Author's response to reviews

Title: The effect of homozygous deletion of the BBOX1 and Fibin genes on carnitine level and acyl carnitine profile

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Author's response to reviews: see over
Reviewer's report:
Reviewer: Audrey Boutron
In their manuscript Rashidi-Nez and co-workers report on a patient with a homozygous deletion of BBOX1 gene and FIBIN gene. Several cases with somewhat similar deletion have been reported on DECIPHER and on literature without relaying BBOX1 deletion to carnitine homeostasis. This case report is well documented and clearly written.

Besides these positive comments I have some concerns:

Major Compulsory Revisions
1) Two genes are involved in the homozygous deletion found. However the authors focused on BBOX1 gene even if the observed clinical phenotype could rather be associated with the absence of the FIBIN gene. Change to be made in the title and background

Answer: following this suggestion we modified the text and background to acknowledge this fact

2) Biochemical evaluation of metabolites involved in FAO could not allowed the authors to conclude on the fatty acid oxidation pathway but only on free and acyl carnitine levels. The results are from one measurement without any indication on fasting duration and/or carnitine dietary intake. The minor change in acyl carnitine / free carnitine ratio could be observed with insufficient dietary intake and/or prolonged fasting or metabolic stress. Surprisingly is the elevation of C: 6 acylcarnitine as only long Chain Fatty Acid (LCFA) needs carnitine to enter FAO pathway. Interpretation of Acylcarnitine profile is more likely than detailed analysis of different acylcarnitine levels. change to be made in conclusion and abstract

Answer: we modified the abstract and conclusion as suggested

Minor Essential Revisions
3) Last sentence in background: unclear.
4) Last sentence in abstract hemizygosity instead of heterozygosity
5) Table 4: CUD, CPT, CACT (and not CACD) CPT2 , are all four diseases in LCFAO and can present with great variability from neonatal period to late infancy. This table is not relevant with the case report

Answer: We modified the text and delete Table 4 as suggested

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests

Reviewer's report
Reviewer: Ayman W El-Hattab

The authors presented a girl with homozygous 11p14.2 deletion that encompasses BBOX1 gene which encodes the last enzyme of de novo carnitine synthesis. Despite the fact that such deletion has not been previously reported in the homozygous state, there are several major
concerns in this report:

1. The literature review is incomplete and this case is not the first reported patient with complete deficiency in de novo carnitine biosynthesis. Deletions of TMLHE gene (on chromosome X) also result in deficiency of de novo carnitine synthesis (Celestino-Soper PB, et al. Proc Natl Acad Sci USA. 2012;109:7974-81).

Answer: we modified the text throughout to correctly pinpoint the discoveries of Celestino-Soper et al. as suggested

2. Making inappropriate conclusions. The acylcarnitine profile and carnitine levels are basically normal. Having a free carnitine level that is closer to the lower limit of normal and such slight increase in AC/FC are not clinically or biochemically significant, especially that this test was done once. So, this acylcarnitine profile results cannot be used as an evidence of carnitine biosynthesis defects and should not receive such emphasis in this report.

Answer: following this comment we subjected the proband to a second round of analysis of acylcarnitine levels. This recall proved more difficult than expected explaining the delay in revising our report. We modified the text and tables to include both the measurements done at 42 and 60 months of age. We also toned down the carnitine biosynthesis defects as suggested

3. Including irrelevant details in this report. There is no need to present normal values (e.g. tables 2 and 3) and data that do not add significant and relevant information (e.g. pedigree and brain MRI pictures).

Answer: we modified Tables 2 and 3 and deleted Figure 1C and 2 as suggested

4. The failure to include important and relevant points like details about what is currently known about the other gene (FIBIN) and measurements of intermediates of carnitine biosynthetic pathway.

Answer: we included new references pertaining to fibin function

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.