Reviewer's report

Title: Contribution of germline BRCA1 and BRCA2 sequence alterations in to breast cancer in Northern India.

Version: 1 Date: 14 February 2006

Reviewer: Mary-Claire C King

Reviewer's report:

General

This manuscript presents heteroduplex analysis of BRCA1 and BRCA2 from 204 patients from Northern India with either early-onset breast cancer or familial breast cancer. BRCA1 and BRCA2 have not previously been evaluated in such a large series from this population, so the information is a valuable addition to the cancer genetics literature.

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

1. It is misleading to state that "genetic susceptibility to breast cancer due to BRCA1/BRCA2 mutations was noticed in 11.3% (23/204) patients." This is not correct, because most of the variants noted in these 23 patients are very likely to be neutral, albeit rare, SNPs. The proportion of patients in this series with genetic susceptibility to breast cancer due to BRCA1/BRCA2 mutations is actually 6/204, or 2.9%. The abstract, Table 1, and the text should be corrected to reflect the frequency only of mutations known to be deleterious.

2. The BRCA1 mutation 4476(+2)T>C, which is probably the same as ivs13(+2)T>C although noted in two different ways on Table 4, was observed by these authors in their previous, smaller study in 2002 and again (independently?) in this series. It is very possible that this mutation alters BRCA1 splicing and is deleterious. This possibility should be tested by evaluation of BRCA1 message from these patients.

3. Please discuss the limits of heteroduplex analysis in this project. Specifically, what fraction of mutations of various classes were detected by heteroduplex analysis in the hands of these experimentalists in blind testing of known mutations?

4. For all families in whom the history of the mutation BRCA1.185delAG has been explored, its ancestry has proven to be Jewish, regardless of the geographic locale of current residence of the family. Furthermore, all haplotypes surrounding this mutation determined so far are the same, suggesting a single occurrence. This does not preclude the possibility of an independent occurrence of this allele, but thus far none has been demonstrated. Text should be corrected for this point.

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

In the title, the word "in" in the phrase "sequence alterations in to breast cancer" should be removed. Other errors of English in the text should be corrected.

Discretionary Revisions (which the author can choose to ignore)

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**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:** No

**Declaration of competing interests:**

I declare that I have no competing interests