nature research

Peer Review Information

Journal: Nature Genetics
Manuscript Title: Genetic architecture of the inflammatory bowel diseases across East Asian and European ancestries
Corresponding author name(s): Dr Hailiang Huang

Reviewer Comments & Decisions:

Decision Letter, initial version:
12th July 2022

Dear Hailiang,

Your Article "Genetic architecture of the inflammatory bowel diseases across East Asian and European ancestries" has been seen by three referees. You will see from their comments below that, while they find your work of interest, they have raised some relevant points. We are interested in the possibility of publishing your study in Nature Genetics, but we would like to consider your response to these points in the form of a revised manuscript before we make a final decision on publication.

To guide the scope of the revisions, the editors discuss the referee reports in detail within the team with a view to identifying key priorities that should be addressed in revision, and sometimes overruling referee requests that are deemed beyond the scope of the current study. In this case, we particularly ask that you provide more details of the fine-mapping results and the imputation methods used, revise the presentation for clarity throughout, and revise the Discussion to better highlight the new insights gained from the analyses. We hope you will find this prioritized set of referee points to be useful when revising your study. Please do not hesitate to get in touch if you would like to discuss these issues further.

We therefore invite you to revise your manuscript taking into account all reviewer and editor comments. Please highlight all changes in the manuscript text file. At this stage we will need you to upload a copy of the manuscript in MS Word .docx or similar editable format.

We are committed to providing a fair and constructive peer-review process. Do not hesitate to contact us if there are specific requests from the reviewers that you believe are technically impossible or unlikely to yield a meaningful outcome.

When revising your manuscript:

*1) Include a "Response to referees" document detailing, point-by-point, how you addressed each referee comment. If no action was taken to address a point, you must provide a compelling argument. This response will be sent back to the referees along with the revised manuscript.

*2) If you have not done so already please begin to revise your manuscript so that it conforms to our Article format instructions, available
here.
Refer also to any guidelines provided in this letter.

*3) Include a revised version of any required Reporting Summary:
https://www.nature.com/documents/nr-reporting-summary.pdf
It will be available to referees (and, potentially, statisticians) to aid in their evaluation if the manuscript goes back for peer review.
A revised checklist is essential for re-review of the paper.

Please be aware of our guidelines on digital image standards.

Please use the link below to submit your revised manuscript and related files:

[redacted]

Note: This URL links to your confidential home page and associated information about manuscripts you may have submitted, or that you are reviewing for us. If you wish to forward this email to co-authors, please delete the link to your homepage.

We hope to receive your revised manuscript within 4-8 weeks. If you cannot send it within this time, please let us know.

Please do not hesitate to contact me if you have any questions or would like to discuss these revisions further.

Nature Genetics is committed to improving transparency in authorship. As part of our efforts in this direction, we are now requesting that all authors identified as 'corresponding author' on published papers create and link their Open Researcher and Contributor Identifier (ORCID) with their account on the Manuscript Tracking System (MTS), prior to acceptance. ORCID helps the scientific community achieve unambiguous attribution of all scholarly contributions. You can create and link your ORCID from the home page of the MTS by clicking on 'Modify my Springer Nature account'. For more information please visit please visit www.springernature.com/orcid.

We look forward to seeing the revised manuscript and thank you for the opportunity to review your work.

Sincerely,
Kyle

Kyle Vogan, PhD
Senior Editor
Nature Genetics
https://orcid.org/0000-0001-9565-9665

Referee expertise:

Referee #1: Genetics, inflammatory diseases, gastroenterology

Referee #2: Genetics, immune-mediated diseases

Referee #3: Genetics, statistical methods, diverse populations

Reviewers' Comments:

Reviewer #1:
Remarks to the Author:

Liu et al. report on an analysis of GWAS and Immunochip data from individuals with inflammatory bowel disease (IBD) and control subjects of East Asian (China, Japan and South Korea) and European descent (EAS, EUR per author terminology), presenting the genetic landscape of IBD associations in EAS and EUR combined and separately, delineating 16 previously unreported EAS associations. The manuscript contains interesting sections on effect size and heritability modeling of genetic architecture across the investigated populations and evaluation of polygenic risk score performance improvements resulting from the introduction of the EAS data. Overall the manuscript is well-written and adds a considerable amount of novel insights to the IBD genetics field, emphasizing the now well-established need to expand on diversity in genetics studies of human disease phenotypes. The discussion is focused, to the extent of appearing underdeveloped (at least with regards to pointing out potential limitations of the analyses done, as well as the broader implications of findings presented, the PRS statements included).

I have the following comments for consideration by the authors:

1) It took this reviewer quite an effort to try figure out which samples were genuinely genotyped for the present study; whilst re-analysis was apparently done for most of the EAS panels included, a significant proportion of data appears to derive from previous publications. This does not diminish the effort, but would be good in fairness to state more clearly than what is currently the case for the Methods chapter (the reviewer had to look up references to check).

2) I don’t think it is appropriate to consider the Immunochip a GWAS array, including some form of “carry on bias” of SNP selection (as this was done for this array based on EUR studies) relevant for the present project, and would in transparency distinguish throughout (including Figure 1, which otherwise would benefit from an improved legend).

3) The finemapping which clearly has been done is served poorly by the Supplementary Tables 5 and 6 and associated manuscript text. Whilst Figure 2 is somewhat the only possible summary authors could have done (and should be retained), it is not useful for the reader as a practical resource and as such please elaborate, to this reviewer preferably including regional association plots for the 80 EAS loci (as Supplementary Material) including the finemapping results. This would greatly enhance the "resource" aspect of the paper, for follow-up studies aimed at scrutinizing the biology of loci claimed (e.g. a "quick check" for classically "challenging" IBD loci like 3p21.31 in EAS does not reveal any meaningful insight in this manuscript).

4) Along the same lines, I do understand that authors are hesitant to embark on a comprehensive and full-scale MHC assessment (including restrictions put by missing relevant imputation panels for the classical HLA loci, put forward by the authors themselves in the Discussion), which I would not request. Nevertheless, some further SNP based assessments and considerations to the observed significant heterogeneity reported across the involved populations, along the overall logic of the manuscript (e.g. relative importance of MHC in EAS vs. EUR for CD and UC, respectively?), would have served the paper well. A minor comment to this end, I would refer to the MHC, not "MHC locus".

5) The authors make an interesting statement "...CD that shows well established ethnicity dependence." Please elaborate; what would be the molecular make-up of such "CD subtypes" based on present data? The reviewer fully understands the topic of CD subphenotypes as from the clinical perspective as a source of bias to this point (and likely authors do not have access to such subphenotypes, as it seems), but the opportunity to scrutinize the point globally for CD in EAS vs. EUR appears still to be there and would be of considerable interest.

Reviewer #2:
Remarks to the Author:

The study reported in this manuscript identified additional novel IBD associated genetic loci, using imputed GWAS data from different EAS groups. Based on the findings, the manuscript is worthy of consideration for NG.

But further improvement should be considered

1. There are significant variations in genetic background among and within SHA1, ICH1, KOR1. A supplementary method section should be given to imputation analysis, since there are limited number of EAS samples in the TOPMed data.

2. Lack of comparison of genetic loci between CD and UC in the result and discussion section. Although MHC was mentioned in the discussion, it seems not highly relevant. There are obvious lack of discussion how these loci can contribute to disease pathogenesis.

3. Authors used most of the discussion to explain methodology used for population stratification, which I think they can be included in the supplementary method section. The discussion section requires major revision.

Reviewer #3:
Remarks to the Author:

The authors have conducted the largest IBD GWAS of East Asian ancestries (specifically Chinese, Korean, and Japanese) with novel findings for discovery, fine-mapping, characterizing the genetic architecture of IBD, CD, and UC, as well as the development of a polygenic risk score (PRS). The methods are solid and it is an impressive amount of work. I only have a few major comments and they are related mostly to the presentation of the results, not the scientific methods per se, to better clarify some points and make it a bit easier on the reader so they don't have to go digging through the supplement or figures for estimates.

- Throughout the manuscript, it would benefit from including the actual estimates in the main text instead of only in figures. For example, page 11 lines 298-300 describes comparable SNP-based heritability across EAS and EUR ancestries. It is in Figure 3A, but it would help to have the actual estimates and bounds in the main text for better interpretation. Another example is page 12, lines 340-346 in which there are no estimates for variance explained except in Extended Data Figure 7.

- One of the reasons the author cite for differential PRS performance increases with a multi-ancestry analysis between UC and CD (page 13, lines 371-372) is that CD genetics is more population specific. However, in the previous section they note that "genetic correlations (per allele) across ancestries (...) not distinguishable from one for UC, indicating overall consistency of genetic effect with a small amount of heterogeneity" (page 11, lines 301-302) and that genetic effects were consistent across ancestries (page 12 line 322). It would be great if the authors could use the estimates (which need to be added to the main text) to better make this argument in the PRS section since they have the data.

- There are a lot of genes mentioned in the different sections, as well as their possible roles in IBD. While the authors summarize these findings in the circular manhattan plot, it would help the reader better contextualize these findings if there were some sort of network analysis presented with a plot to bring it all together.

MINOR COMMENTS

- Page 7, line 176 refers to conducting fine-mapping genome-wide significant loci in EAS (N=50). However, page 5 lines 143-144 state that there were 80 significant associations (54 novel in EAS). I think the authors might have meant that the fine-mapping was only conducted in the novel loci?

- Similarly, Figure 2 has new associations in orange, but is this new from the meta-analysis? Or novel in EAS only?

- What is the previous association's effect estimates for the known locus TNFSF15 (page 12, line 324) for comparison to the non-significant EUR and significantly associated EAS association?

- Please include the actual manhattan plots in the supplement. It is hard to judge things properly from the simplified circos plot.

- The performance of the PRS were only presented in the Chinese population. What was the performance in the other populations? I didn't see anything listed in that paragraph to reference.

- Another option to help the readers visualize the differences would be a Miami plot in which manhattan plots are compared. This isn't necessary, but just a suggestion as it's hard to see how much of it is due to statistical power versus effect size, although this is somewhat already addressed by Figure 3.

Author Rebuttal to Initial comments

We thank all reviewers for their insightful comments and constructive suggestions. We have carefully considered the points made by the reviewers and revised the manuscript accordingly. In summary, we performed an analysis for the comparative contribution to CD and UC across ancestries (reviewers 1-3), an analysis in the MHC locus (reviewer 1), a PRS analysis for Korean and Japanese subjects (reviewer 3), and a network clustering and enrichment analysis (reviewer 3). We also enhanced the presentation of fine-mapping results (reviewer 1), clarified the imputation methods (reviewer 2), overhauled the main result table, added display items to highlight our findings, and edited the manuscript throughout for clarity (reviewers 1-3).

We have provided the following point-by-point response to specific reviewer concerns. Our response is colored in light blue for ease of review. Changes to the text are highlighted in yellow in the updated manuscript.

Reviewers' Comments:

Reviewer #1:

Remarks to the Author:

Liu et al. report on an analysis of GWAS and Immunochip data from individuals with inflammatory bowel disease (IBD) and control subjects of East Asian (China, Japan and South Korea) and European descent (EAS, EUR per author terminology), presenting the genetic landscape of IBD associations in EAS and EUR combined and separately, delineating 16 previously unreported EAS associations. The manuscript contains interesting sections on effect size and heritability modeling of genetic architecture across the investigated populations and evaluation of polygenic risk score performance improvements resulting from the introduction of the EAS data. Overall the

manuscript is well-written and adds a considerable amount of novel insights to the IBD genetics field, emphasizing the now well-established need to expand on diversity in genetics studies of human disease phenotypes. The discussion is focused, to the extent of appearing underdeveloped (at least with regards to pointing out potential limitations of the analyses done, as well as the broader implications of findings presented, the PRS statements included).

We thank the reviewer for these positive comments. Along with additional edits described below, we have substantially expanded the discussion to better highlight the limitations and implications of this study.

I have the following comments for consideration by the authors:

1) It took this reviewer quite an effort to try figure out which samples were genuinely genotyped for the present study; whilst re-analysis was apparently done for most of the EAS panels included, a significant proportion of data appears to derive from previous publications. This does not diminish the effort, but would be good in fairness to state more clearly than what is currently the case for the Methods chapter (the reviewer had to look up references to check).

This is a good idea. In East Asia, Korean and Japanese data have been published, and Chinese data has not. In Europe, the non-Finnish data has been published and the Finnish data has not (but its GWAS summary statistics are available in the FinnGen browser). We have added these information to Figure 1b.

2) I don't think it is appropriate to consider the Immunochip a GWAS array, including some form of "carry on bias" of SNP selection (as this was done for this array based on EUR studies) relevant for the present project, and would in transparency distinguish throughout (including Figure 1, which otherwise would benefit from an improved legend).

We agree with the reviewer. We have revised the Figure 1, its legend and the text accordingly (lines 118-119, 142-143, 505-510).

3) The finemapping which clearly has been done is served poorly by the Supplementary Tables 5 and 6 and associated manuscript text. Whilst Figure 2 is somewhat the only possible summary authors could have done (and should be retained), it is not useful for the reader as a practical resource and as such please elaborate, to this reviewer preferably including regional association plots for the 80 EAS loci (as Supplementary Material) including the finemapping results. This would greatly enhance the "resource" aspect of the paper, for follow-up studies aimed at scrutinizing the biology of loci claimed (e.g. a "quick check" for classically "challenging" IBD loci like 3p21.31 in EAS does not reveal any meaningful insight in this manuscript).

We appreciate this suggestion! In response,

1. We have created regional association plots for all 80 IBD-associated loci in East Asian ancestries with their fine-mapping results when available (Supplementary Data 2).
2. We have designed a new Table 2 to include variants fine-mapped to posterior inclusion probability > 50%, or to 10% if missense or pLoF.
3. We added Box 1 and Supplementary Note to discuss key genes discovered from this study.
4. As an ongoing effort, results from this study will be included in a multi-ancestry genome browser integrating GWAS, exome-sequencing and fine-mapping. The browser, once available, will be listed on the IIBDGC website that can be easily found and accessed.

4) Along the same lines, I do understand that authors are hesitant to embark on a comprehensive and full-scale MHC assessment (including restrictions put by missing relevant imputation panels for the classical HLA loci, put forward by the authors themselves in the Discussion), which I would not request. Nevertheless, some further SNP based assessments and considerations to the observed significant heterogeneity reported across the involved populations, along the overall logic of the manuscript (e.g. relative importance of MHC in EAS vs. EUR for CD and UC, respectively?), would have served the paper well. A minor comment to this end, I would refer to the MHC, not "MHC locus".

We agree with the reviewer and have performed analyses on the lead CD and UC variants in MHC. In summary, we found "In MHC, while EAS and EUR have largely consistent genetic effects (-0.399 ± 0.015 and -0.434 ± 0.026, mean ± s.e.) and variance explained (2.9% vs 2.4%) for the primary UC association (rs6927022), EAS hosts a CD association that explains ~6x greater amount of phenotypic variance than that in EUR (3.5% [rs9270965] vs 0.6% [rs145568234], Supplementary Note)" (lines 340 - 344, Supplementary Note).

5) The authors make an interesting statement "...CD that shows well established ethnicity dependence." Please elaborate; what would be the molecular make-up of such "CD subtypes" based on present data? The reviewer fully understands the topic of CD subphenotypes as from the clinical perspective as a source of bias to this point (and likely authors do not have access to such subphenotypes, as it seems), but the opportunity to scrutinize the point globally for CD in EAS vs. EUR appears still to be there and would be of considerable interest.

We agree this would be a helpful analysis. In response, we performed a CD vs UC comparative analysis across EAS and EUR (Extended Data Figure 9). We found an interesting cross-ancestry difference for the CD specificity. For example, *NOD2* and *ATG16L1*, both involved in the autophagy pathway, are the drivers for CD specificity in EUR due to its elevated MAF. In EAS, in contrast, *TNFSF15* is the driver for CD specificity due to its effect size. (lines 334 - 340)

Reviewer #2:

Remarks to the Author:

The study reported in this manuscript identified additional novel IBD associated genetic loci, using imputed GWAS data from different EAS groups. Based on the findings, the manuscript is worthy of consideration for NG.

But further improvement should be considered

1. There are significant variations in genetic background among and within SHA1, ICH1, KOR1. A supplementary method section should be given to imputation analysis, since there are limited number of EAS samples in the TOPMed data.

We thank the reviewer for raising this important question. We have added the sample size broken down by ancestry to the imputation section (lines 567-570). There are 1,184 individuals of East Asian ancestry. Details in the imputation methods have been provided in lines 558-570 (SHA1, ICH1 and KOR1) and lines 595 - 605 (JPN1).

We would like to note that, while there are indeed variations in genetic background across and within East Asian cohorts, modern imputation methods are capable to account for such heterogeneity, and leverage the shared haplotypes within and across ancestries for better imputation accuracy, as demonstrated by an earlier study which used a similar imputation strategy and the 1000 genome reference panel (~500 EAS subjects) (Lam and Chen *et al.*, Nature Genetics 2019). Here we used the TOPMed reference panel which includes all 1000 genomes samples and additional subjects of East Asian ancestry, for a total of 1,184 EAS subjects. While still quite limited in the EAS sample size, TOPMed represents the best publicly available and tested imputation panel we have access to for the East Asian subjects.

2. Lack of comparison of genetic loci between CD and UC in the result and discussion section. Although MHC was mentioned in the discussion, it seems not highly relevant. There are obvious lack of discussion how these loci can contribute to disease pathogenesis.

The reviewer raised several excellent questions.

1. In response to "Lack of comparison of genetic loci between CD and UC", we have added a CD vs UC comparative analysis and presented results in Extended Data Figure 9 and lines 334 - 340.
2. In response to "Although MHC was mentioned in the discussion, it seems not highly relevant", we have restructured the MHC discussion and focused the discussion on its relative contribution to CD vs UC across ancestries (Lines 340-344, Supplementary Note).
3. In response to "discussion how these loci can contribute to disease pathogenesis", we have expanded the discussion of key genes discovered this study in Box 1, Supplementary Note and added a network analysis (Extended Data Figure 4).

3. Authors used most of the discussion to explain methodology used for population stratification, which I think they can be included in the supplementary method section. The discussion section requires major revision.

We thank the reviewer for pointing this out. We have rewritten the discussion section to better highlight the limitations and new insights from this study. The discussion now includes a summary

of key findings (genetic discovery, comparative analysis across ancestries and PRS) and limitations (sample size, allele frequency limit, and clinical heterogeneity across countries).

Reviewer #3:

Remarks to the Author:

The authors have conducted the largest IBD GWAS of East Asian ancestries (specifically Chinese, Korean, and Japanese) with novel findings for discovery, fine-mapping, characterizing the genetic architecture of IBD, CD, and UC, as well as the development of a polygenic risk score (PRS). The methods are solid and it is an impressive amount of work. I only have a few major comments and they are related mostly to the presentation of the results, not the scientific methods per se, to better clarify some points and make it a bit easier on the reader so they don't have to go digging through the supplement or figures for estimates.

- Throughout the manuscript, it would benefit from including the actual estimates in the main text instead of only in figures. For example, page 11 lines 298-300 describes comparable SNP-based heritability across EAS and EUR ancestries. It is in Figure 3A, but it would help to have the actual estimates and bounds in the main text for better interpretation. Another example is page 12, lines 340-346 in which there are no estimates for variance explained except in Extended Data Figure 7.

We thank the reviewer for pointing this out. We have revised the manuscript accordingly.

- One of the reasons the author cite for differential PRS performance increases with a multi-ancestry analysis between UC and CD (page 13, lines 371-372) is that CD genetics is more population specific. However, in the previous section they note that "genetic correlations (per allele) across ancestries (...) not distinguishable from one for UC, indicating overall consistency of genetic effect with a small amount of heterogeneity" (page 11, lines 301-302) and that genetic effects were consistent across ancestries (page 12 line 322). It would be great if the authors could use the estimates (which need to be added to the main text) to better make this argument in the PRS section since they have the data.

We apologize for the confusion. The "genetic correlation" was calculated using variants shared across ancestries and the claim that CD being more population specific refers to the fact that variants that have a strong preference for CD can be present in one population but not the other (e.g., *NOD2* in EUR). We have expanded the relevant discussions and added quantitative assessments as suggested (lines 277, 315-316, 323-325). For example, we compared the variance explained across populations for CD and UC, of which CD showed a significant difference while UC did not (lines 323-325).

- There are a lot of genes mentioned in the different sections, as well as their possible roles in IBD. While the authors summarize these findings in the circular manhattan plot, it would help the reader better contextualize these findings if there were some sort of network analysis presented with a plot to bring it all together.

We thank the reviewer for pointing this out. We have restructured our discussions so that discussions related to specific genes are presented in Box 1 with further details in Supplementary Note. We also added a network analysis as suggested (Extended Data Figure 4, lines 234-245).

MINOR COMMENTS

- Page 7, line 176 refers to conducting fine-mapping genome-wide significant loci in EAS (N=50). However, page 5 lines 143-144 state that there were 80 significant associations (54 novel in EAS). I think the authors might have meant that the fine-mapping was only conducted in the novel loci?

We apologize for the confusion. We were not able to fine-map all the 80 significantly associated loci in EAS because the Japanese data cannot be included. Due to the data use restriction, Japanese samples cannot be imputed using the TOPMed server thus their variants do not fully line up with variants in Chinese/Korean samples. This is acceptable for GWAS but creates challenges for fine-mapping because the sample size is uneven across variants. We therefore only fine-mapped the 50 loci significantly associated with CD/UC/IBD using only Chinese and Korean samples. We have clarified this in the text (lines 190-191)

- Similarly, Figure 2 has new associations in orange, but is this new from the meta-analysis? Or novel in EAS only?

It's "new from the meta-analysis", i.e., never reported in IBD GWASs of EAS nor EUR before. We have revised the figure legend for clarify. Thank you for pointing this out.

- What is the previous association's effect estimates for the known locus TNFSF15 (page 12, line 324) for comparison to the non-significant EUR and significantly associated EAS association?

What we reported in the manuscript was for a new secondary CD association in *TNFSF15*. The previously reported primary CD association in *TNFSF15* was not included in that analysis due to its low fine-mapping resolution, although its finding has indeed been replicated: the previous study (Liu *et al.*, Nature Genetics 2015) had marginal OR of 1.75 [95% CI: 1.57-1.91] in EAS vs 1.15 [95% CI: 1.11-1.17] in EUR, and our study had marginal OR of 1.89 [95% CI: 1.80-1.99] in EAS vs 1.17 [95% CI: 1.13 = 1.21] in EUR.

We have clarified this in the manuscript (lines 302-307). We apologize for the confusion and thank the reviewer for catching this.

- Please include the actual manhattan plots in the supplement. It is hard to judge things properly from the simplified circos plot.

We have added manhattan plots for CD, UC and IBD for EAS and the meta-analysis as Supplementary Data 1.

- The performance of the PRS were only presented in the Chinese population. What was the performance in the other populations? I didn't see anything listed in that paragraph to reference.

Good suggestion. We have added a leave-one-country-out PRS analysis as Extended Data Figure 10 with discussions in lines 364 - 368. The results largely supported what was found in the Chinese population.

- Another option to help the readers visualize the differences would be a Miami plot in which manhattan plots are compared. This isn't necessary, but just a suggestion as it's hard to see how much of it is due to statistical power versus effect size, although this is somewhat already addressed by Figure 3.

As the reviewer said, we find Miami plot limited in its utility as it's hard to distinguish contributions from power versus effect size using a Miami plot. We hope that Figure 3, Extended Data Figure 8 and the newly added Extended Data Figure 9 will be helpful for the readers to visualize the differences across IBD subtypes and ancestries. Figure 3 compares the effect size while Extended Data Figures 8 and 9 compare the power.

Also, as mentioned in the response to reviewer 1, we are working on an interactive multi-ancestry genome browser integrating GWAS, exome-sequencing and fine-mapping findings for IBD. We hope once available, this browser will further help readers and users to visualize our results. This browser will be listed on the IIBDGC website that can be easily found and accessed.

Decision Letter, first revision:

25th October 2022

Dear Hailiang,

Your revised manuscript "Genetic architecture of the inflammatory bowel diseases across East Asian and European ancestries" (NG-A60370R) has been seen by the original referees. As you will see from their comments below, they find that the paper has improved in revision, and therefore we will be happy in principle to publish it in Nature Genetics as an Article pending final revisions to satisfy the referees' remaining requests and to comply with our editorial and formatting guidelines.

We are now performing detailed checks on your paper, and we will send you a checklist detailing our editorial and formatting requirements soon. Please do not upload the final materials or make any revisions until you receive this additional information from us.

Thank you again for your interest in Nature Genetics. Please do not hesitate to contact me if you have

any questions.

Sincerely,
Kyle

Kyle Vogan, PhD
Senior Editor
Nature Genetics
https://orcid.org/0000-0001-9565-9665

Reviewer #1 (Remarks to the Author):

For the specific points, the authors have responded appropriately. The Discussion chapter is still somehow superficial and fragmented.

Reviewer #2 (Remarks to the Author):

The authors performed a large scale Meta analysis Using existing EAS IBD GWAS data and Immunochip data combining new IBD GWAS data and identified multiple novel IBD loci. Further combining EUR IBD GWAS data, additional IBD loci were identified. The authors conducted multiple statistical analyses to consolidate their discovery. The results offered new findings for our understanding of IBD pathogenesis.

In this revised version of manuscript, the authors are able to incorporate suggestions from reviewers and I feel satisfied to accept the current version for publication.

Reviewer #3 (Remarks to the Author):

First off I want to thank the authors for their patience during the review process. Secondly, they have addressed many of my concerns and I no longer have any major concerns about this manuscript. A few minor comments/suggestions, which are mostly related to presentation, are below:

1. The first paragraph of the results section (Study Populations) currently reads somewhat like a methods section with sections divided into EAS and EUR sample numbers. Some of this information can be removed and put into the Methods sections.

2. I really like figure 2 to show shared signals. It may be worth renaming it though, as it is not a Manhattan plot technically.

3. Table 1 has a minor allele frequency and an effect allele. Is the effect allele always the minor allele? It may be worth clarifying in the legend.

4. Could Table 2 be condensed somewhat? Perhaps limiting it to only Tiers 1 and 2 for the most relevant loci to that specific conclusion?

5. I still think it would be helpful to have the numbers within the text when comparative statements are being made. For example, lines 264-266 say that the h2 between Asian groups are comparable but they are in an extended data figure. Can you add in the range here maybe?

6. I really like Box 1!

Author Rebuttal, first revision:

We again thank all reviewers for your insightful and constructive comments that have led to a much-improved manuscript. We have provided the following point-by-point response to specific reviewer concerns. Our response is colored in light blue for ease of review. Changes to the text have been track-changed in the updated manuscript.

Reviewer #1:
Remarks to the Author:

For the specific points, the authors have responded appropriately. The Discussion chapter is still somehow superficial and fragmented.
We are glad that the reviewer found we have addressed all specific points raised in the previous revision. We have further revised the Discussion for coherence and clarity.

Reviewer #2:
Remarks to the Author:

The authors performed a large scale Meta analysis Using existing EAS IBD GWAS data and Immunechip data combining new IBD GWAS data and identified multiple novel IBD loci. Further combining EUR IBD GWAS data, additional IBD loci were identified. The authors conducted multiple statistical analyses to consolidate their discovery. The results offered new findings for our understanding of IBD pathogenesis.

In this revised version of manuscript, the authors are able to incorporate suggestions from reviewers and I feel satisfied to accept the current version for publication.
We thank the reviewer for your time and efforts leading to a much-improved manuscript!

Reviewer #3:
Remarks to the Author:

First off I want to thank the authors for their patience during the review process.

Secondly, they have addressed many of my concerns and I no longer have any major concerns about this manuscript. A few minor comments/suggestions, which are mostly related to presentation, are below:
We appreciate all your comments leading to this improved manuscript!

1. The first paragraph of the results section (Study Populations) currently reads somewhat like a methods section with sections divided into EAS and EUR sample numbers. Some of this information can be removed and put into the Methods sections.

We agree. We have revised the manuscript so that the first paragraph only has the sample size per ancestry and key QC metrics, which we feel helps interpret the results. All other information is now in Methods.

2. I really like figure 2 to show shared signals. It may be worth renaming it though, as it is not a manhattan plot technically.
Thanks! We agree and have changed the title to "IBD genetic associations."

3. Table 1 has a minor allele frequency and an effect allele. Is the effect allele always the minor allele? It may be worth clarifying in the legend.
We apologize for the confusion. The effect allele is not always the minor allele. We have changed MAF to EAF (effect allele frequency) in Table 1 and clarified this in the legend.

4. Could Table 2 be condensed somewhat? Perhaps limiting it to only Tiers 1 and 2 for the most relevant loci to that specific conclusion?
We agree it's a big table. However, respectfully, since some of the key findings in EAS, as featured in Table 1, have coding variants reported in tier 3 (e.g., *PTAFR* and *ADAP1*) and discussed throughout the manuscript, we feel it'd be easier for readers to have access to this information in a main table. Due to the sample size, many coding variants were inevitably mapped to tier 3, but they are still important findings worth discussing and highlighting. We're flexible, though, in this arrangement and will be glad to revise this table to fit the journal style and for a pleasant visual effect.

5. I still think it would be helpful to have the numbers within the text when comparative statements are being made. For example, lines 264-266 say that the h2 between asian groups are comparable but they are in an extended data figure. Can you add in the range here maybe?
We thank the reviewer for pointing this out. We have revised the manuscript accordingly, including adding the exact numbers for the heritabilities and genetic correlations.

6. I really like Box 1! Thanks! We like it too!

Final Decision Letter:

Pending final acceptance