1. RESPONSE TO REVIEWERS

1) To reviewer 02821831:

Comment 1 The Introduction section is clearly written but the authors must add other recent studies in the same context including the implication of other genes as the multi-drug resistance gene (MDR1) and showing an association between MDR1 gene polymorphisms and the risk of Crohn's disease in pediatric patients, published by Bouzidi et al, 2016 in PEDIATRIC RESEACH.

Response: At the beginning of the Introduction, we added two paragraphs of relevant recent studies as suggested by reviewer:

Pediatric IBD has a distinct clinic phenotype from adult IBD [1]. Few of the 163 genes associated adult IBD have been identified and functionally studied in pediatric IBD. A GWAS in the Polish population revealed that the genetic architecture is different between pediatric and adult-onset IBD [2]. Adult IBD associated genes NOD2 (Leu1007insC) and IRGM have been to be associated with increased risk of CD and ORMDL3 variant with susceptibility to UC in Lithuanian early-onset IBD patients [3]. The TRIM22-NOD2 network and signaling pathways and genetic factors are associated with very early-onset and adult IBD. Function studies showed that variants of the tripartite motif containing 22 gene (TRIM22) disrupted its ability to regulate NOD2-dependent activity of interferon-βsignaling and NFKB [4].

In addition, novel association of a major histocompatibility complex haplotype with pediatric-onset IBD has been reported [5] and the multi-drug resistance gene MDR1 SNPs C1236T and G2577A/T have also been shown to be associated with CD in a cohort of Algerian pediatric patients [6].

Comment 2: The section results is well presented. In section Discussion, the authors must add one sentence indicating the involvement of other signaling pathways

depending of other cytokine as IL-23/IL-17A axis and NO synthase pathway in IBD pathogenesis (Rafa et al, 2013).

Response: Thank you for the comments. The previous studies suggested by reviewer is added before the final summary paragraph of Discussion:
Other cytokines have also shown to be in the inflammatory process in IBD. Studies on correlation between NO and IL17A, IL-23, and IL-6 levels in plasma of IBD patients indicated that the IL23/IL17A axis and NO synthase pathway are involved in inflammation regulation in IBD [65].

2) To reviewer 01429143:
Comment 1: Interesting and well-written paper. I found some minor typos.

Response: All the typos and minor correction in the paper are corrected. The detail is listed in the All of the Revisions.

Comment 2: The only comment I have is regarding the lack of evaluation of potential linkage disequilibrium among those SNPs that were found on epistatic interactions. Please add.

Response: Thank you. We have calculated the LD between the epistatic SNPs and test the significance of these LD. We did not find any significant LD. In the Methods at the end of the "Epistatic interaction analysis of IL-10 and IL-10 pathway genes" section, we added a paragraph:
"We estimated the pair-wise linkage disequilibria (LD) between these epistatic loci, which were detected to be non-significant, showing that these loci are segregating randomly in the population".

2. ALLOF THE REVISIONS

1) Changes in the cited References

We added 3 paragraphs with 7 references according to reviewer 1's suggestions as described above, the reference citation numbers were changed.

2) Changes for Figures and Tables

We separated tables and figures in figure 1 as table 5 and figure 1; figure 3 as table 7 and figure 3; and figure 4 as table 8 and figure 4.

The tables 1-4 were not changed, but table 5 was changed to table 6.

Zhenwu Lin, PhD, Senior Research Scientist

Department of Pediatrics, College of Medicine Pennsylvania State University, 500 University Drive, Hershey, PA 17033, United States

E-mail: zxl13@psu.edu

Telephone: +1-717-2198591