Reviewer's report

Title: Comprehensive Analysis of NuMA Variation in Breast Cancer

Version: 1 Date: 26 September 2007

Reviewer: Janet Hall

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General

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

1. The manuscript of Kilpivaara et al. reports the sequence analysis of the NuMA gene in breast cancer patients. The coding region and exon-intron boundaries were screened in DNA from 92 familial BC patients and this information used to construct haplotypes. The frequency of 5 missense variants detected in the familial cases was determined in an additional 341 patients with a family history of BC cancer and 368 controls, in addition the Ala794Gly sequence variant frequency was determined in 910 familial and 884 unselected BC cases and 906 controls. Based on the results obtained the authors report:

A) A lack of an association between the Ala794Gly variant and BC risk.
B) No association between the Ala794Gly variant and histopathologic parameters in unselected BC cases.
C) No association of specific haplotypes in the NuMA gene and familial cancer risk.

I am not sure that these conclusions come across clearly in the abstract and in particular the haplotype studies. The power of the study to detect associations should be clearly stated and in particular for the haplotype studies and whilst a conclusion that the Ala794Gly is not associated with BC risk is probably justified, can an involvement of other sequence variants in the NuMA gene in sporadic BC be excluded based on this data set? The Ala794Gly variant did in fact show significant associations with p53 status and lymph node involvement in sporadic BC cases. In addition it would be useful to note in the abstract the basis for choosing the five missense variants that were genotyped in the extended population.

2. The description of the BC patients in the material and methods section is muddled and difficult to follow. Is the same inclusion criteria used throughout for the familial BC cancers- it would seem not?

Can a reference be given for how BRCA1 and BRCA2 screening was carried out on the cohort.
3. It would appear from the numbers that the genotyping was unsuccessful on some DNA samples can this be clarified? There was 910 familial BC cases but 893 (378+515) successfully genotyped, was the failure rate the same in those with a strong family history vs. those with a “weaker” family history? The unselected series consisted of 884 cases of which 842 were successfully genotyped but from these women 889 primary tumours were analysed. Some clarification is needed here.

4. How was the p53 status defined, what was the % of cells staining used for the cut-off for positive staining? What antibodies were used for p53 staining?

5. The association between the Ala794Gly allele and histopathologic parameters is presented in table 4 for 842 unselected BC cancers however for the different parameters the number of tumours analysed varies between 653 and 889. Some explanation should be given for the “failures” and how 889 tumours were analysed for 842 individuals. The association between the variant allele and lymph node status was not seen in the familial cases – this observation is based on how many samples? No information is provided on the number of tumours analysed for this group of cases.

6. The p values for the associations should be given in table 2.

7. In table 5 it is not clear what the results presented here represent.

8. Was the significance of any of the variants found at intron/exon boundaries assessed using bioinformatic techniques?

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

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests other than an interest in the identification in breast cancer susceptibility genes.