Reviewer's report

**Title:** A functional polymorphism in the DNA methyltransferase 3A promoter modifies the susceptibility in gastric cancer but not in esophageal carcinoma

**Version:** 2  **Date:** 4 December 2009

**Reviewer:** Yae Kanai

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Fan et al. showed increased promoter activity of the -448 A allele of the DNMT3A gene in vitro. The allele frequency of -448A among gastric cancer patients and controls was 32.9% and 19.9%, respectively. AA homozygotes show a >6-fold increased susceptibility in gastric cancers but not in esophageal cancers. The authors concluded that -448A is a marker to predict and individual susceptibility to gastric cancers.

Although this manuscript potentially contains significant and original findings, there are some points which should be further clarified.

1. AG heterozygotes did not show significant increase of the risk of gastric cancers in Table 3. Therefore, one cannot conclude that “AA+AG” is a potential SNP to evaluate the susceptibility even though the p value is 0.001 (Table 3) due to the strong impact of AA homozygotes. Therefore, description about the significance of AG heterozygotes should be toned down or omitted.

2. The luciferase assay revealed that the promoter activity of the -448 A allele is about twice that of the G allele. The authors should discuss whether the only 2-fold overexpression of DNMT3A may result in alterations of expression levels of tumor-related genes and potentially participate in carcinogenesis or not. In addition, the authors should discuss the reason why the same 2-fold overexpression of DNMT3A does not have impact on esophageal carcinogenesis.

3. The author described that they examined immunohistochemically DNMT3A expression in paraffin sections of gastric cancers (data not shown). Such data should be included in the Methods and Results sections and shown as an appropriate photo. The correlation between DNMT3A expression and AA homozygotes should be examined in gastric and esophageal cancer patients.

4. The authors should mention the informed consent and approval of institutional review board.

**Which journal?:** Appropriate or potentially appropriate for BMC Medicine: an article of importance in its field
What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Quality of written English: Needs some language corrections before being published

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.