Reviewer’s report

Title: Spectrum of mutations in monogenic diabetes genes identified from high-throughput DNA sequencing of 6,888 individuals

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Reviewer: Sian Ellard

Reviewer’s report:

The authors have used a pooled next generation sequencing strategy to sequence a large panel of genes in nearly 7000 individuals; 2872 controls and 4016 patients with type 2 diabetes. They analysed 22 monogenic diabetes genes and identified pathogenic variants in 48 individuals with diabetes. Nearly half of these subjects were diagnosed with GCK MODY which does not usually require pharmacological treatment.

The manuscript is well-written and the data clearly presented. Minor comments:

1) The term "carrier" refers to a person who is heterozygous for a recessively acting disease-causing variant. For example the unaffected parent of a patient with Wolfram syndrome. It should not be used to describe a person with diabetes in whom a dominantly acting pathogenic variant has been identified. In contrast the individuals with heterozygous truncating variants in ABCC8 will be heterozygous carriers of hyperinsulinism.

2) The list of monogenic diabetes genes should be revised as there is insufficient evidence to include PAX4, KLF14 (I think you meant KLF11 in the gene list) or BLK.

3) Variants should be classified according to the ACMG/AMP guidelines (Richards et al 2015 Genetics in Medicine).

4) Is any information available about the impact of the genetic diagnosis? Did the patients found to have GCK variants stop pharmacological treatment? How was this information given back to the study participants?

5) Table 1 - please remove the term "carriers". In addition the ABCC8 truncating variants should be removed because only activating variants in this gene cause diabetes.

6) Table 2 - pathogenic GCK variants cause mildly raised fasting blood glucose from birth so the column heading should be "age at diagnosis" rather than "age at onset".

7) Reference sequences must be provided where HGVS nomenclature is used.

8) The total number of individuals sequenced is 6888 - why round up to 6900 in the title?
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.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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Not relevant to this manuscript

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