Reviewer's report

Title: Aberrations of TACC1 and TACC3 are associated with ovarian cancer

Version: 1 Date: 31 March 2005

Reviewer: Andrew Shelling

Reviewer's report:

General

This is an interesting manuscript reporting for the first time an association between the human Transforming Acidic Coiled Coil (TACC) genes and ovarian cancer. These genes have previously been associated with cancer, and have previously appeared to be interesting candidates based on their location and SAGE analysis.

The authors have used various techniques to make the association between TACC genes and ovarian cancer, including careful analysis of the SAGE data, immunohistochemistry, and mutation detection (by dHPLC) and DNA sequencing. The association is made, and is an important and interesting observation, clearly a larger study is required in the future.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Refer to denaturing HPLC as dHPLC

Methods section.
Last sentence of SAGE expression isn't correctly referenced
Refer to T-BO-1 and IMH-343 as tissue and tumor microarray slides

Why were matched normal siblings used as a control for the genotyping part of the manuscript, is their a danger that they are carriers who have yet to develop symptoms?

Results
Is the HOSE cell line an appropriate control to use for the analysis of expression of TACC1 and 3? Would normal ovary tissue have been more appropriate. The HOSE cell line is not a normal cell line.

In the discussion of the possible role of TACC3 as a new familial predisposition locus (last paragraph of the discussion), the authors may need to substantiate their claims a little further. Is there a known link between clear cell cancers of the ovary and uterine cancer (presumably these would also fit within the HNPCC spectrum). While it is interesting that they make this connection, the coincidence of having the probands mother having uterine cancer is quite high. I would like to see more evidence to be provided, or slightly more cautionary language used for the association between TACC3 and a familial predisposition locus. That also applies to the conclusion
I'm not sure if Fisher's exact test is the right way to analyse this data, an expert statistician may need to consider this.

Discussion
Many cancers show random allele loss, and their will be many genes localised to 4p16, so while it is interesting that there is a potential relationship, it could also be a coincidence. Can the authors just comment in the discussion to recognise this point.

Page 12: what is chTOG, need to provide more background.

Table 2.
It is clear from this table, and difficult in studies like this, that once you break down the tumours into their subtype, that the numbers become very small, and its hard to find significant results, and when you do, you do feel a nervous that it could be a spurious result. Can the authors just comment in the discussion to recognise this point.

Table 3.
Could the authors use correct nomenclature for the annotation of their mutations, according to: den Dunnen JT, Antonarakis SE. 2000. Mutation nomenclature extensions and suggestions to describe complex mutations: a discussion. Human Mutation. 15:7-12.

Discretionary Revisions (which the author can choose to ignore)

What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

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

Statistical review: Yes

Declaration of competing interests:

I declare that I have no competing interests