Reviewer's report

Title: Candidate genes influencing liver metastasis of human uveal melanoma

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Reviewer: Tongwu Zhang

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Major Compulsory Revisions:

The paper reports that using bioinformatics to re-analyze two published microarrays data from uveal melanoma patients. This work integrated two datasets into two groups (Non-metastatic and Liver Metastatic patients), and the result discovered 1138 genes (or probes, need to check) differentially expressed between two groups. Using the GO terms, KEGG pathway, and Signal-Net analyses, authors determined that EXT1, CHL1, the ZNF family, YWHAZ and ATM were most significantly altered between two group cancers, and could be potential candidate genes influencing liver metastasis of human uveal melanoma. In general, the idea and method of this paper is good and very popular used in cancer research to find potential therapy target. However, the detail methods in this paper are too simple, which will result the false positive candidate genes. For example, in differential gene expression analysis, the authors used simple t-test between two groups. There are many methods shown some advantages than simple t-test, such as limma, RVM and SAM (PMID: 20838429). In addition, Authors only highlighted top down/up-regulated gene between two groups, and most of the genes with fold change <3 (sorted with P-value). Missing the genes with large fold change and very significant genes (P-vlaue <1e-3) would decrease the interesting of this paper. It’s hard to believe or prove these candidate genes list here are strong associated with liver metastasis in uveal melanoma if no more detail information of other genes. The paper didn’t compare the differentially expressed gene list in here with original data published paper. For example, what is the expression change of PTP4A3/PRL3 (PMID: 21135111) and SDCBP (PMID: 22267972) between two groups in this paper? These genes were well proved to associate to metastasis occurrence. Also, this paper is not well organized in discussion with too many background information. The authors should focus on the their findings from result and describe the more association between these candidate genes and metastasis occurrence in uveal melanoma. Hence, I would suggest the authors re-analyze data with comparison of published data or gene list and re-organize the paper to make the candidate genes more trustable.

Minor Essential Revisions:

1. In abstract, 1138 genes or probes should be checked and corrected. Because in Figure 2 legend described as 1138 probe sets. One gene many contain multiply probes in Affymetrix Human Genome U133 Plus 2.0 Array.
2. Figure 1 should be in supplement since the outlier did not go through the next analysis.

3. In the methods section, the normalization method for microarray data should be mentioned.

4. The paper used P-value < 0.05 as significant criteria in significant Differential Gene Analysis, Pathway analysis, but P-value <0.01 as the criteria in GO analysis. Then, in the result 4, the author change to O-value <=0.05 in Significant pathway analysis. So Author need to use the same significant criteria.

5. Table 1 is about the clinic pathologic characteristics of Uveal Melanoma patients. The original in data in (PMID: 21135111) is a supplementary summary table and no detail on every patient. So Table 1 summary should be revised according the real published data. Description or marks need make under the table If referring other data.

6. In methods section, delete “All the patients have informed written consent forms”. The method for Signal-Net analysis is redundant. Considering revised or deletion second part of this method. And the last paragraph should be revised.

7. In Figure 2, what’s the heatmap legend key means? standard deviation? It better to understand the gene expression pattern if added two groups with a colored horizontal bar between heatmap and cluster.

8. In Table 2 and Table 3, the titles need to clarify up/down-regulated gene in which group (non- metastatic and liver metastatic patients).

9. In Figure 3, P-value should be added to shown the significant GO terms.

10. In Sigal-network analysis (Figure 5), the interesting nodes (YWHAZ, ATM, etc.) need to add fold change and P-value.

11. The first and second paragraphs in discussion should be integrated into background.

12. “mir-15b and miR-16” change to “miR-15b and miR-16”.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests: I declare that I have no competing interests