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Intra-familial phenotypic heterogeneity of m.3243A>G carriers remains elusive as long as heteroplasmy and mtDNA copy numbers are absent: reply

With great interest, I have read the insightful comments to our case report made by Finsterer[1] and value his opinion greatly, especially since he is a renowned expert in the field of mitochondriopathies. He has raised several issues, to which I would like to respond in an itemized fashion.

Heteroplasmy rates

Finsterer states that heteroplasmy rates and mitochondrial DNA (mtDNA) copy numbers are essential for genetic counselling as phenotype and outcome are influenced by them.[1] I highly agree with this; however, we chose not to include those values in our original report as the main audience was assumed to be of cardiologic background, not human genetics. In fact, heteroplasmy rates were obtained from the index-patient (ca. 25%) and his half-brother KF (ca. 20%). In contrast, mtDNA copy numbers cannot be reported since we rely on information shared by external laboratories. In addition, we were now able to obtain further symptoms in distant relatives, which were unknown at the time of the original draft of the family tree [epilepsy in *Mo*, periodic paralysis in *Je (see original report)*]. *Ma*, the index-patients nephew, was diagnosed as an asymptomatic carrier of the mutation in the meantime.

Diagnostic delay

Finsterer is asking for an explanation of the diagnostic delay of 2 years.[1] It is unclear to me how this timeframe was assumed. As stated in the timeline in the original study, first presentation to the authors of the report was in December of 2018 and the relevant mutation was discovered in June of 2019. This accumulates to 6 months, which I argue can be considered appropriate, when taking the need for an interdisciplinary approach and widespread family history into account.

Medical work-up and genetic testing

I am aware of the multi-system involvement of the disease, which is why the index-patient was referred to the neurologic and ophthalmologic wards of the university hospital. Since the patient is in treatment at the cardiologic ward of the university hospital medical centre, we feel confident that endocrine, renal, and haematological examinations are sufficient, while I agree that determination of lactate is missing and seek to remedy this in the next outpatient consultation. I however strongly disagree with Finsterer's claim that the patient is diabetic.[1] While it is true that current guidelines regard an HbA1c above 6.5% as diabetes, the patient presented with an HbA1c of 7.3 mmol/L, which translates to 6.2%. HbA1c between 5.7% and 6.4% should be regarded as pre-diabetes.[2] Genetic testing poses an ethical challenge and will only be conducted when a patient provides informed consent. Regarding the genetic testing the author is reliant on the co-operation of the individuals. The indication for screening has been forwarded to his relatives through the index-patient. Whether the mentioned relatives did not get tested or did not want to share the results is not within my knowledge. I thank Josef Finsterer for his insightful comments and hope that this response improves the original study in the way he intended.

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