Keyword 1: Mitochondria **Keyword 2:** Basal ganglia **Keyword 3:** Kearns-Sayre syndrome(KSS) **Keyword 4:** Leigh syndrome

Title: Neuropathology of PGC-1α deficiency recapitulates features of mitochondrial encephalopathies but not of neurodegenerative disorders

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Objective: To perform the systematic neuropathological characterization of mature PGC-1α knockout mice.

Background: Deficient PGC-1α axis is an established component of mitochondrial dysfunction in neurodegenerative disorders. The current histopathological classification of such diseases is based on the predominant protein accumulating as intra- or extracellular aggregates. Experimental evidence suggests that mitochondrial dysfunction and impaired protein processing are interrelated. *In vitro* findings further indicate that deficient PGC-1α functioning may contribute to protein misfolding in neurodegeneration. Despite the broad functional spectrum of PGC-1α in mitochondrial physiology, the involvement of its deficiency in mitochondrial encephalopathies has not yet been established.

Methods: 15 PGC-1α knockout and 16 age- and gender-matched wild-type mice were sacrificed. 4-µm-thick sagittal sections of paraffin-embedded brains were evaluated. To assess the pattern of neurodegeneration-related proteins, we performed immunostaining for Tau, p-Tau, α-synuclein, amyloid-β, amyloid precursor protein, prion protein, FUS, TDP-43 and ubiquitin. Furthermore, we used Hematoxylin and Eosin, Klüver-Barrera and Bielschowsky silver stainings, along with anti-GFAP and anti-CD34 immunohistochemistry for the lesion profile analysis.

Results: The immunohistochemical pattern of neurodegeneration-related proteins in knockout brains was not different from the wild-type, and there was a complete lack of neurodegeneration-related protein deposits, or ubiquitin-positive inclusions. The neuropathological alterations consisted of spongiform vacuolation predominating in the cerebral white matter, caudate-putamen, thalamus and brainstem, and reactive astrogliosis in the brainstem and cerebellar nuclei. This phenotype was thus reminiscent of human mitochondrial encephalopathies, in particular the Kearns-Sayre syndrome.

Conclusions: PGC-1α deficiency *per se* is not sufficient to recapitulate major features of neurodegenerative disorders. Our results suggest that polymorphisms in PGC-1α might be valuable targets of investigation in mitochondrial diseases with unidentified origin, and that PGC-1α knockout mice can be a viable animal model for this yet incurable group of diseases.

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