Reviewer's report

Title: Breast Tumor Copy Number Aberration Phenotypes and Genomic Instability

Version: 1 Date: 2 March 2006

Reviewer: Paul A W Edwards

Reviewer's report:

General
1. Is the question posed by the authors new and well defined?
   Yes. This is an important data set which has been analysed in an interesting way.
2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
   I am not competent to assess the statistical analysis, but it is well described and Dr Fridlyand is a leading contributor to the development of such analyses.
3. Are the data sound and well controlled?
   Yes
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   Yes
5. Are the discussion and conclusions well balanced and adequately supported by the data?
   See below. I think the interpretation is somewhat over-stated.
6. Do the title and abstract accurately convey what has been found?
   Again, the abstract focusses heavily on the authors' preferred interpretation to the extent that it distracts from the data and analysis which stand on their own.
7. Is the writing acceptable?
   Good

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
None

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
Please give source of CDP-Star system and Quantity One software.

Discretionary Revisions (which the author can choose to ignore)

My main point of debate with the authors is whether their broader conclusions about genetic instability are over-stated. Their analysis generated a number of interesting observations. Among these they choose to focus the presentation, particularly the Conclusion and Abstract, on the idea that the correlation between expression of genes involved in genome instability processes and number of copy changes suggests that altered expression of (a large number of) genome stability genes causes chromosome instability. They take this a step further and suggest that this might explain the failure to identify the causes of chromosome instability in mutation screens. This is a valid speculation, not unrelated to the much older idea that instability was due to too rapid cycling, but there are several alternative interpretations that seem equally plausible. For example, tumours with more copy number changes may be more unstable and therefore upregulate their genome stability machinery; the demonstrated increased expression of mitosis-related genes may upregulate stability genes; or the tumours may have evolved further and acquired greater resistance to metabolic stress, which may upregulate these genes. The association with telomere attrition may
similarly reflect a later stage of progression/evolution. Our ignorance of gene changes that cause chromosome instability could well be that the key genes have not yet been looked at; that they are epigenetically modified; or that they are altered by genome rearrangements such as translocations that are missed by sequencing screens. (The second sentence of the Abstract is therefore contentious). In essence, association does not imply causality.

Minor point: would it not be better to make Supplementary figures 1 - 3 regular figures? For an online journal, there is less pressure to make material supplementary, and these figures are of interest to most readers.

What next?: Accept after discretionary revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

I declare that I have no competing interests