Reviewer’s report

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

Version: 1 Date: 16 Aug 2017

Reviewer: Martine Vaxillaire

Reviewer’s report:

The authors have addressed most of the reviewers’ concerns, and provided appropriate detailed information in the revised manuscript that is now much improved.

However, some important issues remain to be clarified, as regarding the number of targeted gene regions with a low sequence coverage, like in PDX1, INS and GATA6, making the statistical results not too accurate (such as the % of individuals with a rare likely pathogenic mutation, as well as the OR estimates from the frequency of missense mutations carriers). In the manuscript, the authors clearly report a false negative rate of rare variants to be at 7%.

This reviewer still believe that the strategy of DNA pooling with the use of NGS is not the best appropriate for the discovery of (very) rare genetic variants and further analysis in case-control study for T2D association.

Otherwise, given the range of age at diagnosis of diabetes for the individuals defined as "early-onset cases", that is between 10-40 years, one can expect that a number of these young-onset individuals with a rare (likely) pathogenic mutation in a MODY gene may indeed be considered as belonging to a MODY subtype; in particular for the individuals identified with a GCK mutation, as highlighted by the second reviewer, or the individuals with a protein truncating variant in HNF1A or those with a missense mutation in the MODY genes that have previously been reported in individuals or families with MODY. On this matter, the reviewer believes the clinical criteria used to define the study cases with early-onset diabetes are not stringent enough, and are not discriminant against the MODY subtype. This should be better emphasized in discussing the results.

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.

Unable to assess

**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

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

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