Reviewer's report

Title: Haplotype analysis suggest common founders in carriers of a recurrent BRCA2 mutation in French Canadian hereditary breast and ovarian cancer families

Version: 2 Date: 30 August 2005

Reviewer: Jean-Pierre FRICKER

Reviewer's report:

General

The paper submitted by K.K. Oros & al details a BRCA2 mutation previously reported by the same group in 4 families, and which was later found in 11 breast or breast/ovarian cancer families from the French Canadian population. Recurrent mutations in the BRCA1/2 genes have been reported in several defined populations. They support evidence that mutational events in the BRCA genes are rare events, generally ancient. Their knowledge is useful for optimal mutational analysis strategy in selected populations. They give opportunity for studies on factors which could modify the gene expression. These data are of interest for those involved in genetic testing in breast and ovarian cancer. Therefore, this paper deserves publication but minor essential revisions will be welcome for better clarity.

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

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

The authors have performed genotyping in 11 families harbouring the 3398mutation. The precise characterization of the mutation, namely 3398del AAAAG should appear in the title.

Genotype anlysis is adequately reported and genotypes are shown in Table 2. It is not indicated how many individuals or carriers have been genotyped.

Two haplotypes were observed, differing for only one allele in seven alleles tested. The discussion concerning the existence of 2 different haplotypes differing at D13S1701 (higher mutation rate, slippage in DNA replication or mutation early in the French Canadian population) is of interest.

The data indicate that tested cases shared common genotypes which supports the hypothesis of a common founder genotype, as mentioned in the title. Among eleven families, the phase could be determined in only five families and no linkage disequilibrium could be established. This limitation explains the difficulties for interpreting these haplotypes and «ascertain» a common ancestry. However following statements:

a) the two haplotypes were distinct from those found for the most common French Canadian mutation 8765delAG;

b) although 3 or 4 of the alleles determined in the 3398 mutated cases were also the most frequent in the control panel of «47 French Canadian unaffected with cancer the mutation associated haplotype was not plausible in these« controls»;

c) use of the additional D13S1695 marker excludes recombination event (frequency of D13S1695 alleles in controls should be shown in table 3);

are a set of arguments in favour of a founder effect, but there is no evidence for a founder effect. This study lacks adequate controls to answer the question: What is the probability that the disease-associated (phased) haplotypes might have happened by chance in carriers, by comparison
with those found in unaffected population from French Canadian descent? To address this point, could the haplotypes from the non affected chromosomes not serve as intrafamilial controls?

The authors state they established the « prevalence » of the mutation in cases not selected for family history. Prevalence is the count of all living cases in a population. Although it is nearly always an estimate, in this study it was deduced from the analysis of 60, 127 and 80 cancer cases. What could be the confidence intervals in such limited panels? « Estimate of its frequency » would sound more prudent.

Of interest would be the contribution of this mutation to the number of BRCAs families identified in the Province of Quebec or in the area of Montreal. This would give a comparative information of its contribution to BOC.

Table I shows phenotypic information about the index cases and their families. The type of familial syndrome would be a interesting information to understand how cases and families have been identified. Conversely, so called « cancers at atypical sites » coul be omitted since they are of little help for patient selection and for the determination of a founder effect. Ages at onset of BC or OC are interesting data, especially because the occurrence of OC is discussed in relation with the position of the mutation in the OCCR. Reports are conflicting, and an association is not firmly established. So, the last sentence « Although the association …. is not known » should be omitted, or more detailed. The authors report a frameshift mutation resulting in a stop codon at position 1064, generally considered as deleterious mutation. It is supposed that the disease segregated with the mutation which is located in the OCCR region of the gene. Mutations in this region are supposed to confer enhanced ovarian (or equivalent) cancer risk. OC was observed in approximately half of the families; how many cases were observed; is there any conclusion to draw? The hypothesis of an enhanced ovarian cancer risk is an important issue for optimal patients decision making in genetic clinics.

Finally, several points should be completed or modified:

- Page 5, third line : does « before 80 years » mean between 40 and 80 years?
- Page 6, last line : « ) » should be placed after D13S171 and not after D13S1695
- Page 8, last sentence « in order … »: carriage return
- Page 9, first line : microsatellite
- Page 9, second paragraph, third line : « Presently it is not … »
- Table 1 : Lu, Pan, Brn are not explained in footnote
- Table 2 : italics is not visible

Discretionary Revisions (which the author can choose to ignore)

What next?: Accept after minor essential revisions

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

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

I declare that I have no competing interests.