Author's response to reviews

Title: Evaluation of S1c11a1 as an inflammatory bowel disease candidate gene

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Author's response to reviews:

Thank you for the opportunity to address the reviewer's comments concerning our manuscript "Evaluation of S1c11a1 as an inflammatory bowel disease candidate gene," which is being considered for publication in BMC Medical Genetics. Our responses to the comments are as follows.

Comment 1: From the current version of the manuscript it does not become clear why the authors were unable to sustain their previously reported association of S1c11a1 single nucleotide tandem repeats with Crohn’s disease herein. The potential reasons for the divergent results should be discussed in more detail.
Response: We agree with the reviewer that this divergence needs to be discussed at further length and have concordantly added additional text to page 10 of the manuscript. Briefly, we believe that a number of prominent features of the current study render the results presented here of higher validity than those presented previously. These features include:
1. All histological specimens from subjects included in the current study have been reviewed by a single gastrointestinal pathologist. This was not the case in the earlier study, and diagnostic misclassification (i.e., UC and/or IC incorrectly diagnosed as CD and vice versa) may have been a confounding variable, which in part may have led to what we now consider the false-positive association previously observed in the CD population.
2. The current study contains over two-fold the number of subjects (254 CD, 165 UC, 65 IC, 144 controls) as compared with the previous work (103 CD, 85 UC, 0 IC, 98 controls). Statistical power is therefore far greater in the current study.
3. Statistical methodology is superior in our current work, and we argue that the current analytical protocol rigorously corrects for the effects of multiple testing. This is obviously a vast improvement over the earlier study in which compounding of a type 1 error was not taken into account.
4. Finally, it should be noted that the specimens used for genotyping in the earlier study were rather heterogeneous and consisted of DNA derived from both surgical specimens (i.e., somatic DNA) and leukocytes (i.e., germline DNA), whereas genetic material in the current study was isolated exclusively from leukocytes.

Comment 2: The current pathophysiological concept about IBD is not compatible with a classical autoimmune disorder, but comprises a genetically mediated abrogation of the immunologic tolerance towards luminal (e.g., bacterial) antigens resulting in an excessive largely T-cell driven immunologic activity which leads to a chronic inflammatory process within the bowel wall.
Response: We have corrected this in the manuscript (see page 9, first and second paragraphs).

Comment 3: The numbers of Crohn’s disease patients which had been classified in the different subgroups according to the Vienna classification should be depicted.
Response: These data have been added to pages 4 and 5 of the manuscript.

Comment 4: It is unclear why the authors believe that combining subgroups L2 and L3 does not impair the validity of the statistical analysis.
Response: These groups were combined primarily because IBD affecting the colon is the primary focus of our research. We argue that this approach will not impair the validity of statistical analyses given that the Vienna classification is somewhat arbitrary and that group genetic homogeneity may be increased by combining all those cases with colonic IBD (page 7). In other words, a "colonic" IBD phenotype may well be
a consequence of a common germline variation. Furthermore, the decision to combine these groups was made in an appropriate scientific manner (i.e. prior to initiation of experimentation) and was not made "post hoc."

Comment 5: It should be stated whether Slc11a1 is situated in a previously described linkage region. Response: SLC11A1 is located on chromosome 2p35, a region that has not been identified as being within an IBD susceptibility locus. This fact has been added to page 3.