Reviewer’s report

Title: Genome sequencing analysis of blood cells identifies germline haplotypes strongly associated with drug resistance in osteosarcoma patients

Version: 1 Date: 11 Oct 2018

Reviewer: Claudia Maria Hattinger

Reviewer's report:

In this paper, authors have analysed two next-generation sequencing data sets (INOVA and TARGET) of blood cells obtained from patients with high-grade osteosarcoma with the aim to identify germline SNPs/haplotypes associated with either relapse, percent of tumor necrosis and/or overall survival. The rational for all the analyses undertaken are explained very well by tables, figures and diagrams, in order to enable the reader to follow all the data processing step by step. The same holds true for the presentation of the huge amount of data elaborated and results obtained as well as the discussion of them. This is very much appreciated.

This paper is very interesting and provides important data for further whole-genome studies in the difficult field of osteosarcoma research.

The authors have replied to the reviewers' 1 and 2 comments sufficiently and have added the additional information in this revised version of the manuscript.

Minor comments:

SupplementaryFile2, page 2, last paragraph
Figure S2(A) shows a block diagram representation of this methodology and Figure S2(B) shows the filtering steps.

Should read Figure S3(A) and S3(B).

Results:
Page 8
It would be helpful to indicate in Table 2 the 4 genes associated with relapse and the 6 genes associated with pathways by symbols as was done in Table 6.

Discussion:
Page 11, line 9
Should be: "adherens" instead of "Adherens"

Page 11, lines 23-25
The genes previously linked with drug resistance could be mentioned here. There is also a typing error: haplotypes_found

Page 13, lines 19-22
Luizon et al, the authors reviewed all published pharmacogenomics genome wide association studies (GWAS) and found that 96.4% of the SNPs reside in noncoding regions [50].

Should be: Luizon and Ahituv reviewed all ..... 

Page 14, lines 9-14
In this paragraph "hence" is used three times and could be substituted.

Conclusion:
Page 14, lines 22-23
Studies of osteosarcoma tumor genomes so far have not been revealing of treatment response.

References:


44. Institute NC: Understanding Cancer Genomics. 2015.


These references are incomplete.

43. Reactome
As done for the other databases, the whole link should be provided.

64. This reference has a formatting error.

25. and 26.
In these references the date of last access is missing.

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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