Reviewer’s report


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Reviewer: Tatsuya Kondo

In this manuscript, the authors presented a case report of atypical possible MODY5 diabetic patient, having a significant family history. Exome sequencing revealed a novel mutation in codon 1580 G to A, and predicted a potential pathogenicity using in-silico prediction system. The sequencing also provided the multiple common susceptibility variants associated with obese type 2 diabetics.

Clinical approach to identify a genotype-phenotype relationship is important, and this manuscript provides methodological advances to enhance the diagnostic precision in monogenic diabetes. However, in-silico prediction may not be enough to achieve a conclusive diagnosis of MODY5 in this case, because the phenotype in this patient is not typical in MODY5.

Major comments

1) The proband's insulin sensitivity and insulin secretory capacity should be described, such as M/I value investigated by euglycemic hyperinsulinemic glucose cramp, OGTT with insulin and C-peptide secretion, and urinary excretion of C-peptide a day.

2) Exome sequencing from samples in family and relatives will improve the reliability of responsibility of this specific mutation.

3) Even if the reliability of computational analysis in pathogenicity is increasingly expanded, the in vitro functional analysis of this mutation in insulin secretion and/or insulin sensitivity should be evaluated, because the authors belong to the academic institute.
4) The proband doesn't have kidney anomaly but significant kidney dysfunction. How was the blood pressure control? Any medications for BP?

5) The scores in individual in-silico prediction fluctuate from 0 to 35. How much reliable in those prediction scores.

Minor comments

6) In line 80, the approved number of this project provided by IRB should be indicated.

7) In line 85, do not use "3 ug of DNA", use "3 μg of DNA" instead.

8) In line 226, "atrophy" may not be suitable to express the developmental problem in pancreas. "hypoplasia" may be compatible.

9) Some part, HNF1β and HNF1B mixed up.

10) Is there any association between HNF1β mutation and obesity?

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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