Reviewer's report

Title: Epigenetic loss of heterozygosity of Apc and an inflammation-associated mutational signature detected in Lrig1+/-driven murine colonic adenomas

Version: 0 Date: 18 Nov 2019

Reviewer: Gulshan Singh

Reviewer's report:

Comments to author:

Manuscript number: BCAN-D-19-03040

Epigenetic Loss of Heterozygosity of Apc and an Inflammation-associated Mutational Signature Detected in Lrig1+/---driven Murine Colonic Adenomas

The study presented by Preston and Stiffler demonstrates that early tumors can contain complex patterns of mutations and that oncogenic mutations can become fixed in a latent genomic reservoir prior to advanced disease. The authors used Lrig1-CreERT2/+; Apcfl/+ mouse model and performed mRNA and exomic DNA sequencing. The research findings are informative and showed adenomas are genetically heterogeneous. There are few concerns and suggestions mentioned below:

The background information is good, but it needs to be more focused. Authors can reformat background and shorten it to include only highly relevant information.

Line 54-55: Insert citation/reference for "CRC rates are sharply increasing in younger patients".

Line 58-59: It would be good, if authors can provide the name of 4 broad subcategories of CRC in background section.

Line 134: It is not clear whether 2mg tamoxifen is given per mice or per kg body weight. Authors can include this in materials and method section.
Line 133: Authors can also add background of Lrig1-CreERT2/+;Apcfl/+ mice used in this study as they have mentioned the background of wildtype and Lrig1-CreERT2/+;Apcfl/+ mice in later section.

In this study, authors described the exomes and transcriptomes of conditionally induced murine colonic adenomas from Lrig1-CreERT2/+;Apcfl/+ mice. It would be nice if authors validate their findings with some follow up experiments.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

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