Reviewer’s report

Title: Familial Xp11.22 microdeletion including SHROOM4 and CLCN5 is associated with intellectual disability, short stature, microcephaly and Dent disease

Version: 0 Date: 30 Oct 2018

Reviewer: Arend B Bökenkamp

Reviewer's report:

Danyel et al describe a patient with a micro-deletion involving the SHROOM4 and CLCN5 genes resulting in a combined phenotype of Dent disease and X-linked intellectual disability and short stature. The clinical manifestations in the patient presented overlap with the phenotype of a patient with a microdeletion in the same region described by Armanet et al.

The paper is relevant for the genetic counseling of families with this deletion. While the renal phenotype of CLCN5 mutations is well-known the neurological findings attributed to the deletion of SHROOM4 are relevant as there is only a small number of publications on SHROOM4 mutations.

Major comments:

1. There is considerable overlap of the clinical picture between the observed microdeletion and Lowe syndrome due to OCRL1 mutations. The comparable renal phenotype, growth failure and neurological symptoms/retardation should be discussed as a clinical pitfall as the clinical picture of Lowe may be incomplete (cf. review Ped Nephrol 31 (2016): 2201 - 2212)

2. A number of reports show a comparable neurological phenotype in patients with microduplications in the region involving SHROOM4 (e.g. Am J Med Genetics 2015, Am J Med Genetics 2016). I am not aware of the renal phenotype of these patients but find it remarkable that the duplications apparently lead to a phenotype which is comparable to the deletion reported here.

3. I find the description regarding physical examination and neurological findings rather lengthy while the renal findings are very scant. Here, quantitative findings on kidney function, fractional excretions of electrolytes, low-molecular proteinuria/albuminuria and hypercalciuria should be presented.

4. Which parameters were tested in the mother's urine? Did she have hypercalciuria, LMW proteinuria, nephrocalcinosis (cf recent paper by Li et al, J Pediatr 174 (2016): 204-10)

5. As the the molecular genetic study is central to this paper I believe that the figures presented as supplements should be incorporated in the body of the text. If there are space restraints I believe that the description of the methods could be shortened.

6. While the entire CLCN5 gene is missing, only a small part of SHROOM4 is missing. This is different from the patient reported previously in whom the deletion involved the entire SHROOM4 gene. Can the effect of the deletion on gene expression/function be modeled?
Minor comments

1. The authors should consult a native speaker to check the manuscript (e.g. "phosphatise" to indicate phosphate supplementation).

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.

Unable to assess

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?
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Not relevant to this manuscript

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

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