Author's response to reviews

Title: The TCF7L2 locus and type 1 diabetes

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TCF7L2 response to the Editor and reviewers

The Editor:
1. Please remove the meta-analysis.
   >We agree. The meta-analysis was removed.
2. Provide an appropriate statistical calculation of the power of the study.
   >Please see Page 3 Line 31-34 and Fig.1.
3. Please improve the discussion. In particular our Editorial Board has highlighted the need to discuss, in greater detail than is done currently, the recent publication by John A Todd and colleagues that also reports a negative association between type 1 diabetes and TCF7L2.
   >Accepted. To discuss in greater detail, 2 paragraphs were added to the discussion part in Page 4.

Reviewers
1. Alan Shuldiner
   This reviewer has no major criticisms. The meta analysis for type 2 diabetes is probably not necessary. The main point that can be described simply in the manuscript is that other studies of TCF7L2 in similar ethnic backgrounds to that studied in this manuscript were strongly associated with type 2 diabetes. At the very least, the author should acknowledge publication bias of positive studies over negative studies that could inflate the effect size in the meta analysis.
   >Accepted. The meta-analysis part is removed.

2. John Todd
   (1) Can the authors please use a much larger sample size since the current one is statistically powered to detect only quite large effects. The new sample set would need to be larger than the previously published study of TCF7L2 in T1D (Diabetologia). Negative studies are only interesting if the dataset is very large and has good power to detect very small effects, otherwise the claim "TCF7L2 is not associated with T1D" may not be that informative.
a. As shown in our power calculation (Page 3 Line 38-41 and Fig.1.), our study on 886 T1D nuclear families have reasonable statistical power to detect all but very weak genetic associations.

b. Also, added to the results from Dr. Todd's group, our data strengthen the finding of absence of even a very small effect.

(2) Can the authors please make clear what the new insight into the association of the TCF7L2 gene in T2D brings to the analysis of this gene in T2D? Have the authors performed any fine mapping of the TCF7L2 region? which is the most associated SNPs/DIPs? Is there any association between SNP genotypes and expression of TCF7L2?

> The intronic SNP rs7903146 is the most significant known T2D association shown by our own T2D data and the literature. Proper resequencing and fine mapping, still lacking in the literature as the reviewer suggests, is in progress in our lab; however, this question was outside the thrust of our paper. In the revised version (page 4, line20-23) we mention our unpublished data showing no association between SNP genotypes and the mRNA level of TCF7L2 in human lymphablast cells. However, tissue-specific effects need to be investigated in other human tissues.

3. Colin Palmer
This is a relevant replication of a negative association. The power and limitations of the study are well acknowledged. The T2D metanalysis is completely unnecessary. Accept after discretionary revisions.

>Accepted. The meta-analysis part is removed.

4. Arno G Motulsky
I recommend rejection based on its minimal interest to most readers and its small sample size. An article of insufficient interest to warrant publication in a scientific/medical journal.

> We believe that testing a strong T2D locus for T1D effects is important and the other reviewers seem to agree with us. On sample size and statistical power, please see our answer to Dr. Todd.

5. Alex MacGregor
Minor: Please provide additional referencing for Table 1. Accept after minor essential revisions. An article whose findings are important to those with closely related research interests.

> The data in Table 1 is from our own study of type 1 diabetes, on the same cohort. We have added this information in the table legend.

Thanks!