Reviewer's report

Title: The identification and characterization of the p.G91 deletion in CRYBA1 in a Chinese family with congenital cataracts

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Reviewer: Yaqin Wang

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Manuscript number: MGTC-D-19-00143R1
Manuscript title: An example of the role of a small in-frame deletion in congenital cataracts: a genetic study in a Chinese family

Comments:

Although the CRYBA1 gene is not a new causal gene for congenital cataracts, in which 15 different mutations have been reported (HGMD). Interestingly, the CRYBA1 p.G91 in-frame deletion is frequently present in patients from different races, suggesting a critical role the residue G91 in the encoded protein. Using WES analysis, this study identified the same mutation of CRYBA1 in a two-generation Chinese family with cataracts. Further experiments showed a markedly decreased CRYBA1 mRNA and protein expression in cataract lens capsular tissues and also the mutant CRYBA1 cell lines, possibly due to an unstable transcript of CRYBA1 missing that three "specific" nucleotides. Overall, the manuscript is acceptable with a revision.

Here are my comments and suggestions:

1. In the results, both of the mRNA and protein levels of CRYBA1 are found to be significantly decreased in cataract lenses and mutant cells. However, it is not clear in the abstract why to conclude this mutation only destabilized the encoded protein. In fact, much lower mRNA levels are shown compared to the protein levels. Therefore, the reasons of significantly reduced mRNA level of the gene also has to be discussed.

2. Genetic compensation in response to gene mutations can lead to the transcriptional upregulation of homologous genes. For example, the CRYBA4 gene is also highly expressed in lens. Mutations of CRYBA4 curated in HGMD database are also the causes of cataract. It would be interesting to check if the CRYBA4 expression is compensatorily increased or not.

3. Phenotype-genotype correlation analysis is encouraged to look if any differences can be found in terms of the in-frame deletion versus missense mutations or LoF mutations.
4. In terms of evolutionary conservation, MutationTaster program and/or other algorithms may show if the deleted amino acid is critical or not.

5. In the clinic part, more detailed information is encouraged to provide, which will be important for phenotype-genotype correlation analysis across all the CRYBA4- mutation-related literature.

6. In background of the abstract, line 3, A small in-frame one amino acid deletion”, small can be deleted.

7. The study compared the CRYBA1 expression between the anterior capsule pieces from age-related cataract patients and lens capsular tissues form normal donors. The author may need to explain which site of lens capsular for normal donors is extract from, the anterior, posterior or whole tissues?

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

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I am able to assess the statistics

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