Reviewer’s report

Title: Fetal ERAP2 variation is associated with preeclampsia in African Americans in a case-control study

Version: 1 Date: 26 February 2011

Reviewer: Matthew Peter Johnson

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The manuscript “Fetal ERAP2 variation is associated with preeclampsia in African Americans in a case-control study” by Hill et al. is a hypothesis driven genetic association study that lends support to the potential role of the ERAP2 gene in preeclampsia genetic susceptibility, now in a third ethnic cohort. The fact that there are both maternal and fetal (paternal) contributions to preeclampsia pathogenesis, additional studies from within the field will be needed determine whether the ERAP2 gene has a role in either the maternal or fetal, or both the maternal and fetal genetic contributions to preeclampsia susceptibility. This study’s rationale is sound and its results warrant addition to the literature, with minor revision.

Major Compulsory Revisions

None

Minor Essential Revisions

ABSTRACT: Conclusions

“…this gene in a New Zealand population…” needs to be changed to read “…this gene in an Australian/New Zealand population…”

RESULTS: African American Population

Was the genetic similarity assessment between the Pennsylvania and Michigan African American cohorts formally tested or were the minor allele frequencies “eyeballed” prior to the decision to merge the two cohorts? Between the Pennsylvania and Michigan cohorts, do the ERAP2 minor allele frequency differences of ~3% and ~3.8% in the maternal and fetal groups, respectively, constitute enough of a difference to potentially stratify the association results? If formal statistical tests were performed to assess these differences, then they should be included in the manuscript.

DISCUSSION: 6th paragraph

“While the Johnson et al. reports a maternal association, they did not include fetal samples in their study, and thus cannot rule out that the observed association was driven by fetal genes that were shared with the mother.”

This reviewer acknowledges the plausibility about shared genetic components between the mother and fetus and their contribution to preeclampsia
susceptibility. However, in stating the highlighted sentence (above) the authors need to be aware of, and make the reader aware of, ERAP2 residing within a region of known genetic linkage for maternal preeclampsia susceptibility (Johnson et al. Molecular Human Reproduction 2007). The study design in the Johnson 2007 article interrogated maternal preeclampsia susceptibility in a sub-set of families that were used in the Johnson 2009 article. Therefore, there is good evidence that ERAP2 may contribute to both the maternal and fetal genetic components of preeclampsia susceptibility. Given the heterogenic nature of preeclampsia, ERAP2 may very well have independent effects primarily towards the maternal and fetal components in the Australian/New Zealand and African American cohorts, respectively.

CONCLUSIONS
The rs2549782 association with maternal preeclampsia risk was specific to the Australian/New Zealand population and not the Norwegian population. An association of maternal preeclampsia risk in the Norwegian population was specific to the rs17408150 SNP. Therefore, the third sentence needs to be changed accordingly.

Discretionary Revisions
None

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

**Quality of written English:** Acceptable

**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.