The MELAS phenotype may not only be determined by heteroplasmy of causative mtDNA variants

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I read with interest, the article by Chae *et al.* about a study of 32 paediatric patients with MELAS of whom 25 underwent next-generation sequencing (NGS) (1). It was concluded that heteroplasmy rates correlated inversely with age at onset and age at diagnosis (1). This raises the following comments and concerns.

The main shortcoming of the study is that heteroplasmy rates were determined in blood lymphocytes, which are usually not severely affected in MELAS. Thus, heteroplasmy rates in blood lymphocytes may not represent heteroplasmy rates in other more severely affected tissues. This is why the results provided remain questionable. Heteroplasmy rates should also be determined in tissue such as buccal mucosa cells, hair follicles, urine epithelial cells, skin fibroblasts, or the skeletal muscle.

A second shortcoming is that the phenotypic expression of the m.3243A>G variant may not only depend on heteroplasmy rates but also on the mtDNA copy number, on the haplotype, and on polymorphisms. Thus, the authors should provide at least mtDNA copy numbers to assess if the severity of the phenotype depended on the amount of available mtDNA or not.

Furthermore, heteroplasmy rates may depend on the disease stage, which is why it is important to know if heteroplasmy rates were determined only once or repeatedly during follow-up. Heteroplasmy rates may increase over time even in less severely affected tissues.

Also missing is the current medication the 25 included patients received. As a number of drugs (e.g. steroids, antibiotics) may influence the phenotype of

mitochondrial disorders (MIDs), it is crucial to know the drugs the included patients were regularly taking.

According to Table 1, the family history was positive in seven patients (1). However, if this means that the mothers of these seven patients had MELAS or that they had diabetes without MELAS is not reported.

MELAS may not only manifest in the CNS, eyes, ears, endocrine organs, heart, intestines, or kidneys, but also in the vestibular organs (2), as sudden unexpected death (3), and in peripheral nerves (4). How many of the 25 patients included had vestibular involvement or neuropathy is not reported as well as in how many of them neuropathy was attributed to diabetes, with reference to the underlying mutation.

Overall, the study has a number of shortcomings which need to be addressed before the conclusions drawn can be justified. Heteroplasmy rates in blood lymphocytes may not be related to phenotypic severity and the phenotype may not only be determined by heteroplasmy rates.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this letter.

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Informed consent

The study was approved by the institutional review board.

Author contribution statement

J F was involved in the design, literature search, discussion, first draft and critical comments.

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