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Clinicopathological features associated with the BAG3-Pro209Leu mutation

Recently, we analyzed in detail the histopathology of a heart explant from a child with BAG3-Pro209Leu mutation and found evidence for dysregulated autophagy in the mutant cardiac tissue [1]. Finsterer and Zarrouk-Mahjoub have summarized the phenotypic spectrum of pathologies that have been associated with BAG3 mutations in the literature and have compiled some open questions related to our patient and those reported by others [2]. We agree that a more detailed description of clinical symptoms associated with BAG3 mutations can be useful. We therefore provide herein additional information for our patient, but kindly refer to the original reports for questions concerning other patients. Our patient fulfilled the diagnostic criteria for restrictive cardiomyopathy since left ventricular end-diastolic pressure was 22 mmHg at age 6 years (heart catheterization), whereas systolic function was normal (EF > 60%). Additionally, both atria were enlarged and echocardiography revealed a restrictive filling pattern. Electroneurography disclosed affection of sensory and motor fibers, whereas, clinically, there was no evidence for involvement of autonomic fibers. He had no rigid spine, and a cranial MRI was normal. However, the patient's respiratory muscle involvement and degree of cardiac dysfunction appeared insufficient to explain his degree of nocturnal hypoventilation, which suggests that a central component contributed to his early ventilatory failure.

Further characterization of the patient's pathology, e.g. in nerve and skeletal muscle, would have been interesting, but the lack of consent from the patient's parents precluded the taking of the required biopsies. In some patients, the combination of c.626C > T with other variants within *BAG3* [3] may in part contribute to the explanation of the heterogeneous phenotypes elicited by *BAG3* mutation, but many of the questions raised by Finsterer and Zarrouk-Mahjoub remain unaddressed in the literature so far.

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