Reviewer’s report

Title: Genome-wide Gene by Lead Exposure Interaction Analysis Identifies UNC5D as a Candidate Gene for Neurodevelopment

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Reviewer: Pam Factor-Litvak

Reviewer's report:

This interesting paper assesses the associations between lead and the mental and performance scores on the Bayley Scales of Infant Development in the context of a genome wide interaction analysis. The investigators use data from two studies - one in Mexico City and one in Bangladesh - which used similar methods to collect data. Using the cohort data, the find a possible interactive association between prenatal Pb exposure and one gene (2 SNPs) and child development, however, the direction of the interaction is not in the expected direction. The authors explain this finding by drawing on hypotheses regarding the possible 'protective' pathway whereby Pb may protect against the neurological harmful expression of the gene. Here, it would be interesting if the investigators could give examples of other such associations. Further, the authors perform in vitro work using neurological stem cells to find genetic variants possibly associated with child neurodevelopment and influenced by prenatal Pb exposure.

In all, this is a very interesting paper which provides both in vivo and in vitro examples of the difficulty of performing GWIS. I have some specific comments:

1. Please provide age adjusted scores for the Bayley in table 1 so comparisons between cohorts are facilitated.

2. Please address the seemingly lack of a main Pb effect for both MDI and PDI in table 4. This is in direct contradiction to the bulk of the literature relating Pb to both mental and motor performance. Do the investigators think that this lack of association may in part be due to the relatively high levels of arsenic in this population?

3. Related to the point above, contrary to what the authors state, my read of table 4 is that the estimated betas for the SNPs, Pb and the interaction differ in the two cohorts. Is that true, are the estimated betas statistically the same or different?

4. Several key covariates for child development do not seem to be controlled, namely maternal IQ and HOME score. Did these not matter, i.e. did they not change the estimated beta by some predetermined value?
5. Would the investigators please comment on the limitations of not having a discovery and a confirmatory data set? In light of this, how should the results be interpreted?

6. In the in vitro portion of the study, it does not appear that the UNC5D gene was identified in any of the key pathways. Would the investigators please comment on this?

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