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Letter to the Editor Open Access

12S-rRNA and *COX1* carriers require comprehensive individual and family investigations and follow-up

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Letter to the Editor

In a recent article, Ding et al. reported about the diagnostic-work up of non-syndromic hearing loss in a Han Chinese family revealing two different mtDNA mutations [1]. The two variants were made responsible for the phenotype but there are some concerns with regard to the reliability of the presented data. The main shortcoming of the study is that no heteroplasmy rates of the m.1494C>T and m.7444G>A variant were provided. Phenotypic expression of an mtDNA variant may not only depend on the type and location of a mutation, on the penetrance, haplotypes, and polymorphisms, but also on heteroplasmy rates. Thus, we should be informed about heteroplasmy rates in hair follicles, fibroblasts, buccal mucosa cells, lymphocytes, muscle cells, or urine bladder epithelial cells and if heteroplasmy rates differed between these cell types. It should be also provided if heteroplasmy rates correlated with the severity of the phenotype.

A second shortcoming is that except for aminoglycosides, the history of pharmaceuticals the included patients were currently taking was not provided. Not only aminoglycosides (streptomycin, kanamycin, tobramycin, gentamycin, neomycin) may be ototoxic but also compounds such as viomycin, vancomycin, chemotherapeutics, furosemide, ethacrynic acid, salicylates, or quinones. Before establishing a genotype-phenotype correlation it needs to be excluded that any of the included patients was regularly taking any of these drugs.

Concerning the family history, we should be informed if any of the first-degree relatives presented with clinical manifestations of a MID other than hearing impairment. This is of

particular interest since the variant m.7444G>A has been reported in association with diabetes and congenital visual loss [2]. There are also reports showing that the m.7444G>A variant can cause Leber's hereditary optic neuropathy [3,4]. Since mitochondrial disorders (MIDs) may manifest subclinically [5], it is essential that all MID patients are prospectively investigated for subclinical involvement in the metabolic defect. At least imaging of the brain, heart, endocrine organs, liver, pancreas, guts, and kidneys and determination of serum hormone levels should be carried out. If no prospective investigations were carried out, previous such studies should be revised in retrospect. In this regards it also essential that standard and long-term ECG recordings, blood pressure monitoring, nerve conduction studies, and values of serum parameters, such as creatine-kinase, lactate, pyruvate, amino acids, acyl-carnitines, and urine parameters, such as organic acids, or acyl-carnitines are provided. Were asymptomatic first-degree family members screened for the mutations and were any of the index patient's variants detected? Concerning follow-up investigations, it turned out that most patients were not followed up. However, MID patients with mono-organ involvement should be routinely invited for regular follow-ups, to monitor if there is clinical progression or only subclinical progression of the disease.

In summary, this interesting study could be more meaningful if heteroplasmy rates, current medication, and carrier status of all first-degree relatives would have been provided. We should also be informed about the results of follow-up investigations and about results of prospective investigations for subclinical multiorgan involvement.

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