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Response to Letter to the Editor: "Endocrine Disorders in Primary Mitochondrial Disease"

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We recently published an observational, cross-sectional study designed to provide estimates of the prevalence of endocrine disorders in the North American Mitochondrial Disease Consortium (NAMDC) cohort [1]. In their letter, Finsterer and Zarrouk-Mahjoub [2] highlight multiple potential opportunities for leveraging this cohort to enrich further our understanding of the etiology, burden, and management of endocrine disorders in the setting of mitochondrial disease. However, although the NAMDC registry provides a wealth of informative and well-curated patient data, it does not currently collect information with sufficient granularity to answer some of the important questions Finsterer and Zarrouk-Mahjoub raise [2]. For example, specific queries regarding endocrine neoplasms, the type of adrenal insufficiency or thyroid disorder, familial clustering of endocrine disorders, and importantly, response to therapies were not included. The NAMDC registry does systematically collect data about specific endocrine conditions that were expected to be more prevalent. Clinicians also had the opportunity to note the presence of additional conditions; polycystic ovarian syndrome and irregular menses are examples of these. In our paper, we presented data on conditions with systematically collected information separately from those noted via free text to account for potential biases introduced by these methodological differences [1].

Finsterer and Zarrouk-Mahjoub [2] also raise a question about the methods by which clinical syndromes related to mitochondrial disease were defined. Definitions of clinical syndromes were made according to standardized, consensus-based diagnostic criteria developed by NAMDC mitochondrial disease clinical experts. A category of multisystemic syndrome was assigned to those individuals with phenotypes not characteristic of a well-defined syndrome; individuals with multisystemic syndrome account for 8% of the cohort. Details on mitochondrial disease clinical syndromes included our cohort can be found in Supplemental Table 3 of our paper [1]. We also agree that there is an interesting association between mitochondrial DNA (mtDNA) deletions and/or duplications and endocrinopathies in our cohort, and we refer the reader to Supplemental Table 2 of our paper [1] for additional detail. Patients with large-scale rearrangements (*i.e.*, deletions and/or duplications) accounted for 1.7% of our cohort. Individuals with multiple mtDNA point mutations accounted for 3% of the total cohort, whereas individuals with single mtDNA point mutations made up 51% of the cohort. Although beyond the scope of our study [1], some case reports have

Abbreviations: mtDNA, mitochondrial DNA; NAMDC, North American Mitochondrial Disease Consortium.

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suggested that the nature of the mtDNA change may influence the degree of multisystem involvement. For example, pleioplasmic mtDNA rearrangements may be distributed more widely across tissues and thus may explain the simultaneous occurrence of multiple endocrine disorders in the same individual [3].

With regard to the preponderance of mtDNA molecular genetic diagnoses in the NAMDC registry, we speculate that many of these individuals may have been diagnosed prior to the current availability of advanced molecular diagnostic techniques that permit ready identification of pathologic nuclear DNA defects. It will be interesting to appreciate how the genetic epidemiology of mitochondrial disorders changes over time as these diagnostic techniques are more widely adopted.

In summary, much remains to be learned about the etiology and management of endocrine disorders in mitochondrial diseases. The NAMDC registry provides a critical resource to support future prospective studies and, importantly, for the development of evidence-based screening guidelines for endocrine disorders in this high-risk population.

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References and Notes

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