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Letter to the Editor

Pathogenicity of the Variant M.4414T>C in MT-TM Remains Unproven

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With interest we read the article by Hellebrekers *et al.*, about a 66yo female with depression, glaucoma, arterial hypertension, diabetes, sarcoma, and myopathy being attributed to the variant m.4414T>C in *MT-TM* (Hellebrekers, D. M. *et al.*, 2019). The variant was classified as pathogenic and thus causative for the phenotype (Hellebrekers, D. M. *et al.*, 2019). We have the following comments and concerns.

We strongly disagree that the presented variant is definitively pathogenic. A strong argument against definite pathogenicity is the modified Yarham-score (Finsterer, J. *et al.*, 2018). According to this score at most 9 points can be assigned (>1 independent report: 0, heteroplasmy: 2, disease segregation with variant: 0, biochemical respiratory chain complex defect: 0, variant segregation with biochemical defect in single-fiber studies: 3, cybrid studies: 0, evolutionary conservation: 2, evidence on histopathology: 2). Thus, the variant has to be re-classified as possibly pathogenic. Since no measurements of respiratory chain complex activity was carried on the muscle homogenate and since the validity of quadruple immune-florescence is uncertain, there is no evidence for a combined oxidative phosphorylation defect. A further argument against pathogenicity is the low heteroplasmy rate of 30% in muscle and zero heteroplasmy in hair follicles, buccal mucosa, urinary epithelial cells, or blood lymphocytes (Hellebrekers, D. M. *et al.*, 2019). Since not only the muscle was affected, heteroplasmy can be expected also in tissues other than the muscle.

The authors claim that the variant occurred sporadically. A variant can be classified as sporadic only if it is absent in both parents. Since the parents were not tested for the variant, the mutation cannot be classified as sporadic. Since pathogenic mtDNA variants are maternally inherited in 75% of the cases (Poulton, J. *et al.*, 2017), the probability that the m.4414T>C variant was inherited from the mother is high. To assess if she was clinically affected it would be helpful to know at which age she deceased, which was the cause of death, and which her last medication was.

We also disagree with the notion of a "myopathic phenotype" in the index patient. Mitochondrial disorders (MIDs) are usually multisystem disorders affecting the brain, eyes, ears, endocrine organs, heart, lungs, intestines, kidneys, skin, bone marrow, immune cells, and the cartilage. Accordingly, the index patient presented with a multisystem MID affecting the brain (depression), muscles (myopathy), eyes (glaucoma), cardiovascular system (hypertension), and the endocrine system (diabetes). Since multisystem involvement in MIDs

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may be mild or subclinical, these patients need to be prospectively investigated for multiorgan disease.

Concerning the wording "progressive external ophthalmoplegia and myopathy" it would be more suitable to talk about myopathy of the extra-ocular and the limb muscles. External ophthalmoplegia means myopathy.

Concerning the malignancy of the patient, it should be mentioned that the frequency of neoplasms is generally increased in MIDs (Finsterer, J., & Frank, M. 2016) and that there are indications that mitochondrial dysfunction is involved in cancerogenesis (Abdelwahab, E. M. M. *et al.*, 2019).

Overall, the study may profit from more profound confirmation of the pathogenicity of the variant, from prospective investigations for multisystem disease, and from clarifying if the variant was truly sporadic or inherited.

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