Title: Similar effects of active and passive maternal tobacco smoke exposure on in utero mutagenesis at the HPRT locus

Authors:
Stephen G Grant (sgg@pitt.edu)

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Author's response to reviews: see over
We thank the reviewer’s for their time and efforts. Responses to specific points raised by each reviewer are given below.

Dr. Husgafvel-Puriainen:

Minor essential revisions

1) the suggested reference has been added to the text, and is now cited several times in the introduction

2a) a sentence addressing the potential limitations of the data has been added to the discussion

2b) references to the induction of VDJ recombination-related deletions in the \textit{HPRT} gene by environmental pesticide exposure and chemotherapy regimen including the topoisomerase inhibitor etoposide have been added to the discussion

Dr. Bofettha:

Major compulsory revisions

1a) the differences in the mutation frequencies of the exposed populations were noted in Manchester et al. [21] and attributed to the overall lower socioeconomic status of the Colorado population, although nothing was proven. This comment has been added to the initial comparison of the two populations.

1b) quantitative exposure was measured in both studies, but by different methods (estimated pack-years in the Colorado study, cotinine levels in the Vermont study), making it hard to compare between the two. However, \textit{HPRT} M_{f} was not significantly associated with these dose measurements in either study (from their own analysis and my re-analysis).

2) done.

3) we were collaborators on the Manchester et al study and were provided with the raw data from the McGinniss et al study for comparison. The raw data on these studies used for analysis in the present paper are not necessarily available in the published papers but could be reconstructed (i.e. modeled) from what has been published. The data from the papers of Finnette et al. are reconstructed from the data presented in these papers, which fortunately included individual \textit{HPRT} measurements. We have not found a good way to describe this in the manuscript other than to thank the Finette group for publishing their results in such a way as to allow for this re-analysis.

Minor essential revisions
4) “at the HPRT locus” has been added to the title, and to be sure the point is not lost, a sentence emphasizing that these data have been obtained at a single locus has been added to the discussion.

5) paragraph 1 of the background section attempts to clarify the position of reporter gene mutagenesis in the molecular epidemiological model, stating it is clearly a function of both exposure and susceptibility and, if anything, somewhat closer to disease outcome than initial exposure. Since this report deals only with the re-interpretation of HPRT data, it may convey the impression of “over-interpretation”.