It Remains Unproven That the Variant M.8231C>A Causes Coronary Atherosclerosis

Abstract:

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Letter to the Editor

With interest we read the article by Heidari et al., 2020 about a study on the association between mtDNA mutations coronary heart disease (CHD) in 109 Iranian patients (Heidari, M. M. et al., 2020). The authors found 10 missense mutations, 9 synonymous polymorphisms, and 6 variants in tRNA genes and that particularly the novel, heteroplasmic variant m.8231C>A in MT-CO2 is associated with CHD (Heidari, M. M. et al., 2020). We have the following comments and concerns.

The main shortcoming of the study is that the pathogenicity of the variant m.8231C>A was assessed only upon in-silico methods (Heidari, M. M. et al., 2020). Though the variant occurred in a heteroplasmic distribution, caused a non-synonymous amino acid exchange, and was significantly more prevalent in CHD patients than controls, pathogenicity remains unproven. To confirm pathogenicity it is crucial that segregation of CHD with the variant within the family is documented, that biochemical studies confirm a defect in the respiratory chain, that immune-histological studies show reduced respiratory chain activity, and that cybrid studies show that this particular variant induces the mitochondrial defect (Finsterer, J. et al., 2018).

The second shortcoming is that patients carrying probably pathogenic mtDNA variants were not systematically investigated for multisystem disease. Mitochondrial disorders (MIDs) are usually multisystem diseases either already at onset or progress from a mono-organ disease to a multisystem disease during the disease trajectory (Finsterer, J., & Zarrouk-Mahjoub, S. 2017). Though we agree that a pathogenic mtDNA variants may cause atherosclerosis (Finsterer, J. 2020), most patients with mitochondrial artery disease also present with typical manifestations of a MID also in other organs.

A third shortcoming is that the authors describe the m.8231C>A variant as heteroplasmic but the heteroplasmic is not provided. To assess the pathogenicity, we need to know the degree of heteroplasmia, preferably not only in a single tissue but various tissues, such as hair follicles, skin fibroblasts, buccal mucosa, lymphocytes, muscle, or urinary epithelial cells. We need to know in which tissue the heteroplasmia rate was determined and to which degree it varied between the eight patients carrying this variant. Additionally, we should be informed about the mtDNA copy number as it may strongly determine the phenotype (Scholle, L. M. et al., 2020).
The fourth shortcoming is that no explanation is provided why the culprit mtDNA variant only affected the coronary arteries but no other territory. Usually mtDNA mutations are present in all cells throughout the body, why it can be expected that atherosclerosis may occur ubiquitously.

The fifth shortcoming is that no information about the classical risk factors (arterial hypertension, smoking, diabetes, hyperlipidaemia) was provided. Only after exclusion of these highly prevalent risk factors for atherosclerosis, it can be assigned to the mitochondrial defect.

In summary, the conclusions drawn have to be regarded with caution before the shortcomings outlined above were met. To establish stringent genotype phenotype correlations and accuse an mtDNA variant to cause coronary heart disease, extensive in-depth investigations are a prerequisite.

REFERENCES