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The phenotypic spectrum of *NFU1* variants is broader than anticipated

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1 CORRESPONDENCE

With interest we read the article by Birjiniuk et al. about two patients with multiple mitochondrial dysfunction syndrome-1 (MMDS-1) due to the compound heterozygous variant c.622G>T and c.544C>T in *NFU1* who both developed fatal pulmonary hypertension [1]. We have the following comments and concerns.

Pulmonary hypertension has been repeatedly reported as a manifestation of a mitochondrial disorder (MID) [2,3] . Pulmonary hypertension may not only be associated with mutations in *BMPR2, SMAD9, CAV1, KCNK3, TBX4,* or *ACVRL1* but also with mutations in *MT-TL1* (m.3243A>G) [4, 5], *VARS2* [2], *MT-ND5* [6], *COX5A* [7], SARS2 [8], or *TMEM79* [9]. Pulmonary hypertension can be hereditary or acquired, acute or chronic, due to an identifiable cause or idiopathic. The most frequent causes of pulmonary hypertension are drugs, scleroderma, dermatomyositis, right ventricular hypertrophy, pulmonary valve stenosis, pulmonary artery stenosis, lung disease, chronic, obstructive pulmonary disease, congenital heart disease, persistent pulmonary hypertension of the newborn, infec-tions (e.g. HIV, schistosomiasis), liver disease, or pulmonary embolism. We should know if all these causes of pulmonary hypertension were excluded in the two index patients.

Missing in the study are imaging studies of the brain. Knowing the results of cerebral MRI is crucial as *NFU1* mutations may manifest in the brain as cavitating leukoencephalopathy [10], cystic leukoencephalopathy [11], symmetric, T2-hyperintense white matter lesions [12], T-2 hyperintens white matter lesions periventricularly and in the posterior corpus callosum [13], and atrophy of the corpus callosum [13]. MR-spectroscopy may show a reduced NAA peak, increased choline peak, and a doublet, inverted lactate peak [13]. Knowing the imaging findings is also crucial to assess if respiratory distress and arrest in patient-1was due to involvement of the brainstem, which could explain central respiratory failure.

The authors mention that alveolar growth abnormalities with an open broncho-pulmonary anastomoses suggest pulmonary hypertension [1]. However, these findings can also occur in association with genetic disease [14] or as a developmental abnormality [15]. Accordingly, pulmonary hypertension is speculative why patient-1 should not be presented as MMDS-1 with pulmonary hypertension. It is also conceivable that the pulmonary findings on autopsy in patient-1 simply resulted from primary involvement of the lungs in the underlying metabolic defect, as has been previously reported [16].

NFU1 variants may not only manifest phenotypically with pulmonary hypertension or leukoencephalopathy, but also as spastic paraplegia [13], quadruspasticity [12], or with lactic acidosis [1]. Since MIDs frequently progress to multisystem disease, we should know if the index patients were prospectively investigated for mulitorgan involvement. This is of particular interest as both died from pulmonary receptively cardiac arrest, which both can be multifactorial.

Missing is a description about the clinical features of both parents .Since they carried either pathogenic allele it is conceivable that they were mildly affected as well.

The term “multiple mitochondrial dysfunction syndrome” is only rarely used in the literature. It describes a non-syndromic MID with multiorgan involvement. Since many of the readers will not be familiar with this term it

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should be replaced by a more descriptive and accurate terminology.

Overall, the interesting article by Birjiniuk et al. could profit from providing cerebral MRI images, from clinical investigations of the parents, from discussing differentials of the pulmonary abnormalities on autopsy, and from discussing more deeply the phenotypic heterogeneity of *NFU1* variants.

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