



HAL
open science

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

Josef Finsterer, Sinda Zarrouk-Mahjoub

► **To cite this version:**

Josef Finsterer, Sinda Zarrouk-Mahjoub. Pathogenicity of the Homoplasmic m.8701A>G Variant Requires Confirmation. Chinese Medical Journal, 2016, 10.4103/0366-6999.186655 . pasteur-01444599

HAL Id: pasteur-01444599

<https://riip.hal.science/pasteur-01444599>

Submitted on 24 Jan 2017

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

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

Josef Finsterer¹, Sinda Zarrouk-Mahjoub²

¹Krankenanstalt Rudolfstiftung, Vienna, Austria

²Genomics 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?

dCMP has been reported to be associated with cardioembolism, ventricular arrhythmias, and sudden cardiac death.^[4] Proband II/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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Zhu Y, Gu X, Xu C. A mitochondrial DNA A8701G mutation associated with maternally inherited hypertension and dilated

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

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

© 2016 Chinese Medical Journal | Produced by Wolters Kluwer - Medknow

Received: 25-04-2016 **Edited by:** Yuan-Yuan Ji
How to cite this article: Finsterer J, Zarrouk-Mahjoub S. Pathogenicity of the Homoplasmic m.8701A>G Variant Requires Confirmation. *Chin Med J* 2016;129:1889-90.

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.4103/0366-6999.186655

- cardiomyopathy in a Chinese pedigree of a consanguineous marriage. *Chin Med J* 2016;129:259-66. doi: 10.4103/0366-6999.174491.
2. Zhao Y, Cao H, Song Y, Feng Y, Ding X, Pang M, *et al.* Identification of novel mutations including a double mutation in patients with inherited cardiomyopathy by a targeted sequencing approach using the Ion Torrent PGM system. *Int J Mol Med* 2016;37:1511-20. doi: 10.3892/ijmm.2016.2565.
 3. Yoshii S, Suzuki S, Hosaka S, Osawa H, Takahashi W, Abraham SJ, *et al.* Partial left ventriculectomy in pediatric end-stage dilated cardiomyopathy. *Jpn J Thorac Cardiovasc Surg* 2002;50:235-40.
 4. Kumar S, Stevenson WG, John RM. Arrhythmias in dilated cardiomyopathy. *Card Electrophysiol Clin* 2015;7:221-33. doi: 10.1016/j.ccep.2015.03.005.
 5. Finsterer J. Cardiogenetics, neurogenetics, and pathogenetics of left ventricular hypertrabeculation/noncompaction. *Pediatr Cardiol* 2009;30:659-81. doi: 10.1007/s00246-008-9359-0.