Reviewer's report

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

Version: 1 Date: 19 Sep 2017

Reviewer: Hiroto Furuta

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In this study, Mohan et al. investigated causal genes of patients with MODY like characteristics in south India. They screened 152 clinically diagnosed MODY cases with target, whole exome or whole genome sequencing for 35 genes that included known MODY genes and others implicated in early onset diabetes including neonatal diabetes. Although this study is informative to clarify the etiology of MODY like patients, I have several comments.

Major comments

1. The author described that "HNF1A (MODY 3) was most frequently mutated at 8.6% (n=13), followed by ABCC8 at 4.6% (MODY 12; n=7), BLK at 3.9% (MODY 11; n=6) and KLF11 at 2% (MODY 7; n=3). Other MODY genes that were mutated included CEL (MODY 8; n=2), HNF4A (MODY 1; n=2), GCK (MODY 2; n=1), HNF1B (MODY 5; n=1), KCNJ11 (MODY 13; n=1) and PDX1 (MODY 4; n=1), although these mutations were infrequent." However several patients have a mutation in two or three different genes (Fig. 2b). For example, sample No 201 has a mutation in both HNF1A and BLK. The author should clarify which gene mutation is associated with diabetes in this case families and recalculate the frequencies of causal genes in south India.

2. Several mutations are predicted as "benign" or "tolerated" with Polyphen2 or SIFT. The author should explain the reason that the author judged the variant as the causative mutation in the family.

3. The author described that "In addition to known MODY genes, we report the identification of variants in WFS1, MNX1, RFX6, NKX6-1, NKX2-2, AKT2, EIF2AK3, and SLC19A2 that may contribute to development of MODY." In addition to functional study of mutation, it is very important to check that the mutation is cosegregated with diabetes in the family. This point should be checked for all causative mutations.

Minor comments

In page 8, lines 9, the author described that "Combined together, we identified 58 unique candidate variants in 51 of the 152 MODY sample". However, I think the number of candidate variants is 63, which is shown in the Supple. Table 4b.
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

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Not relevant to this manuscript

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