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Metabolomics of MNGIE Depends on the Individual *TYMP* Variant, Secondary mtDNA Defects, and Current Medications

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LETTER TO THE EDITOR

We read with interest the article by Du, *et al*., on metabolomic changes and homeostatic regulation in three TYMP-deficient patients assessed by targeted and non-targeted metabolomic techniques applied to serum and skin fibroblasts [Du, J. *et al*., 2023]. The results were compared to those of three m.3243A>G carriers and four healthy controls [Du, J. *et al*., 2023]. Specific changes in nucleosides, bile acids, and steroid metabolism have been found in the plasma of MNGIE patients [Du, J. *et al*., 2023]. In skin fibroblasts mitochondrial dysfunction, decreased cholesterol metabolism and decreased fatty acid biosynthesis and degradation have been found [Du, J. *et al*., 2023]. The study is excellent but has limitations that should be discussed.

The first limitation of the study is that secondary changes in mtDNA caused by TYMP deficiency have not been examined [Du, J. *et al*., 2023]. Since *TYMP* variants can cause multiple mtDNA deletions, mtDNA point mutations, and even mtDNA depletion due to defective mtDNA replication and since the secondary mtDNA defects vary between the types of *TYMP* variants but also between patients carrying the same *TYMP* variant, each individual MNGIE patient represents a unique phenotype that also concerns the metabolic profile.

A second limitation is that the current medications that the included patients were regularly taking were not provided. Since all included patients were multimorbid, it is very likely that they all received regular medication. Since medications can strongly influence the blood composition of metabolites examined in the index study, it is imperative to be aware of them and to include them in the discussion of the results.

A third limitation is that dependence of serum metabolite composition on the underlying mutation was also not considered in the discussion. Differences between MNGIE patients1/2 and patient-3 could simply be due to the different genetic defects. Differences between MNGIE patients and MELAS patients can be explained simply by the different mutated genes.
A fourth limitation is that no reference limits are given in table 1 making it difficult to judge which values are normal and which are not.
A fifth limitation is that the group size was small, making the statistical comparison unreliable. The comparison of three patients with four controls respectively three MELAS patients can lead to incorrect results, especially given the wide phenotypic heterogeneity of MNGIE patients. Before comparing MNGIE patients with healthy or disease controls, the inter-individual variability between MNGIE patients must be calculated.
Skin fibroblasts are usually not or only mildly affected in MELAS patients. Surprisingly, the heteroplasmy rates of the variant m.3243A>G were high with numbers of 66, 76, and 85% [Du, J. *et al*., 2023]. We should know if these three MELAS patients also manifested in the skin, which is usually not the case in MELAS patients.
In summary, the interesting study has limitations that put the results and their interpretation into perspective. Addressing these issues would strengthen the conclusions and could improve the status of the study. Because the metabolic profile in MNGIE patients is highly dependent on the underlying *TYMP* mutation, current medication, and secondary mtDNA defects, it is crucial to include these parameters in the assessment and discussion.

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Ethical compliance statement: The authors confirm that the approval of an institutional review board or patient consent was not required for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those

guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors

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