Reviewer’s report

Title: Mutation analysis of the MDM4 gene in German breast cancer patients

Version: 1 Date: 27 September 2007

Reviewer: Robert Winqvist

Reviewer’s report:

General

Reinicke et al have here comprehensively screened 40 BRCA1 and BRCA2 mutation-negative German familial breast cancer cases for constitutional mutations in the MDM4 gene, the protein of which that cooperates with MDM2 and is a negative regulator of p53 in the cellular response to DNA damage. Based on its biological function MDM4 is a very good candidate to be assessed for possible involvement in hereditable cancer susceptibility beyond BRCA1 and BRCA2, particularly as there are no previous reports evaluating this particular candidate gene.

Among the eight observed NDM4 variants two occurred in protein-encoding regions of the gene (exons 4 and 7) and are not currently listed in the NCBI data base, whereas all of the 6 non-coding changes have also been seen previously. Of the two novel variants only c.458A>G changes an amino acid (D153G) in the protein product and therefore potentially interesting, but everything indicates that c.222A>T (V74V) is only a harmless neutral change.

The heterozygous D153G variant was observed only in 1/40 (2.5%) of the studied familial breast cancer cases, but in none of the subsequently tested 200 female controls or 140 bilateral breast cancers. Interestingly, the index case displaying this variant had been diagnosed with breast cancer at the age of 24. Also her mother that had breast cancer at age 41 tested positive for the D153G variant, but the index patient’s maternal aunt having the disease at age 44 was found negative, thus suggesting an incomplete segregation pattern. Although the observed change seem rare and maps to a less conserved region of the MDM4 protein, it may affect a predicted casein kinase II phosphorylation site, and could therefore potentially be of importance in DNA repair and cell cycle control functions. However, no functional assessments were carried out in the present study. Therefore, at present there is insufficient evidence to conclude that the D153G variant exerts any effect at the functional level.

This interesting, well and also critically enough written paper presents the first assessment of MDM4 as a candidate gene for heritable predisposition to breast cancer. Although there were some potentially relevant novel findings, the general conclusion is that germ-line MDM4 alterations are extremely rare and currently seem to be of only limited importance, if any. More knowledge about the occurrence and possible biological effect of different MDM4 gene variants, such
as D153G, certainly is required.

I would recommend publishing of the current paper.

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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)

- page 3, second paragraph, line 2: P53 should be p53
- Figure 1: MDMX should be MDM4

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Discretionary Revisions (which the author can choose to ignore)

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What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

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