Reviewer's report

Title: Integrative genome-wide expression profiling identifies three distinct molecular subgroups of renal cell carcinoma with different patient outcome

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Reviewer: Daniel Heng

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This is a very interesting project that examines complex genome wide expression profiles to determine if there are novel molecular subgroups in patients with renal cell carcinoma. Currently, we have pathologic subtypes, grade, stage and other prognostic factors to separate patients into groups but we do not have molecular classifications. This manuscript is representative of a lot of work and effort and the authors should be applauded.

Major comments:

1) The clinical characteristics of the patients (in the 97 +15 RCC patients and the 189 external validation TMA patients) should be included in the main manuscript and not the supplementary files (file 8). There needs to be a table that describes the patient stage, grade, sarcomatoid features, pathologic subtype and it can be stratified by groups A, B, C (cell cultures N/A). There is no mention of whether this molecular classification has any value added beyond normal clinical characteristics/subtypes and prognostic factors (eg. SSIGN). It appears that there are more high grade, high stage patients in group C … so does knowing you are in group C more helpful then just knowing the grade and stage? In the metastatic samples, are they from patients from which their primary tumor is also included in this analysis?

2) A multivariable analysis is mentioned but it is unclear what variables were used.

3) An unsupervised analysis may lead to clusters of expression for which the significance and association is unknown. This should be discussed in the limitations section. There should be a limitations section.

4) The methods section should come after the introduction and requires a lot more detail. These can be appendices if they are too long.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

I declare that I have no competing interests