LETTER TO THE EDITOR

FREQUENCY OF THE m.3243A>G ANDm.3316G>A VARIANTS AMONG DIABETIC PATIENTS

Josef Finsterer, Marlies Frank
Krankenanstalt Rudolfstiftung, Vienna-Austria

Dear Editor

We read with interest the article by Wahid *et al*. about the frequency of the m.3243A>G and m.3316G>A variants in 25 patients with type-1 diabetes requiring insulin (T1DM) and 25 patients with early onset type-2 diabetes requiring oral hypoglycemics (T2DM).[1] Despite maternal transmission of diabetes in all 50 patients, neither of the two mtDNA variants was found in any of the patients in group T1DM or group T2DM.[1] We have the following comments and concerns.

There are several reasons why the authors did not find the m.3243A>G or m.3316G>A variants in their cohort. First, the sample size could have been too small to detect the expected mtDNA variants. Their frequency may be lower than estimated among the local population. Second, diabetes was not mitochondrial but due to other causes and the transmission rather autosomal than maternal. Did transmission over at least three generations strictly follow a maternal trait of inheritance? Third, abundance of the variants in blood was too low to reach the detection level. mtDNA variants are frequently heteroplasmic and heteroplasmy rates may vary significantly between different tissues. To overcome this potential flaw, tissues other than blood, such as muscle, fibroblasts, hair follicles, buccal cells, or urinary cells could be tested.

Mitochondrial diabetes may not only occur in maternally inherited diabetes and deafness (MIDD) but also in other specific or non-specific mitochondrial disorders (MIDs). Among the specific MIDs in which diabetes may be one of the clinical manifestations are MELAS syndrome, MERRF syndrome[2], chronic progressive external ophthalmoplegia (CPEO), Leigh syndrome[3], Kearns-Sayre syndrome[4], NARP syndrome, and Pearson syndrome[5]. More frequently than with specific MIDs, diabetes is associated with non-specific mitochondrial multiorgan disorder syndromes (MIMODSs).[6] Mitochondrial diabetes may not only follow a maternal but also an autosomal trait of transmission.

Since the genetic background of mitochondrial diabetes is heterogeneous, mutations other than the m.3243A>G and the m.3316G>A may be causative. Thus, future studies could investigate if T1DM or T2DM is associated with mutations in mtDNA located or nDNA genes other than the *tRNA(Lys)* or *ND1*. To select diabetic patients for genetic work-up and evaluation if mitochondrial diabetes is present, diabetic patients could be screened for the presence of phenotypic features typical for MIDs, such as short stature, dysmorphism, epilepsy, migraine, ptosis, ophthalmoparesis, cataract, thyroid dysfunction, cardiomyopathy, arrhythmias, hepatopathy, gastrointestinal compromise, renal insufficiency, hypogonadism, osteoporosis, arterial hypertension, myopathy, polyneuropathy, anemia, or mild hyper-CKemia.

Since arterial blood gas analysis was carried out in all 50 patients it would be interesting to know how many of the included patients had lactic acidosis. Was acidemia attributed to lactic acidosis or the presence of ketone bodies? In how many of the patients was acidosis attributable to renal dysfunction?

Overall, this interesting study could be more meaningful if the sample size would have been increased, if heteroplasmy rates would have been determined, and if variants in nuclear genes would have been considered as causative for mitochondrial diabetes.

Keywords: Mitochondrial; mtDNA; Phenotype; Genotype; Diabetes; Insulin; Glucagon

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Address for Correspondence:

Finsterer J, MD, PhD, Postfach 20, 1180 Vienna-Austria
Tel: +43-1-71165-72085, **Email:** fifigs1@yahoo.de