Reviewer’s report

Title: Identification of a novel CHEK2 variant and assessment of its contribution to the risk of breast cancer in French Canadian women

Version: 1 Date: 21 March 2008

Reviewer: Mieke Schutte

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The paper by Novak et al. reports on a whole gene mutation screen of CHEK2 in 25 French Canadian familial breast cancer cases and 25 controls. They have identified two variants: the well-known E84E polymorphism and the novel R406H variant. The R406H variant was then screened in two larger cohorts of breast cancer cases (124 and 543 cases) and in 6432 controls. The prevalence of R406H among cases was similar to that among controls. They conclude that R406H is a non-pathogenic variant and that no other CHEK2 alleles than 1100delC influence breast cancer risk in the French Canadian population.

Major compulsory revisions

1. The conclusion of the paper is too far stretched. The conclusion that R406H is a non-pathogenic polymorphism appears justified (see comment #2). Yet, the authors can not conclude that 1100delC is the only other CHEK2 variant of importance in their population. Specifically, the cohort of 25 breast cancer cases is too small to identify all CHEK2 alleles present in their population. This is exemplified by the fact that 1100delC had not been detected in the 25 breast cancer cases, while screening of 149 cases identified the mutation in 2.0% of cases (which certainly is not ignorable). The authors can not exclude that they have missed other variants as well and they therefore should rephrase their conclusion.

2. The prevalence of the R406H variant among the different cohorts of cases is a bit suspicious. The variant was present in 1 of 25 cases of group 1, in 1 of 124 cases of group 2 and in 1 of 543 cases from group 3. They either have been quite lucky to detect the variant in the first two groups, or they have missed a few in group 3. This raises questions on the mutation detection methods, which were different for each of the three groups: sequencing for group 1, allele-specific PCR for group 2, and restriction assay for group 3. To answer the questions raised, the authors should indicate in the methods section which and how many positive controls have been used for each method. They should also indicate whether the wild-type or mutant allele is being cut in the restriction assay and how the quality of digestion was controlled.

3. The overview on CHEK2 literature is disturbingly inaccurate. Currently, a breast cancer risk has been shown for FIVE variants of CHEK2: 1100delC, I157T, IVS2+1G>A, the 5.4 kb deletion and the Jewish S428F mutation. The I157T mutations is completely ignored by the authors (except for its colorectal
cancer risk in the Discussion). The 1100delC mutation, which is the most important variant, is underrepresented. For example, the fifth para in the discussion starts with "To date, THREE interesting CHEK2 founder alleles have been identified,...". Also, the references in the Background section are inaccurate. At the end of the 2nd para of the Background, the references that CHEK2 has been confirmed as a low-penetrance breast cancer susceptibility allele should be refs 3 and 9 in stead of ref 8. Next line, in the 3rd para, ref 9 should be replaced by ref 3. Next line, add to ref 3 also refs 9 and 8. Last line of 3rd para, refs 10-12 should be significantly extended (currently near 25 papers touch on this subject) or should be replaced by ref 8 (which was the first to state the variation in population frequencies). In the discussion, 1st line of the 4th para, ref 30 is weird and ref 8 should be included. Same para, 2nd line, replace "many Eastern European populations" with "many other populations". Same para, 3rd and 4th lines are inaccurate and should be deleted or rephrased: The five CHEK2 variants mentioned above under comment #1 have all convincingly been shown to confer a breast cancer risk. Each of these variants consistently confers a breast cancer risk in different populations, PROVIDED they are present in that population. Please change the text. Fifth para, first sentence, again, there are five interesting variants, so please include 1100delC and I157T.

Minor essential revisions

1. In the Materials section, please add details on the family history of the group 2 cases
2. Also in the Materials section, indicate whether the group 3 cases have been screened for BRCA1 and BRCA2 mutations.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory 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, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

'I declare that I have no competing interests'