Reviewer's report

Title: Comparing the frequency of common genetic variants and haplotypes between carriers and non-carriers of BRCA1 and BRCA2 deleterious mutations in Australian women diagnosed with breast cancer before 40 years of age

Version: 2 Date: 18 January 2010

Reviewer: Nancy Hamel

Reviewer's report:

This manuscript compares the frequency of common variants in the genes BRCA1 and BRCA2 between individuals affected with breast cancer who are either carrier or non-carrier of deleterious mutations in these same genes. A subset of 4 tag SNPs per gene are chosen for analysis and their frequency in the “deleterious” and “non-deleterious” subgroups of patients for each gene are compared. In addition, the various haplotypes in which these SNPs are found are inferred using statistical methods, and the relative frequencies of these haplotypes are again compared between the “deleterious” and “non-deleterious” groups of breast cancer patients.

The study design is simple and the statistical approaches used to reconstruct the haplotypes and perform genotype and haplotype frequency comparisons are accepted in the field as appropriate to this type of study.

Major Compulsory Revisions

1. The goal of the study is not immediately obvious from the abstract. Allele frequencies are compared, but what the authors were looking for and how the observations answered the questions is not clearly understood without reading the entire manuscript. I was unsure whether the authors were interested in the frequency of variants in cis with the deleterious mutation, or variants in trans (modifiers), or both.

2. There is a lack of raw data in the paper. In the various tables the total number of variants observed for each gene is listed, but there is no sense of how many individuals were observed to be carriers of these variants. Was each deleterious mutation observed only once, with the total number of distinct mutations and the total number of mutation carriers being equal? This seems unlikely, as some of the deleterious mutations listed are known to be more common than others, and the number of mutation carriers would thus be very low. If some mutations were observed more than once, what was the total number of deleterious mutation carriers for each gene? For each mutation? Is it possible that the weak genotype/haplotype associations observed in this study were driven by one particular deleterious mutation rather than associated with the presence of several deleterious variants? With no data available for review, this is impossible to assess.
3. Throughout the article, the authors refer to mutation carrier patients as opposed to carrier chromosomes. Was phase between the deleterious mutation and the other variants established? Understandably, this would be difficult without several carriers for the same mutation available to identify the haplotype linked to the mutation. However, without phase information, a positive association between a given haplotype and presence of a deleterious mutation does not necessarily reflect a physical association between mutation and haplotype, as seems to be assumed by the authors throughout the article. It could reflect a functional association, such as modifying penetrance in trans and increasing the disease-causing potential of the deleterious variant. Would this affect the interpretation of any association observed?

Minor Essential Revisions

4. The number of variants listed in Table 2 is 22 (and not 23 as stated in the text). In addition, the first two mutations listed, 188delAA and 189 delAA are incorrect because 1) they would theoretically be the same mutation and should have the same name, yet they appear to be different since they have different minor allele frequencies and 2) there are no AAs in the vicinity of nucleotides 188 and 189 so the labeling must be wrong. Please verify the accuracy of these 2 listings.

5. Please indicate where the minor allele frequencies in Table 2 and 3 were obtained (public databases, or are these the MAF as observed from the data in this study)?

Discretionary Revisions

6. There is no hypothesis offered by the authors as to why an association between deleterious mutations and one or a few particular haplotypes should be expected to exist in BRCA1 and BRCA2. According to the BIC database, 890 alterations in BRCA1 and 975 alterations in BRCA2 were reported to occur only once; novel variations in these genes arise frequently and are spread throughout the gene sequence. By chance alone, a rare haplotype may be in strong LD with a given mutation but by virtue of being rare would provide little useful predictive power. Common haplotypes, on the other hand, may harbor many deleterious variants, but would also be present often enough in non-carriers that most people who carry them would need to be sequenced regardless, especially since they would be likely to carry them on the 2nd allele as well. So why is this study worth doing? Certainly, identifying one or several haplotypes associated with the presence of deleterious mutations would be highly desirable (in the end it may not matter why it works, as long as it does), but are there any reasons to suggest that finding an association strong enough to be useful for mutation testing is even possible?

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.