Reviewer's report

Title: Comprehensive genomic analysis of pathogenic variants in Maturity-Onset Diabetes of the Young (MODY) patients in south India

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Reviewer: Kazuya Yamagata

Reviewer's report:

Mohan et al. carried out a comprehensive genomic analysis of MODY patients in south India and identified that HNF1A and ABCC8 genes are most frequently mutated genes. Furthermore, they found variants in Nkx6.1 and other genes. The findings by the authors are potentially interesting, but there are several questions that deflate the value of the present study.

Major criticisms

1) The authors found many missense and nonsense mutations. Please clarify whether they are novel or previously reported mutations.

2) The clinical features (e.g. BMI, age at diagnosis, CPR, and treatment) of patients with MODYs should be clarified.

3) Fig. S3: The label of Y-axis is RPKM. What is RPKM? Clearly, expression of WT is much higher than that of mutant. This reviewer thinks that the differentially regulated gene expression may be simply due to the difference of Nkx6.1 expression levels (rather than WT vs MUT). In addition, the induction levels of Nkx6.1 compared to endogeneous Nkx6.1 is unclear. Overexpression of proteins in beta-cells easily induce ER stress. Please show the induction levels compared endogenous Nkx6.1. The authors have to show equal expression between WT and mutants (after induction) by western blotting. If the authors claim that S317L and S329L are functionally impaired, they should examine transcriptional activities of mutant Nkx6.1 by classical reporter gene assay. Alternatively, the authors should investigate insulin secretion or apoptosis using stable cell lines. Fig. 4d seems to be not informative.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.
Yes

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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