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**Letter to the Editor**

# Renal Involvement in Carriers of the COX-I Variant M.6145G>A

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With interest we read the article by Fervenza *et al.*, (2019) about a 42 years old male with renal insufficiency and myopathy attributed to the variant m.6145G>A in the *COX-I* gene (Fervenza, F. C. *et al.*, 2019). We have the following comments and concerns.

We do not agree with the statement that electromyography and nerve conduction studies showed "diffuse myopathy without inflammation, necrosis, vacuolisation, or fiber splitting" (Fervenza, F. C. *et al.*, 2019). Electromyography can be normal, neurogenic, myogenic, or non-specific (Oaube, J. R. 1991). Nerve conduction studies may show normal/reduced nerve conduction velocity or normal/reduced compound muscle action potentials (England, J. D. *et al.*, 2005). Neuropathological features cannot be found on electromyography or nerve conduction studies.

To demonstrate the pathogenicity of a mtDNA variant it is not sufficient to investigate the effect on the protein level. It is crucial to demonstrate that the genotype/phenotype correlation is strong, that the genetic defect segregates with the phenotype through the generations, that COX-negative fibers have higher heteroplasmy rates than COX-positive fibers, that the genetic variant has a negative effect on various mitochondrial functions, that the variant is not present in healthy controls, and that pathogenicity can be demonstrated in cybrid studies (Finsterer, J. *et al.*, 2018).

Light microscopic and immunehistological findings on muscle biopsy are reported but, unfortunately, no results of electron microscopy are presented. Patients with mitochondrial myopathy frequently show abnormally shaped and structured mitochondria, an increased/decreased amount of mitochondria, and subsarcolemmal accumulation of mitochondria (McAfee, J. L. *et al.*, 2017). Ultrastructural investigations are particularly helpful, if light microscopy is normal (McAfee, J. L. *et al.*, 2017).

Overall, the interesting case lacks confirmation of the pathogenicity of the variant and presentation of ultrastructural abnormalities of the muscle. Description of electrophysiological investigations needs to be corrected.

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