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Letter to the Editor

Pathogenicity of the M.1630A>G Variant Remains Questionable If First Degree Relatives with Similar Heteroplasmy Rates Remain Asymoptmatic

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In a recent article, Uittenbogaard *et al.*, reported about a 24yo female with MELAS due to the variant m.1630A>G with a heteroplasmy rate of 75% (blood), 95% (urine), and 89.6 (fibroblasts) (Uittenbogaard, M. *et al.*, 2019). Her mother was clinically unaffected but carried the same variant with similar mutaton loads (Uittenbogaard, M. *et al.*, 2019). We have the following concerns.

Patients carrying mtDNA variants may be asymptomatic (Weerasinghe, C. A. L. *et al.*, 2018). Thus, the mother should be investigated for asymptomatic involvement of the brain, eyes, ears, endocrinium, myocardium, lungs, intestines, kidneys, bone-marrow, cartilage, and skin.

We do not agree with the statement about a big difference in the similar heteroplasmy rates between proband and mother in urine and fibroblasts. The difference in blood heteroplasmy rates is not striking either as heteroplasmy rates in blood frequently do not correlate with the severity of the phenotype (Kärppä, M. *et al.*, 2018).

The strongest difference between mother and daughter in addition to the phenotype is the fact that the daughter, but not the mother, was regularly taking antiepileptic drugs (AEDs) and immunosuppressants. Since some AEDs (e.g. phenytoin, valproate, phenobarbital carbamazepine) can be mitochondrion-toxic and strongly influence the condition (Finsterer, J. 2017), we should know which AEDs and immunosuppressants the proband was regularly taking. There are also reports about immunsuppressive medication deteriorating MELAS (Serkova, N.J. *et al.*, 2004).

The asymptomatic mother with heteroplasmy rates similar to those of her symptomatic daughter suggests that the m.1630A>G variant was not pathogenic and that a mutation in another gene may be causative. Since the results of WES do not convincingly explain the phenotypic difference between mother and daughter, whole genome sequencing is recommended.

Overall, this study could be more meaningful if heteroplasmy rates in affected organs were compared, if the mother was investigated for subclinical involvement, if the effect of the medication on the phenotype was discussed, if single-fibre PCR was carried out, and if deletions, indels, duplications, insertions, and repeat-sequences were excluded.

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