ANSWERING REVIEWERS

March 26, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 1569-review.doc).

Title: Analysis of single nucleotide polymorphisms in the region of *CLDN2 - MORC4* in relation to inflammatory bowel disease

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 1569

The manuscript has been improved according to the valuable suggestions of the reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) Reviewer No. 227487
Abbreviations (IBD, CD, UC, and IBD-U) have been explained in the footnotes of Table 1, 4, and 7.

(2) Reviewer No. 291381
We agree with the reviewer that the passage concerning an effect of single nucleotide polymorphisms on putative transcription factor binding sites is speculative. Therefore, the following paragraph has been removed from the Results section.

"The C-variant of the rs62605981 polymorphism was located in the last position of the Sp1 matrix consensus sequence (nCCAGnGkGy). The G allele disrupted this sequence motif and revealed another, downstream Sp1 binding site (nyyCCTCmyC), with the SNP in the first position. The normal variant of the rs72466477 polymorphism was located in the middle of the USF matrix consensus sequence (kCnCAyGTGn), and the binding site was abolished by the deletion variant."

Further, since neither of the two novel single nucleotide polymorphisms located in putative transcription factor binding sites showed any significant association to CD, we consider that further experimental studies probably will not contribute to the understanding of the genetic background of Crohn's disease.

(3) Reviewer No. 13033
We agree with the reviewer that our case-control study is small compared to large-scale GWAS studies. However, in comparison to the GWAS studies our case-control population is geographically

more homogenous. A clear genetic heterogeneity due to geographic stratification is presented in the meta-analysis by Jostins *et al.* (2012). Geographically homogenous populations should be beneficial for uncovering regionally confined genetic variants that affect disease susceptibility.
An association between Crohn's disease and the single nucleotide polymorphisms of our study could not have been reported by Jostins *et al.* (2012), since their study only covered the autosomal chromosomes. The *CLDN2 – MORC4* region is located on the X chromosome.
However, given that Jostins *et al.* (2012) is the latest GWAS study regarding inflammatory bowel disease and points to a genetic heterogeneity due to geographic stratification, we have included Jostins *et al.* (2012) in the reference list. We have therefore added the following paragraph in the Discussion section.

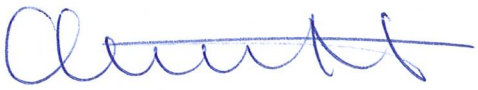
"Substantial genetic heterogeneity due to geographic stratification has been demonstrated in genome-wide association studies (Jostins *et al.*, 2012). A geographically homogenous population (this study) should be advantageous for unveiling regionally restricted genetic risk factors."

The lack of replication and a possible regional heterogeneity is already addressed in the Discussion.

3 References and typesetting were corrected

We thank you once again for considering our manuscript for publication in the *World Journal of Gastroenterology* and hope that we now have paid sufficient attention to the reviewers' comments.

Sincerely yours,



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