Author's response to reviews

Title: TCF7L2 and therapeutic response to sulfonylureas in patients with type 2 diabetes

Authors:

Andreas Holstein (Andreas.Holstein@t-online.de)
Michael Hahn (mhahn78@googlemail.com)
Antje Körner (antje.koerner@medizin.uni-leipzig.de)
Michael Stumvoll (michael.stumvoll@medizin.uni-leipzig.de)
Peter Kovacs (peter.kovacs@medizin.uni-leipzig.de)

Version: 3  Date: 31 January 2011

Author's response to reviews: see over
Re: Revision of Manuscript

Dear Dr. Meyre,

thank you very much for your encouraging letter and for the opportunity to revise our manuscript entitled “TCF7L2 and therapeutic response to sulfonylureas in patients with type 2 diabetes” (Holstein et al.). We considered the remaining comments raised by the reviewers and revised our manuscript accordingly. We thank the reviewers for their constructive criticism which, we feel, substantially improved the quality of our manuscript. All changes in the revised manuscript are indicated in red and underlined. Please also find attached our point-by-point response to the reviewers’ concerns.

We sincerely hope that we satisfactorily addressed all issues and the paper could now be accepted for publication in BMC Medical Genetics.

With best regards,
sincerely,

Peter Kovacs
Comments to the Reviewers:

Reviewer: Jose Florez

We thank the reviewer for the very constructive comments which we addressed in the revised version. We really appreciate it!

1. First paragraph of the Discussion: under the new analyses, diabetes duration was no longer a predictor of SU failure.
   - We regret this and apologize for not revising the first paragraph of the Discussion. We now corrected this part.

2. First paragraph of the Discussion: allele frequencies refer to the prior analyses, and should be changed to refer the new definition of SU failure.
   - Has been corrected accordingly.

3. First paragraph of the Discussion: was there an adjustment for diabetes duration, even if not significant? If not, the sentence should be removed; but the authors could consider performing this additional analysis, although this is not required.
   - Primarily, we did not adjust for diabetes duration since it did not predict SU treatment failure in the univariate analyses. However, according to the reviewer’s suggestion, we now run the analyses also with adjustment for diabetes duration and found materially unchanged results. Therefore, we added (page 7, first para of the Discussion): “After adjusting for diabetes duration the odds ratio did not change (OR=1.57) and the p-value reduced just minimally (from P=0.046 to P=0.057), thus indicating independent effect of the TCF7L2 genotype.”

4. First paragraph of the Discussion: carriers of the T allele were 57% more likely to fail SU; TT homozygotes were twice as likely as CC homozygotes.
   - Many thanks; we now revised the sentence accordingly (page 8).

There is one discretionary revision:
While the new HbA1c-based definition is preferable as suggested, it may be worthwhile to strengthen the paper to state that an alternate definition based on addition of insulin yielded similar results. As long as all the caveats expressed on initial review are included, the authors may not need to discard their prior analyses, but include them as secondary confirmatory analyses while specifying they are not independent from the previous analyses. The interesting piece of how diabetes duration differed between the two groups, and how adjustment for this covariate only reduced the odds ratio minimally (from 1.73 to 1.66, even if the P-value went from 0.04 to 0.06) would also be nice to present.
   - We thank the reviewer for this remark since we also believe that the data based on alternate definition of SU treatment failure (addition of insulin) support our findings and strengthen the conclusions. Therefore, as suggested by the reviewer we now included secondary confirmatory analyses (in the Results; page 6-7) and addressed the main points in the Discussion (page 8-9).

“It is noteworthy that an alternate definition of SU treatment failure in our cohort based on addition of insulin after at least 6 months of SU therapy and corresponding A1C...
measurement of ≥7.0% yielded similar results. Even though not independent from the previous analyses, these findings provide further support for the role of TCF7L2 genotypes in altered hypoglycaemic response to SUs. Interestingly, when using this definition of SU treatment failure, diabetes duration appeared to be a predictor of treatment failure along with the TCF7L2 genotype. Nevertheless, the genotype effect was independent as even after adjustment for diabetes duration, the results remained materially unchanged. Although the P-value went from 0.04 to 0.06 the odds ratio reduced only minimally (from 1.73 to 1.66).