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NDUFA9 Variants Exhibit a Broad Phenotypic Spectrum, Including Generalised Dystonia or Leigh Syndrome

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LETTER TO THE EDITOR

We read with interest the article by Singh, *et al*., reporting a 26 year-old female with Leigh syndrome due to the homozygous, missense variant c.727G>A in *NDUFA9* [Singh, R. *et al*., 2023]. The patient phenotypically showed generalised dystonia and cognitive impairment [Singh, R. *et al*., 2023]. She benefited from trihexyphenidyl and clonazepam and additionally was supplemented with carnitine, coenzyme Q10, riboflavin, thiamine, vitamin E, and biotin [Singh, R. *et al*., 2023]. The study is impressive, but some points require discussion.

Leigh syndrome due a variant in *NDUFA9* was reported not only in the two cases listed in table 1 and the index case, but also by Nesti *et al*. and Shirazi *et al*. [Nesti, C. *et al*., 2023,3]. Nesti *et al*. reported a 12 year-old male with late-onset Leigh syndrome due to a variant in *DNAJC30* and the heterozygous likely pathogenic variant c.801-1G>C in *NDUFA9* [Nesti, C. *et al*., 2023]. The patient presented clinically with developmental regression, cognitive decline, epilepsy, ataxia, dysarthria, and myopathy [Singh, R. *et al*., 2023]. It was concluded that the two variants had a synergistic effect and therefore may have caused a more severe phenotype than either variant alone [Nesti, C. *et al*., 2023]. The patient reported by Shirazi *et al*. was a neonate with consanguineous parents, who presented with failure to thrive, respiratory insufficiency, and epilepsy [Shirazi, P. G. *et al*., 2022]. The cause of Leigh syndrome in this patient was the homozygous missense mutation c.1069C>G in *NDUFA9* [3]. The patient died of respiratory failure at the age of four months [Shirazi, P. G. *et al*., 2022].

Leigh syndrome is characterised by brain and serum lactic acidosis as mentioned by the authors in the introduction [Singh, R. *et al*., 2023]. Surprisingly, the index patient had neither serum nor CSF lactate elevation. Even magnetic resonance spectroscopy, which is usually more sensitive for documenting CSF lactate elevations than direct measurement, was negative. Since complex-I activity was severely reduced to 17% of normal, respiratory chain dysfunction and thus lactic acidosis are to be expected. We should know how to explain this surprising finding.

A limitation of the study is the neither the father nor the consanguineous mother were clinically or genetically examined. To assess whether the *NDUFA9* variant was inherited or occurred sporadically, it is important to also test the parents of the index patient. Was either or another first-degree relative of the index patient clinically affected by a mitochondrial disorder?

In muscle biopsy complex-I activity was reported to be reduced to 20% [Singh, R. *et al*., 2023]. What method was used to determine complex-I activity? Through a calorimetric assay such as UV VIS spectroscopy or through biochemical measurement [Rasmussen, T. *et al*., 2001]? With such low complex-I activity, one would expect skeletal muscle to be clinically affected. However, no weakness was reported [Singh, R. *et al*., 2023]. How can this surprising finding be explained? Did the patient have at least ptosis or ophthalmoparesis?

We should know whether strained voice quality was due to laryngeal muscle impairment caused by dystonia or other causes. In particular, did the patient have spasmodic dysphonia? How was dysphonia treated? The patient apparently did not receive botulinum toxin [Singh, R. *et al*., 2023]. What was the reason? Clonazepam has a strong addictive potential.

In summary, the interesting study has limitations that put the results and their interpretation into perspective and should be discussed.

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