Reviewer's report

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

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Reviewer: Jose Florez

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In this paper, the authors follow up on a previous retrospective study in the GoDARTS cohort which reported that carriers of the risk allele at the well established type 2 diabetes locus TCF7L2 fail sulfonylurea therapy, whereas metformin does not have a genotype-specific effect. While that study examined close to 1,000 patients per treatment modality, in this manuscript only 189 patients were studied. Sulfonylurea failure was defined as the addition of insulin after at least 6 months of sulfonylurea therapy and a concomitant glycated hemoglobin (HbA1c) #7%, which typically demands escalation of therapy. The authors find that diabetes duration predicted sulfonylurea failure, and that the risk genotype at TCF7L2 rs7903146 was more frequent among people who required insulin in addition to a sulfonylurea (P=0.03). When adjusting these results for diabetes duration, the P value became 0.06 (0.04 under a recessive model). They conclude that their study confirms that the risk genotype at TCF7L2 is associated with a worse response to sulfonylureas.

This paper is interesting in the following respects:

1. Study of the gene with the strongest effect on type 2 diabetes identified thus far
2. Corroboration of a previous pharmacogenetic finding
3. A result that is consistent with the known mechanism of action at this locus

However, while the conclusion reached here is consistent with a previous well powered pharmacogenetic study on the same variant, this study suffers from several limitations that require clarification:

1. The definition of sulfonylurea failure: the addition of any other antidiabetic medication (e.g. metformin, thiazolidinediones, exenatide, DPP-IV inhibitors), not just insulin, could also be indicative of sulfonylurea failure. Some information on whether other options were available to the physicians in this study would be helpful. Furthermore, the decision to escalate therapy is also driven by physician inertia; given the availability of HbA1c as an index of treatment response, this biochemical measure alone would seem to be more objective and less prone to non-genetic environmental factors. Why not simply use HbA1c #7% as the definition of failure, regardless of how treatment was escalated?

2. Confounding by severity of disease: the authors show that patients who
required insulin in addition to a sulfonylurea were also younger at the onset of disease and had longer duration of type 2 diabetes. Therefore their genotype at TCF7L2 may have simply affected the manifestation of disease (in timing and/or severity), and not be specific to sulfonylurea response per se. This suspicion is further supported by the effect of adjustment for diabetes duration, which makes the P value under the additive model non-significant. A study where participants are matched for clinical characteristics at baseline (preferably in a prospective fashion) would be a more definitive way to answer this question. To bolster their claims, the authors should draw attention to the small change seen in the odds ratio after adjustment for diabetes duration, suggesting that the attenuation of effect is small even if the P value becomes non-significant.

3. Lack of another treatment modality to support specificity: in contrast with the previous GoDARTS report, which compared the effect of genotype in people treated with metformin or a sulfonylurea, this study only examines sulfonylurea-treated patients. To demonstrate that the TCF7L2 effect is specific to the mechanism of action of sulfonylureas, it would have been nice to show that this genotype does not influence response to a non-insulin secretagogue. Can the authors repeat their analyses on the 72 metformin-treated individuals only?

4. Incomplete analyses: it is not clear why genotype was not used as a predictor in the univariate regression analysis presented in Table 2 (although it is mentioned as an independent predictor in the Abstract and Discussion). A stepwise regression in this model would have helped sort out to what extent the effect of genotype is confounded by other variables.

5. Unclear justification for the recessive model: multiple studies have demonstrated that this locus exerts its effects via an additive model. Thus there is no a priori justification to use a recessive model, unless it is being used simply to attain statistical significance.

6. Low sample size: for genetic variants that confer a modest effect on risk, a much higher sample size is typically needed. The authors should provide power calculations describing the magnitude of the effect they are expected to detect, and how that compares with the previous publication.

7. Other endpoints: if genotype at rs7903146 makes patients more resistant to the action of sulfonylureas, one would expect that carriers of the risk genotype should be less likely to become hypoglycemic. This endpoint could provide supportive evidence, particularly in the context of a protocol originally designed to study hypoglycemia.

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.
Declaration of competing interests:

I declare that I have no competing interests