

Leukocyte Heteroplasmy Rates of the m.3243A>G Variant may not Correlate with Phenotype or Prognosis

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Letter to the Editor

In a recent article Langdahl et al. reported a study about 46/32 m. 3243A>G mutation carriers who were followed up for 10 years with regard to progression of the phenotype and the heteroplasmy rates in lymphocytes [1]. We have the following comments and concerns.

A major disadvantage of the study is that the medication taken during the observational period was not mentioned. Since mitochondrial disorders frequently require therapy for epilepsy, heart failure, arrhythmias, diabetes, hypothyroidism, arterial hypertension, hyperlipidemia, or neuropathic pain, we should know if mitochondrion-toxic compounds were administered. Particularly antiepileptic drugs, such as phenobarbital, carbamazepine, valproic acid, and phenytoin, can be mitochondrion-toxic [2]. Mitochondrion-toxic are also statins, which may cause asymptomatic hyper-CKemia, myalgia, soreness, exercise intolerance, tiredness, weakness, or even rhabdomyolysis. It should be also mentioned how many of the included patients underwent general anaesthesia during the 10 year observational period and developed side-effects. Anaesthetics, muscle relaxants, and analgesics can strongly deteriorate the clinical manifestations [3] and thus determine the outcome. How many took steroids, which are potentially mitochondrion-toxic or even fatal in some patients with a mitochondrial disorder [1]. Two patients had undergone transplantation [4]. Did they tolerate the immuno-suppressants without adverse reactions? How many of the patients required anti-retroviral treatment, from which it is well-known that it can be mitochondrion-toxic as well [5].

A further disadvantage of Langdahl's study is that heteroplasmy rates from lymphocytes may not represent heteroplasmy rates in other more affected tissues. It is well appreciated that heteroplasmy rates can vary significantly between tissues why it is recommended to determine heteroplasmy rate in various different tissues particularly in those most severely clinically affected.

A further shortcoming is that deterioration of the phenotype despite reduction of the heteroplasmy rate was not discussed. Is this finding an artefact or an attempt of the body to compensate for the pathogenic effect of high heteroplasmy rates? If heteroplasmy rates are related to phenotypic severity, we would rather expect a clinical improvement than deterioration.

Furthermore, how can patients have been followed-up for 10 years if they were recruited until 2014? If there were 44 matched samples

leukocyte/urinary epithelial cells, and leukocytes/buccal-mucosa each, how to explain that only 42 paired samples urinary epithelial cells/ buccal-mucosa were available? If initial investigations were carried out between 2003 and 2006, how to explain that methods to determine heteroplasmy were the same at inclusion and at follow-up? Only 32 patients underwent determination of longitudinal changes of the heteroplasmy rate.

The retrospective design of the study may have promoted that essential information from the history was not taken and that no instrumental investigations for subclinical involvement of organs had been carried out.

Overall, this interesting study could be more meaningful if supplementary data would have been provided. Particularly, mitochondrion-toxic drugs taken during the observational period need to be discussed for their potential to influence heteroplasmy rates. Additionally, a number of inconsistencies need to be addressed.

Declarations

Both authors contributed equally, JF: design, literature search, discussion, first draft, SZ-M: literature search, discussion, critical comments. Both authors read and approved the final manuscript and there are no conflicts of interest.

References

1. Finsterer J, Frank M (2015) Glucocorticoids for mitochondrial disorders. *Singapore Med J* 56: 122-123.
2. Finsterer J, Mahjoub SZ (2012) Mitochondrial toxicity of antiepileptic drugs and their tolerability in mitochondrial disorders. *Expert Opin Drug Metab Toxicol* 8: 71-79.
3. Finsterer J, Stratil U, Bittner R, Sporn P (1998) Increased sensitivity to rocuronium and atracurium in mitochondrial myopathy. *Can J Anaesth* 45: 781-784.
4. Langdahl JH, Larsen M, Frost M, Andersen PH, Yderstraede KB, et al. (2017) Leucocytes Mutation load Declines with Age in Carriers of the m. 3243A>G Mutation. A 10-year Prospective Cohort. *Clin Genet* 4: 925-928.
5. Velinov M, Dolzhanskaya N, Mendez H (2009) Mitochondrial T9098C sequence change in the MTATP6 gene and development of severe mitochondrial disease after in utero antiretroviral prophylaxis. *Pharmacotherapy* 12: 1491.