Reviewer's report

Title: Variations in the NBN/NBS1 gene and the risk of breast cancer in non-BRCA1/2 French Canadian families with high risk of breast cancer.

Version: 3 Date: 25 February 2009

Reviewer: Eva Seemanova

Reviewer's report:

The paper presents an interesting project, which extents our knowledge in the field of genomic instability and breast cancer. The authors explored very well defined material of a large group of familial breast cancer for study of new aspect - an association with broad spectrum of 24 variants in NBS1/NBN gene - in possible etiological contribution of this genetic heterogenous disease. This view on gene variants, which can act as modifier and so contribute to the cancerogenesis can have relevance for preventive management in clinical practise. The authors emphasize limitations of genetic testing of variants associated with malignancy.

Minor Essential Revisions:
1) The goal of the study is precisely defined and logically maintained
2) The used methods are appropriate
3) The data are clearly explained and sound
4) The manuscript adheres well to all formal standards for such publication
5) There are mentioned practically all relevant papers, dealing with the related problematics. I would recommend also to discuss the results of Someya M. et all paper " association of ionizing radiation-induced foci of NBS1 repression".
6) The conclusion strongly respects limitation of the results with respect to the multifactorial etiologic causes of breast cancer
7) According to my knowledge the authors did not forget any recent and relevant publications, which are connected to this problematics with only exception - I would see useful to discuss also the new paper Vineis P. et all.: " A field synopsis on low-penetrance in DNA repair genes and cancer susceptibility" in JNCI from Jan 7 2009.
8) The Abstract is clearly formulated and gives good information about the aim, material, methods and results of this study
9) The paper is written acceptable with many explaining details for interseants, who are not familiar with molecular basis of NBS1 gene and its function. I am not aware that any part of this paper has been published elsewhere.
10) I believe, that this manuscript is suitable for publication in BMC Cancer and can be accepted with small revision.
11) The study revealed two new, undescribed variants in NBS1 gene - the
insertion of 50bp of the intron between exons 2 and 3 and the in-frame deletion of 113 amino acids of exons 12 to 14 - both exclusively present among breast cancer patients. Particularly the finding of significant increased incidence of variant in promotor region - c.242-110delAGTA - is of interest, because it shows a probably new important factor or marker for the risk of development of malignancy

12) As non-native speaker I believe that the English language of this article is good enough and acceptable for publication

13) Statistical review is acceptable - I think that this manuscript does not need to be seen by a statistician any more, but I do not feel adequately qualified to assess the statistics and its conclusion in this paper

**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