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Reply to Comment on: Progression of Retinopathy Secondary to Maternally Inherited Diabetes and Deafness – Evaluation of Predicting Parameters

REPLY

MATERNALLY INHERITED DIABETES AND DEAFNESS (MIDD) presents with different phenotypes associated with the individual percentage of affected mitochondria (heteroplasmy).[1,2] In this study we demonstrated that atrophy of the retinal pigment epithelium (RPE) is a meaningful and reliable endpoint that allows for designing proof-of-concept clinical trials with small numbers of patients.[3]

Drs Finsterer and Scorza seem to miss much of the intent of our article. Instead they want to state that MIDD is due not only to m.3243A>G mutation but to other mutations, which, while interesting, has no relevance to the focus of the article. A second point they want to establish is that MIDD can affect organs other than the eyes, which is widely known and already mentioned in our manuscript. Actually, this is the point of the manuscript, as extraocular manifestations of MIDD are problematic in terms of potential endpoints for clinical trials.

In addition, they requested to know the heteroplasmy rate of each patient. While we agree that knowing tissue-relevant rates of heteroplasmy would be of interest, as it is understood that the heteroplasmy rate differs from one tissue to the other, retinal tissue must be obtained, as peripheral tissue heteroplasmy rates may not relate to that of the RPE. Given that we are dealing with living humans with MIDD in this study, we would need to undertake a macular retina/RPE biopsy; this might not only be ethically incorrect but also sight-threatening, while not leading to any change in our conclusions. As non-ophthalmologists, Drs Finsterer and Scorza may not be aware of this issue of biopsy risk. Dr Finsterer refers to a study by Laloi-Michelin and associates to support the importance of measuring heteroplasmy rates of blood lymphocytes on retinopathy. However, this report shows the converse and argues against his point, in that about the same proportion (three quarters) of eyes with the highest heteroplasmy levels and the rest of eyes had macular pattern dystrophy.[2] In addition, Dr Finsterer demonstrates inconsistency, as he has previously argued against the utility of heteroplasmy in ocular studies, as he previously stated in the correspondence to Spaide that correlation between heteroplasmic mtDNA point mutations and clinical severity is usually poor[4] and is associated with marked phenotypic heterogeneity between family members and between generations.[5]

The medical history and daily medication of every patient might be nice to have. Giving the retrospective character of our article, we might include this as a factor for further upcoming prospective studies. Finally, Drs Finsterer and Scorza mentioned the lactate value in the cerebrospinal fluid of MIDD patients. It is not evident how this statement is germane to the focus of our article given the differences in retina/RPE vs central nervous system metabolism.[6]

They finish their comment by stating that "RPE atrophy is currently no suitable endpoint of MIDD." As shown in this reply, this statement is based on an untenable argument. As we could show throughout our manuscript, RPE atrophy is indeed a reliable and suitable endpoint for disease progression and, therefore, treatment effects. It is simple to quantify, in contrast to other endpoints both ocular and nonocular, and is an accepted endpoint by the U.S. Food and Drug Administration and European Medicines Agency for other ocular conditions.

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CONFLICT OF INTEREST DISCLOSURES: SEE THE ORIGINAL article for any disclosures of the authors.

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