Title: Polymorphisms in gene encoding TRPV1-receptor involved in pain perception are unrelated to chronic pancreatitis.

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Reviewer's report:

Polymorphisms in gene encoding TRPV1-receptor involved in pain perception are unrelated to chronic pancreatitis in a Dutch population.

Overall, this is an excellent paper. The background sets the scene well: providing a clear rationale for the study. The aim is clearly stated. The laboratory methods are well described. The statistical analysis is appropriate. The results are clearly presented. The discussion puts the results in the context of TRPV1 research in general and in pancreatitis, in particular. The limitations of the study are acknowledged. The references are appropriate and up to date. The tables and figures are well constructed and enhance the text.

We thank the reviewer for his comments and are really happy that the manuscript meets with the expectations.

Minor Essential Revisions

1) Insert “A” before “few” (Background 2nd para, 2nd sentence), if the meaning is intended to convey that there are sufficient studies to implicate TRPV1 in chronic pancreatitis, rather than too few.

2) Methods (Subjects): insert “daily” or “per day” into the definition of alcoholic chronic pancreatitis.

3) Methods (Genotyping – sentence 4): Substitute “accept” with “except”.

4) Discussion (4th para, 2nd sentence): typographical error; “at” rather than “art”.

We thank the reviewer for his accurateness and have made changes throughout the manuscript as per indication.
Discretionary Revisions

1) Methods (Statistical analysis); perhaps define the sample size where Fisher’s exact size was used).

We added the note that we used the two-sided Fisher’s exact test in case values in any of the cells within the table were below 10.

2) Discussion (limitations); consider addressing those who would wish to see an alcoholic control group.

Indeed this point consistently pops up when performing a case control study in alcoholic chronic pancreatitis. The issue here is that researchers want to perform a highly rigorous trial and therefore want to control for alcohol use as well. The question is whether this rigorous set-up is required at all for these types of studies. At this point of time we do not know whether the effect size of alcohol use relative to the effect of a genetic variant. We do know that the risk conferred by genetic variants is usually small with odds ratios between 1.1 and 1.3, but also that only a small minority (~5%) of alcoholics will get ACP. Indeed when setting up this type of study we should aim to recruit exact data on environmental exposures (alcohol use) and other covariates in all controls in a sample size large enough to allow detecting interaction between gene polymorphisms and environmental exposure. Within the framework of the current study it is not reasonable to assume that this (or any other cohort study with sample size <2000-3000) will allow dissection of all gene-environmental effects.

Thus, we agree with the reviewer on the importance of this aspect, and we have added remarks to this effect to the limitation section of the paper.

Reviewer #2

Reviewer’s report:

This study examines the potential contribution by TRPV1 to chronic pancreatitis. The hypothesis appears to be that these mutations cause disease. In a mixed etiology population of patients with chronic pancreatitis the authors found no such association.

Comments

1) Most studies of chronic pancreatitis that have examined TRPV1 have linked it to pain perception and not pancreatitis inflammation. The one study (15) linking it to inflammation was as study of acute and not chronic inflammation. Also, these were studies in knockouts and compensation by other receptors could not be excluded. These issues need to be discussed.

We agree with the reviewer that this is an important issue. The study addressed to is indeed a study in acute pancreatitis and not in chronic inflammation. Since the pathogenesis of chronic pancreatitis is unclear it is not known whether the same pathogenesis in acute pancreatitis holds for chronic pancreatitis. Therefore, the reviewer is correct in stating that one cannot extrapolate results from a secretagogue-induced acute pancreatitis to chronic pancreatitis. We added this information.
2) The study appears to be organized to address the issue "are polymorphisms in TRPV1 associated with chronic pancreatitis" in a broad sense, but an equally important issue (suggested by most studies) would be "is it associated with pain? This is a much more difficult study to do than the one undertaken by these authors—they would have to find patients with other manifestations of chronic pancreatitis (calcification, insufficiency, similar duration and etiology) and ask whether the levels of pain differ. At a minimum this issue needs to be discussed. Although their population is small, it might be worthwhile assessing whether pancreatitis pain differed in accordance with TRPV1 polymorphisms.

This question is a key question in this study. The difficulty in measuring the pain, as experienced in CP patients, is that we currently fail to have an objective means of measuring pain. As far as we know there is no validated CP pain scoring system. In most part this is due to the fact that CP patients are known to have an unpredictable course with attacks and remissions. Pain in CP is variable ranging from mild to severe and from intermittent to persistent, it varies greatly during the lifetime of the disease, and may be scored differently from time to time. In an earlier effort we created a composite score in order to distinguish those patients with a protracted course with painful attacks from those with a more benign course, but even this rather crude tool was in our view insufficient to distinguish those patients with severe and those with mild pain. We have mentioned these limitations and included extra sentences to discuss this aspect.