Molecular Genetics and Metabolism Reports 15 (2018) 65–66

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

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BAG3-related myofibrillar myopathy requiring heart transplantation for restrictive cardiomyopathy

ARTICLE INFO

Keywords:
Mitochondrial
mtDNA
Phenotype
Genotype
Epilepsy
Seizures
Lymphocytes
MELAS
Lactic acidosis

We read with interest the article by Schänzer et al. about a 9 yo male with restrictive cardiomyopathy (rCMP), myofibrillar myopathy (MFM), and neuropathy due to the *BAG3* mutation c.626C > T [1]. The explanted heart was investigated for mutant cardiac tissue abnormalities. We have the following comments/concerns.

rCMP is clinically characterised by enlargement of both atria, diastolic dysfunction with a restrictive filling pattern (EA-ratio > 1, deceleration time < 150 ms), and normal systolic function [2]. Were these diagnostic criteria fulfilled in the index patient and all patients of table-1?

Which was the reason why one patient carrying the *BAG3* variant in table-1 manifested with hypertrophic cardiomyopathy, whereas 11 patients had rCMP? [1] It should be also discussed why one patient had long-QT syndrome and one patient no cardiac involvement [1]. Did the patient with long-QT syndrome [3] carry a second mutation associated with hereditary long-QT syndrome?

Was respiratory failure in 10/14 patients of table-1 due to affection of the brainstem, the primary respiratory muscles, or secondary due to heart failure? Differentiation of the causes of respiratory insufficiency is crucial with regard to treatment and outcome.

According to table-1 the patient reported by Kostera-Pruszczyk presented with myopathic features on muscle biopsy but did not have a myopathy according to Table 1. This discrepancy should be explained.

The index patient manifested clinically with myopathy, neuropathy, and rCMP. Did he manifest in other systems as well? Was he prospectively investigated for other phenotypic manifestations as frequently observed in *BAG3*-related FMF (Table 1).

Concerning the neuropathy, it would be interesting to know which types of fibers were affected, motor, sensory, or autonomic fibers alone or in combination. Additionally, nerve biopsy in *BAG3*-related neuropathy may show giant axons [4,5]. Were giant axons found also in the index patient?

Overall, this study requires a more widespread clinical description and a more in depth discussion of any inconsistency.

Table 1
Phenotypic spectrum of *BAG3* mutations.

Phenotype	Mutation	NOP	Reference
rCMP	c.626C > T	14	[Schänzer [1], Konersman [5], Lee [6]]
hCMP	c.626C > T, c.772C > T	1	[Schänzer [1]]
dCMP	c.913delC	1	[Rafiq [7]]
long-QT syndrome	c.626C > T	2	[Kostera-Pruszczyk [3], Lee [6]]
Respiratory insufficiency	c.626C > T, c.772C > T	11	[Schänzer [1], Lee [6], Selcen [8], Kostera-Pruszczyk [3]]
Restrictive lung disease	c.626C > T, c.772C > T	1	[Lee [6]]
Myopathy	c.626C > T	> 20	[Schänzer [1]]
Neuropathy (giant axons)	c.626C > T	> 10	[Schänzer [1]]
Intracytoplasmic inclusions	c.626C > T	6	[Schänzer [1]]
Disintegration, disarray of fibers	c.626C > T	> 10	[Schänzer [1]]
Dysphagia	c.626C > T	1	[Semmler [9]]
Hypoacusis	c.626C > T	1	[Semmler [9]]
Rigid spine	c.626C > T	> 15	[d'Avila [10], Odgerel [11]]

rCMP: restrictive cardiomyopathy, hCMP: hypertrophic cardiomyopathy, dCMP: dilative cardiomyopathy, NOP: number of patients.

https://doi.org/10.1016/j.ymgmr.2018.02.002
Received 31 January 2018; Accepted 1 February 2018
Available online 22 February 2018

There are no conflicts of interest.
No funding was received.

Author contribution

JF: design, literature search, discussion, first draft, SZ-M: literature search, discussion, critical comments.

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