Reviewer's report

**Title:** Genome-wide screening of microsatellite markers associated with acute adverse effects following radiotherapy for cancer patients

**Version:** 1  **Date:** 26 January 2010

**Reviewer:** Marie Fernet

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The manuscript describes a two round genome-wide association study using 23,244 microsatellite markers on DNA from 360 cancer patients who had been treated with radiotherapy. The authors have identified 47 autosomal markers showing a significant association with radiosensitivity and focused on the D7S0338i marker associated with the Semaphorin 3A gene.

Overall this is an interesting and well-written manuscript, the results obtained for the microsatellite markers analysis are very complete and the statistical analysis done very carefully, however the data presented were insufficient to convince me about the clinical applications of a potential test using the marker identified.

Here are some suggestions to improve the quality of the manuscript:

**Minor Essential Revisions**

1. The background section would benefit from removing the details on previous results using a different approach (ref. 15) and adding additional information on microsatellite sequences, especially is there any previous association studies using this marker?

2. Instead of « Assessment of protein synthesis » the methods section about Sema3A protein quantification should be named simply « Western blotting » and the complete reference of the Sema3A antibody should be given. In the radiosensitivity assay section, an « appropriate number of cells » should be defined, is it the number of cells that gives the same number of colonies for all the radiation doses used ?

3. Abbreviations in table 1 should be defined in the table legend : LGG, HGG, TNM. In the last sentence of the legend, « suppression » have to be replaced by « suppression ». The definition of « hg18 » should be given in the legend of table 2.

4. Explanations would be given at the end of the section « Individual patient typing of selected markers » about the choice of D7S0338i for further analysis. Why not D1S0288i ?

5. In the table 5 legend, « Conchran-Armitage » have to be replaced by « Cochran-Armitage ». The genotype association analysis of D7S0338i is interesting and raises questions that, unfortunately are not discussed in the
discussion section. To extend the characterisation of the genotypes, a useful experiment to do would be to measure the expression of the SEMA 3A gene for the LGG and HGG patients groups homozygous for 292/292 and 296/296, to establish a direct correlation between the SEMA 3A gene genotype, the level of expression of this gene and the modulation of the radiosensitivity risk.

6. The cell survival curve of the figure 2 would benefit from extending the dose range used, only 2 doses is not very convincing and details on the number of experiments done and the statistical analysis to validate the significance of the difference would be useful. A lot of details are given in the discussion on SM-216289, an inhibitor of Sema 3A, the cell survival of human skin fibroblasts in presence of this inhibitor would nicely confirm the effect seen with the siRNA.

7. The limitations of this work are not well stated in the discussion. The composition of the cohorts of patients, regardless of their cancer type is justified by the need for statistical power but in my opinion it is really non realistic to imagine that we can find an « universal » test for all cancer patients and the results have to be validated on groups of patients with a unique cancer type. Another point is the lack of reflexion about the feasibility (time, cost) of the potential test using SEMA 3A genotyping for routine preclinical diagnosis.

**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