Reviewer’s report

Title: Fainting Fanconi syndrome clarified by proxy. A case report.

Version: 0 Date: 08 Apr 2017

Reviewer: João Paulo Oliveira

Reviewer’s report:

This a very interesting case report, illustrating the utility of multigene panels in the diagnosis of rare, genetically heterogeneous disorders; furthermore, to the best of my knowledge, ultrastructural evidence of a mitochondrial cytopathy in patients with renal Fanconi syndrome (RFS) due to the ‘HNF4A’ p.Arg63Trp variant has never been published.

I have two suggestions for the authors:

#1. To report the final genetic diagnosis in the abstract.

#2. To consider in their discussion the results of a recently published study in the Drosophila model [Barry WE, Thummel CS. The Drosophila HNF4 nuclear receptor promotes glucose-stimulated insulin secretion and mitochondrial function in adults. Elife. 2016 May 17;5. pii: e11183. doi: 10.7554/eLife.11183] providing evidence that ‘dHNF4’ promotes mitochondrial oxidative phosphorylation by regulating nuclear and mitochondrial gene expression. This might help the readers to better understand why a pathogenic variant in a nuclear gene (i.e., ’HNF4A’) manifests a mitochondrial phenotype. Moreover, as the authors have pointed out, the p.Arg63Trp variant is peculiar among pathogenic ‘HNF4A’ variants in that it is the only one known to be associated with proximal tubular dysfunction. The replacement of arginine by tryptophan at HNF4A polypeptide position 63 is thought to affect its DNA binding affinity, but does not explain why it is the only HNF4A mutation causing RFS. Therefore, the finding of abnormal mitochondria in the proximal tubular cells might be a clue to the molecular mechanism(s) explaining the peculiar genotype-phenotype correlation of this ‘HNF4A’ variant.

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

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests in relation to this paper.

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.
I agree to the open peer review policy of the journal