Reviewer's report

Title: Maternal iron metabolism gene variants modify umbilical cord blood lead levels by gene-environment interaction: a birth cohort study

Version: 1 Date: 6 May 2014

Reviewer: Joseph H Graziano

Reviewer's report:

Comments for the Authors: This is a beautifully written manuscript that is a pleasure to read. The question posed by the investigators is very straightforward and implied in the title, i.e., do variants in several genes involved in iron metabolism alter the transfer of lead (Pb) from mother to the fetus during pregnancy. The findings are conceivably important in Pb exposed populations, though they are not particularly of “clinical concern” in this particular study population, whose blood Pb (BPb) levels are remarkably low (mean maternal and cord BPbs < 1 ug/dL), particularly given the environmental legacy of the Tar Creek mining activities. This does not detract from the fundamental findings concerning hemochromatosis gene variants and Pb transfer to the fetus. All of my comments represent minor revisions:

1. The description of the study population and methodologies are fine, as is the approach to the statistical analyses. I found the first two paragraphs under “Potential Confounders” (page 8) to be somewhat unnecessary as it seems to me quite obvious that SES parameters would not influence the biological processes concerning maternal-fetal Pb transport. Indeed they did not when probed in sensitivity analyses in this paper. They could be deleted.

2. With regard to the results, the observation that maternal blood Pb (MBL) and umbilical cord blood Pb (UCBL) are strongly associated is not novel, and has been observed in many other study populations, a point which should be mentioned in the discussion.

3. However, the finding that infants born to women with the hemachromatosis HFE C282Y gene variant have lower UCBLs is completely novel. The first paragraph of the discussion (page 13) ends by saying that this observation is “…both statistically and clinically significant.” I find this conclusion to be a bit strong (particularly in this population) and suggest that it be modified to indicate that it is “…potentially clinically significant in exposed populations.” To their credit, the authors do mention (in the limitations section) that the low range of BPbs in this population may limit the generalizability of the observations.

4. Page 5, line 76, should read: “…iron transport [16], while…

5. Page 7, line 141: Define “…TE buffer…”

6. Page 9, line 172, should read: “…were available: serum ferritin…”
7. Page 15, lines 309-310, should read: “…proteins and thereby lessen gastrointestinal lead absorption.”

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

No competing interests