Point to point reply for Reviewers

Dear editor,

We thank the editors for allowing us to revise our manuscript and the reviewers for their constructive comments. We have revised our manuscript according to the comments and suggestions. Following is a point-to-point response for the questions raised by the reviewers.

Reviewer #1:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This is an interesting and clinically relevant study.

Answer: Thanks.

Reviewer #2: In the manuscript, "A 10-bp deletion in the OTC gene results in ornithine transcarbamylase deficiency by early translation termination: A case report", Wang and colleagues present an affected boy with Ornithine transcarbamylase deficiency (OTCD) due to a novel deletion variation in OTC.

Specific comment: There are more than 500 OTC reported pathogenic variants (http://www.hgmd.cf.ac.uk/ac/gene.php?gene=OTC). Therefore, the statement "…results confirm the pathogenic variation in OTC and provide strong evidence for further OTCD screening and clinical consultation.", should be revised to highlight the contribution of the current report.

Answer: Thanks for this crucial suggestion. We have revised it (Line26, Page1).

Minor Comment:

1. On page 2, please provide OMIM number for phenotype Ornithine transcarbamylase deficiency (OTCD).

Answer: Thanks for this suggestion. We have added it (Line36, Page2).

2. On page 2, in the statement "The OTC gene (OMIM:300461) is located on position Xp11.4, contains 10 exons and 9 introns, and encodes 354 amino acids." Please replace "position" with "chromosome" and add "encodes a 354 amino acids protein", instead of the current wording.

Answer: Thanks for this suggestion. We have revised it (Line47-48, Page2).

3. On page 3, statements "in the neonatal onset group, it was completely lost," and "the late onset group, it was partially lost"; please replace "was" by "is".

Answer: Thanks for this suggestion. We have revised it (Line58-59, Page2).

4. On page 3, statement "They are normal at birth, but gradually refuse …" please re-word, "they have no symptoms at birth, but gradually refuse…"

Answer: Thanks for this suggestion. We have revised it (Line60, Page2).

5. On page 3: What are the "molecular function experiments" referred to? The data for biochemical investigations, exome sequencing and treatment is presented but there is no experiment regarding function.

Answer: Sorry for this mistake, we have deleted this sentence (Line76, Page3).

6. On page 5, Please state that the variant is "absent" in all publicly available databases including gnomAD instead of writing "included".

Answer: Thanks for this suggestion. We have revised it (Line107, Page4).

7. For page 5: Please deposit the variant in ClinVar or other comparable databases such as LOVD and insert the accession number in the manuscript.

Answer: Thanks for this suggestion. We have uploaded this variant to ClinVar (accession number: VCV001256051) (Line110, Page4).

8. On page 6: In the statement "other ornithine circulatory disorders; other genetic metabolic diseases, including organic acid hematic disease, fatty acid, beta oxygen defects, …", please

replace "other" with "different" and "miscellaneous" respectively, in order to avoid the use of the word "other" multiple times.

Answer: Thanks for this suggestion. We have revised it (Line148, Page5).

9. On page 7: Please re-word the statement "Sanger sequencing fails in the detection of OTCD in approximately 20% of patients [10, 11], whereas NGS has the advantage of detecting small insertions or deletions". In the cited papers, array CGH or multiplex ligation-dependent probe amplification were used to detect relatively large exon level insertions and deletions which are usually missed by both Sanger and exome sequencing. In special circumstances, exome sequencing may be used to detect these exon level duplications and deletions. However, this does not apply in the case presented here since Sanger sequencing is able to detect small 10bp deletion or insertion which is comparable to the detection by exome sequencing.

Answer: Thanks for this suggestion. We are sorry that the cite here is not appropriate, we have revised the sentence and delete the reference here (Line168-170, Page6).

10. On page 7, "Our results provide evidence for the pathogenicity of our variant and accurate diagnosis for patients with the same variant." Please re-word since the results do not provide evidence of pathogenicity since no such experiments were performed. However, the pathogenicity is inferred due to the extreme severity of the variant which is present in the gene known to cause the phenotype as detected in the patient.

Answer: Thanks for this suggestion. We have revised it (Line174, Page6).

11. On page 6: In the statement: "…there was no response to stimulation, and the patient was in a coma. The patient died soon after discharge." Please clarify; did the patient recover from coma before discharge? Or was he discharged while in a coma? If he had recovered from coma, then please state whether he had a relapse at home.

Answer: Thanks for this question. The patient has been in a coma since admission with weak heart sound. After various treatments, he still can't maintain spontaneous breathing without any signs of improvement. He was still in a coma when discharge, and died soon after that.

We have updated this in the manuscript (Line127-131, Page4).

12. On page 9, in table 2, please specify in the footnote what NE stands for.

Answer: Thanks for this suggestion. We have added it (Line211, Page8).