Reviewer's report

Title: GSTM1 and APE1 genotypes affect arsenic-induced oxidative stress: a repeated measures study

Version: 1 Date: 1 October 2007

Reviewer: Kenneth Cantor

Reviewer's report:

General

This paper shows a significant association between urinary arsenic levels and levels of urinary 8-OHdG among GSTM1-null subjects in a cross-sectional study of 97 Bangladeshi women exposed to arsenic in drinking water. A negative association of urinary 8-OHdG with a specific APE1 SNP is also described. The manuscript is generally well written and many, but not all, items needing further attention are editorial in nature. Comments, relating to both major and minor issues, follow:

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

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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)

Abstract:

- results for APE1 and GSTM1 genotypes are liberally spread through the ‘results’ section of the abstract. However, there is no mention of genotyping in ‘methods’. A brief sentence or two about genotyping is needed in the ‘methods’ section, including mention of the specific genes that were evaluated.
- Terms for which the authors use abbreviations (eg. TUA, APE1, GSTM1) should be spelled out the first time they appear. This applies separately to the abstract and in the body of the paper.

Methods:

- More clarity is required in describing how many samples were collected from each woman, etc. For example, on top, p.7, we read “the cohort was restricted to women who provided at least one urine sample from … … .” and that ‘This restriction yielded 97 women and 290 urine samples for analysis.” Later on p. 7: “… … urine samples were collected … on three consecutive days and stored … ….” Does this mean that 3 samples were collected from each of the 97 women in the study (and that one was lost or otherwise inappropriate for analysis (3 x 97 = 291)) ? This needs to be spelled out more fully.
- with no further information available, it seems that conducting five replicate
analyses of each toenail sample was excessive. Why was this done?

Results:
- Bot. of first parag: “The adjusted within-person … was 0.51.” Is this a correlation coefficient? How was this done with three measurements for each subject?
- P.12 (and later, in discussion). The authors use the term ‘wildtype’ in at least two places here and later in the manuscript (discussion & Table 5). I suggest that this term not be used, here or elsewhere in the paper, and that the specific form of the gene in question be described in lieu of ‘wildtype’.
- P. 12. Typo on line 7. Probably should be CI=0.33.
- P. 12. In the ‘methods’ section (p.10), it is mentioned that an interaction term was included in models to test for effect modification of the association between arsenic and 8-OHdG by polymorphisms in GSTM1, APE1, and hOGG1 … … . A statistical measure, such as the p for interaction, should be reported in the results section, especially in the case of GSTM1.
- p.12. While the regression coefficients for logged 8-OHdG levels are elevated among GSTM1-null respondents with TUA above 13.5 µg/L, there is no apparent increase in 8-OHdG with increasing TUA level. i.e., the response plateaus at relatively modest levels of exposure. This should be explicitly mentioned in the results section, and possible reasons for this raised in the discussion. In addition, this raises the issue as to whether the authors looked at the top 10th or 15th percentile of TUA (or, for example, among persons with TUA >200 or 300 µg/L) to see if an incremental increase in logged 8-OHdG could be detected among subjects with extreme levels of TUA.

Discussion:
- p.14. line 4. The authors use the term ‘gene-environment’ interaction here and elsewhere. I recommend that this term not be used, and that the specific interaction be referenced. For example, in this case, the sentence could read “… powered to detect an interaction of 8-OHdG level with GSTM1 genotype”.

Discretionary Revisions (which the author can choose to ignore)
Discussion:
- p.13. The authors cite literature reports showing that the proportion of MMA is elevated among women with a null genotype (ref 33). Was this also observed in these data? Will this be the topic of another paper from this database?

What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable
**Statistical review:** No, the manuscript does not need to be seen by a statistician.