Reviewer's report

**Title:** Association of common variants in mismatch repair genes and breast cancer susceptibility: a multigene study.

**Version:** 1  **Date:** 15 May 2009

**Reviewer:** Karen Curtin

**Reviewer's report:**

**General comments:**

The authors present findings from a hospital-based case-control association study of several DNA mismatch repair polymorphisms and discuss potential mechanisms involved in defects in DNA mismatch repair and breast cancer susceptibility. The Tables have a well-organized appearance, and generally clear in presentation.

(Major Compulsory Revisions)

1. However, the manuscript contains several English language errors throughout including: misspellings, incorrect use of tense, incorrect grammar, faulty syntax, and awkward sentence structure that should be corrected and carefully proofread prior to any resubmission.

2. Methods: Did the authors test for two-way SNP interactions using an additive or multiplicative interaction model (Table 4)? For example, a likelihood ratio test of a model including a multiplicative interaction term and a model in which the independent (main) effects of each SNP only are considered. The authors’ approach to testing for interaction using Chi-squared test of independence between cases and controls for each combined 2-SNP genotype is simplistic and does not test for the presence of an interaction, modeled as either multiplicative or additive, beyond the independent or main effects of each SNP in the joint model. The results should be modified to include significance of an interaction term between each pair of SNPs.

3. In Table 2, for the MLH3 Leu844Pro G>A variant, the authors show that A is the minor allele. However, the genotype frequencies they list for Pro/Pro, Leu/Pro, and Leu/Leu genotypes indicate that G is the minor allele in their population, and Pro/Pro is used as the reference group. This discrepancy should be addressed.

4. Discussion: The authors should distinguish more clearly between protein or enzyme interactions from in-vitro studies, and potential associations of joint assessment of two SNPs; see page 12, final paragraph, first sentence.

5. Discussion: Page 14 paragraph 2: The authors state that “However, our study demonstrates that MSH3 Ala1045Thr/MSH6 Gly39Glu interaction is associated with a reduced risk for breast cancer.” This appears to be based on the
comparison of the MSH3 Ala1045 Thr AA genotype in combination with the MSH6 Gly39Glu CT genotype. As the confidence intervals for the other genotype categories contain one, an interaction term between the two SNPs may not be significant and the findings do not clearly demonstrate the reduced risk of this combined genotype as the authors suggest. Also, how was the choice of reference group made in this comparison? G is the minor MSH3 “risk” allele as indicated in Table 2 while C is the common “low-risk” allele in MSH6 in the single-SNP table.

(Minor Essential Revisions)

1. The authors should consider rounding all odds ratios and confidence intervals to one or two decimal places throughout the manuscript and tables. These are estimates, and precision at that level is unnecessary and distracting in its presentation. P-values>0.01 can also be rounded to two decimal places.

2. Introduction: Page 5, paragraph 2: reference [14] appears to be incorrect. Are the authors referring to the work of Moinfar, et al., Modern Pathology 2008 21, 39-646? If so, the Moinfar study is based on an analysis of 12 mastectomy specimens and the size of the study should be mentioned.

3. Results: In the Methods, the authors state that a histological diagnosis was available for all cases. Was tumor stage or grade available from the pathology? A distribution in cases of the stage of disease (i.e. local or distant), and potentially estrogen receptor status, and histological grade, if available, could be stated in the text or added to Table 1.

4. Table 3 presents the results of combined genotypes between two polymorphisms within the same gene, either MSH3 or MSH6. The title to this table and the text should state this, rather than presenting the data as the effects of haplotypes. An analysis of haplotype pairs (phase known, or estimated for compound heterozygotes) in case-control subjects is not presented in this table or discussed in the Results.

5. In Table 4 (page 30), the combined genotype for MSH4 Ala97Thr and MSH3 Leu844Pro used as the reference genotype includes the low-risk MSH3 G (Leu) allele, which appears to be the minor allele in their population. For consistency, the authors could use homozygous carriers of the minor G allele of this MSH3 SNP as the reference (low risk) genotype.

(Discretionary Revisions)

1. Abstract: The methods paragraph should clearly state that this was a study of hospital-based cases and controls. The conclusion that common variants in MMR genes contribute significantly to breast cancer susceptibility is not supported by the data. This was a fairly small hospital-based study and confidence intervals are fairly wide; the authors might consider rewording the conclusions to more cautiously interpret their findings.

2. Table 4 could be significantly shortened to show only the two-way SNP
combined genotype association between MSH4 Ala97Thr and MLH3LEu844Pro on page 30 that achieved nominal significance<0.05 for a chi-squared association test of combined genotype and case-control status. The entire table could be included as supplementary data available online.

**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, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

'I declare that I have no competing interests'