Reviewer's report

Title: TCF7L2 Gene Polymorphisms do not Predict Susceptibility to Diabetes in Tropical Calcific Pancreatitis

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Reviewer: Joost P Drenth

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TCF7L2 Gene Polymorphisms do not Predict Susceptibility to Diabetes in Tropical Calcific Pancreatitis


Dr. Mahirkar and colleagues were interested in the genetic background of tropical calcific pancreatitis (TCP), a type of chronic pancreatitis that is diagnosed in the tropics. They note that progression to diabetes occurs in the large majority. This phenotype led them to investigate the role of 2 diabetes mellitus associated polymorphisms in the TCF7L2 gene using a case-control approach in 478 well-characterized TCP patients and 661 healthy controls. They found that the genotype and allele distribution of the 2 TCF7L2 SNP's was similar among groups. This leads to the conclusion that "TCF7L2 is a major susceptibility gene for type 2 diabetes, hence lack of association of TCF7L2 variants with TCP or FCPD as observed in this study suggests that the diabetes in TCP patients may not be similar to type 2 diabetes or T2D associated TCF7L2 variants are not associated with diabetes in TCP."

This study fulfills the requirements of a solid genetic case control study. The sample size (~1100) participants is large enough to power the study, the biological plausibility is there, and the methods (sequencing) are fine. I would like to commend the authors that they were able to collect this sample size which allows independent gene discovery studies.

I have only few comments that I would like the authors to address

1. The introduction mentions Cathepsin B, CFTR, and SPINK1. Many studies have confirmed the association between SPINK1 N34S variant and TCP (1, 2, 4, 5) yet the authors only mention their own study. I think that it is appropriate here to refer to other landmark studies as well here. Furthermore, in addition to the genes mentioned, I think it is good to add a recent gene discovery study on trypsin-degrading enzyme chymotrypsin C (CTRC) which is clearly associated with TCP. (3)

2. One major issue is the subdivision of the TCP population in of Dravidian and Indo-European ethnic groups. Although there has been debate on the origin of the Dravidian ethnic group and the assumed dissimilarity with Indo_europeans
recent studies have settled this issue and indicate that there is no real separate biological Dravidian "race" distinct from non-Dravidians in the Indian subcontinent. (J Hum Genet. 2005;50(10):497-506, & Am J Hum Genet. 2006 February; 78(2): 202–221). Thus, despite the geographic and linguistic diversity of the population groups in India, Indians as a whole display a low level of genetic heterogeneity. (BMC Genet. 2008 Feb 4;9(1):13) As a consequence, the results from both groups should be lumped together: TCP vs controls. The meta analysis with forrest plots can be deleted from the manuscript.

3. Perhaps I missed it, but I would like to see how many patients in their respective cohorts suffered from fibro-calculous pancreatic diabetes. Table 2b gives results but I cannot see the number of patients that fit into the group.

4. Other TCF7L2 variants have also been associated with diabetes. Why did the authors limit their analysis to rs7903146 and rs12255372?

5. Were rs7903146 and rs12255372 in linkage disequilibrium in the population under study?

6. The authors state that “Both patients and the controls filled a detailed questionnaire” What questionnaire and which questions? There is no reference to the questionnaire in the remainder of the text.

7. I failed to see the relevance of the lines “TCF7L2 gene variants…. important role in T1D ……understanding….. diabetes in FCPD patients” in the context of the results obtained.

8. I have difficulties with the conclusion of this paper, and I fear that the authors use an overstatement. Personally I would not go so far in concluding that the pathogenesis of type 2 diabetes is dissimilar from diabetes in TCP on the basis of study of 2 single nucleotide polymorphisms.

Reference List


**What next?:** Accept after minor essential revisions

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

none