Reviewer’s report

Title: Genetic and clinical characteristics of Chinese children with Glucokinase-Maturity-Onset Diabetes Of The Young (GCK-MODY)

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Reviewer: Monique Losekoot

Reviewer's report:

The aim of the study by Li et al is to investigate the clinical and molecular characteristics of Chinese children with GCK-MODY. The authors describe that in 587 children with diabetes, 24 patients presented with possible MODY. Eleven patients suspected of GCK-MODY were tested for the presence of a mutation in GCK and in 9 patients a GCK mutation was detected. The remaining 2 patients were tested by targeted NGS for other MODY genes and no mutation was detected. It is unclear if the other 13 possible MODY patients were tested for a MODY mutation. Clinical data of the patients and affected relatives are presented and discussed. There is no difference with Caucasian patients. The paper is written in a clear and concise way.

Comments:

- The possibility that in the original population of 587 children other GCK-MODY patients could be present is not discussed and these patients were not tested for MODY mutations.

- Mutations were compared with HGMD and NCBI; only Polyphen-2 was used to predict pathogenicity while other prediction tools exist (SIFT, GVGD) are also available. In addition, it is unclear how splice mutations were predicted. Polyphen-2 predictions can be used for missense mutations only. In the paper the novel mutations are: 2 in frame deletions; one frame shift and one splice mutation for which Polyphen-2 is not useful.

- In Fig. 1 the frame shift and splice mutations are depicted in GCK protein crystal structure. This is useless since these mutations will give a completely different (truncated) protein or no protein at all due to NMD. If you want to show the effect on the protein structure, the structure of the mutated protein should be predicted in order to illustrate the effect of the mutation. Both Fig 1 and 2 do not add much to the text and can be omitted. If you do show this figure you should also discuss it in the text and elaborate on the implications of the mutation and the possible effect on protein structure and function.

- Targeted NGS is described in ref 13. Checking this reference I noticed that the MODY genes are not present in the 193 genes in the target gene panel (Table S1 in this paper). It is not
clear how the NGS procedure for the 13 MODY genes en 31 monogenic diabetes genes was performed and data concerning coverage and other relevant information on the targeted experiment are not provided.

- Also for splice site mutations HGVS nomenclature should be used e.g. IVS6+1G>A should read c.679+1G>A.

- Method: DNA extraction using standard procedure: please provide reference.

- The authors describe 4 novel mutations which they state add to the diversity of GCK mutations. Over 620 GCK mutations have been described so far; 4 more is not really a significant addition.

**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

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
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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Please indicate the quality of language in the manuscript:

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