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Letter to the Editor

Rule out subclinical multiorgan disease in m.3243A>G and m.14502T>C carriers with diabetes

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We read with interest the article by Ding *et al*. about two Chinese families with mitochondrial diabetes due to the variant m.3243A>G in *MT-TL1* (family 1) and due to the variants m.3243A>G plus m.14502T>C in *MT-ND6* [1]. It was found that the variants m.3243A>G in *MT-TL1* and m.14502T>C are associated with mitochondrial diabetes with or without visual or otologic impairment [1]. The study also showed that the variant m.14502T>C increased the penetrance of diabetes in m.3243A>G carriers [1]. It was concluded that in patients with maternally transmitted diabetes and those at risk of carrying mtDNA variants associated with mitochondrial diabetes should undergo mtDNA sequencing [1]. The study is appealing but raises concerns that should be discussed.

There is a discrepancy between figure 1 (family tree) and the results section [1]. In the results the index patient III/7 of family 1 is described as female, whereas the family tree in figure 1 shows a male [1]. This discrepancy should be solved.

A limitation of the study is that heteroplasmy rates of either variant were not provided [1]. Knowing heteroplasmy rates is crucial as they may influence the phenotype and the phenotypic heterogeneity between family members [2]. Knowing heteroplasmy rates in various family members is also useful for genetic counselling of those at risk of transmitting the disease.

History and clinical exam are insufficient to determine if a family is affected or not. Multidisciplinary instrumental investigations are obligatory to assess if a given subject is subclinically affected or not. These investigations include, in addition to what has been carried in the study, extensive blood and urine tests, cerebral magnetic resonance imaging (MRI), electroencephalography (EEG), hormone levels, echocardiography, pro-brain natriuretic peptide (pro-BNP), electrocardiography (ECG), long-term ECG recordings, abdominal ultrasound, needle electromyography (EMG), nerve conduction studies, and eventually muscle biopsy and genetic testing. These investigations are particularly necessary in family members without apparent manifestations on clinical examination.

A further limitation is that lactate levels were not provided for any of the family members. Lactic acidosis is a common phenotypic feature of mitochondrial disorders (MIDs), particularly of patients carrying the m.3243A>G variant [3]. Therefore, it is crucial to know serum lactate levels of clinically affected and non-affected members. Missing are also serum creatine-kinase (CK) levels, organic acids in the urine, renal function tests, and myoglobin levels. They are frequently abnormal in m.3243A>G carriers [4].

Surprisingly, some family members were tested for mutations in *GJB2*, *GJB3*, and *GJB6* [1]. What was the reason for this approach? There was obvious maternal inheritance of diabetes suggesting that hearing impairment was most likely due to an mtDNA variant.

Visual impairment was found in proband II/10 of family 1. We should know if visual impairment was due to diabetes or if there were other causes, such as cataract or pigmentary retinopathy [5], explaining visual impairment.

Coronary heart disease was ruled out in patients II71, II/10, and III/7 [1]. We should know if only the history was negative for angina chest pain or myocardial infarction, or if these three patients truly had undergone coronary angiography or stress testing.

Overall, the interesting study has some limitations that call the results and their interpretation into question. Clarifying these weaknesses would strengthen the conclusions and could improve the study. Families carrying mtDNA variants require systematic comprehensive investigations of clinical affected and unaffected family members, including genetic testing to assess who is affected and how mutation loads are distributed among family members.

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