# NDUFA2 mutations cause multisystem mitochondrial disorder.

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## Letter to the Editor

In a recent article by Perrier et al. two paediatric patients with a nonspecific mitochondrial multiorgan disorder syndrome (MIMODS) due to a mutation in the NDUFA2 gene were presented [1]. One of these patients also carried a second mutation in the SLC25A4 gene, manifesting as primary carnitine-deficiency [1]. The paper raises a number of comments and concerns.

Patient-1 obviously had a double trouble from mutations in the NDUFA2 and the SLC25A4 genes [1]. Which of the clinical manifestations were attributable either to the one or the other mutation? Which of the clinical manifestations were attributable to both mutations?

Patient-1 is reported to have had severe carnitine-deficiency [1]. Was the patient substituted with L-carnitine and did the clinical manifestations attributable to carnitine-deficiency improve? Particularly patients with primary carnitine-deficiency have been reported to respond favourably to substitution with L-carnitine [2].

One sibling of patient-1 died at age 3y but it is not reported if this particular sibling was also affected by RRM1B-associated disease. Did this sibling undergo genetic testing before or after decease?

Did any of the heterozygous parents of patient-1 manifest clinically and which were the clinical manifestations in the parents? Did the parents of patient-1 also carry the SLC25A4 mutation? Did they also manifest with carnitine-deficiency?

Contrary to the statement provided by the authors, the case presented by Vanderver et al. [3] lacks a detailed clinical description and supplementary material is not accessible via the provided link, thus cannot be compared on a clinical basis with the case presented by the authors (Table 1). There is also a marked discrepancy between the phenotype provided by the present study and the phenotype reported by Hoefs et al. in [4].

Overall, this interesting study may profit from provision of more clinical and genetic data and from discussing in more detail the differences between the three patients so far reported.

**Table 1**. *Clinical manifestations in the three patients carrying a NDUFA2 mutation so far reported. Nm: not mentioned, c: corpus, cs: corticospìnal*

| Phenotype | Patient-1 | Patient-2 [3] | Patient-3 [4] |
|---|---|---|---|
| Microcephaly | no | yes | nm |
| Failure to thrive | no | yes | nm |
| Seizures | yes | nm | yes |
| Dystonia | yes | nm | nm |
| Developmental delay | yes | nm | nm |
| Spasticity | yes | nm | nm |
| Hepatomegaly | yes | nm | nm |
| Hyperammonemia | yes | nm | nm |
| Carnitine deficiency | yes | nm | nm |
| Poor feeding | yes | nm | nm |
| Lethargy | yes | nm | nm |
| Cerebellar signs | yes | nm | nm |
| Hypertrophic cardiomyopathy | no | no | yes |
| Cerebral atrophy | nm | nm | yes |
| Hypoplasia of c callosum | nm | nm | yes |
| Optic atrophy | nm | nm | yes |
| Vomiting | nm | nm | yes |

## References

1. Perrier S, Gauquelin L, Tétreault M, et al. Recessive mutations in NDUFA2 cause mitochondrial leukoencephalopathy. Clin Genetics. 2018;93(2):396-400.
2. Asai T, Okumura K, Takahashi R, et al. Combined therapy with PPARalpha agonist and L-carnitine rescues lipotoxic cardiomyopathy due to systemic carnitine deficiency. Cardiovasc Res. 2006;70(3):566-77.
3. Vanderver A, Simons C, Helman G, et al. Whole exome sequencing in patients with white matter abnormalities. Ann Neurol. 2016;79(6):1031-37.
4. Hoefs SJG, Dieteren CEJ, Distelmaier F, et al. NDUFA2 complex I mutation leads to Leigh disease. Am J Hum Genet. 2008;82(6):1306-15.

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