**Reviewer’s report**

**Title:** Novel PYGL mutations in Chinese children leading to glycogen storage disease type VI: two case reports

**Version:** 1  **Date:** 20 Nov 2019

**Reviewer:** Andreas Janecke

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MGTC-D-19-00379R1

The authors report 2 patients with glycogen storage disease type VI (GSDVI).

The clinical presentation is within the known spectrum of this disease.

A homozygous multi-exon deletion was identified in one patient. Compound-heterozygosity for 2 mutations, one which is novel, was found in the other patient.

The authors emphasize that

1. The phenotype of patient 1 with the deletion is surprisingly mild, as the mutation removes inframe 22% of the protein

2. The authors employ whole-exome sequencing (WES) to detect the mutations, and conclude that this method is superior to a targeted sequencing approach (TS), that earlier missed the deletion

GSDVI is a very rare disorder and publication of very detailed clinical information of two further cases can be helpful for clinicians and geneticists.

However, in the current form the manuscript is unacceptable.

1. Patient 1 with the deletion displays the typical growth delay and laboratory abnormalities. While the authors claim that the otherwise typical symptom of hepatomegaly was not present, this observation does not justify to call it a mild expression of GSDVI. Neither ultrasound data are presented nor liver biopsy was performed to assess the extent of changes in the liver (a procedure not necessary after successful genetic and clinical diagnosis).

2. WES is compared in the manuscript to TS. However, no details on TS are provided, and it remains unexplained how this form of testing could have missed a homozygous multi-exon deletion. All addressing of this comparison is therefore unnecessary.
3. The authors emphasize that they did a SNV and CNV analysis of their WES data sets. This is state-of-the-art and needs no emphasizing, briefly mention variant calling software.

4. WES or Clinical ES is in my opinion justified to perform in the case of children presenting with unclear hepatopathies.

5. The biochemical laboratory parameters were determined at what patient age, and earlier to causal treatment?

The manuscript is much too long and there is a great redundancy of data and sentences.

A most recent and comprehensive review on the topic should be cited and can replace older references, Prishnani KS et al. Genet Med 2019.

**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.

No

**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

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Acceptable

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