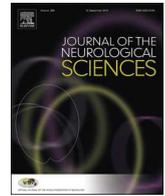




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Letter to the Editor

Response to "Letter to the editors" in regard to the article 'Genetic heterogeneity of mitochondrial genome in thiamine deficient Leigh syndrome patients'



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Dear Editor,

We would like to thank Dr. Josef Finsterer for the inquiry regarding our study [1]. As per the main concern of Dr. Josef towards the pathogenic nature of all the identified variations of mitochondrial DNA of Leigh syndrome (LS) patients, we would like to mention that in our study [1], we have primarily highlighted the level of genetic heterogeneity in mitochondrial DNA of thiamine deficient LS patients. Further based upon the association of these nucleotides with other diseases, their status in controls as well as results of *in-silico* analysis we proposed the possible pathogenic nature of these variation. The outcome of our study did not prove the pathogenicity of these variations rather identified some important variations which may further be studied by cybrid assays to functionally validate their pathogenicity.

Based upon the above-mentioned criteria, we have suggested that "Out of all the 100 non-synonymous nucleotide changes, several reported variations such as A3796G, T6253C, G6267A, G7830A, G7859A, T8594A, T8987C T10237C, A10398G, C10980G, G14831A and few novel variations such as G8863A, A7746G, G7269A, G6036A, and T13994A. Based on their *in-silico* predictions, these variations may possibly affect the activity of respective protein and in turn the ATP level too. However, functional assays (cybrid generation) are an important and final step to validate their role in the disease [1]." Here all the variations except A10398G is exclusively present in patients only. A10398G is also suggested to be pathogenic because of its proven association with AD, PD and Breast cancer [2,3]. Hence based upon the concept of phenotypic heterogeneity of mtDNA mutations, this variation may be influencing the effect of other mt DNA variations observed in respective patients.

With respect to the concern raised towards the homoplasmic nature of variations identified in our study, we would like to mention that though the heteroplasmic nature of a variation is indicator for its pathogenicity, however the possibility of homoplasmic variation exhibiting pathogenicity cannot be completely ruled out. A good number of literatures have indicated the pathogenic nature of homoplasmic variations too. Interestingly these variations are reported in Leigh syndrome and other mitochondrial diseases too [4–12]. In case of Lebers' hereditary optic neuropathy, more than 90% of patients have one of three, often homoplasmic, pathogenic mtDNA mutations

(3460G > A, 11778G > A, and 14484T > C) [13].

In his letter, Dr. Finsterer also pointed out that four variants m.8701A > G, m.8860A > G, m.10398A > G, and 15326A > G were observed in a large number of patients and may not be pathogenic. We compared the frequencies of these variations in patients and controls and as a result it was observed that there was no significant difference in prevalence of A10398G and A8701G ($p = .0516$ and $p = .795$, respectively) However, the difference in the frequencies for nucleotide variation A15326G and A8860G was significantly high ($p = .0001$) [1]. These two variations are also known to be found in different mitochondrial diseases as a polymorphism. We suggested that on different nucleotide background in patients, A8860G and A15326G may act like a secondary variation and influence the effect of primary nucleotide changes in those patients. It may emphasize upon the phenotypic heterogeneity of A15326G and A8860G variations and their possible pathogenic nature too.

As Dr. Finsterer noted that histopathological findings are no argument for pathogenicity as only 23 of 165 patients underwent muscle biopsy. We also accept it and mentioned about the unavailability of many biopsy samples, as most of these infants were admitted in acute life-threatening condition [1]. Also we have not correlated any specific genetic defect with particular abnormalities on muscle biopsy. This part of the study is just an attempt to showcase the structural and functional defect in muscle biopsy of these patients.

As a clarification towards the last point regarding the association of 4216T > C with multiple sclerosis (MS) it may be noted that though T4216C variation has frequently been investigated in MS patients; nonetheless, controversy has existed about the evidence of association of this variation with susceptibility to MS. However an extensive systematic review and meta-analysis based study exploring the association of T4216C variation with susceptibility to MS, have led to a common conclusion. This systematic review and meta-analysis done by the group of Andalib S et al. suggested that T4216C variation is a contributory factor in susceptibility to MS [14]. The study conducted in year 2016 by Andalib S et al. was also followed and cited by Barcelos IP et al. in current year [15].

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Declaration of Competing Interest

None.

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