Author's response to reviews

Title: Inherited KIF21A and PAX6 gene Mutations in A Boy with Congenital Fibrosis of Extraocular Muscles and Aniridia

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Author's response to reviews: see over
Dear Editors,

We thank all reviewers for their thorough inspections and constructive comments on our manuscript “Inherited KIF21A and PAX6 gene mutations in a child with Congenital Fibrosis of Extraocular Muscles and Aniridia”. According to their suggestions, we revised the text as follows:

Reviewer #1

1. “In Conclusion”: Include that both CFEOM type I and aniridia are AD disorders. The proband's children have 50% risk of inheriting each of these disorders. His children can inherit both CFEOM and aniridia from him.”
Yes, we think so.

2. “Risk for parents to have additional children with the 2 disorders should also be mentioned in discussion”.
Thanks. According to your suggestion, we added some discussion about the risk for parents to have additional children.

3. “In isolated aniridia with mutations in PAX6 -- THERE IS NO INCREASED
RISK OF WILMS tumor. WILMs tumor risk is increased only in individuals with deletion of PAX6 along with involvement of neighbouring gene "WT1". Explain about importance of differentiating the 2 so that now that a PAX6 mutation has been identified, screening for abdominal tumors by routine U?S not required any longer and this is important for families and reduces anxiety about tumors.

Thanks for your suggestion. We added some contents to the second paragraph of introduction and some details to the Material and Methods for explaining the differences between WAGR syndrome and aniridia.

4. "Describe other clinical features and recommendations for follow up of these Patients"

Thanks for your suggestion. We added some sentences into the Material and Methods for describing other clinical features and follow-up of the patients, for example, the outcome of the CFEOM patients after surgery.

5. “Please correct on page 3, 2nd para last line -- "WAGR" caused by contiguous gene deletion syndrome”.

Thanks for your suggestion. We corrected it in the second paragraph of introduction.

6. “In Materials and methods: Change "accepted" to "underwent" strabismus surgery. Change line 7 & 8 to proband was found to have limited extraocular movement soon after birth.”

Thanks. As proposed, we changed the word "accepted" to “underwent”, and modified the sentence into “The grandfather was found to have limited extraocular
movement soon after birth and underwent strabismus surgery for treatment of CFEOM in 1991”.

7. “Page 5 paragraph 3 - please provide additional details as to why the authors feel the transcript will be subject to NMDA. Describe when a truncated protein may be formed versus when it will be haploinsufficiency because of NMDA.”

Thanks for your suggestion. We added some statements in the discussion to explain why we think the truncated protein in our study undergoing NMDA.

8.”indications and prognosis in CFEOM1 when surgical options are sought.”

Thanks for your suggestion. We added some sentences for describing the outcome of our patients with CFEOM before and after surgery.

Reviewer #2
1. “In addition, aniridia is usually associated with kidney nephroblastoma, genitourinary anomalies, or mental retardation and cerebellar ataxia[5,6].” Aniridia can be associated with these findings but they are part of the WAGR spectrum and usually associated with a contiguous gene deletion syndrome or WT1 deletion – not related to PAX6 mutations. However, PAX6 mutations can be associated with brain malformations, for example, “PAX6 aniridia and interhemispheric brain anomalies.”, Abouzeid H, Youssef MA, ElShakankiri N, Hauser P, Munier FL, Schorderet DF.Mol Vis. 2009 Oct 17;15:2074-83. The authors need to clarify this point.”

Thanks for your suggestion. According to your suggestion, we added some sentences to the second paragraph in the introduction to explain the differences
between WAGR syndrome and aniridia, and mentioned Dr Abouzeid’s work in the introduction and discussion.

2. “Here we report a boy carrying with dominant mutations in KIF21A and PAX6 gene – omit ‘with’ and italicize PAX6”

Thanks for your careful reviewing. We corrected these errors.

3. “7-years old boy – 7-year old boy”

Thanks. We corrected it.


Thanks. We fixed it.

5. “p.L249Yfs should be written p.Leu249TyrfsX22 according to what you have written in the text”

Thanks. We changed the “p.L249Yfs” to “p.Leu249TyrfsX22” according to your suggestion.

6. “bilateral optic nerve hapoplasia – bilateral optic nerve hypoplasia”

We are sorry for this spelling error and corrected it.

7. “Argnine (A) – Arginine”

We are sorry for typing error and corrected.

8. “ Gene names should be italicized”

Thanks for your suggestion. The gene name is italicized.

9. “In Figure 1, the pedigree shading could be standardized – so that shading of the left hand side of the pedigree symbol represents CFEOM, regardless of gender.”

Thanks for your suggestion. We re-edited the pedigree in figure 1.