Author’s response to reviews

Title: Novel likely pathogenic variants in TMEM126A identified in non-syndromic autosomal recessive optic atrophy: two case reports

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Author’s response to reviews:

We thank the reviewers and editors for their insightful comments and suggestions. Below are our point-by-point responses to all comments.

Technical comments

1. In the ‘Funding’ statement, please declare the role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Authors’ response: We have added the following sentence to the Funding statement (page 11, lines 275-276): “The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.”

2. In the ‘ethics approval and consent to participate’ and ‘consent for publication’ section, please clarify who gave informed consent in the case of the 16- and 14-year old children involved in the second case study.
Authors´ response: We have added the following sentence to the Ethics approval and consent to participate section (page 11, lines 265-266): “For the probands of family B who are underage, informed consent for participation in this study was obtained from the probands’ parents.”

In addition, we have added the following sentence to the Consent for publication section (page 12, lines 292-294): “For the probands of family B who are underage, informed consent for publication of this study was obtained from the probands’ parents.”

3. In the ‘ethics approval and consent to participate’ section, please add any reference number of ethics approval

Authors´ response: We have adapted the following sentence in the Ethics approval and consent to participate section (page 11, lines 266-269): “The study was approved by the institutional review board of the Ethics Committee of the University Hospital of Tübingen (study number 637/2017BO1, dated October 23, 2017) and the Ethics Committee of the Hamburg Chamber of Physicians (study number PV3802, dated March 1, 2016).”

Editor Comments

In addition to the reviewers’ comments I would like to add the following: In your study you conclude that more information on the effect of TMEM126A alterations on mitochondrial function is needed to confirm the exact pathogenic mechanisms that cause autosomal-recessive non-syndromic atrophy. Therefore, we kindly ask you to revise the portions of the text that state a causal relationship between the variant and the disease.

Authors´ response: We carefully read the manuscript and found only one statement that postulates a causal relationship between the variants we identified and arOA, namely in the Background section of the Abstract, stating: “Here we report two novel variants in the TMEM126A gene from non-Maghreb patients, both resulting in an arOA phenotype.” We have changed this sentence into: “Here we report two novel variants in the TMEM126A gene from non-Maghreb patients, both found in patients with an arOA phenotype.” (page 2, lines 33-34).

Throughout the manuscript, we make use of wordings like “putative pathogenic” or “likely to be deleterious”. We also point out that the missense variant we identified has to be categorized as variant of unclear significance according to the guidelines for the classification of sequence variants by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology.

We also changed the title of the manuscript into “Novel likely pathogenic variants in TMEM126A identified in non-syndromic autosomal recessive optic atrophy: two case reports”
Reviewer 1

• Please change the term "mutation" to "pathogenic variant" or "likely pathogenic variant" in the text and in the title as well.

Authors´response: We replaced the term “mutation” with “pathogenic variant” except for “mutational spectrum” and “founder mutation” as these are collocations.

• Please prefer the term "affected individuals" to "patients"

Authors´response: We replaced the term “patient” with “affected individual” or “proband” except for “index patient” as this is a collocation.

• Put TMEM126A in Italic type when dealing with the gene throughout the manuscript and abstract.

Authors´ response: TMEM126A is in italics only if we refer to the gene. If we refer to the protein, it is not in italics.

Reviewer 2

• The manuscript contains too many figures (n=6). The results of the molecular genetic analysis and the pedigrees could be merged. Also, clinical data should be presented in one figure, which will provide more concise information. There is no need to show all the sequence chromatograms. Just the one showing the mutation is sufficient.

Authors´response: For the sake of clarity and visualization we rather leave the clinical data as it is. However, we have merged the sequence chromatograms into the pedigree and thereby reduced the number of figures to five.

• Line 37 A diagnostic gene panel revealed a splice donor variant (c.86+2T>C) in the TMEM126A gene

It would better for clarity to add that that the mutation was found in a homozygous state

Authors´response: We changed the sentence accordingly (page 2, line 38).

• 39 aberrant transcript lacking exon 2, presumably representing a functional null allele.

Authors´response: We are not sure what the reviewer wants us to do with this sentence.
• Line 105 visual acuity testing, Which charts were used for visual acuity testing?
Authors´ response: We have added this information (BCVA, Snellen) (page 5, line 107).

• Line 124 variants were called (VarScan 2.4.2, CeGaT extended version) with a minimum variant allele frequency of 5%
Why the 5% threshold?
Authors´ response: Variants showing the mutant allele in less than 5% of reads are considered technical artefacts.

• 41 early childhood. A missense variant (p.S36L)
I would recommend to describe the mutation at protein level using HGVS guidelines, i. e. with ()
Authors´ response: We replaced the mutation descriptions at protein level according to the HGVS guidelines.

• Line 147 Please add to the methods which OCT device was used.
Authors´ response: We added this information (spectral domain optical coherence tomography (SD-OCT; Heidelberg Engineering GmbH, Heidelberg, Germany)) (page 5, lines 108-109).

• Line 160 The girl was diagnosed with poor vision and achromatopsia in early childhood.
Was she misdiagnosed? This should be noted for clarity to avoid readers thinking that she had two different ocular traits.
Authors´ response: We modified the paragraph into:” The girl was initially diagnosed with poor vision and achromatopsia in early childhood. The clinical diagnosis was revised to optic atrophy when visual evoked potentials showed reduced potentials and delayed latency periods at the age of 14.” (page 7, lines 164-166)

• Line 205 TMEM126A was proposed as the genetic defect underlying non-syndromic autosomal-recessive optic atrophy (arOA)
Abbreviation orOA has been introduced already in the Introduction.
Authors´ response: We changed the sentence accordingly (page 9, lines 209-210).
•Line 239 needed to confirm the exact pathogenic mechanisms that cause autosomal-recessive non-syndromic

The same comment as above.

Authors´ response: We changed the sentence accordingly (page 10, lines 242-243).

•Line 210 the current manuscript, we provide additional evidence for the implication of biallelic TMEM126A mutations in arOA, as we diagnosed two additional cases

Avoid using additional twice in the same sentence.

Authors´ response: We changed the sentence accordingly (page 9, lines 214-216).