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Letter to the Editor

Letter to the Editor from Finsterer and Scorza: “”The m.7479G>A Variant in MT-TS1 Manifests not only with Diabetes, but as a Multisystem Disease

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Letter to the Editor

We read with interest the article by Danek *et al*. about a 71-year-old female patient with mitochondrial diabetes due to the m.7479G>A variant in the MT-TS1 gene, with a heteroplasmy rate of 14%. This variant was also suspected in her brother, mother, and a maternal uncle [1]. The patient also presented with hypothyroidism, arterial hypertension, hyperlipidemia, an intraductal papillary mucinous neoplasm of the pancreas, and hepatopathy [1]. Adequate glycemic control was achieved with metformin and gliclazide [1]. The study is interesting but raises some questions.

First, we disagree with the assumption that the m.7479G>A variant in the MT-TS1 gene is exclusively associated with diabetes. Since the patient also presented with hypothyroidism, hypertension, hyperlipidemia, a malignant disease, and hepatopathy, and these manifestations represent classic phenotypic features of mtDNA variants [2], it is highly likely that the variant caused a multisystem disease rather than a single-organ disease. In this regard, the patient was not prospectively screened for involvement of organs other than the pancreas [1]. Mitochondrial diseases are frequently multisystem diseases, either at the onset of the disease or during its progression. Multisystem involvement is often subclinical or mild, necessitating an active search for involvement of affected organs. Frequently affected organs in MIDs include the brain, spinal cord, eyes, ears, endocrine organs (except for the islet cells), heart muscle, gastrointestinal tract, and kidneys. Did the index patient exhibit mild or subclinical symptoms in any of these areas?

Second, no results of genetic tests or clinical examinations of first-degree relatives, particularly the mother of the index patient, were presented [1]. Since mtDNA variants are inherited maternally in 75% of cases [3], it is highly likely that at least those relatives of the index patient who also developed diabetes carried the causative mtDNA variant. Was at least the daughter of the index patient tested for the variant?

Third, it was not explained why the mother of the index patient developed diabetes significantly earlier than the index patient himself [1]. The variable onset of diabetes may be due to various factors besides heteroplasmy that influence the phenotypic expression of mtDNA. These include age, sex, haplotype, tissue distribution and energy requirements, mtDNA copy number, environmental and lifestyle factors, mitonuclear interactions, and nuclear genetic background [4].

The fourth point is that serum lactate levels were not reported. Since mitochondrial disorders (MIDs) are frequently associated with lactic acidosis in serum or cerebrospinal fluid, it is possible that the index patient also had elevated lactate levels. Knowledge of the serum lactate level is particularly important because the patient was taking metformin, which can increase lactate levels [5].

In summary, the m.7479G>A variant in the MT-TS1 gene likely causes a multisystem disease, but not a monosystem disease. Carriers of this mtDNA variant should be prospectively screened for multisystem diseases, and first-degree relatives of patients with a MID require clinical and genetic testing to assess phenotypic heterogeneity and provide optimal genetic counseling.

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