Reviewer's report

Title: Lymphotoxin-alpha polymorphisms and prevalence of whole cancer: a study in 1,536 consecutive autopsy cases

Version: 1 Date: 18 February 2008

Reviewer: Marc J. Gunter

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consecutive autopsy cases

Takei et al.

This manuscript describes a study of the association of 2 non-synonymous SNPs in LTA, a gene that encodes a pro-inflammatory cytokine with anti-tumorigenic activity, with cancer prevalence in a Japanese hospital-based investigation of 1,536 individuals. Both SNPs were associated with overall cancer prevalence, albeit the association was restricted to male patients. The SNPs were specifically associated with prevalence of lung and gastric cancers. Both SNPs have been related to functional changes in LTA activity and the authors conclude that LTA may play a functional role in tumorigenesis.

Overall the study has several strengths including a large sample size and a focus on SNPs with significant minor allele prevalence, that give rise to changes in LTA activity, thus enhancing the biologic plausibility of the findings.

However the study has a number of deficiencies that limit enthusiasm. The LTA gene lies adjacent to TNF, another pro-inflammatory cytokine that also has anti-tumor activity and several SNPs in TNF have been associated with various malignancies (refs). There is a high degree of linkage disequilibrium across the LTA-TNF gene region and it has been suggested that these 2 loci be analyzed together in cancer association studies (as many other studies have done). The associations observed for LTA SNPs in this investigation may reflect the effect of variants in TNF, thus a more comprehensive assessment of the entire TNF-LTA region would be desirable. In any case, the authors should address this point in the discussion as a possible limitation.

The authors should also discuss any potential bias that may arise as a result of the study design-specifically the use of autopsy patients. This is really a study of cancer-related death versus non-cancer-related death, and not cancer prevalence-this needs to be highlighted in the manuscript.

Specific points

1. The patient recruitment criteria are not clearly described. What was the definition of "elderly" for this study? Were the 1,536 subjects all the deaths/autopsy patients that arose during the period 1995-2004? The eligibility criteria and definition of study population need to be more explicitly described.
2. What proportion of samples were re-genotyped? (Last sentence, para 1, p.5) Were the re-genotyped specimens part of a quality assurance procedure?

3. Page 7, third paragraph, the authors mention haplotype data but there is no description of haplotype estimation methods or how they reconstructed haplotypes from the genotype data.

4. Please insert P-trend values for the genotype data.

5. The manuscript requires significant editorial work to sharpen the language.

Recommendations:
- Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest
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- An article of importance in its field

Quality of written English
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- Not suitable for publication unless extensively edited

Statistical review
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- No, the manuscript does not need to be seen by a statistician.