Author’s response to reviews

Title: A novel compound mutation in GLRA1 cause hyperekplexia in a Chinese boy- a case report and review of the literature

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Version: 1 Date: 17 Aug 2017

Author’s response to reviews:

2017-8-17

Dear editor,

We are grateful for the opportunity to revise our paper (MGTC-D-17-00157) entitled” A novel compound mutation in GLRA1 cause hyperekplexia in a Chinese boy- a case report”, and the helpful comments of your reviewers.

We feel that the comments have allowed us to improve the paper and hope you convey our gratitude to the reviewers.

We attach a version showing the tracked changes in red words and, separately list our point-by-point responses.

We also had the manuscript edited by a native English speaker about grammar.

Yours sincerely,

Zhiliang Yang,MD,PhD.
Technical Comments:

1. Results

Please remove this header as Case reports do not have a Results section. The results of the genetic investigation can be part of the Case presentation.

Answer: I removed the header.

2. Ethics approval and consent to participate

Please include a statement describing the type of consent to participate obtained from the parents of the proband.

Answer: I edited the part again and the statement was included (Page 12 row 9-11).

Reviewer reports:

Márta Széll (Reviewer 1):

This is a well-written paper on the genetic background of an extremely rare monogenic disease. These reports are absolutely needed to unravel the genotype-phenotype associations in rare monogenic diseases. Analyzing and reviewing the literature is the next step in this process. This is why papers like Yang et al submitted have high importance in clinical genetics.

I arranged a list of major comments and suggestions and a list of minor comments and suggestions.

MAJOR COMMENTS AND SUGGESTIONS:

Title:

I suggest to modify the title: … - a case report and a review of the literature

Answer: I modified the title to be “… -a case report and review of the literature”.

Abstract and Background

Well written parts, I have no suggestions.
Case presentation

1. Why did you need the approval of the ethics committee for a routine molecular genetics diagnostic procedure? This is not an experimental process which would need the permission of an ethical committee. But if this is the case in China, of course, I accept this sentence.

Answer: We do not perform genetic test routinely now, the genetic test should be obtain the consent from patient or parents of patient firstly, and we are requested to have the qualification for genetic tests if we do some researches associated with genetics. The qualification is given by the ethical committee.

2. Did the authors perform the NGS procedure by themselves? If not, please indicate what the name of the service company is. The same applies for the direct capillary sequencing for the validation of the NGS identified mutations.

Answer: We did not perform the NGS procedure or validation by ourselves, the third party inspection services has been added to the manuscript (Page 7 row 9-11).

3. Is there any connection between the target(s) of clonazepam and the glycine transmission system? If yes, please add 1-2 sentences about at the relevant part of the paper.

Answer: Clonazepam (CZP) is a GABARAI agonist and can enhance GABA-gated chloride channel function. The glycine receptor and γ-aminobutyric acid (GABAA) receptor are members of same superfamily of ligand-gated ion channels and share common transmembrane topology, structural and functional features. CZP was presumed to compensate for the defective glycine-gated chloride channel function by enhancing GABA-gated chloride channel function in hyperekplexia(Zhou L et al, Brain Dev. 2002;24:669-74.).

These sentences have been added to manuscript (Page 7 row 17-22-Page 8 row 1-2).

Results:

1. Do we have any data on the mode of heredity of the 2 novel mutations mentioned at Page 8 row 10? Dominant? Recessive? If there are no data about them, you should tell that the papers that first described these mutations could not define it.

Answer: The compound mutation was first reported, we cannot define whether it is dominant or recessive.

This has been added to manuscript (Page 9 row 1-2).
Discussion and conclusions

1. Please delete the sentence at Page 9 row 9. It is obvious and no need to emphasize it in a paper like this.

Answer: I deleted the sentence.

2. The same applies for the last sentence of the first paragraph on page 10. Please delete this sentence or re-phrase it. My suggestion would be: This suggests that these recessive mutations of the GLRA1 gene in a compound heterozygote state are pathogenic and cause hyperekplexia.

Answer: Thank you, I rephrased to the sentence from the suggestion(Page 10 row 16-18).

Tables and Figures:

1. Please delete (%) from the heading of the second column of Table 2. You show only numbers but no percentages in this column.

Answer: I deleted it.

2. I suggest to show Table 3 as a Supplementary material.

Answer: I accepted the suggestion.

3. Figure 2: please re-phase the explanation of the color code. Regions harboring mainly recessive mutations AND Regions harboring mainly dominant mutations

Answer: I edited the explanation with the suggestions.

MINOR POINTS AND SUGGESTIONS:

Page 2 row 4: … most of the mutations…

Page 4. row 14: … most of the mutations…
Barbara Steinborn (Reviewer 2):

Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format. Please overwrite this text when adding your comments to the authors. Hereditary startle disease is caused by genetic defects in inhibitory glycine receptor and transporter genes. Missense, nonsense, frameshift, splice site mutations, and large deletions in the human glycine receptor α1 subunit gene (GLRA1) are the major known causes of this disorder. However, mutations are also found in the genes encoding the glycine receptor β subunit (GLRB) and the presynaptic Na+/Cl−-dependent glycine transporter GlyT2 (SLC6A5). The reasons of hyperekplexia may be connected with other mutation in other genes. We report for the first time a clear association of mutation in CTNNB1 with an atypical syndromic hyperekplexia expanding the phenotype of CTNNB1-related syndrome. Consequently CTNNB1 should be added to the growing list of genes to be considered as a cause of startle disease or syndromic hyperekplexia.[1]

I proposed to mention in this article about other mutation in hyperekplexia.


Answer: I edited the manuscript again and added the suggested gene from the article. I am sorry about the missing in lecture searching(Page 4 row 13-16).