Author’s response to reviews

Title: A novel mutation in the OAR domain of PITX3 associated with congenital posterior subcapsular cataract

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Author’s response to reviews:

Dear Sir/Madam,

Thank you very much for your letter and for the reviewers’ comments concerning our manuscript entitled “A novel mutation in the OAR domain of PITX3 associated with congenital posterior subcapsular cataract” (MGTC-D-18-00300R2).
We greatly appreciate both your help and that of the reviewers concerning improvement to this paper. Based on the comments, we have made careful modifications on the original manuscript. All changes are marked in red in the revised manuscript. We hope that the revised manuscript will meet your journal’s standard.

We thank you again for considering our manuscript. We sincerely hope that this revised manuscript is now suitable for publication.

Yours sincerely,

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Response letter:

To Reviewer #1's comments:

General comments

1. Overall, there are still some awkward or difficult to understand phrases (for example- Pg 5, line 13- 'two of them were associated with...' should be 'two of them were affected with'; pg 7, lines 15-17 the sentence beginning with 'Finally, according to' and pg 9, line 26-27 starting with 'for the downstream' are poor English and difficult to understand).

Response: Thank you very much for kindly pointing this out.
The sentence “two of them were associated with…” has been revised to “two of them were affected with…” (Revised manuscript: Methods section, line 12, page 5).

The sentence “Finally, according to the inheritance mode and literature retrieval, we excluded the genes that were independent of isolated congenital cataract” has been revised to “Based on valuable information in published literatures, we included the genes that were of autosomal dominant genetic inheritance pattern and congenital cataract” (Revised manuscript: Results section, line 14-15, page 7).

The sentence “For the downstream codons to be translated properly, folding of the OAR domain cannot be disrupted” has been deleted in the revised manuscript.

Background

2. References are missing for some statements, such as the assertion that 8.3-25% of congenital cataracts are hereditary

Response: Thank you very much for kindly pointing this out. The reference has been included in the revised manuscript. (Yi J, Yun J, Li ZK, Xu CT, Pan BR. Epidemiology and molecular genetics of congenital cataracts. Int J Ophthalmol. 2011;4:422-32. Revised manuscript: Background section, line 9, page 4).

3. For consistency, please use the HGNC approved gene names in paragraph 2 (ie, ABCA3 rather than 'ATP-binding cassette protein A3') since this is what is used elsewhere in the manuscript

Response: Thank you very much for kindly pointing this out. The HGNC approved gene names have been applied to all the genes in the revised manuscript (Revised manuscript: Background section, line 11, page 4).

Results

4. When family is first described on Page 6, lines 25-27, authors should note that only the proband and her parents were enrolled. It would also be helpful to specify this on Figure 1, perhaps with an asterick (*) added to indicate enrolled individuals.
Response: Thank you very much for your valuable suggestions. When family is first described in results section, we have stated that only the proband and her parents were enrolled in the study (Revised manuscript: Results section, line 24-25, page 6). And astericks (*) have been added to indicate enrolled individuals on Figure 1(Revised manuscript: Figure Legends section, line 5, page 14).

5. I suggest deleting Supplementary Table 1 (14076 raw variants) as this is excessive and impossible to interpret without additional annotation.

Response: Thank you very much for your valuable suggestions. We have deleted Supplementary Table 1 in the revised manuscript (Revised manuscript: Results section, line 12, page 7).

6. It would be helpful to provide frequency info in Supplementary Table 2.

Response: Thank you very much for your valuable suggestions. We have provided frequency info in Supplementary Table in the revised manuscript.

7. The authors state that the variant meets ACMG criteria to be classified as likely pathogenic (pg7, line 23) - they should note which criteria they used to make this determination. In my opinion, the variant meets criteria PM2, PM4, and PP1, which would classify it as uncertain significance

Response: Thank you very much for your valuable suggestions. According to your sugesstion, the variant was identified as an uncertain clinical significance mutation according to the ACMG guidelines (criteria PM2, PM4, and PP1) (Revised manuscript: Results section, line 20-22, page 7).

Discussion

8. Page 8, line 12, the authors call the variant 'a novel pathogenic deletion variant', but this is not certain. While the uncertainty is expressed elsewhere in the discussion, this phrase should also acknowledge the uncertainty.

Response: Thank you very much for kindly pointing this out. The sentence “a novel pathogenic deletion variant” in the original manuscript has been revised to “a novel deletion variant” in the revised manuscript. (Revised manuscript: Discussion section, line 10, page 8).
9. Page 8, lines 27-page 9 line 2: the mutation nomenclature needs to be consistent. In some, the distance to stop codon after the frameshift is given, for others only fs is noted. In some, * is used to indicate the stop, in others X is used. In some, parentheses are applied to the protein name, in others this is omitted, etc.

Response: Thank you for your valuable suggestion. The mutation nomenclature has been consisted in the revised manuscript (Revised manuscript: Discussion section, line 26-29, page 8).

10. Pg 8, line 28-pg 9 line 1: Two mutations are incorrectly listed as delT, but are actually delC (c.573delC and c.669delC). If the review reference cited lists incorrect nomenclature, I suggest going back to the original article or find a different review article.

Response: Thank you for your valuable suggestion. Two incorrect mutations have been revised to “c.573delC” and “c.669delC” in the revised manuscript (Revised manuscript: Discussion section, line 26 and line 28, page 8).

11. Pg 9, line 3: the authors state- 'all these mutations are in exon 4 and are frameshift', but the p.Ser13Asn mutation is not.

Response: Thank you very much for kindly pointing this out. The statement “all these mutations are in exon 4 and are frameshift” in the original manuscript has been revised to “Except c.38G>A, p.Ser13Asn mutation, other mutations are in exon 4 and are frameshift mutations” in the revised manuscript. (Revised manuscript: Discussion section, line 1-2, page 9).

12. Pg 9, line 26- I think the authors mean to use the word 'deletion' rather than 'disruption of the OAR domain, since later in the sentence they state this deletion would not do so, yet they claim that this mutation does disrupt…

Response: Thank you very much for kindly pointing this out. The statement “disruption of the OAR domain” in the original manuscript has been deleted in the revised manuscript.