Reviewer's report

Title: TCF7L2 variant genotypes and type 2 diabetes risk in Brazil: significant association, but not a significant tool for risk stratification in the general population

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Reviewer: André Scherag

Reviewer's report:

In 'TCF7L2 variant genotypes and type 2 diabetes risk in Brazil: significant association, but not a significant tool for risk stratification in the general population' Marquezine et al. report results of genetic association analyses in two samples for one variant (rs7903146) of TCF7L2 which has previously been shown to be robustly associated with type 2 diabetes mellitus (T2DM). Even though this variant has been analysed multiple times before, their manuscript focuses on results in a South American population and investigates the question if genotype status adds to the area under the receiver operating characteristic (ROC) curve of a diagnostic test already constructed on the basis of other non-genetic variables.

In sum, this is a concisely written paper which addresses an important, potential application of genetic association findings - their usefulness for predictive genetic testing. Nevertheless, to further improve the manuscript I would like to add some major and minor remarks which I would like to see addressed in a revised version of the paper.

Major Compulsory Revisions
- the authors analyse rs7903146 assuming a recessive genetic model which might both not be the correct one or which might be less powerful than the (log-)additive model – so I strongly recommend using the latter for the basic as well as for the ROC analyses
- the authors should give all genotype counts (CC, CT, TT) for each sample which offers the option to compare results more easily across studies
- please clearly distinguish for which statistical tests hypotheses exist from the literature (a-priori information) and if the reported data point into the same direction
- for all statistical tests please report unadjusted p-values as well as point estimators and confidence intervals for the genetic effects; for all tests with a-priori information do also report adjusted p-values and mark them as such
- in case of sparseness of the data the authors should use exact tests (e.g. Fishers test instead of Chi-squared test)
- what is the purpose of including the highly selected MASS II data?
- what would happen if you analyse both samples jointly (say for your main finding)?

- what is the practical purpose of the prediction model and to what population should it be applied (e.g. if it is a screening tool for T2DM it’s application to MASS II would make little sense and a variable like “obesity” should be assessed a the time of screening while T2DM status should be assessed later in time)?

- please give a citation for the prediction model without genetics and give more detail on the variables (e.g. was “obesity” assessed at the same time of T2DM diagnosis?) and their weights for the prediction; a clear improvement of the manuscript would be a an inclusion of other non-genetic prediction models (please give citations) and a comparison of their AUC (estimator and confidence interval) with and without rs7903146 genotype status

- please revise the statistical analysis part and use non-parametric tests instead of e.g. t-tests or ANOVA

- please give detail on the power calculation

Minor Essential Revisions

- mentioning SPSS only once in the statistical analysis part

- use commas to denote the thousands digit throughout

Discretionary Revisions

- as your data nicely underlines the limits of predictive genetic testing, your discussion would benefit from a critical review of the recent papers of Chachi S et al. or A Cecile J W Janssens

- genotype distributions cannot be in Hardy-Weinberg equilibrium; correctly there can only be no evidence for (strong) deviations from Hardy-Weinberg equilibrium (report the smallest 2-sided exact p-value to underline your statement)

- what would be the practical consequences of applying either predictive model – given an example e.g. for testing say 1,000 subjects (how many wrong decisions will there be?)

**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