Author's response to reviews

Title: A comprehensive analysis of common genetic variation in prolactin (PRL) and PRL receptor (PRLR) genes in relation to plasma prolactin levels and breast cancer risk: the Multiethnic Cohort

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Author's response to reviews: see over
Response to Reviewer Comments

Reviewer#1:

The authors have done an excellent job in revising their manuscript ‘A comprehensive analysis of common genetic variation in prolactin (PRL) and PRL receptor (PRLR) genes in relation to plasma prolactin levels and breast cancer risk: The Multiethnic Cohort’.

We thank the reviewer for the positive comments regarding the previous revision. We appreciate the detailed comments, providing us the opportunity to strengthen the paper.

Major Compulsory Revisions

None

Minor Compulsory Revisions

1) I just would like to see one addition/correction/clarification on the paragraph starting on p.7, where the authors describe the effects of four SNPs (for which the Illumina assay was not working) on haplotype analysis. If I understood correctly, due to the inability to analyze the SNPs one cannot distinguish between the haplotypes 1A1, 1A2 and 1A3, which were rather common in LA (16.9%, 6.4%, and 6.6%), and 1A1 and 1A2 in NH and WH (17.2% and 4.5% in NH and 34.6% and 5.9% in WH) and 1A1 and 1A3 in AA (9.2% and 2.2%); NOT ‘between two common haplotypes in AA and LA’, as the authors write on the last line on p.7. Additionally, I’m not quite sure, why the authors have left the haplotypes 1G and 1H out from supplemental table 11.

We thank the reviewer for pointing out this detail on page 7. Without the four SNPs, we are unable to distinguish between haplotypes 1A1, 1A2, and 1A3 in AA, NH, LA, and WH. We have now corrected the statement to read “This resulted in the inability to distinguish between haplotypes 1A1, 1A2, and 1A3 in LA (minor allele frequency 16.9%, 6.4%, and 6.6%), between haplotypes 1A1 and 1A3 in AA (9.2% and 2.2%), and between 1A1 and 1A2 in NH (17.2% and 4.5%) and in WH (34.6% and 5.9%)” (page 7, last paragraph).

Regarding the reviewer’s second comment about haplotypes 1G and 1H: the original MEC panel included 70 individuals in each racial/ethnic group, whereas the case-control panel included approximately 400 to 800 individuals (number of cases and controls by racial/ethnic group: 345/426 AA, 109/290 NH, 425/420 JA, 335/386 LA, 401/440 WH). There were small differences in haplotype frequencies between the MEC panel and case-control, and therefore, we decided to only show those haplotypes ≥ 5% in cases or controls in Supplemental Tables 10 and 11. Thus, haplotypes 1G and 1H are not shown in Supplemental Table 11 since these two haplotypes were not common in the case-control panel. For haplotype 1G, the haplotype frequencies in cases and controls, respectively, are AA (1.38/0.55), NH (1.09/1.07), JA (3.61/2.96), LA (1.76/1.73) and WH (0.98/0.63). For haplotype 1H, the haplotype
frequencies are AA (0.23/0.30), NH (1.03/0.21), JA (1.53/1.48), LA (4.49/3.70), and WH (0.67/0.15).

We have now included a sentence “Therefore, only haplotypes with ≥ 5% frequency in cases or controls, per each racial/ethnic group, are shown in Supplemental Tables 10 and 11” (page 8, first paragraph).

In addition, we have added edited the legends for Supplemental Tables 10 and 11 to read “Associations between common . . . haplotypes and breast cancer risk,” to clarify that only haplotypes ≥ 5% in the case-control panel are shown (page 31).