Author’s response to reviews

Title: The CTLA4 variants may interact with the IL23R- and NOD2-conferred risk in development of Crohn's disease

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Author’s response to reviews: see over
Response to reviewers:

Reviewer Kazuhiro Tsukamoto:

1. In Table 1a, the gender ratio of 482 healthy control subjects was not matched to that of 333 Czech CD patients. Chi-square test indicates that there is a statistically significant difference in the gender ratio between CD patients and control subjects at P value of less than 0.0001. Since this study has a selection bias by selecting healthy control subjects, authors should perform multivariate logistic regression analysis using gender and polymorphisms of CTLA4 as variable factors in order to investigate whether these two factors contribute to the pathogenesis of the onset of CD. Because, it is important to evaluate environmental backgrounds between patients and control subjects on an association study by case-control study.

As we wrote in answer 1b to reviewer Kazuhiro Tsukamoto previously, “we have adjusted the analyses of associations between CD and tested SNPs to gender; the adjusted results were numerically nearly identical to those without adjustment for gender (detailed results of these models are available, and can be added to the manuscript at the discretion of the reviewer and / or editor).”

Newly we have replaced OR in the Table 2 by the adjusted one by gender.

2. In Table 1b, there is a discrepancy between text of this manuscript and Table 1b. The authors described “… who developed CD under or at the age of 18 years and were diagnosed …” in Line 5 of Page 7 in the “Methods” section. In Table 1b, however, CD patients were divided into three groups according to the age at diagnosis. For example, A1 group involves the CD patients under 17 years at diagnosis. A2 indicates those at 17 to 40 years at diagnosis. Which is true, 18 or 17 years?

According to standards of health care in the Czech Republic, patients are considered as pediatric in case that diagnosis was arranged at the age of 18 years or earlier. Table 1b respects the Montreal criteria which divide patients into three groups (< 17 years; 17-40 years and >40 years). As you can see, the group A1 include 111 patients and A2 26 patients from the pediatric-onset group of patients which indicates that 26 patients were diagnosed at the age of 18 years.

3. It is very difficult to understand Tables 3a and 3b. Could you show us easier and simply?

We have corrected mistake in description of Table 3b which make table more demonstrable.

4. The P value should be added in Table 4.

The P values have been added.
5. In the "Discussion" section, authors should explain in more details why the polymorphisms of CTLA4 were associated with early onset of CD as well as those of NOD2 or IL23R.

Unfortunately, the study had focused to find genetic associations and possible interactions between variants. No functional study has been performed so we are not able to answer the questions.

Similarly to association of other genetic factors with early-onset CD, we can only speculate that also the CTLA4 polymorphisms expresses strongly in early-onset CD than in adult-onset patients. Please see second paragraph on page 12.

6. In the last sentence of Page 12 in the "Discussion" section, "... genetic background between Chinese and Czech populations differs markedly." was wrong. Authors should change "Chinese" to "Japanese", because Machina reported in the Japanese population (see Ref. 19).

According to reviewer suggestion we have corrected the mistake.

Reviewer Jürgen Glas:
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Reviewer Bing Xia:
1. The revised manuscript does not shown clearly where revision was made compared with previous manuscript. I can not find changes to answer my questions.

We have highlighted changes of previous version of manuscript according to questions of reviewer Bing Xia by blue color.

2. there are several mistakes in missing names of authors in references.

We have add names of authors where missing (Citation 7, 8, 22).