Reviewer’s report

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

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Reviewer: Alison M Dunning

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This report has used genome wide microsatellite markers in a case-control association study of 180 patients with high-grade and 180 with low grade acute radiation toxicity using a DNA pooling strategy in the initial screen.

Discretionary Revisions:

(i)- It is currently unusual to see microsatellites, rather than SNPs, used in such a case-control study. The authors claim this method has advantages of allele frequency over the use of SNPs, but there are other differences that also need to be considered. For instance repeat length polymorphisms mutate, on average, more frequently than SNP alleles. This means they have more value for discovering more recent, and hence rarer and more highly penetrant variants, than SNPs.

(ii) It may be due to the above reasons, as well as the heterogeneities in cancer site, radiation dose and type of adverse reaction inherent in the study design, that the authors discovered only two markers, from the 23,244 tested, that were reproducibly associated with adverse reactions. In reality there must be many more such loci to discover and the authors might like to comment on this.

Major Compulsory Revisions:-

The authors concentrate on just one marker that showed reproducible allelic association of the two most common alleles. They report that this marker lies 1500bp upstream of the SEMA3A gene, but do not (iii) report the extent of linkage disequilibrium across this region. (iv) Do neighbouring markers also detect the same association? (v) If not, why not? (vi) Do other genes fall within the same linkage disequilibrium block? (This could be investigated using the HAPMAP.)

Unless SEMA3A is the only gene within linkage disequilibrium range of this marker, or the authors have additional information supporting a role for this gene, it seems strange to have concentrated so much subsequent work on this gene alone.

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 have no competing interests.