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LETTER

Mitochondrial Diabetes May Not Be the Only Phenotypic Presentation of the m.5826A>G mtDNA Variant [Letter]

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Dear editor

We read with interest the article by Li et al about a four-generation Chinese family with maternally-inherited diabetes due to the novel mtDNA variant m.5826A>G at the conjunction between tRNA(Cys) and tRNA(Tyr).[1] Cybrid cells carrying the variant m.5826A>G showed a 36% reduction in ATP production, a 22% reduction in mitochondrial membrane potential, and a 33% increase in ROS production compared to wild-type cells.[1] It was concluded that the m.5826A>G variant is pathogenic and presents as mitochondrial diabetes.[1] The study is attractive but raises concerns that should be discussed.

The first point is that the clinically affected and unaffected family members have not been studied prospectively for multisystem disease.[1] Since mitochondrial disorders (MIDs) due to mtDNA variants manifest phenotypically maximally initially in a single organ or tissue but become a multisystem disease either at the onset or during disease progression, it is imperative to prospectively screen these patients for multisystem involvement. Multisystem involvement can occur not only in the brain, eyes or kidneys due to complications of poorly controlled diabetes, but also in organs not normally affected by diabetic complications. These include the heart, endocrine organs, gastrointestinal tract, immune system, skin, bone marrow, and the reproductive organs. Multisystem involvement is often not obvious but is only present subclinically. A comprehensive description of the phenotype, including subclinical involvement, is crucial not only for prognostic purposes but also for genetic counselling of affected and unaffected family members.

The second point is that according to table 1, two patients had hypoacusis.[1] Therefore, these patients should be classified as having maternally inherited diabetes and deafness (MIDD) syndrome.[2] If these two patients also have additional phenotypic features, they should even be classified as MIDD plus. Although MIDD is usually due to the m.3243A>G variant, other mtDNA variants have occasionally also been reported to manifest with the MIDD phenotype.[3]

The third point is that heteroplasmy rates have not been reported.[1] Knowledge of the heteroplasmy rates of affected and unaffected tissues is important for assessing the pathogenicity of the causative variant, the expected disease progression and future phenotype, as well as for genetic counselling.

A fourth point is that determining visual acuity is not sufficient to assess whether or not ocular involvement was present. Ocular involvement in diabetes most commonly manifests in the retina as diabetic retinopathy, requiring funduscopy, optical coherence tomography (OCT), and OCT angiography. Because ocular involvement varies widely in MIDs, it is important to rule out optic atrophy, retinal atrophy, astigmatism, or cataract.

A fifth point is that the treatment of these four affected patients has not been reported. Knowledge of therapeutic management and its effects is crucial for assessing whether or not the phenotype can be positively influenced and whether therapeutic measure could have a prophylactic effect.

Received: 2 June 2024
Accepted: 23 July 2024
Published: 25 July 2024

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A sixth point is that at least one of the included patients was treated with metformin for diabetes. Since metformin is known to causes lactic acidosis and the mtDNA variants often manifest in lactic acidosis,[4] metformin should not be administered to MID patients with diabetes.

In conclusion, this interesting study has limitations that put the results and their interpretation into perspective. Removing these limitations could strengthen the conclusions and reinforce the study's message. All unsolved questions must be clarified before readers can uncritically accept the study's message. Patients carrying an mtDNA variant must be prospectively screened for multisystem disease and heteroplasmy must be reported. There is also a need to treat these patients with antioxidants, vitamins, and cofactors.

Data Sharing Statement

All data are available from the corresponding author.

Funding

There is no funding to report.

Disclosure

The author reports no conflicts of interest in this communication.

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https://doi.org/10.2147/PGPM.S481009