REPLY

We appreciate the interest shown by Drs Finsterer and Zarrouk-Mahjoub in our study.[1] Although we agree with the comments made on the mode of transmission of several mtDNA-associated disorders, the analysis of the families and the patterns of inheritance were beyond the scope of our study.

As we stated in the Discussion, we do admit the possibility of a selection bias towards mitochondrial disorders with skeletal muscle involvement. However, we did not base our inclusion criteria on the existence of suggestive histological features. Instead, we selected all the patients with a molecularly confirmed diagnosis who also had a muscle biopsy performed and analyzed at the neuropathology unit that participated in this study, regardless of the results of the histology. Moreover, as per the supplementary tables, this study included several patients with predominant central nervous system or multisystem features who probably had a muscle biopsy only because it was more straightforward than obtaining other tissue for analysis.

We agree that it would be invaluable to have more detailed clinical information about these patients and that the source of clinical information in this study is indeed an important drawback, something we ourselves pointed out in the Discussion. We also acknowledge the potential value of biochemical and molecular data derived from the analysis of other tissues. Nevertheless, despite the limitations, we believe the results provided by this study fulfill our major objectives which were, on one hand, to offer a broad clinical description and to indentify the most frequent clinical features and, on the other hand, to analyze the relative diagnostic utility of both muscle histological analysis and respiratory chain enzyme assay in patients with suspected mitochondrial disorders. Unfortunately, the study design did not allow us to provide follow-up data, and, therefore, it precluded us from drawing any conclusion on the progression of these patients.

We believe that it is important to clarify that we have not stated that muscle biopsy worsens with age because we do not have follow-up analysis of our patients. Instead, our results suggest that older patients are more likely to show histological features of mitochondrial disorders than younger subjects.

We have, indeed, analyzed a group of 183 patients with mitochondrial histological features independently of their molecular diagnosis. In 98 of these subjects, a molecular diagnosis was pursued, and, in 46, a diagnosis was established. It was decided not to include this analysis because we thought that this might have made our report less clear for the reader.

Simão Cruz, MD[1]

Ricardo Taipa, MD[2]

Célia Nogueira, PhD[3]

Manuel Melo-Pires, MD, PhD[2]

Laura Vilarinho, PhD[3]

[1]Neurology Department, Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal

[2]Neuropathology Unit, Hospital Santo António/Centro Hospitalar do Porto, Porto, Portugal

[3]Newborn Screening, Metabolism and Genetics Unit, Human Genetics Department, Dr Ricardo Jorge National Health Institute, Porto, Portugal

1. Cruz S, Taipa R, Nogueira C, Pereira C, Almeida LS, Neiva R, Geraldes T, Guimarães A, Melo-Pires M, Vilarinho L. Clinical, biochemical, molecular and histological features of 65 Portuguese patients with mitochondrial disorders. Muscle Nerve 2017 Jan 27 Jan 27. doi:10.1002/mus.25593.

Published online 25 March 2017 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/mus.25650