Reviewer’s report

Title: Clinical and whole-exome sequencing findings in two siblings from Hani ethnic minority with congenital glycosylation disorders

Version: 2 Date: 04 Jul 2019

Reviewer: Kent Lai

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Review for MGTC-D-19-00057R2

The authors of this manuscript reported the identification, based upon whole exome sequencing, of nucleotide changes - c.241-242 del and c.679 G>A in the PMM2 and MYH9 genes, respectively, in two siblings from Hani ethnic minority with congenital disorders of glycosylation (CDG). Although such gene variations have not been described in this population and the implications could potentially be significant, this reviewer has serious concerns for the findings.

1) Despite the authors claimed that both patients suffer from CDG, the clinical presentation shown in Table 1 offered little support for such diagnosis. At the very least, the authors should show the glycosylation status of serum biomarkers such as transferrin to support the diagnosis.

2) The sequencing results shown in Fig. 3 are confusing. In the text, the authors claimed "The heterozygous PMM2 c.241-242 del was identified in the proband's affected brother, the proband's unaffected mother (Fig. 3)....... But in Fig. 3, the PMM2 c.241-242 del does NOT appear to be present in the "affected" brother. The brother's sequence is the same as the father's.

3) Another major concern is that PMM2-CDG is a well-documented autosomal recessive disorder and therefore, even if the c241-242 del is "pathogenic by prediction", it will not make much sense a heterozygous change identified could result in disease manifestation. In fact, if this were the case, why is the mother "unaffected"? This reviewer appreciates the authors' mentioning that total absence of PMM2 activity is incompatible with life, but most patients do have homozygous hypomorphic mutations (see https://www.ncbi.nlm.nih.gov/books/NBK1110/). Were there any PMM2 enzyme activities measurement done on patient cells?

<END>
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

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I am able to assess the statistics

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