**Reviewer’s report**

**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

**Version:** 0  **Date:** 28 May 2019

**Reviewer:** sara missaglia

**Reviewer's report:**

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This manuscript represents an interesting report that associates ETFDH gene mutations with neonatal GA II (type I and II) onset. Moreover, as ETFDH protein alterations are described in only 16 patients with these clinical phenotypes, the present case description expands the spectrum of ETFDH mutations causing GA II type I and II.

In this study the authors describe in detail clinical presentation of patient, as well as molecular and bioinformatic analysis. Furthermore, the authors accurately undertake and discuss their research.

However, some issues should be addressed:

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.

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.

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).

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).

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".

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.

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

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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