Reviewer's report

Title: Prevalence and predictors of germline CDKN2A mutations for melanoma cases from Australia, Spain and the United Kingdom

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Reviewer: Veronica Höiom

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M Harland and colleagues submitted a manuscript entitled: "Prevalence and predictors of germline CDKN2A mutations for melanoma cases from Australia, Spain and the United Kingdom", in which they reported the prevalence and predictors of carrying a pathogenic CDKN2A or CDK4 mutation in three different populations.

The prevalence of pathogenic mutations was very similar in all investigated populations, an overall frequency of 2.2%, and the prevalence was increased with the presence of multiple primary melanomas (MPMs) and a family history of melanoma. About ¼ of the cases with both MPMs and a family history of melanoma carried a mutation. Although the correlation between MPMs/family history of melanoma and mutation status of CDKN2A has been described before, the study is interesting, with solid data and is well written. The result of this study is important to give support for example clinical geneticist in their work; in identifying patients/relatives suitable of genetic testing for CDKN2A mutations. Based on this data, patients with at least two 1st or 2nd degree relatives with melanoma, patients with 3 or more primary melanomas and patients with a family history of melanoma and MPMs should be offered genetic testing. I have only a few questions and comments.

- Minor Essential Revisions
  1) In additional file 3, the classification of a variant as "pathogenic" or "non-pathogenic", is not consistent. For example, the D156A is classified as non-pathogenic despite an overall score of 2, no data on function or segregation in melanoma families. Other variants with similar outcome have been classified as pathogenic (for example G111S).

  2) For classification of intronic variants, were any analyses done on for example effect on splicing, CADD-scores etc?

- Discretionary Revisions
  1) Was there any difference in prevalence regarding predicted non-pathogenic variants?

  2) For the Spanish patients, were all patients diagnosed with invasive melanoma and were the controls sex-matched? Were the gender known for the Spanish controls? Because, mutations were about 3 times more common among male carriers, the proportion of males among Spanish controls might be of importance.
3) The p.A148T seems to be a low-risk variant. Was this variant seen alone or present with another (pathogenic) CDKN2A-mutation?

**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