Phenotypic Expression of the m.3243A>G Variant Not Only Depends on Heteroplasmy Rates

Abstract:

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Letter to the Editor

With interest we read the article by Shand, J. A. et al., (2020) about renal involvement in monozygotic twins carrying the mtDNA variant m.3243A>G at heteroplasmy rates 20%/40% (twin-1) respectively 10%/40% (twin-2) in blood lymphocytes respectively buccal mucosa (Shand, J. A. et al., 2020). Variable onset of end-stage kidney disease (ESKD) in both patients was attributed to their different heteroplasmy rates (Shand, J. A. et al., 2020). We have the following comments and concerns.

Heteroplasmy rates from blood lymphocytes/buccal mucosa (not affected) are not representative for disease severity in clinically affected organs (kidneys) (Ganetzky, R. D. et al., 2019). More appropriate than heteroplasmy rates from a tissue not affected, such as lymphocytes, would be urinary epithelial cells or renal tissue. We should know heteroplasmy rates in both twins from urinary epithelial cells and in the explanted kidneys. In patients with renal involvement in a mitochondrial disorder (MID) due to the variant m.3243A>G heteroplasmy rates in the kidneys may as high as 89% (Finsterer, J., & Zarrouk-Mahjoub, S. 2014).

Phenotypic expression, and thus disease severity, progression, and outcome, may not only depend on the heteroplasmy rate but also on mtDNA copy number (Rudnicki, M. et al., 2016). We should know if mtDNA copy number was reduced (mtDNA depletion) or not in index patients.

Since the grandfather of the index patients had deafness but not the grandmother and since two uncles had deafness as well, it is more likely that the phenotype of the index patients is not only attributable to the mtDNA variant alone but to a second mutation in a yet unidentified nuclear gene with autosomal dominant inheritance. Thus, genetic work-up should be expanded to whole exome sequencing (WES).

We do not agree with the statement that “The level of organ impairment relates to its metabolic demand, rate of cell turnover, and individual tissue-level mutation load, or heteroplasmy” (Shand, J. A. et al., 2020). Other factors that determine the phenotype include mtDNA copy number, haplotype, polymorphisms, drugs, oxidative stress, diet, and environmental toxins. Renal function may also depend on drinking habits. Were they the same in both twins?

The m.3243A>G variant may manifest in the kidneys not only as focal segmental glomerulosclerosis (FSGS) or as ESKD (Shand, J. A. et al., 2020), but also with nephrolithiasis (Scholle, L. M. et al., 2020), granular swollen epithelial cells (Bargagli, M. et al., 2019), macroalbuminuria (Sugai, K. et al., 2018), interstitial fibrosis (Finsterer, J., & Zarrouk-Mahjoub, S. 2014), renal insufficiency (Zhu, J. et al., 2017), non-specific glomerular changes (Koene, S. et al., 2015), abnormal mitochondria in podocytes and tubular epithelial cells (Alcubilla-Prats, P. et al., 2017), or renal cysts (Yanagihara, C. et al., 2001).
The variable phenotypic expression even in monzygotic twins can be explained by the bottleneck effect and tissue segregation. The copy number of mutated mtDNA may be different in both halves of the fertilised oocyte after the first division and mutated mtDNA may be distributed to different progenitor cells in both twins.

We do not agree with the statement in the abstract that “The mtDNA mutation mt.3243A>G is most commonly associated with maternally inherited diabetes and deafness” (Shand, J. A. et al., 2020). The syndrome most frequently associated with the m.3243A>G variant is mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) (Finsterer, J., & Scorza, F., 2017).

Overall, this interesting study has a number of shortcomings, which need to be addressed before conclusions as those presented, can be drawn. Heteroplasmy rates in urinary epithelial or renal cells need to be determined, mtDNA copy numbers need to be presented, all factors influencing disease severity should be considered, and heteroplasmy rates and mtDNA copy numbers should be determined in other first degree relatives.

REFERENCES


