Reviewer's report

Title: A Novel Mutation in the Glycogen Synthase 2 Gene in a Child with Hypoglycemia Due to Glycogen Storage Disease Type 0

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Reviewer: David A Weinstein

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Dr. Soggia and her colleagues present a convincing case of glycogen storage disease type 0 along with the description of a new mutation. GSD type 0 is still being under-recognized, and it is valuable to have more cases reported. While the clinical evaluation and mutation analysis in the patient are convincing, the relationship between being a carrier and clinical manifestations is less clear and lacks support. This is an important observation if it is true, and the investigators should attempt to more formally gain evidence supporting their assertion. The authors may want to consider dividing this into 2 papers: One reporting the case and new mutation with a second characterizing the carriers in a much more formal way.

MAJOR COMPULSORY REVISIONS:
Case Description and Results Sections:

1. Much more information is required about the parents if a relationship between haploinsufficiency and clinical manifestations is going to be established.
   • What is the mother's weight and BMI? What was the hemoglobin A1c and fasting insulin level in the mother? In GSD 0, the fasting insulin should be normal while it would be possibly elevated if the post-prandial hyperglycemia were due to developing diabetes.
   • What happened to the ketones in the parents with fasting?
   • Much more information is needed about the father's hypoglycemia if it is going to be attributed to haploinsufficiency. How low was the blood sugar and how did he present? When was the hypoglycemia in relationship to the drinking and how high was the EtOH concentration?

2. How were the glucose and lactates measured? Were they plasma glucose concentrations or meter readings?

Discussion Section:

3. If the glucose intolerance in the mother was due to GSD 0, why didn't the lactates go up? This finding should be addressed.

4. Studies have been done looking at mutations in the GYS2 gene in people with
type 2 diabetes. It would be very important to compare these findings with the published literature on this topic.

5. Both of the sisters were hypoglycemic at 2 hours, yet only one of the girls had a mutation. Was this related to the GYS2 gene? Please discuss the hypoglycemia in the siblings.

6. Why was the patient with GSD 0 hypoglycemic at the beginning of the fast?

MINOR ESSENTIAL REVISIONS:
7. There are a number of grammatical and spelling errors throughout the document (i.e. "toa" in the title of Table 3). Please review the text carefully.

DISCRETIONARY REVISIONS:
8. It may be useful to have more of a family history. Did they have European ancestry that could explain the common mutation?

9. The authors may want to discuss the rise in the glucose concentration after glucagon.

10. Do carriers for other forms of GSD develop hypoglycemia? The authors may want to discuss clinical manifestations due to haploinsufficiency in other diseases.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests