Reviewer's report

Title: Comparative analysis of histologically classified oligodendrogliomas reveals characteristic molecular differences between subgroups

Version: 0 Date: 05 May 2017

Reviewer: Laila M Poisson

Reviewer's report:

The authors have obviously done a lot of work and put thought into the analyses conducted in the paper. Unfortunately, it is not obvious how these results progress the knowledge of glioma subtyping beyond what was shown by others. First, since the analysis relies on TCGA samples, a comparison of the results in this paper should be made against those in the two TCGA Working Group papers that deal with diffuse astrocytoma (TCGA, NEJM, 2015 and Ceccereli et al, Cell 2016). Finding that oligodendrogliomas contain IDH mut/codel, IDHmut-non-codel, and IDHwt tumors was already discussed in NEJM 2015. Showing that some IDHmut-non-codel tumors behave poorly (GCMIP-low) and some IDHwt grade II/III tumors do very well (PA-like) was discussed in Cell 2016. How does the author's derivation of RNA expression classes and GCMIP differ from what is reported in supplemental files for Cell 2016 and NEJM 2015? How do the 7-subtypes of the Cell 2016 paper relate to the classes discovered by the authors? Second, the WHO2016 update has been interpreted by leading neuropathologists as using histology to distinguish diffuse astrocytoma from glioblastoma and then subdivision by molecular typing. While this does mean that some oligodendroglioma-looking tumors will be called astrocytoma-wt if IDHmutation is absent, we have seen in the previous TCGA work that the molecular profile is more strongly associated with IDH/codel status than with histology. What would the authors make of their results if they were to classify the tumors first by the WHO2016 classification? The networks are interesting but, again, should be described in the context of past results. How do these hub genes relate to those identified in other TCGA work? Smaller details that require clarification or attention are given here:* On page 2, bottom left column, the case TCGA-P5-A5F6-01A is referenced using the 12-digit TCGA barcode and the 3-digit specimen identifier. Of the cases included, are the recurrent samples (-02) excluded? If so, the authors might clarify to say "primary tumors" when describing the sample set.* Please clarify which source was used for the survival data? If TCGA LGG refers to table S1 from the NEJM 2015 paper then please cite this paper. If the primary data were downloaded from GDC please clarify whether/how enrollment data were updated using follow-up form data. * On page 4, col 2, lines 28-32, there are quite a few samples with missing survival information. The supplemental table from the Cell 2016 paper would give more complete data than the NEJM 2015 paper. Direct download from GDC would give the most current data as of the end of the study.* When considering grade II/II at the top-left of page 5, what are the sample sizes in each of these groups? In summary, the work appears acceptable but the authors need to better relate and distinguish their results in the context of other major TCGA papers so that the reader can clearly see the progression of knowledge.

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

**Declaration of competing interests**
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below.
If your reply is yes to any, please give details below.
I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal