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LETTER TO THE EDITOR

Genotype/phenotype correlations are crucial for establishing pathogenicity of mtDNA variant

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1 | CORRESPONDENCE

With interest we read the article by Loos et al. about 27 patients with mtDNA-associated mitochondrial disorders (MID) from Argentina [1]. MELAS was the most common phenotype and the variants m.13513G>A in *MT-ND5* and m.9185T>C in *ATP6,* phenotypically manifesting as Leigh syndrome, occurred sporadically [1]. The report is interesting but raises the following comments and concerns.

Concerning the pathogenicity of the variant m.13513G>A, the heteroplasmy rate of 20% in lymphocytes argues against causality. If clinically more severely affected tissues did not carry higher heteroplasmy rates, the patient should be investigated for mutations in alternative genes associated with MELAS. Using quantitative real-time PCR and hair follicles or urinary epithelial cells might be more efficient in this respect [2].

According to table-1 only 10 of the 11 MELAS patients had a stroke-like episode (SLE) [1]. We should know if the patient without a SLE fulfilled the Hirano or Japanese criteria for diagnosing MELAS [3].

According to table 1 only 2 of 3 patients with Kearns-Sayre syndrome had cardiac involvement. Since cardiac conduction defects are part of the diagnostic criteria [4], we should be told if the patient without cardiac involvement fulfilled the diagnostic criteria.

Most MELAS patients present with lactic acidosis on magnetic resonance spectroscopy (MRS) or investigations of the cerebro-spinal fluid. We should be told why only 2/11 MELAS patients had elevated lactate in the brain.

Since mtDNA variants are inherited via the maternal line in 75% of the cases [5], we should know in how many of the 27 patients the family history was positive for the disease. Furthermore, we should know

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how many of the 27 mothers carried the mutation of their child.

Since most of the MIDs are non-syndromic, it should be explained why no patient with non-syndromic MID was included.

Overall, the report is appealing but has several limitations which challenge the results and their interpretation.

Declarations

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Data availability: not applicable

Consent to participate: not applicable

Consent for publication: not applicable

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