Reviewer's report

Title: Single nucleotide polymorphisms in the APC genes of Taiwanese subjects and colorectal cancer risk: a case-control study

Version: 2 Date: 23 January 2006

Reviewer: Gregory Tranah

Reviewer's report:

General

The manuscript 'Single nucleotide polymorphisms in the APC genes of Taiwanese subjects and colorectal cancer risk: a case-control study' by Shee-Ping SPC Chen, Shih-Tzu STT Tsai, Yen-Lun YLH Huang, Yu-Chen YCC Chao, Shinn-Zong SZL Lin and Horng-Jyh HJH Harn is a well-written and worthwhile manuscript. The study presents some interesting and novel information and once the two major issues are addressed the manuscript should be acceptable for publication.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1) Several clarifications need to be provided regarding the colorectal cancer cases and controls:

a) Please describe the exam used to screen for colorectal tumors (colonoscopy, sigmoidoscopy).

b) Were the controls also screened? This is not clear.

c) Please list the location of the tumors when reporting mutations (proximal, distal, rectal).

d) Is there any information on tumor grade (Duke's stage)?

2) The logistic regression analysis is not acceptable as it is currently presented.

a) In the methods section please describe your logistic regression analyses - were there matching factors (age, gender?) and were any additional variables adjusted for in the model (smoking, BMI, etc.)? The sample size is probably too small to adjust for many covariates but adjusting for gender and age (~5 year groups) should be tolerable.

b) In the results and in Table 2 please report the ORs for all genotypes relative to the wild-type/common genotype. It is more informative to see the ORs for each genotype even if the rare allele prevalence requires collapsing heterozygotes and homozygous variant genotypes into a single category. Knowing the number of cases and controls would also be helpful for interpreting the ORs and this information could be moved to Table 2 from Table 1.

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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)

1) In two places within the discussion the authors mention that a particular mutation may alter function of APC without giving a reference. Are the authors suggesting this or are there studies that
demonstrate functionality of the mutations in question? The authors should be more cautious when suggesting that a particular mutation is functional if there are no studies to support these claims.

a) page 10, second paragraph - "Such substitutions may result in disruption of the putative cell signaling function of the APC protein".

b) page 11, second paragraph - "...B-catenin binding repeat (amino acids 1840-1866) and may disrupt the function of the APC gene product".

If these statements do not have a reference then the author's should revise these comments by adding, "...; however, this needs to be demonstrated experimentally".

2) In the discussion, the authors refer to two papers (Slattery et al. 2001 and Tranah et al. 2005) suggesting that each of these studies report genetic modification (gene*environment interaction) between the APC D1822V polymorphism and dietary fat intake. Slattery et al. did report a significant interaction between fat intake and the APC D1822V polymorphism; however, this was not replicated in the Tranah et al. study. One major difference between the studies was the retrospective ascertainment of diet in the Slattery et al. study and the prospective ascertainment of diet in the Tranah et al. study, suggesting that the Slattery et al. is potentially more prone to recall bias. This needs to be clarified in the discussion.

Also, Tranah et al. observed a significant interaction between the APC D1822V polymorphism and postmenopausal hormone use.

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

I declare that I have no competing interests