Molecular Genetics and Metabolism Reports 19 (2019) 100462

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Correspondence

The importance of the nuclear background on the phenotypic signature caused by the MELAS m.1630 A > G variant

ARTICLE INFO

Keywords:
MELAS
M.1630 A > G variant
Phenotypic variability
Nuclear background
Heteroplasmic threshold

Dear Editor,

We appreciate the Letter to the Editor by Dr. Finsterer [1] in response to our publication in *Molecular Genetics and Metabolism* "The nuclear background influences the penetrance of the near-homoplasmic m.1630A > G variant in a symptomatic proband and asymptomatic mother" [2].

Though the heteroplasmic threshold concept explains most MELAS symptomology, some patients with high heteroplasmy are asymptomatic, suggesting that unknown factors could modulate the variant's penetrance and its phenotypic expression [2–4]. With only 13 proteins encoded by the mitochondrial genome, the nuclear genome contributes to mitochondrial functions via 1158 proteins [5].

The pathogenicity of the m.1630 A > G variant was demonstrated in previous studies [3,4]. The role of the nonsense *VARS2* variant as a nuclear modifier is congruent with its sole expression in the proband, and removal of two-third of the VARS2 protein reducing the valine charge of the mutated mt-tRNA^{val}. Although whole genome sequencing could reveal additional variants, the majority of pathogenic mutations are found in coding regions [6]. The differential chromatin landscape between the proband and her mother lends credence to the idea of the nuclear epigenomics modulating MELAS symptomology.

Since the mother's phenotype was reported in the original 2011 study [3], we only took detailed history and performed non-invasive tests. Over the last nine years, she remains asymptomatic with consistent higher levels of heteroplasmy in blood, urine and fibroblasts than her daughter [2,3].

The proband has not taken antiepileptic drugs for many years and at the time of the skin biopsy, which was performed prior to her kidney transplant, making the study of immunosuppressants irrelevant.

No Institutional Review Board responsible to protect the rights and welfare of human research subjects would approve measuring heteroplasmy in multiple affected organs, which could only be performed on autoptic tissues. To this day, the proband and her mother remain alive.

Conflict of interest

There are no conflict of interest to disclose.

Funding

This work was funded by the NIH National Institute of Neurological Disorders and Stroke [NS085282 to AC].

References

[1] J. Finsterer, Pathogenicity of the m.1630A > G variant remains elusive if related mutation carriers with similar heteroplasmy rates are asymptomatic, Mol. Genet. Metab. Rep. 19 (2019) 100461, https://doi.org/10.1016/j.ymgmr.2019.100461.
[2] M. Uittenbogaard, H. Wang, V.W. Zhang, L.J. Wong, C.A. Brantner, A. Gropman, A. Chiaramello, The nuclear background influences the penetrance of the near-homoplasmic m.1630A > G MELAS variant in a symptomatic proband and asymptomatic mother, Mol. Genet. Metab. (2019), https://doi.org/10.1016/j.ymgme.2019.01.022.
[3] C. Glatz, A. D'Aco, K. Smith, S.N. Sondheimer, Mutation in the mitochondrial tRNA(Val) causes mitochondrial encephalopathy, lactic acidosis and stroke-like episodes, Mitochondrion 11 (2011) 615–619, https://doi.org/10.16/j.mito.2011.04.003.
[4] R. Horvath, A. Bender, A. Abicht, E. Holinski-Feder, B. Czermin, T. Trips, P. Schneiderat, H. Lochmuller, T. Klopstock, Hetreoplasmic mutation in the anticodon -stem of mitochondrial tRNA(Val) causing MNGIE-like gastrointestinal dysmotility and cachexia, J. Neuro 256 (2009) 810–815, https://doi.org/10.1007/s00415-009-5023-8.
[5] S.E. Calvo, K.R. Clauser, V.K. Mootha, MitoCarta2.0: an updated inventory of mammalian mitochondrial proteins, Nucleic Acids Res. 44 (2016) D1251–D1257, https://doi.org/10.1093/nar/gkv1003.
[6] C.J. Carroll, V. Brilhante, A. Suomalainen, Next-generation sequencing for mitochondrial disorders, Br. J. Pharmacol. 171 (2014) 1837–1853, https://doi.org/10.1111/bph.12469.

Andrea Gropman[a], Anne Chiaramello[b,*]
[a] *Children's National Medical Center, Division of Neurogenetics and Developmental Pediatrics, Washington, DC 20010, USA*
[b] *Department of Anatomy and Cell Biology, George Washington University School of Medicine and Health Sciences, Washington, DC 20037, USA*
E-mail address: achiaram@gwu.edu (A. Chiaramello).

* Corresponding author.

https://doi.org/10.1016/j.ymgmr.2019.100462
Received 11 February 2019; Accepted 12 February 2019
Available online 16 February 2019
2214-4269/ © 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/BY-NC-ND/4.0/).