Author’s response to reviews

Title: Xp11.22 Duplications in Four Unrelated Chinese Families: Delineating the Genotype-phenotype Relationship for HSD17B10 and FGD1

Authors:

Qingming Wang (wqm0404@sina.com)
Pengliang Chen (goodcpl@163.com)
Jianxin Liu (dgfyrsk@163.com)
Jiwu Lou (598337047@qq.com)
Yanhui Liu (yh523120@sina.com)
Haiming Yuan (haimingyuan@sina.cn)

Version: 3 Date: 23 Mar 2020

Author’s response to reviews:

Dear Editor:
We are delighted to resubmit the manuscript entitled “Xp11.22 Duplications in Four Unrelated Chinese Families: Delineating the Genotype-phenotype Relationship for HSD17B10 and FGD1” after revising it following reviewers’ comments and suggestions. Please see our point by point response to your reviewers’ comments.

Editor Comments:
As one of the original reviewers was unable to assist us in evaluating the revised manuscript, we involved an additional referee. They have been fully informed that the manuscript was previously evaluated and have been asked to take the revisions and the point-by-point response into consideration when assessing the manuscript.
As you can see from the feedback below, they are overall satisfied with the revisions, however, they point out some outstanding concerns that we kindly ask you to address further.

Reviewer reports:
Aleksander Jamsheer, Ph.D., M.D. (Reviewer 2): The authors have corrected the manuscript according to the reviewer's suggestions. I have no further questions.
Reviewer 2 (Reviewer 3): PEER REVIEWER ASSESSMENTS:
OBJECTIVE - Full research articles: is there a clear objective that addresses one or several testable research questions? (Brief or other article types: is there a clear objective?)
No - there are minor issues
DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?
No - there are minor issues
EXECUTION - Are the experiments and analyses performed with sufficient technical rigor to allow confidence in the results?
No - there are minor issues
STATISTICS - Is the use of statistics in the manuscript appropriate?
Response: Xp11.22 duplications have been reported to contribute to nonsyndromic intellectual disability (ID). Currently, few Xp11.22 duplication cases have been reported in the Chinese population, with limited knowledge regarding the role of other genes in this interval. In this paper, WES identified Xp11.22 duplications in four unrelated Chinese patients and CMA confirmed and refined these duplications. The two experimental techniques have been recommended as the first-tier clinical diagnostic tests for individuals with neurodevelopmental disorders. Thus, both techniques are precise and the resulting data are reliable. Here, four unrelated Chinese patients carried Xp11.22 duplications, and presented with similar clinical features such as nonsyndromic ID, which further implicated the role of Xp11.22 duplication in ID. By comparing the genotype-phenotype relationships of all patients with Xp11.22 duplications, HSD17B10 and FGD1 were identified as potential dosage-sensitive genes responsible for the clinical presentations observed in our patients. I think that this paper has a clear objective. I have tried my best to answer the questions requested by reviewer 3.

REQUESTED REVISIONS:
There are Study design problems. Also authors need to include - as requested by Reviewer 1 in Discussion some sentences about: "The authors should discuss whether some of the CNVs could be mediated by these polymorphisms." The same holds true for comment of Reviewer 1 for FDG1 and HUWE1 genes - here the authors cannot just answer this point in the answer to the reviewers comments and include not all what they answered completely in the article; this must be added in discussion - and it seems that this was not really done yet completely.

In reviewing the previous reviewers' comments and reading the manuscript, my main concern is about being able to document the number of women who chose to receive treatment, which would allow the readers to interpret all prevalence data in a more informed context. I understand the reasoning for not including this information in the regression analysis, but could the authors include simple percentages of women who, after being referred to treatment, followed through with referral? Perhaps I have missed it, but I did not find this information easily available in the paper.

Response: I have answered the question requested by Reviewer 1 “whether some of the CNVs could be mediated by these polymorphisms”, as follows: it was well known that recurrent copy number variants (CNVs) was mediated by non-allelic homologous recombination-prone low copy repeats (LCRs). Currently, no studies or published literatures show that sporadic CNVs could be mediated by these
polymorphisms. So, I think it is superfluous to add this sentence “Currently, no studies or published literatures show that sporadic CNVs could be mediated by these polymorphisms.” to the discussion section since no medical literatures could be cited. Furthermore, females carrying Xp11.22 duplication are usually asymptomatic due to X-inactivation, so they would not be likely to receive treatment.

I really hope you would be satisfied with my answer.
I appreciate your reviewers’ input and your help. We look forward to hearing from you.

Best regards!

Haiming Yuan