

## Peer Review Information

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**Journal:** Nature Microbiology

**Manuscript Title:** Histone acetylome-wide associations in immune cells from individuals with active *Mycobacterium tuberculosis* infection

**Corresponding author name(s):** Shyam Prabhakar

## Reviewer Comments & Decisions:

### Decision Letter, initial version:

Dear Dr. Prabhakar,

Thank you for submitting your revised manuscript "Histone acetylome-wide association study of tuberculosis" (NMICROBIOL-21092305-T). It has now been seen by the original referees and their comments are below. The reviewers find that the paper has improved in revision, and therefore we'll be happy in principle to publish it in Nature Microbiology, pending minor revisions to satisfy the referees' final requests and to comply with our editorial and formatting guidelines.

If the current version of your manuscript is in a PDF format, please email us a copy of the file in an editable format (Microsoft Word or LaTeX)-- we can not proceed with PDFs at this stage.

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

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

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Reviewer #1 (Remarks to the Author):

The authors have done a thorough job of attending to previously identified comments. They now include an independent longitudinal cohort from South Africa and address statistical issues along with addressing other technical issues. There is now a focus on apoptosis rather than autophagy which is clearer.

Reviewer #2 (Remarks to the Author):

The authors have effectively addressed all my concerns and I have no additional comment.

Reviewer #3 (Remarks to the Author):

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Rosario et al present a significantly revised version of their initial manuscript transferred from Nature Medicine. The authors have taken great care to address all issues raised in my previous review of their work. I appreciate the additional replication analysis, power analysis, TF motif analysis and the many clarifications that the authors provide. Overall, the revision has improved the manuscript substantially. I only have minor remaining comments:

Re comment 5 (replication of haQTL):

I would recommend the authors to include a statement on the use of allelic imbalance (as indicated in their response) also to the main text (between lines 373-388), to help the reader better understand the reasons for the differences in power relative to the sample size between the cohorts / analyses.

## Decision Letter, final checks:

Dear Dr. Prabhakar,

Thank you for your patience as we've prepared the guidelines for final submission of your Nature Microbiology manuscript, "Histone acetylome-wide association study of tuberculosis" (NMICROBIOL-21092305-T). Please carefully follow the step-by-step instructions provided in the attached file, and add a response in each row of the table to indicate the changes that you have made. Please also check and comment on any additional marked-up edits we have proposed within the text. Ensuring that each point is addressed will help to ensure that your revised manuscript can be swiftly handed over to our production team.

We would like to start working on your revised paper, with all of the requested files and forms, as soon as possible (preferably within two weeks). Please get in contact with us if you anticipate delays.

When you upload your final materials, please include a point-by-point response to any remaining reviewer comments.

If you have not done so already, please alert us to any related manuscripts from your group that are under consideration or in press at other journals, or are being written up for submission to other journals (see: <https://www.nature.com/nature-research/editorial-policies/plagiarism#policy-on-duplicate-publication> for details).

In recognition of the time and expertise our reviewers provide to Nature Microbiology's editorial process, we would like to formally acknowledge their contribution to the external peer review of your manuscript entitled "Histone acetylome-wide association study of tuberculosis". For those reviewers who give their assent, we will be publishing their names alongside the published article.

Nature Microbiology offers a Transparent Peer Review option for new original research manuscripts submitted after December 1st, 2019. As part of this initiative, we encourage our authors to support increased transparency into the peer review process by agreeing to have the reviewer comments,

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Please use the following link for uploading these materials:  
{redacted}

If you have any further questions, please feel free to contact me.

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Reviewer #1:

Remarks to the Author:

The authors have done a thorough job of attending to previously identified comments. They now include an independent longitudinal cohort from South Africa and address statistical issues along with addressing other technical issues. There is now a focus on apoptosis rather than autophagy which is clearer.

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I only have minor remaining comments:

Re comment 5 (replication of haQTL):

I would recommend the authors to include a statement on the use of allelic imbalance (as indicated in their response) also to the main text (between lines 373-388), to help the reader better understand the reasons for the differences in power relative to the sample size between the cohorts / analyses.

Author Rebuttal to Initial comments

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[Response: We appreciate the remarks of Reviewer 1.](#)

Reviewer #2 (Remarks to the Author):

The authors have effectively addressed all my concerns and I have no additional comment.

[Response: We thank Reviewer 2 for his/her comment.](#)

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Rosario et al present a significantly revised version of their initial manuscript transferred from Nature Medicine. The authors have taken great care to address all issues raised in my previous review of their work. I appreciate the additional replication analysis, power analysis, TF motif analysis and the many clarifications that the authors provide. Overall, the revision has improved the manuscript substantially. I only have minor remaining comments:

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their response) also to the main text (between lines 373-388), to help the reader better understand the reasons for the differences in power relative to the sample size between the cohorts / analyses.

Response: We appreciate the remarks of Reviewer 3. We have now added the following sentences between lines 373-388 of the original submission to Nature Microbiology:

“We also note that our haQTL analysis approach exploited additional information present in the data, namely allelic imbalance in ChIP-seq reads at heterozygous sites. By modeling the effect of genotype on both peak height and allelic imbalance, our approach had relatively high statistical power.”

## Final Decision Letter:

Dear Shyam,

I am pleased to accept your Article "Histone acetylome-wide associations in immune cells from individuals with active *Mycobacterium tuberculosis* infection" for publication in Nature Microbiology. Thank you for having chosen to submit your work to us and many congratulations.

Over the next few weeks, your paper will be copyedited to ensure that it conforms to Nature Microbiology style. We look particularly carefully at the titles of all papers to ensure that they are relatively brief and understandable.

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