Journal of Human Genetics (2017) 62, 865–866

www.nature.com/jhg

CORRESPONDENCE

A commentary on homozygous p.(Glu87Lys) variant in *ISCA1* is associated with a multiple mitochondrial dysfunctions syndrome

Journal of Human Genetics (2017) **62,** 865–866; doi:10.1038/jhg.2017.64; published online 15 June 2017

We read with interest the article by Shukla *et al.*[1] about two unrelated families in which one member each carried the same ISCA1 mutation manifesting as multiple mitochondrial dysfunction syndrome (MMDS). Comparison with previous investigations was not possible due to missing earlier description of ISCA1 mutations in humans. We have the following comments and concerns.

So far, MMDS was attributed to mutations in the NFU1 (15 patients),[2–6] ISCA2 (6 patients),[7] BOLA3 (5 patients)[8,9] and IBA57 (5 patients) genes,[10,11] respectively (Table 1). Altogether, MMDS has been described in 30 patients so far, including the present two.[1–11] Irrespective of the underlying mutation, MMDS predominantly manifests as encephalopathy or leukoencephalopathy (Table 1).[3] Cerebral manifestations in the 30 patients with MMDS so far reported include absence of head or trunk control, feeding difficulties, lethargy, failure to thrive, psychomotor retardation, neurological regression, spastic quadruparesis, hypotonia, dystonia, tremor, extrapyramidal signs, epilepsy, myoclonus, ataxia, optic atrophy, respiratory insufficiency, muscle hypotonia and cerebral cyst formation (Table 1).[1–11] In addition to leukoencephalopathy, patients carrying NFU1 mutations may present with pulmonary hypertension.[2,5] In patients carrying BOLA3 mutations, optic atrophy, cardiomyopathy, diabetes and diarrhea were additionally reported.[8,9] Patients carrying BOLA3 mutations may present with Leigh syndrome.[8] In one patient carrying an IBA57 mutation recurrent vomiting was reported.[10] Patient P2 presented with retinopathy.[1] Were any other features of MMDS detected in patient P2 and P4?

From mitochondrial disorders (MIDs) it is well known that they manifest with multiorgan involvement either already at onset of the disease or during progression of the disease (mitochondrial multiorgan disorder syndrome (MIMODS)). Were the two patients prospectively investigated for multisystem disease, particularly for endocrinological, pulmonary, gastrointestinal, renal, bone or dermal involvement? Did any of the two develop MIMODS? Particularly mtDNA depletion syndrome may manifest in organs other than the cerebrum.

Table 1 Manifestations of MMDS syndrome

Mutation	*NFU1*	*ISCA2*	*BOLA3*	*IBA57*	*ISCA1*
NOP	15	6	5	5	2
MOI	AR	AR	AR	AR	AR
Zygosity	chez, hoz	hoz	hoz	hoz	hoz
mtDNAdepl	nr	yes	nr	nr	nr
CNS	LE, EL, DD, SP DT, EPS, cysts	LE, DD, SP, OA	LE. SP, OA, MC EL, EPS, AT	LE, DD, SP, RI EL, cysts	LE, EL, DD, SP, TR
Eye	nr	nr	nr	nr	RP
Cardiac	nr	nr	CMP	nr	nr
Endocrine	nr	nr	Diabetes	nr	nr
Blood	Lactate ↑, glycin ↑	normal	Lactate ↑, glycin ↑	Lactate ↑	CK ↑, lactate ↑
CSF	Lactate ↑ on MRS	normal	Lactate ↑, glycin ↑	Lactate ↑ on MRS	Lactate ↑ on MRS
Muscle	SDH ↓ C2+C1 ↓ PDH ↓	atrophic MF	C1+C2+C3 ↓ PDH ↓	C1+C2+C3 ↓	nr
Fibroplasts	SDH ↓ C2+C4 ↓ C3 ↓, PDH ↓	C1 ↓	normal	nr	nr
Reference	2–6	7	8,9	10,11	1

Abbreviations: AR, autosomal recessive; AT, ataxia; chez, compound heterozygote; CK, creatine-kinase; CMP, cardiomyopathy; DD, developmental delay; DT, dystonia; EL, epilepsy; EPS, extrapyramidal signs; hoz, homozygous; LE, leucencephalopathy; MC, myoclonus; MF, muscle fibers; MOI, mode of inheritance; mtDNAdepl, mtDNA depletion; na, not reported; NOP, number of patients so far reported; OA, optic atrophy; RI, respiratory insufficiency; RP, retinopathy; SP, spasticity; TR, tremor.

Patient P2 had CK elevation.[1] Was CK elevation attributed to previous seizure activity, myopathy, cardiomyopathy or macro-CK? Were CK isoenzymes determined?

ISCA2 mutations have been reported to cause mtDNA depletion.[7] mtDNA depletion syndromes may manifest as isolated encephalopathy.[12] Were the two described patients investigated for mtDNA depletion? Was the amount of mtDNA reduced?

Was pigmentary retinopathy in patient P2 attributed to ISCA1 mutations or due to a double trouble?

Patient P2 is reported to have undergone biochemical investigations.[1] What biochemical investigations were carried out? Did patient P2 undergo muscle biopsy and biochemical investigations of the muscle homogenate? Did muscle biopsy show any histological or ultrastructural features of a MID, such as ragged-red fibers, COX-negative fibers, glycogen or fat depositions, SDH-hyperreactive fibers, or abnormally structured mitochondria?

Overall, this interesting case study shows that MMDS refers not only to cerebral abnormalities but also to multiorgan disease, including the eyes, endocrine organs, heart, lungs and the gastrointestinal tract. Although extra-cerebral manifestations may be rare in MMDS, these patients should be actively screened for MIMODS, since some of these manifestations, particularly cardiac involvement, may strongly determine their outcome.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

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

Josef Finsterer[1,3] and Sinda Zarrouk-Mahjoub[2,3]

[1]Krankenanstalt Rudolfstiftung, Vienna, Austria and [2]University of Tunis El Manar and Genomics Platform, Pasteur Institute of Tunis, Tunis, Tunisia
E-mail: fifigs1@yahoo.de
[3]These authors contributed equally to this work.

1 Shukla, A., Hebbar, M., Srivastava, A., Kadavigere, R., Upadhyai, P., Kanthi, A. *et al.* Homozygous p.(Glu87Lys) variant in *ISCA1* is associated with a multiple mitochondrial dysfunctions syndrome. *J. Hum. Genet.* **62**, 723–727 (2017).

2 Cameron, J. M., Janer, A., Levandovskiy, V., Mackay, N., Rouault, T. A., Tong, W. H. *et al.* Mutations in iron-sulfur cluster scaffold genes NFU1 and BOLA3 cause a fatal deficiency of multiple respiratory chain and 2-oxoacid dehydrogenase enzymes. *Am. J. Hum. Genet.* **89**, 486–495 (2011).

3 Invernizzi, F., Ardissone, A., Lamantea, E., Garavaglia, B., Zeviani, M., Farina, L. *et al.* Cavitating leukoencephalopathy with multiple mitochondrial dysfunction syndrome and NFU1 mutations. *Front. Genet.* **5**, 412 (2014).

4 Navarro-Sastre, A., Tort, F., Stehling, O., Uzarska, M. A., Arranz, J. A., Del Toro, M. *et al.* A fatal mitochondrial disease is associated with defective NFU1 function in the maturation of a subset of mitochondrial Fe-S proteins. *Am. J. Hum. Genet.* **89**, 656–667 (2011).

5 Nizon, M., Boutron, A., Boddaert, N., Slama, A., Delpech, H., Sardet, C. *et al.* Leukoencephalopathy with cysts and hyperglycinemia may result from NFU1 deficiency. *Mitochondrion.* **15**, 59–64 (2014).

6 Seyda, A., Newbold, R. F., Hudson, T. J., Verner, A., MacKay, N., Winter, S. *et al.* A novel syndrome affecting multiple mitochondrial functions, located by microcell-mediated transfer to chromosome 2p14-2p13. *Am. J. Hum. Genet.* **68**, 386–396 (2001).

7 Al-Hassnan, Z. N., Al-Dosary, M., Alfadhel, M., Faqeih, E. A., Alsagob, M., Kenana, R. *et al.* ISCA2 mutation causes infantile neurodegenerative mitochondrial disorder. *J. Med. Genet.* **52**, 186–194 (2015).

8 Baker, P. R. 2nd, Friederich, M. W., Swanson, M. A., Shaikh, T., Bhattacharya, K., Scharer, G. H. *et al.* Variant non ketotic hyperglycinemia is caused by mutations in LIAS, BOLA3 and the novel gene GLRX5. *Brain* **137**, 366–379 (2014).

9 Haack, T. B., Rolinski, B., Haberberger, B., Zimmermann, F., Schum, J., Strecker, V. *et al.* Homozygous missense mutation in BOLA3 causes multiple mitochondrial dysfunctions syndrome in two siblings. *J. Inherit. Metab. Dis.* **36**, 55–62 (2013).

10 Debray, F. G., Stümpfig, C., Vanlander, A. V., Dideberg, V., Josse, C., Caberg, J. H. *et al.* Mutation of the iron-sulfur cluster assembly gene IBA57 causes fatal infantile leukodystrophy. *J. Inherit. Metab. Dis.* **38**, 1147–1153 (2015).

11 Torraco, A., Ardissone, A., Invernizzi, F., Rizza, T., Fiermonte, G., Niceta, M. *et al.* Novel mutations in IBA57 are associated with leukodystrophy and variable clinical phenotypes. *J. Neurol.* **264**, 102–111 (2017).

12 Kollberg, G., Moslemi, A. R., Darin, N., Nennesmo, I., Bjarnadottir, I., Uvebrant, P. *et al.* POLG1 mutations associated with progressive encephalopathy in childhood. *J. Neuropathol. Exp. Neurol.* **65**, 758–768 (2006).