Reviewer's report

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

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Reviewer: Valeriya Lyssenko

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The paper by Mahurkar et al. evaluates influence of the genetic variants in thus far strongest gene for type 2 diabetes, TCF7L2, on the risk for fibro-calculous pancreatic diabetes (FCPD) in 478 subjects with tropical calcific pancreatitis (TCP) and 661 healthy controls from Indian. The authors conclude that the findings point to a lack of association of variants in TCF7L2 with FCPD.

To date TCF7L2 is the most important gene for T2D. It was also shown to be a major genetic risk factor for gestational diabetes and LADA (Latent Autoimmune Diabetes of Adults), whereas it has shown no association with T1D. The mechanisms whereby variants in TCF7L2 increase risk of T2D is not known, but seems to involve an impaired beta-cell function, and impaired incretin effect. It is therefore of value to explore whether variants in TCF7L2 could also be associated with secondary forms of diabetes.

In this study authors addressed the question whether TCF7L2 would be associated with FCPD and/or TCP.

Major Compulsory Revisions to be addressed:

1. Authors should provide available clinical characteristics of the studied patients and control. Particularly important is information on family history of T2D. If there is none for FCPD with family history for T2D it is unlikely to give a signal for TCF7L2.

2. It has been earlier reported by this group and others that whereas environmental factors have been implicated in the development of TCP, a strong genetic predisposition to the disease exists. It has been suggested that nearly 50% of TCP is attributable to mutations in SPINK1 gene. Also authors have earlier reported an association of variants in cathepsin B gene with FCPD and/or TCP. Thus it seems reasonable to test effect of TCF7L2 on risk of FCPD and/or TCP conditioning on established genetic risk factors for FCPD such as SPINK1 and cathepsin B genes. This would take us into additional genetic risk factors contributing to developing FCPD in patients with TCP who do not carry risk variants in SPINK1 gene and/or in carriers of the protective haplotype in cathepsin B gene who despite develop the disease.

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:
I declare that I have no competing interests