Reviewer's report

Title: Linkage disequilibrium mapping of a breast cancer susceptibility locus in the RAI gene region

Version: 2 Date: 30 August 2007

Reviewer: Jan Lubinski

Reviewer's report:

General

Nexo et al. in the manuscript „Linkage disequilibrium mapping of a breast cancer susceptibility locus in the RAI gene region” describes the results of analysis of specific region located in 19q13.2-3 in a group of Dutch breast cancer patients. The defined investigated region included four different genes, two DNA repair (XPD alias ERCC2 and ERCC1), one relating to apoptosis (RAI) and one involved in rRNA transcription (ASE1 alias CD3EAP). The analyses of over 60 different SNPs (first 22, and later 44) were performed on 434 postmenopausal breast cancer cases and matched controls.

Authors used different techniques: linkage disequilibrium mapping to define specific haplotype blocks, sequencing and finally SNPs genotyping using Lightcycler, Taqman and ABI3100.

Authors found that a new tandem repeat marker in a RAI gene, called RAI-3’d1 (duplication of 5 bp) is strongly associated with breast cancer risk (RR 2.44, CI 1.41-4.23, p=0.0008), with higher risk for breast cancer diagnosed before 55 y (RR 6.29, CI 1.49-26.6, p=0.01).

Generally, the manuscript presents very interesting issue and the used analytical methods and obtained results are convincing.

-------------------------------------------------------------------------------

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

-------------------------------------------------------------------------------

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

1. All parts: Background, Results, etc. are written chaotic and should be improved according to the guidelines for authors on BioMed Central websites

2. The description of tested controls is not sufficient and some information’s are missing, e.g. information’s about selection criteria of controls, their disease status, population etc. Authors wrote that the controls were matched individually to cases for age, HRT use and menopausal status. When the matching was done
and how was done the age-matching, by age at diagnosis of cases or current age, when this was performed? What is the median age at diagnosis of cases and controls?

3. In Results the description of analysed fragments is confusing, i.e. RAI intron 8-3 (is it a fragment of the RAI gene between intron 8 and intron or exon 3?) or ASE1 exon 3-3 (exon 3/intron 3 or only exon 3 of ASE1 gene?)

4. Table’s numbers used in the text are wrong and confusing; the table’s legends are not sufficient, all superscripts and used abbreviation should be explained (the same apply to figures)

5. Confusing are numbers of tested cases and controls found in the table 2: if the study group consisted of 434 cases and 434 controls why in the table are included only 365 cases and 374 controls tested for RAI-3’d1, and 383 cases and 400 controls tested for rai-3’d2? What is the reason of such differences? Would be helpful if in the tables authors will include a total numbers of testes samples.

6. pp. 14, it is written that “Three polymorphism, RAI-3’d1, RAI-3’, and RAI-3’d2 were determined as length polymorphisms on ABI3100 (Applied Biosystems, Nærum, Denmark). Information about the assay conditions can be found in the Additional File 1: SNP typing and SNP identification.”, these data are partial and confusing (how RAI-3’3 was analyzed, by ABI3100 or Lightcycler?), where are primer sequences for RAI-3’d2 and reaction conditions for all three analyzed on ABI3100?

Discretionary Revisions (which the author can choose to ignore)

What next?: Accept after minor essential revisions

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.