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Pathogenicity of the variant m.15990C>T in progressive external ophthalmoplegia remains unproven

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ABSTRACT

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Key words: respiratory chain–mtDNA–tRNA–heteroplasmy–pathogenicity–myopathy

1 CORRESPONDENCE

With interest we read the article by Joshi et al. about a 34yo female from Kosovo with progressive external ophthalmoplegia (PEO) due to the variant m.15990C>T in *mt-tRNA(Pro)* (*MTTP*) [1]. The phenotype was classified as pure PEO and the culprit variant was classified as pathogenic [1]. We have the following comments and concerns.

The authors claim that the variant m.15990C>T occurred as a de novo mutation in the index patient. However, in the mother they looked for the variant made responsible for the phenotype only in blood, urothelial cells, buccal cells and hair shafts but not in muscle [1]. Since the mutation in the index patient was only found in muscle and not in blood, urothelial cells, buccal cells and hair shafts [1], it is crucial that the mother's muscle is investigated for the mutation before classifying the variant as de novo. Additionally, muscle mtDNA of the nine clinically asymptomatic siblings of the index patient needs to be tested before grading m.15990C>T as de novo.

The variant m.15990C>T was classified as definitively pathogenic [1]. However, the Yarham score for assessing the pathogenicity of a mt-tRNA variant was not applied [2]. Application of the modified Yarham score [3] yielded the following results: >1 independent report: 0; heteroplasmy: 2; disease segregation with the variant: 0; biochemical CI, CIII, or CIV defect: 0; variant segregation with the bio-chemical defect in single fiber studies: 3; mutant mt-tRNA steady state level studies or evidence of pathogenicity on trans-mitochondrial cybrid studies: 0; evidence of normality in cybrid studies: 0: evolutionary conservation of nucleotide: 2; mitochondrial histopathology: 2. Thus, with a scoring result of nine points the variant has to be classified as only "possibly pathogenic" [3].

The authors classified t he p henotype a s p ure P EO [1]. However, except for cardiac investigations, the patient was not prospectively investigated for subclinical or mildly manifesting multisystem disease (PEO plus) [4]. *MTTP* variants may also manifest as retinopathy [5], retinitis pigmentosa, dilated cardiomyopathy, myoclonic epilepsy, ataxia, leukoencephalopathy, hearing loss, dysarthria, or nystagmus.

Missing in this report is the information about the relation between the parents. We should know if the parents were consanguineous or not. This is of relevance since the patient originated from Kosovo, where consanguinity rates may be increased compared to non-Muslim countries.

Overall, this interesting case report has a number of shortcomings which do not allow currently classifying the culprit variant as pathogenic and the phenotype as pure.

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