Reviewer's report

Title: Digenetic inheritance of SLC12A3 and CLCNKB genes in a Chinese girl with Gitelman syndrome

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Reviewer: Helena Gil

Reviewer's report:

The report is very interesting and the methodology is new and well applied. Although not in the context of Gitelman Syndrome, digenetic mechanism in other tubulopathy (Distal Renal Tubular Acidosis), has been previously described (Gomez J et al. Pediatr Res. 2016).

Therefore, the suspicion that a known mutation in a gene may be affected by the synergistic effect of a variant of uncertain significance is in line with the authors' conclusion.

Minor comments:

- Although in-silico predictors can not reproduce real molecular interactions, the authors have used excellent functional predictions that provide a well-evaluated approach to variant tolerance. However, there are not functional assays to be certain about the pathogenicity of the CLCNKB gene variant, which is an important limitation on the interpretation of the results.

- An interesting fact is the growth retardation observed in the diagnosis (-1.62 SD in length), which means a severe form of the disease, although laboratory tests did not reveal extreme values for hypokalemia or metabolic alkalosis. Do the authors believe that the effect of growth may be due to a negative effect of the p.L94I variant of CLCNKB on the p.N359K mutation of SLC12A3?

- The authors mention the HNF1B gene referred to in the Blanchard publication (Kidney Int, 2017). However, they do not explain why this gene should be taken into account for genetic testing of Gitelman syndrome. They should include the study of Verhave JC (J Am Soc Nephrol, 2016).

- Fig 3 about the protein-protein interaction analysis is referenced in the text as Fig 2.
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?
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

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Please indicate the quality of language in the manuscript:

Acceptable

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