

Author Response: Penetrance of the LHON Mutation m.11778G>A May Depend on Factors Other Than Haplotype or Heteroplasmy Rate

We appreciate the effort shown by the authors and their comments¹ on our article “Leber’s Hereditary Optic Neuropathy-Specific Mutation m.11778G>A Exists on Diverse Mitochondrial Haplogroups in India.”² Leber’s hereditary optic neuropathy (LHON) is the most common, well-diagnosed, and maternally inherited mitochondrial disease. In this case, we would emphasize the statement that LHON is one of the most well characterized maternally inherited mitochondrial disease.

We do agree with the statement that penetrance may depend on the age of individuals who carry the mutation. To date, our follow-up data do not reveal nonsymptomatic mutation carriers to have developed visual impairment and LHON. The data presented are to the best of our knowledge, till the time the manuscript was written. However, most of the families are in contact with the clinicians and have been informed about their genetic diagnosis. The families were followed up for the period of study (2005–2016), and patients were included if they developed visual disturbance.

As discussed in the article,² 13 out of 64 LHON families with m.11778G>A mutation were observed in heteroplasmic condition, and the remaining 51 were homoplasmic. In total (22 out of 145), 15% of manifesting mutation carriers was present with heteroplasmic form, while 31% of mutation carriers (124 out of 398) were present with homoplasmic condition.

We do agree with the authors that knowledge of environmental factors (tobacco smoke) would greatly help in answering the penetrance of these LHON pedigrees. However, we realized during the study that quite a significant percentage of participants were not ready to share the details about their smoking and alcohol consumption history in an accurate way. At present, we lack proper details of the tobacco smoke and alcohol consumption for all the pedigrees and the amount of information, which we have, is not sufficient to make any specific conclusion about this issue. Keeping this in mind, we have decided to exclude this information from this study.

During the initial analysis, 41 out of 64 index cases had positive family history of LHON. Seven affected individuals have mothers clinically manifesting LHON. During the course of this study, all the index cases were investigated for multiorgan involvement. We observed one patient from the index case had mild hepatosplenomegaly, while the other patients from index cases do not have any organ involvement. Hence, we would not be able to make conclusions about the multiorgan involvement and heteroplasmy level.

None of the tRNA variants scored >11 on the Yarham score.³ One of the limitations was that we do not have all the information required for predicting the Yarham score for each patient due to absence of histology and transmittochondrial cybrid study for all the mutations.

During initial clinical diagnosis of LHON-like symptoms for the patients, blood samples were collected for genetic diagnosis, which was confirmed by the presence of mutation. We, therefore, do not agree with collection of invasive samples like muscle biopsy in all the cases, but it was collected for a few cases where patients gave their consent. Hence, we were not able to perform all the analysis for predicting the Yarham score for additional variants observed together with m.11778G>A mutation. We also think it would be very difficult to segregate the effect of additional variant, since patients already have pathogenic mutation.

We do agree with authors that pathogenicity of variants may be confirmed by using single fiber and cybrid analysis. However, it is not possible for us to make cybrids for all the variants; nevertheless, for the continuation of this project, we have a plan to select a few of the potential variants to study their role in different haplogroup backgrounds.

Nabid Akhtar Khan¹
Periyasamy Govindaraj^{2,3}
Nagasamy Soumitra⁴
Sonika Sharma¹
Sundaramoorthy Srilekha⁴
Selvakumar Ambika⁵
Ayyasamy Vanniarajan^{1,6}
Angamuthu Kanikannan Meena⁷
Megha S. Uppin⁸
Challa Sundaram⁸
Parayil Sankaran Bindu^{3,9}
Narayanappa Gayathri^{3,9}
Arun B. Taly^{3,9}
Kumarasamy Thangaraj¹

¹CSIR–Centre for Cellular and Molecular Biology, Hyderabad, India; ²Department of Neuropathology, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, India; ³Neuromuscular Laboratory, Neurobiology Research Centre, NIMHANS, Bengaluru, India; ⁴SNONGC Department of Genetics and Molecular Biology, Vision Research Foundation, Sankara Nethralaya, Chennai, India; ⁵Department of Neuro-Ophthalmology, Medical Research Foundation, Sankara Nethralaya Chennai, India; ⁶Department of Molecular Genetics, Aravind Medical Research Foundation, Madurai, India; ⁷Department of Neurology, Nizam’s Institute Medical Sciences (NIMS), Hyderabad, India; ⁸Department of Pathology, Nizam’s Institute Medical Sciences (NIMS), Hyderabad, India; and the ⁹Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, India.

Correspondence: thangs@ccmb.res.in

NAK and PG contributed equally to the work presented here and should therefore be regarded as equivalent authors.

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