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Phenotypic Heterogeneity of *RRM2B* Mutations

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Letter to the Editor

In a recent article Kropach *et al.* reported about two brothers, carrying a novel *RRM2B* mutation, which manifested as fatal encephalomyopathy with hypotonia, lactic acidosis, and developmental delay [1]. The study raises a number of comments and concerns.

We should be informed if genetic testing was also carried out in patient-1 or other first-degree relatives. Did the mutation occur in the homozygous or heterozygous state? Did patient-2 inherit the mutation from his father, mother, or both? Which was the amount of mtDNA depleted? Which other family members were clinically affected?

MIDs are usually multisystem diseases (MIMODS) [2]. Did the authors also prospectively look for cardiac, endocrine, hematological, orthopedic, dermal, or pulmonary involvement? Patients carrying *RRM2B* mutations not only manifest with features observed in Kropach's patients but also with other features (Table 1).

Patient-1 presented with focal seizures [1]. He received midazolam, hydantoin and phenobarbital [1]. Hydantoin and phenobarbital are potentially mitochondrion-toxic [3]. Did the phenotype deteriorate upon application of these compounds?

Seizures may be a manifestation of stroke-like episodes/lesions (SLEs/SLLs) [4]. Did patient-1 undergo cerebral MRI at the time seizures occurred and did it show SLLs?

Patient-1 had marked hyper-CKemia but no EMG is reported [1]. Was hyper-CKemia due to epilepsy, myopathy, or due to both? Were fatigue, exercise intolerance, cramps, or myalgia observed? Was respiratory failure due to affection of respiratory muscles, brain-stem involvement, or due to infection or heart failure?

Overall, these interesting two cases would by more meaningful by providing data about prospective investigations for MIMODS, about the family history, and more extensive genetic work-up [5-15].

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Table 1. *Phenotypic manifestations of RRM2B mutations.*

	Manifestation	Patient 1	Patient 2	Literature
Central nervous system				
	Hypotonia	yes	yes	[1]
	Missed milestones§	yes	nm	[1]
	Absent social smile	yes	nm	[1,5]
	Not recognising parents	yes	nm	[1]
	Head lag	yes	yes	[6]
	Recurrent vomiting	yes	yes	[7,8]
	Seizures	yes	nm	[1]
	Abnormal pacing reflexes	nm	yes	[1]
	Abnormal stepping reflexes	nm	yes	[1]
	Failure to thrive	yes	nm	[9]
	Failure to gain weight	yes	yes	[1]
	Nystagmus	nm	nm	[10]
	Dystonia	nm	nm	[10]
	Brisk tendon reflexes	nm	nm	[10]
	Microcephaly	nm	nm	[1]
	Elevated CSF protein	yes	yes	[1]
	Abnormal EEG	yes	no	[1,5]
	Abnormal cerebral MRI	no	no	[6]
	Cerebral hypomyelination	no	no	[11,12]
	Cerebral atrophy	no	no	[9]
	MRS lactate peak	nm	yes	[6]
Eyes				
	Myopia	nm	no	[5]
	Megacornea	nm	no	[9]
Ears				
	Deafness	nm	yes	[1]
Gastrointestinal				
	Dysmotility	nm	nm	[11,12]
	Diarrhoea	nm	nm	[7]
Renal				
	Hypocalcemia	yes	no	[1]
	Keton bodies	yes	yes	[5]

	Microalbuminuria	no	yes	[1]
	Aminoaciduria	no	yes	[1]
	Fanconi-like tubular dysfunction	no	yes	[1]
	Nephrocalcinosis	nm	yes	[1]
	Glucosuria	no	yes	[1]
Hematological				
	Anemia	nm	nm	[13]
Myopathy				
	Reduced tendon reflexes	yes	yes*	[1]
	Limb muscle weakness	nm	nm	[1,5]
	Ophthalmoplegia	nm	nm	[11,12]
	Ptosis	nm	nm	[11,12]
	Hyper-CKemia	yes	no	[13]
Neuropathy	no	no	[11,12,14]	
Others				
	Lactic acidosis	yes*	yes	[1]
	Elevated serum pyruvate	yes	no	[1]
	Elevated amino-acids	no	yes	[1]
	Increased urinary organic acids	yes	no	[1]
	Dysmorphism	yes	nm	[1]
	Respiratory failure	yes	yes	[1]
	MtDNA depletion (AR)	yes	yes	[1]
	MtDNA multiple deletions (AD)	nm	nm	[1]
	Dysphagia	nm	nm	[15]

AD: autosomal dominant transmission, AR: autosomal recessive transmission, *: not initially, §: developmental delay, nm: not mentioned

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