Reviewer’s report

Title: High-Resolution Analysis of Copy Number Alterations and Associated Expression Changes in Ovarian Tumors

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Reviewer: Bauke Ylstra

Reviewer’s report:

• Major Compulsory Revisions

A series of different tumors all of ovarian origin have been profiled for copy number aberrations and expression. 54 patients were sampled and 57 tumors. To my knowledge ovarian tumors have not been evaluated before for copy number and expression. Such combined analysis have been performed for several malignancies including Non-hodgkin lymphomas, glioblastomas, hepatocellular, mammary and cervical carcinomas (Pollack et al., 2002; Nigro et al., 2005; Chin et al., 2006; Zender et al., 2006; Chin et al., 2007; Wilting et al., 2008; Oudejans et al., 2008)

The reason to combine chromosomal copy number aberrations with expression is that CNA’s are hallmark of tumorigenesis and copy numbers can directly influence gene expression, but only in the tumor cells. By adding CNA’s to expression array data, downstream effects or effects of invading cells (without chromosomal aberrations) can thus be eliminated. Thus, fundamental genes in ovarian tumorigenesis can thus be identified with this strategy which were not identifiable by analysis of expression data alone.

The manuscript seems statistically thorough.

The manuscript is very technically written, this makes it unnecessarily complicated to read I am afraid. I would suggest to have a non-statistician/clinician go through this before resubmission (a small example under minor revisions).

In addition, the (clinical) reason(s) why certain analysis were made are not justified, introduced or explained; i.e. Why check the profiles of metastasis? This is done even diagnostically with LOH panels, but has also been performed and published before using arrayCGH by us and others.

Reading is furthermore impaired by the amount of figures; 5 figures + 17 supplementary files, many consisting of 1 to 7 subfigures, I roughly count >40 figures, this is out of control and readability impaired. Also the size need to be reduced (figure S4 was 11Mb and initially timed out at my home computer.

The tumors are diverse as the authors describe in great detail, yet for GISTIC analysis and integration are all thrown on one heap. I suspect the authors will have to agree with me that this would dilute the quality of the results and fundamental genes for a specific type of ovarian tumor may not be identified anymore. The authors need to comment on the fact that not one specific type of
tumors have been selected with clinical arguments or redo all analysis and select one specific type.

Much to much and speculative discussion and literature reviewing is ad randomly done—possibly by authors interest—on pages 10-14 and 16. This needs to be majorly shortened, especially since no clinical data are (made) available and no follow up or survival data is available and the tumor group was too diverse.

At last, in my opinion the authors make a large mistake by using the genes identified in pathway analysis. Combining array CGH with expression would identify fundamental (oncogenes and tumor suppressor genes) not the downstream genes or genes of invading tumors. With pathway analysis using only expression data all these downstream and invading genes are included and pathway analysis could give an insight in which pathways are affected. This is NOT the situation here, we just got rid of all downstream genes thus I think this section is wrong. It looks like, “o, what else can we do”. This would not help science and our knowledge on ovarian tumors forward. Thus delete. (in my humble opinion, and I am aware of all the corrections etc.; If I give a pathway program any extensive list of genes identified from a-set of- tumors it will give me pathways and I will find in PUBMED enough literature to make a nice story. I suspect that this is what is happening here. Again a strong introduction why the analysis is necessary or needs to be performed is necessary, or

Minor Essential Revisions

All array data is uploaded in GEO, great!
The author can be trusted to make these. For example, missing labels on figures, the wrong use of a term, spelling mistakes.

In abstract and introduction the Term GISTIC is introduced without any further explanation; I suggest say to instead say that smallest regions of overlap (SROs) were indentified or a sentence alike, rather than a non descriptive acronym.

Tumors of Ovarian origin have been profiled before by others including one of Haverty’s colleagues and coworkers J. Fridlyand (Snijders et al., 2003; Nowee et al., 2007) strange there is no reference to this first and follow up articles from the UCSF group on ovarian tumors

Page 3 “methods from 1 – 4 Mb” is not correct anymore, higher res CGH arrays are published meanwhile.

Intro: 47 “significant” gains on 5 chromosomes; also in the results the authors talk about "regions". Region and gain need to be defined the number 47 is otherwise useless.

• Discretionary Revisions

Figure 1 can be made more intuitive and readable in B/W by adding the patient numbers above the cluster.

References


**Level of interest:** An article whose findings are important to those with closely
related research interests

**Quality of written English:** Not suitable for publication unless extensively edited

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

**Declaration of competing interests:**

I declare that I have no competing interests’