Author’s response to reviews

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

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Author’s response to reviews:

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For the attention of :-

The Editor of Biomed Central Medical Genetics

Dear Editor,

I wish to thank the reviewers for their comments and am now enclosing our revised manuscript titled "TCF7L2 Gene Polymorphisms do not Predict Susceptibility to Diabetes in Tropical Calcific Pancreatitis but May Interact with SPINK1 and CTSB Mutations in Predicting Diabetes”. I am highly obliged to the reviewers for giving valuable advice towards investigating the interaction between TCF7L2 variants and SPINK1 and CTSB variants. We have now performed this analysis and have got interesting results which have been incorporated in the modified manuscript. This has also led to slight modification in the title from the original title.

I am happy to note that there are no serious concerns from all the reviewers and there are only minor revisions focusing mainly on the language and grammatical errors in the manuscript. We have incorporated all the suggestions made by the reviewers. These changes are mentioned point by point below and have also been highlighted in the revised manuscript. Please let me know if any clarification is required.
Thank you once again for taking time to consider this manuscript.

I look forward to hearing from you.

Yours sincerely

(G R Chandak)

Response to comments from the Reviewers

Reviewer 1 (Cedric Le Marechal):

Minor Revision

1. We agree with the reviewer’s comment and have now modified the statement "evidence for association...significance criteria" for the sake of clarity as, “as the overall evidence for association of TCF7L2 gene variants exceeds genome-wide significance criteria (P=10-5) and clearly establishes TCF7L2 as a T2D susceptibility gene of substantial importance in majority of populations world-wide [Zhang et al. Diabetes 55: 2645–48, 2006] including Indian population [Chandak et al. Diabetologia 50: 63-67, 2007], it is likely that TCF7L2 may be the strongest susceptibility factor for T2D”.

Discretionary Revisions

We are extremely thankful to the reviewer for this important suggestion and have now included the SPINK1 mutation as another criterion for stratification to look for association of TCF7L2 variants with TCP between carriers and non-carriers of N34S SPINK1 mutation. We have done similar analyses taking L26V CTSB mutation as another criterion for stratification. Sections added in the revised manuscript are highlighted in bold. In view of the results of this analysis, we have made minor modifications in the title of the revised manuscript.

Reviewer 2 (Joost P Drenth):

1. We thank the reviewer for pointing this out; suggested references have been included in the revised manuscript.

2. We agree with the reviewer that the inter-linguistic group heterogeneity in India has been reported to be low, however, there are reports which, though did not detect an evidence of clustering based on ethnic linguistic geographic or socio-cultural affiliations, detected genetic sub-structuring among populations originating from northeastern and southern India reflective of their migrational
histories and genetic isolation respectively [Kashyap et al. BMC Genet 2006, 7: 28, 2006]. Some studies have used the linguistic groups such as Bengalis, Gujaratis in their study etc, which are truly not populations and may still have evidence of sub-structuring [Rosenberg NA et al. PLoS Genet 2(12): e215, 2006; Pemberton TJ et al. BMC Genet 4(9): 13, 2008]. We therefore felt that this is still a matter of debate and it may be better to initially analyse them as separate groups and subsequently pool the results by meta-analysis, which is what has been followed and presented in the manuscript.

3. We are extremely sorry for missing out on number of FCPD patients and are thankful to the reviewer for pointing the same, which has now been included in the legend of table 2b.

4. We genotyped the SNPs rs7903146 and rs12255372, as they showed the strongest association in the study by Grant et al., 2006 and in our earlier study, Chandak et al., 2007.

5. We did not observe a strong LD between the two SNPs rs7903146 and rs12255372. The D` value was 0.86 whereas r2 was 0.55.

6. We are thankful to the reviewer for the query on questionnaire. The detailed questionnaire included, apart from the routine personal and anthropometric data, information on frequency of attacks, nature of pain, age at onset, age at diagnosis, family history, diabetic status, age at onset of diabetes, family history of diabetes, etc. and the information obtained from this has been published earlier [Chandak et al. J Med Genet 39(5): 347–51, 2002].

7. We are sorry for the confusion. As elaborated in the Introduction, the diabetes in TCP is known to have features of both type 1 diabetes (T1D) and type 2 diabetes (T2D) and this statement was to convey that since the role of TCF7L2 variants in T1D has been ruled out through the well-powered study as mentioned in the reference, and its role in T2D very strongly proven across the globe, investigating the TCF7L2 variants in TCP may give an idea about the type of diabetes in TCP. I hope the explanation provided makes it clear now.

8. We thank the reviewer for his suggestion and have following to comment. This study was conducted with 2 objectives, one to investigate the association of TCF7L2 variants with TCP and the other, to try to understand the type of diabetes in this disease, which has had several contrasting evidence of insulin resistance as well as insulin secretion defect. Since TCF7L2 variants have been one of the strongest predictors of T2D and hence, lack of association in a cohort with adequate power may suggest that there could be differences between T2D and the diabetes in TCP. We have tried to put across this as one of the suggestions and not as a strong conclusion. Hence, we feel that it may be appropriate to retain this in the manuscript. However, we have modified the statement in the light of reviewers’ concerns.
Reviewer 3 (Atsushi Masamune)

Major

Please see response to comment no. 8 from Prof Drenth.

Minor

1. We are thankful to the reviewer for pointing this, we have now uniformly used the abbreviations for type 2 diabetes, tropical calcific pancreatitis, and fibro-calculous pancreatic diabetes throughout the manuscript.

2. We thank the reviewer for his observations and have now incorporated the necessary changes with regard to the reference style.

Reviewer 4 (Struan Grant)

Minor

1. We agree with the reviewer that merging table 1 and 2 would facilitate the interpretation of data but would need cutting down on some crucial information for the sake of brevity, hence we have still retained them as separate tables.

2. We are thankful to the reviewer for the suggestion on English; we have attempted to work on language and modified wherever appropriate.

Reviewer 5 (Valeriya Lyssenko)

1. We are extremely thankful to the reviewer and agree with the suggestion that stratification based on N34S SPINK1 and L26V CTSB mutation status would give information on additional susceptibility factors for development of diabetes in TCP patients. We have analysed the data and results have been included in the text. Sections added in the revised manuscript are highlighted in bold.

References included in the modified manuscript


