND2* is known to be associated with Leigh syndrome *[La Morgia, C. et al., 2014]*, we should know whether the variant was also detected in blood lymphocytes and whether this particular patient developed phenotypic features of Leigh-syndrome. Likewise, we should know whether the variant m.11665C>T, which is known to manifest phenotypically as mitochondrial encephalopathy, lactic acidosis, and stroke-like episode (MELAS) syndrome *[Choi, B. O. et al., 2008]* or Leber's hereditary optic neuropathy (LHON) *[Zhang, J. et al., 2010]*, was also detected in blood lymphocytes and whether the patient had phenotypic features of MELAS or LHON.

The fourth point is that only two single base pair deletions and one single base pair insertion have been reported *[Khair, S. Z. N. M. et al., 2024]*. Since it is known that large-scale deletions can occur in several malignancies *[Fontana, G. A. et al., 2024]*, we should know whether mtDNA analysis also included search for single or multiple mtDNA deletions or insertions and if so, how to explain the fact that none of these were detected in the index cohort.

In conclusion, the outcome of the primary brain tumors depends not only on the prevalence of mtDNA mutations, but also on several other more significant factors.

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