Reviewer's report

**Title:** Genetic Variation of NEDD4L Is Associated with Essential Hypertension in Female Kazakh General Population

**Version:** 1  **Date:** 24 August 2009

**Reviewer:** Amy I Lynch

**Reviewer's report:**

Major compulsory revisions: none

Minor essential revisions: none

Discretionary revisions:

1) The authors provide a mechanism that possibly explains the gender-specific findings, but it would also be appropriate to include in the discussion whether any previously published reports have found gender-specific effects of gene variants in general (and the gene variants reported in this manuscript in particular) on blood pressure traits, particularly significant gene-by-gender interactions. It would lend support to their findings.

2) I did not see data for a statistical test of the gene-by-gender interaction in the results section. It would seem that to conclude there is a difference between men and women with respect to the effect of the genetic variants on hypertension one would need to test for an interaction.

3) There is a striking difference between men and women for self-reported smoking status in this study population - over 50% of men and only about 1% of women report being smokers according to Table 2. It would be interesting to know whether the apparent gene-by-gender interaction is only a proxy for an underlying gene-by-smoking interaction — there is some prior work on gene-by-smoking interactions; for example the NHLBI Family Heart Study has reported on a genotype-by-smoking interaction on calcified coronary atherosclerosis. The authors could try stratifying the data by smoking status rather than gender to see if differences are observed. They could also perform a statistical test of the gene-by-smoking interaction and compare it to a statistical test of the gene-by-gender interaction to see which is stronger.

4) Table 3 would be improved if column percentages were added to the allele frequency data.

**Level of interest:** An article of importance in its field

**Quality of written English:** Not suitable for publication unless extensively edited

**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.