Reviewer's report

Title: SNP-SNP Interactions in Breast Cancer Susceptibility

Version: 2 Date: 19 January 2006

Reviewer: David Goldgar

Reviewer's report:

General
This article describes the analysis of 19 SNPs in a set of functionally relevant cancer genes comprising key pathways in a set of ~400 breast cancer cases and controls form the Ontario BCFR. Although no main effects were found, the authors detected a few two-way interactions that remained significant after (some) correction for multiple testing. The meaning of this is not totally clear as one would have thought that the sample size of the study would a priori not have a great deal of power for detecting such interactions.

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

There should be an additional table describing in more detail the significant interactions, in terms of the effect size for particular combinations of SNP 2-locus genotypes.

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

It would be useful to add a column to table 1 or 2 describing any previous evidence for association of the SNPs with Breast Cancer in other (and perhaps larger) studies. Also the column in table 1 labeled 'Interacting SNPs' is not clear as to what is meant by interacting.

On page 10, what sample size was used for the bootstrap samples?

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Discretionary Revisions (which the author can choose to ignore)

Table 4 might be better as the first table since it more or less describes the study population.

It might be interesting to use the family history data to increase power for the main effects analysis using e.g., the method outlined in Thompson D, Witte J, Slattery M, Goldgar D. (2004) Increased power for case-control studies of single nucleotide polymorphisms through Incorporation of family history and genetic constraints. Genetic Epidemiology27:215-24.

What next?: Accept after minor essential 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.