Author's response to reviews

Title: Transcription factor 7-like 2 (TCF7L2) variant is associated with familial breast cancer risk: a case-control study

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Author's response to reviews: see over
Dear Dr. Puebla,

We are pleased that you consider our manuscript for publication in BMC Cancer after substantial revision. In the following, you will find the response to the reviewers´ comments. Changes within the manuscript are highlighted in red.

Reviewer: Arto Mannermaa:

Minor Essential Revisions:

The typing error in the Methods section was corrected (Line135).
The sentence in the Results and Discussion section was rewritten, and the citing was removed (Line 163).

Discretionary Revisions:
Familial breast cancer cases were used to increase the power of the study as described in the Results and Discussion section (references 14 and 15). Unfortunately, DNA material of family members was not available, so that an evaluation of TCF7L2 variant inheritance was not possible. We added this information to the Methods section (Line 112).

We deleted the entire part of the analysis on pancreatic cancer risk.

Reviewer: Hiltrud Brauch:

General:

1. The patient description is part of the Methods section. Unfortunately, epidemiological parameters, such as type 2 diabetes, were not available.

2. Age adjustment showed that the distribution of genotypes is not age-dependent ("Adjustment for age did not change the ORs, assuming that the distribution of the TCF7L2 rs12255372 genotypes is age-independent."). We added this statement to Table 1.

3. The fact that 1.00 was included in the 95% C.I. made us carefully recalculate our data, coming across a rounding error (C.I. = 1.005-..... = C.I. = 1.01-...). However, this part of the Results and Discussion section was rewritten more cautiously including the chance of a type 1 error ("The minor T allele of rs12255372 was significantly
overrepresented in cases, and we found an allelic association with an increased familial BC risk (OR = 1.19, 95% C.I. = 1.01-1.42, \( P = 0.04 \), Table 1). Given the borderline significance, a finding by chance cannot be excluded. However, according to the Cochran-Armitage test for trend the association was allele dose-dependent (\( P_{\text{trend}} = 0.04 \), Table 1), adding some consistency to our data.”, Line 149).

4. see 1.

5. Power calculation was implemented using the power and sample size software PS before exploring the genotyping data. However, we moved the statistical calculation to the Methods section (Line 141).

6. We deleted the entire part of the analysis on pancreatic cancer risk.

7. The final statements were carefully reformulated (“In summary, our data suggest that TCF7L2 variants may contribute to the risk of familial BC. Regarding the borderline significance level of our results, confirmation in an independent BC cohort is essential. Moreover, it would be of interest to estimate their impact on further types of human cancer.”, Line 175) and “Our data suggest a possible influence of the TCF7L2 rs12255372 variant on the risk of familial BC.”, Line 58).

**Reviewer: Jörg Epplen:**

**General:**

Since DNA material of family members was not available, an evaluation of TCF7L2 variant inheritance was not possible. We state this fact in the manuscript (“The TCF7L2 rs12255372 analysis comprised one index case per family. DNA of further family members to evaluate segregation of the variant with BC risk was not available.” Line 112).

We deleted the entire part of the analysis on pancreatic cancer risk from the manuscript (including authors, references and Table 2).

The Discussion and Conclusion sections were written more cautiously (“In summary, our data suggest that TCF7L2 variants may contribute to the risk of familial BC. Regarding the borderline significance level of our results, confirmation in an independent BC cohort is essential. Moreover, it would be of interest to estimate their impact on further types of..."
human cancer.”, Line 175) and “Our data suggest a possible influence of the TCF7L2 rs12255372 variant on the risk of familial BC.”, Line 58).

According to Grant et al., their five investigated SNPs are located within an ~ 100 kb linkage disequilibrium block. For this reason, we chose rs12255372 as a representative, showing the strongest correlation to DG10S478. We added a new paragraph to the Methods section (SNP selection, Line 122).

In addition, we updated our manuscript by including two recent publications on TCF7L2 variants and risk of type 2 diabetes (Line 79, references 3 and 4).

We hope that we have answered the questions raised and look forward to hearing from you.

Sincerely yours
Bernd Frank