Reviewer’s report

Title: Type 2 diabetes gene TCF7L2 polymorphism is not associated with fetal and postnatal growth in two birth cohort studies.

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Reviewer: Nicolòment of Pulizzi

Reviewer’s report:

Mook-Kanamori and colleagues investigated whether the most replicated type 2 diabetes gene, TCF7L2, is associated with growth pattern during fetal life and early infancy, a concept in the frame of the fetal insulin hypothesis. To do so, they used data from 2 cohort, (Generation R, representative of general population, and SGA cohort, including subjects small for gestational age). Of Generation R, fetal measurements during the second and third trimester were available.

The issue addressed by this manuscript is of interest, and there are some potentially relevant data on TCF7L2 genotype and fetal measurements. Though, I do not agree on the way some data were presented.

The authors found:
1. The minor allele (T) frequency of the variant rs7903146 in TCF7L2 gene was similar between Generation R and SGA cohorts.
2. Birth size was similar among genotypes in both cohorts.
3. TCF7L2 was not associated with pre- and post birth growth characteristics in both cohorts.

The authors concluded that “TCF7L2 would therefore not appear to be involved in the previously demonstrated associations of low birth weight with T2D”.

A key strength of the study is the availability of fetal measurements in Generation R cohort, which adds some exciting information in the puzzle of the fetal insulin hypothesis. As the authors clearly state, birth weight can be the result of very different growth pattern during fetal life, thus representing a rough proxy of fetal development. The manuscript is clear, even if throughout the text there is some redundancy (see Discretionary Revisions). However, there are some important areas of concern:

Major Compulsory Revisions:
1. Dominant, recessive and additive models are tested. This approach can be acceptable in a preliminary analysis of data, but according to the literature in this field, only the additive model earns credit. When testing different models, a Bonferroni correction for multiple testing multiple is usually required, and this often turns nominal significant findings into non significant results. Here the dominant and recessive models do not add any information, so I would suggest to skip them, showing only results drawn from the additive model.
2. Comparing the allele distribution between the general population (Generation R) and SGA cohort gives the reader some qualitative hint to think about, but, as it is, it sounds to me somehow misleading, whereas from that the authors seem to draw too strong conclusions.

The ideal would have been to compare in the Generation R cohort the allelic distribution between SGA subjects and non SGA subjects, adjusting for available confounding factors and looking for eventual interactions. From table 1 it appears that the low number of SGA subjects in the Generation R cohort makes the suggested approach weak in terms of statistical power. If the authors want to compare the allelic frequency between the two cohorts, not merely to describe the data, but in a “case-control” approach, I suggest, at least in this specific analysis, to remove from the Generation R cohort subjects small for gestational age. Even after doing so, there will be left some newborn labeled as non SGA, but still with a birth weight lower than 2500 g, if I interpret correctly the data shown in table 1: in Generation R cohort 1.6% is SGA and 2.5% has a birth weight <2500 g. On the other hand in The SGA cohort there is 17.3% with a birth weight >2500 g. The authors should either to redesign this analysis or to better comment the results from the chi-square. Consistently, I would advocate more caution to state: “Furthermore, minor allele frequency was not different in SGA subjects than in non-SGA subjects from which we can conclude that there was no association between genotype and risk of being born SGA”.

Discretionary Revisions:
1. The final statement in the abstract: “TCF7L2 would therefore not appear to be involved in the previously demonstrated associations of low birth weight with T2D” cannot be drawn from the data presented.

2. The authors are redundant in the Introduction and in the Discussion sections, repeating some information from the literature, not strictly related to their own results.

3. The authors cite previous studies from Cauchi and Freathy. To be more complete they might cite also the findings from the Helsinki Birth Cohort, which consistently did not show any association between this variant of TCF7L2 and birth size.

4. “Furthermore, we demonstrated that this polymorphism is not related to size at birth...” : I would rather use “replicate”or “confirm”. On the other hand I would stress more throughout the text what seems the real novelty of this study. Since TCF7L2 is likely associated with impaired insulin secretion and insulin is a main anabolic factor during fetal life, it arises as a candidate gene of impaired fetal development, as well stated by the authors. Previous studies failed to demonstrate this hypothesis, but their findings were not definitive, being birth weight a proxy of development. In this unique study, the authors demonstrate that this variant of TCF7L2 does not influence the fetal development, by direct fetal measurements.

Minor Essential Revisions

Introduction; 3rd line: These associations may be explained by common genetic
variants: better to use “influenced”.

Introduction; 4th line: “factor” is repeated twice in the same sentence.

Results; 11th line: I would say nominal p value, to make clearer that it may a false positive

Discussion; 2nd line: “early life” I would specify “fetal life” for general population and early postnatal life for both cohorts.

Discussion; 24th line: These fetal genetic factors could also (partially) explain the association between low birth weight and T2D risk

Materials and Methods/The Generation R study/Fetal growth...; 8th line: "using" is repeated twice in the same sentence.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I have cooperated with the interpretation of the genotyping in Helsinki Birth Cohort.