Reviewer's report

Title: Non-Replication Study of a Genome-Wide Association Study for Hypertension and Blood Pressure in African Americans

Version: 2 Date: 23 January 2012

Reviewer: Adebowale Adeyemo

Reviewer's report:

This revision of the earlier manuscript has provided more information that permits better evaluation of the manuscript. The text has been revised in response to the previous comments and is much clearer than the previous version. However, there are still a couple of major issues which need to be addressed.

1. In reading the text, it is uncertain which p-values are presented in the tables and/or in the Results/Discussion. Is it a test of difference between cases and controls in genotype frequencies? Or the one way ANOVA (described in the methods)? Or the multiple regression analysis? Or the genetic association model done with PLINK with case-control comparisons/qtl analysis? This needs to be clarified. Most papers reporting association present a "definitive" model (e.g. association of the phenotype with each SNP under an additive model, adjusting for age, gender, BMI...) and then deal with other considerations (e.g. adding or dropping a covariate, multiple testing) arising from that reference point. This facilitates the presentation of the results and the discussion, as well as helps the reader to follow the story. The current manuscript has several tables (Tables 2, 4 and 5) each with with over 90 rows, as well as p-values in each table that seem to represent basic analysis (e.g. differences in frequency between cases and controls) rather than what the authors consider the definitive model. I would suggest:

(a) presenting a table of the definitive model for each of phenotype (HTN, SBP, DBP) that is run in PLINK under an additive genetic model and and adjusting for age, gender, BMI and creatinine. The table would look like the current Table 3 but would have only one row per SNP and the beta would have the SE included. Relevant points arising from these (e.g. a better p value under another model) can be discussed in the text.

(b) moving Tables 2, 4 and 5 to supplementary material.

2. The explicit aim of the study was to attempt to replicate the findings of the first GWAS of hypertension and blood pressure in African Americans (Adeyemo et al 2009). However, the text does not directly compare and contrast the two studies, except for values. At least two important differences between the studies ought to be discussed: (a) The allele frequencies for the five genome wide significant loci differ considerably (~ 2 to 9 fold)between the two studies (supplementary table) - CACNA1H (0.015 vs 0.109), IPO7 (0.013 vs 0.123), YWHAZ (0.012 vs 0.113), SLC24A4 (0.067 vs 0.178), PMS1 (0.352 vs 0.148). This means that the
two study populations show considerable genetic differences at the markers of primary interest. (b) The two studies did not use the same association model because the present study could not adjust for admixture proportions (and indeed, apparently has no markers to do so). This is in contrast to the GWAS that used genome wide markers to compute PCs and used these in the association model. Given the role of admixture in a mixed ethnic group such as African Americans, this is an important difference.

Minor point

1. The title can be rephrased slightly differently for better flow, e.g. "Non-replication of a genome-wide association study for hypertension and blood pressure in African Americans."

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

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests as listed above.
I am the first author of the study this paper is attempting to replicate.