Reviewer's report

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

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Reviewer: Detlef Bockenhauer

Reviewer's report:

The authors report on patient with a clinical diagnosis of GS, in whom genetic testing identified a heterozygous mutation in SLC12A3 and a VUS in CLCNKB. They claim that the disorder in this patient is caused by "digenetic"[sic] inheritance.

The paper is full of spelling and grammar mistakes and would clearly benefit from review by a native speaker.

I have several comments:

1) If the authors really want to propose this paradigm change in the genetics of GS, they better have good data. The authors should check databases to assess the frequency of SLC12A3 and CLCNKB variants in the general population. Current papers suggest a frequency of SLC12A3 mutations around 2-3%. Presumably, there are less variants in CLCNKB, but if one were to include VUS (as the authors do in this paper), the frequency is probably around 0.5%. Which would mean that the frequency of digenic GS would be roughly 1:10.000. Thus, in a country like China with a population of 1 billion, there would be about 100.000 such GS patients! How amazing that nobody has discovered this before!

2) The other way to look at this, is that the likelihood to find such digenic variants is quite high and coincidental to the phenotype.

3) There are a number of reports of GS patients with only heterozygous identified mutations and a few papers from Taiwan suggest that intronic variants on the other allele may be causative. Have the authors looked at this?

4) They should also perform functional studies of the VUS in CLCNKB, before asserting pathogenicity.

5) The idea to go into protein interaction databases for SLC12A3 and CLCNKB is really quite bizarre, since the physiology and location of these transport molecules is well known and described!
Minor:

1) what is the definition of "slight hypokalaemia"?

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

No

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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