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# Pathogenicity of the Homoplasmic m.8701A>G Variant Requires Confirmation

**Josef Finsterer[1], Sinda Zarrouk-Mahjoub[2]**

[1]Krankenanstalt Rudolfstiftung, Vienna, Austria
[2]Genomics Platform, Pasteur Institute of Tunis, Tunis, Tunisia

Josef Finsterer and Sinda Zarrouk-Mahjoub contributed equally to this study.

To the Editor: We read with interest the article by Zhu *et al*. about a family with dilated cardiomyopathy (dCMP) and arterial hypertension (AHT) in four members being attributed to the m.8701A>G variant in the *ATP6* gene.[1] We have the following comments and concerns.

We do not agree with the conclusion that dCMP and AHT in the presented family are due to the m.8701A>G variant. Transmission of dCMP and AHT in this family could not only follow a maternal trait but also an autosomal dominant or even autosomal recessive trait of inheritance. Did the authors exclude mutations in nDNA-located genes which have been shown to cause dCMP, such as *MYH7*, *MYBPC3*, *LMNA*, *TNNI3*, *TNNT2*, *ACTC1*, *TPM1*, *SCN5A*, *MYL2*, *MYH6*, *MYL3*, *PLEKHM2*, *HAND1*, *RBM20*, *FBXO32*, *DES*, *YBPC3*, *MYPN*, and *PRKAG2*?[2] Arguments against the m.8701A>G variant as being causative are that the variant has not been reported as pathogenic, was homoplasmic, that no biochemical defect was demonstrated neither in skeletal muscle nor in skin fibroblasts, that the heteroplasmy rate was not tested in tissues other than lymphocytes, that a maternal trait is not the only possible transmission, that no other organs except the myocardium were affected, and that the variant occurred also in a subject of the control group. The authors themselves admit that the m.8701A>G variant has not been reported in association with cardiovascular disease.

A further objection concerns the missing investigation for chromosomal abnormalities. Chromosomal defects have been reported to result from consanguineous marriage and may also be associated with dCMP.[3]

Mitochondrial disorders (MIDs) are usually multisystem disorders manifesting as mitochondrial multiorgan disorder syndromes (MIMODS). Although MIMODS were excluded in the index patient, we should be informed if any other of the affected patients had developed involvement of organs other than the heart. Was diabetes in patient II/5 regarded as a manifestation of an MID?

Were causes of AHT other than the mitochondrial DNA variant, such as hyperthyroidism, renal artery stenosis, renal parenchymatous disease, hyperaldosteronism, or pheochromocytoma, excluded as alternative causes of AHT?

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dCMP has been reported to be associated with cardioembolism, ventricular arrhythmias, and sudden cardiac death.[4] Proband I/2 died suddenly being attributed to heart failure.[1] Were ventricular arrhythmias, asystole, and cardioembolism excluded as alternative causes of sudden death? Did any of the probands carrying the m.8701A>G variant undergo long-term electrocardiograph (ECG) recordings and which were the results?

Was any of the family members investigated for noncompaction, frequently associated with MIDs?[5] In how many were echocardiographies retrospectively reviewed for noncompaction?

We should be informed about the results of coronary angiography in the index case and their brothers. Was coronary angiography normal or indicative of coronary heart disease at least in patients II/1 and II/5 who were smokers?[1] Normal coronary angiography is required for the diagnosis of dCMP.

Overall, this interesting case requires profound confirmation of the pathogenicity of the m.8701A>G variant, all patients need to be investigated for multiorgan involvement, and long-term ECG data need to be presented. Alternative causes of dCMP and AHT need to be thoroughly excluded.

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## Conflicts of interest

There are no conflicts of interest.

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**Address for correspondence:** Dr. Josef Finsterer, Postfach 20, 1180 Vienna, Austria
E-Mail: fifigs1@yahoo.de

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