

Peer Review Information

Journal: Nature Genetics

Manuscript Title: Increased somatic mutation burdens in normal human cells due to defective DNA polymerases

Corresponding author name(s): Professor Michael Stratton

Editorial Notes:

Transferred manuscripts This manuscript has been previously reviewed at another journal that is not operating a transparent peer review scheme. This document only contains reviewer comments, rebuttal and decision letters for versions considered at Nature Genetics.

Reviewer Comments & Decisions:

Decision Letter, initial version:
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Our ref: NG-A56992

17th Mar 2021

Dear Mike,

I hope you're well.

First of all, please accept my apologies for the delay in returning this decision to you. Your patience is appreciated.

Thank you for submitting your revised manuscript "Elevated somatic mutation burdens in normal human cells due to defective DNA polymerases" (NG-A56992). 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 Genetics, pending revisions to satisfy Reviewer #2's final requests (these are minor) 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 Genetics. It's a lovely paper and I look forward to seeing it online and in print.

Kind regards,

Safia

Safia Danovi
Senior Editor
Nature Genetics

[Ed; please note that we have used the same numbering of reviewers as in your previous round. Note also that Reviewer #1 has signed their report]

Reviewer #1 (Remarks to the Author):

The authors have made a good job in addressing the comments by the reviewers and the new version of the manuscript has improved. I am satisfied with their answers to comments and no further changes are requested from my side.

Nuria Lopez-Bigas

Reviewer #2 (Remarks to the Author):

In their manuscript, Robinson et al. described a landscape of somatic mutations caused by defective DNA polymerase in patients with germline mutations in POLE and POLD1. The authors fully address the concerns raised by the reviewers for their original submission. The manuscript has now been substantially improved. This reviewer has only a few minor comments.

- Lines 219-222: No data is presented for ID in Fig. 3a.
- Labels in Fig. 3 should be corrected: Fig 3b (L244), Fig. 3d (L274), and Fig. 3e (L275) should be Fig. 3c, Fig. 3c, and Fig. 3d, respectively. No Fig. 3e.
- As for the discussion on the distinction between SBS56 and SBC10c, authors are requested to confirm replication strand bias of SBS56.

Reviewer #3 (Remarks to the Author):

I feel that the authors have addressed all my concerns.
I think that this is an important paper and data that should be published.

Final Decision Letter:

In reply please quote: NG-A56992R Stratton

28th Jul 2021

Dear Mike,

How are you?

I am delighted to say that your manuscript "Increased somatic mutation burdens in normal human cells due to defective DNA polymerases" has been accepted for publication in an upcoming issue of Nature Genetics.

Prior to setting your manuscript, we may make minor changes to enhance the lucidity of the text and with reference to our house style. We therefore ask that you examine the proofs most carefully to ensure that we have not inadvertently altered the sense of your text in any way.

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Acceptance is conditional on the data in the manuscript not being published elsewhere, or announced in the print or electronic media, until the embargo/publication date. These restrictions are not intended to deter you from presenting your data at academic meetings and conferences, but any enquiries from the media about papers not yet scheduled for publication should be referred to us.

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I'll just close by saying how pleased I am that you sent this paper to Nature Genetics - we are excited to be publishing it.

With best wishes,

Safia

Safia Danovi
Senior Editor
Nature Genetics