Reviewer's report

Title: No germline mutations in supposed tumour suppressor genes SAFB1 and SAFB2 in familial breast cancer with linkage to 19p.

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Reviewer: Tadahide Izumi

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SAFB1 and SAFB2 genes, nucleosomal scaffolding factors whose functions are not understood well, have been implicated to be breast cancer risk factors due to somatic LOH implicated by their earlier statistical analysis. The present study sought to find germ line mutations (DNA from blood cells) of the genes from 31 patients of 14 families. With the results, the authors conclude that the two genes are not causative of the hereditary breast cancer, at least in the west Swedish families. This is a rather simple work for a negative conclusion.

The SAFB1/2 genes are mapped in the gene locus 19p13 which is linked to a tumor suppressing factor. Testing germ line mutations on the two genes is thus an important topic and would have been highly significant if indeed such mutations were found. Although the scale of analysis is not quite large enough to completely exclude the possibility of the hereditary risk factor in the broader human population, the authors describe that the families were linked to the 19p13 deficiency in a past study (citation to this study is essential). Therefore, the analysis is valid for the small focused group.

<Major compulsory revisions through the bottom>

However, the mutation analyses were done only on the exon regions of the two genes and epigenetic changes were not considered either. Therefore, unusual gene expressions of SAFB1/2 could not be detected, and the lack of these experiments may confound their conclusion. Probing the expression of the genes by different strategies, i.e., analysis of methylation, levels of transcripts by RT-PCR, or tissue staining/immunoblot of the patients specimen should strengthen their conclusion. The authors discussed the possibility of STK11/LKB1 gene mutation instead of SAFB. It would be necessary to include similar genetic analyses on STK11/LKB1 genes.

Another concern is that PCR might not detect possible deletions of the locus. In this case a PCR reaction using DNA from blood cells would not react the deleted allele, but still would amplify the unaffected, normal allele which would result in a pseudo-normal genotype in their sequencing analyses. Have the authors determined the structures of the genes in a larger scale by Southern blotting or any other methods? Discussion and precaution to exclude this possibility is missing.

Level of interest: An article of limited interest
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.