Reviewer's report

**Title:** Mutation analysis of the AATF gene in breast cancer families

**Version:** 1  **Date:** 9 September 2009

**Reviewer:** Csilla Szabo

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BMC Cancer Csilla Szabo review of Research Article: 8279902172892439

1. Is the question posed by the authors well defined?
   This is a comprehensive analysis of a biologically plausible candidate breast cancer susceptibility gene in 121 Finnish breast cancer families (104 of whom do not carry mutations in known or suspected predisposition genes).

2. Are the methods appropriate and well described?
   Methods are both appropriate and clearly described. Statistical analyses are appropriate.

3. Are the data sound?
   Data are solid – as with previous work of this group.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   Relevant standards for reporting and data deposition are adhered to in the manuscript.

5. Are the discussion and conclusions well balanced and adequately supported by the data?
   Discussion and conclusions are in keeping with the results of the study.

6. Are limitations of the work clearly stated?
   Limitations of the work are clearly delineated.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
   This is an exploratory study to determine whether a novel gene that is involved in the critical cellular processes of genomic integrity maintenance and cell-cycle checkpoint control might play a role in cancer susceptibility. The rationale for the study is sound.

8. Do the title and abstract accurately convey what has been found?
   The title and abstract reflect the aim of the study and the resultant negative findings.

9. Is the writing acceptable?
   Apart from a few minor revisions (see below), the writing of the article is clear and concise.
Discretionary Revisions:
(recommendations for improvement but which the author can choose to ignore)

DR.1) Abstract-Background, last sentence: The authors may wish to strengthen their biological rationale in the following manner: “Based on its biological function, and direct interaction with the known risk genes, ATM/ATR and CHEK2, the AATF gene is a good candidate for being involved in breast cancer susceptibility.

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

MER.1) Background, 1st paragraph: “Mutations in two major high penetrance genes BRCA1 and BRCA2 are well known, but they seem to be responsible for only ~16% of heritable disease predisposition [3],[4].” A more correct way of stating is this is less than 20% of excess familial risk.

MER.2) Background, 1st paragraph, typo: “As most of the known cancer susceptibility genes are involved in the maintenance of genomic integrity, potential candidate genes could have similar functions.”

MER.3) Results, 1st paragraph, typo: “All the other seen variants were all intronic.”

MER.4) Results, 2nd paragraph: “These two amino acids display very different characteristics. Alanine is a small hydrophobic and aliphatic aa, whereas serine is a polaric and hydrophilic aa.”

Please define the abbreviation or refrain from using it.

MER.5) Discussion, 2nd paragraph, typo: “Furthermore, none of the intronic changes seemed to affect consensus splicing sequences.”

MER.6) Table 1: Please correct the format of the table so that the Intron 12 data is all in a single row.

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

MCR.1) Background, 2nd paragraph: Please re-work the description of AATF function, including a bit more detail from additional literature references.

MCR.2) Subjects and Methods – Cases and controls: Please better define the meaning of the following sentence:
“All high-risk families were previously screened for germline mutations in known or potential susceptibility genes and disease associated changes in BRCA1, BRCA2, CHK2, TP53, RAD50, RAP80 or PALB2 [6,15-19], and disease associated alterations were seen in altogether 17 of the families.”
If you are describing germline changes observed in AATF, this should be reserved for the Results section.

If there were disease-associated mutations in known or suspected susceptibility genes, why were these samples not excluded from the AATF analysis (especially if the mutation was in BRCA1, BRCA2, TP53 or PALB2, which are known to confer high risks)? It would be better to exclude data from families carrying mutations in these genes.

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

No competing interests.