Author’s response to reviews

Title: A novel electron transfer flavoprotein dehydrogenase (ETFDH) gene mutation identified in a newborn with glutaric acidemia type II: A case report of a Chinese family

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Author’s response to reviews:

Dear editor and reviewers,

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript, we appreciate editor and reviewers very much for their comments and suggestions on our manuscript entitled “A novel electron transfer flavoprotein dehydrogenase (ETFDH) gene mutation identified in a newborn with glutaric acidemia type II: A case report of a Chinese family” (ID: MGTC-D-19-00138). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied reviewer’s comments carefully and have made revision which used track changes in the paper. Attached please find the revised version, which we would like to submit for your kind consideration. We appreciate for Editors/Reviewers’ warm work earnestly,
and hope that the correction will meet with approval. Once again, thank you very much for your comments and suggestions. The main corrections in the paper and the responds to the reviewers’ comments are as follows:

Responds to the reviewer’s comments:

sara missaglia, PhD (Reviewer 1):

1) In the Background, page 3 line 45, the authors state that: "GA II is caused by a defect in the electron transfer flavoprotein (ETFα, ETFβ) or ETF dehydrogenase (ETFDH) resulting in deficiencies in multiple acyl-CoA dehydrogenases". GA II is a disorder with a heterogeneous etiology. The majority of patients show ETFα, ETFβ or ETFDH gene mutations. However, some researchers recently identified defects in FLAD1 (Olsen et al, Am J Hum Genet. 2016;98(6):1130-1145; Ryder et al, JIMD Rep. 2019;45:37-44) involved in GA II onset. The authors should add this information in the section.

Response 1): We have added the information in the Background according to the reviewer’s comments.

2) In the Background, page 4 line 68, the authors say: "Recently, several adult onset GA II cases have been reported with ETFDH mutations…..". Subjects affected by adult-onset GA II have been described since 1982 (Gregersen et al, Pediatr. Res. 1982;16: 861-868). The authors should remove "recently" from the sentence and should add this reference: Angelini et al, Ther Adv Neurol Disord. 2019;12:1756286419843359.

Response 2): We have made correction according to the reviewer’s comments.

3) In the Background, page 4 line 69, the authors state that:"….more than 30 mutations have been identified." Considering all patients with adult-onset GA II caused by ETFDH mutations, almost 190 different variations of this gene have been identified. The authors should correct the sentence and should add other references (Grunert, Orphanet J Rare Dis. 2014;9:117; Angelini et al, JIMD Rep. 2018;38:33-40; Missaglia et al,Lipids Health Dis. 2018;17(1):254).

Response 3): We have corrected the sentence and added references according to the reviewer’s comments.

4) In the Case presentation, page 7 line 138, the authors should add the reference in which the mutation c.1399G>C has been reported for the first time (Wen et al, J Neurol Neurosurg Psychiatry 2010;81(2):231-6).

Response 4): The reference has already cited in our paper on page 9 line 180 in the Discussion and Conclusions.
5) In the Discussion and Conclusion, page 8 line 157, the authors should replace "two neonatal-onset male patients" with "three neonatal-onset male patients".

Response 5): We have made correction according to the reviewer’s comments.

6) In the Discussion and Conclusion, page 9 line 158, the authors use ETF: QO abbreviation without definition. They should explain the abbreviation and clarify that this is an alternative definition of ETFDH.

Response 6): We have explained ETF: QO abbreviation in Discussion and Conclusions which used track changes.

7) The Figures are not numbered in the correct order. The authors should correct the numbers in the Figure files.

Response 7): We are very sorry for our negligence of Figures are not numbered in the correct order, and we have made correction according to the reviewer’s comments.

Special thanks to you for your good comments and suggestion.

Andrea Bordugo (Reviewer 2):

2.1 LINE 113 page 6 Is glucose value truly 0.06 or 0.6?

Response 2.1: We checked medical records of the patient carefully and the glucose value is truly 0.06

2.2 LINE 115 Could you please indicate the anion gap?

Response 2.2: The anion gap was not determined but metabolic acidosis was based on the arterial blood gas results: pH 7.342, pCO2 17.7 mmHg, pO2 77 mmHg, SO2 95%, and BE−16 mmol/L (reference ranges: arterial pH 7.35–7.45, pCO2 35–45 mmHg, pO2 60–90 mmHg, SO2 95–98%, and BE 0±3 mmol/L).

2.3 LINE 132 Can you better clarify why second tier testing procedure was performed in such a case and for what metabolites?

Response 2.3: The second-tier NBS testing performed to confirm the infant was positive for GA II and make a definite diagnosis according to acylcarnitine concentrations including C4, C6, C8, C10, C12, and C14.
This is just a suggestion to authors: It would have been of interest to perform a Fatty acid flux oxidation study on skin fibroblasts to add a functional correlation.

Response: We thank the reviewer for the professional suggestion and we would take it into consideration of our later research.

Special thanks to you for your good comments and suggestion.

Francesco Porta (Reviewer 3):

Please add the results of in silico prediction tools for the pathogenicity of the novel variant.

Response: In silico prediction tools MutationTaster demonstrate the novel variant is disease causing but SIFT and Polyphen2 cannot provide the pathogenicity of the novel variant due to it is a frameshift deletion but not nonsynonymous or synonymous mutation. We have made correction in Table 2.

Please indicate MAF (minor allele frequency). It is difficult to understand the differential impact of neonatal sepsis and GAIi on neonatal clinical picture.

Response: There is no MAF data in NHLBI Exome Sequencing Project (ESP esp6500siv2 all) and 1000 Genome Project of these two variants in this study.

The clinical picture of the infant is special due to neonatal sepsis and we just want to demonstrate the different clinical feature compared with reported GA II infants.

Functional testing would be useful to document the effect of the claimed new variant.

Response: The functional testing of the new variant will be investigated later in our laboratory.

There are many typos in the text.

Response: We have made correction and used track changes in the paper.

Special thanks to you for your good comments and suggestion.

Sincerely yours,

Qi Hu and Wenjun Wang on behalf of the authors.

Corresponding author: