Reviewer's report

Title: Complicated Gitelman syndrome and autoimmune thyroid disease: A case report with a new homozygous mutation in the SLC12A3 gene and literature review

Version: 2 Date: 20 Jul 2018

Reviewer: Katarzyna Ziemnicka

Reviewer's report:
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Dear Authors,
Thank you for all corrections you have made, but still the description of molecular study results and methods needs improvement.

See comments below:

For the legends, the minimum information that authors should include refers to the method, gene, mutation and patient i. e.:

Figure 1: Sequencing of the SLC12A3 gene fragment encompassing homozygous mutation g.15042_15044delTCA in patient

And similarly

Figure 2: Sequencing of the SLC12A3 gene fragment encompassing heterozygous mutation g.15042_15044delTCA in patient mother
ATTENTION!
The mutation description is wrong. And do not follow HGVS recommendation. Authors did not inspect the automatically generated mutation calls from software.
The mutation call c.1556_1558delTCA, p.520Ile should be corrected for c.1562_1564delTCA, p.522Ile (g.15042_15044delTCA) everywhere it appears
It is precisely determined by HGVS recommendation, named 3’rule:

3'rule: for all deletions, duplications and insertions the most 3' position possible is arbitrarily assigned to have been changed
* the 3’rule also applies for changes in single residue stretches and tandem repeats (nucleotide or amino acid)
* the 3'rule applies to ALL descriptions (genome, gene, transcript and protein) of a given variant
* exception: deletion/duplication around exon/exon junctions using c., r. or n. reference sequences (although SLC12A3 mutation is very close to the exon border but not applies here since there is no interference with splice recognition signal)

Authors also did not mentioned that at the same position of Ile repeat (p.520-522) another deletion was submitted to HGM (CD117081) and published by Vargas-Poussou (2011) J Am Soc Nephrol 22, 693.
Authors should pursue this change since the p.520-522Ile tract may represent a mutational hot-spot.
By the way this is very important paper for GS, presenting summarized mutation in SLC12A3 and should be also included in references.

In the Figure 1, the software used by authors automatically introduced a break on a first TCA repeat and not third (TCA_ _ _ TCG). That is leading to erroneous description of the mutation (it was explained before). In Figure 2 authors included also a three-nucleotide gap which is a major mistake since there one can see a typical heterozygotic deletion/insertion picture presenting overlap of differing sequences.
My recommendation is to include unmodified chromatogram sequences and just add below text sequences (human reference+patient sequence showing missing 3rd TCA repeat for Figure 1 and only human reference for Figure 2)

**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.
Yes

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

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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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