Reviewer's report

Title: Carboxypeptidase 4 gene variants and early-onset intermediate-to-high risk prostate cancer

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Reviewer: Jennifer Beebe-Dimmer

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Carboxypeptidase 4 gene variants and early-onset intermediate-to-high risk prostate cancer

This is a well-written and organized manuscript examining the contribution of variants in a gene suspected to function in prostate cancer progression and therefore predictive of aggressive disease. This paper is illustrative of the direction taken by most researchers in the field of prostate cancer genetics. Despite evidence of a strong heritable component, localizing regions of the genome associated with increased susceptibility has been difficult to reproduce between studies in part because prostate cancer is a clinically heterogeneous disease. Creating a more homogenous case sample and focusing on men with clinically meaningful disease may provide us with new insight. The case-control study estimates the relative risk associated with 6 SNPs in the CPA4 gene in a sample of 1012 prostate cancer cases and controls and finds that homozygotes for the variant allele in SNP (rs2171492) associates with “aggressive disease” in men with early onset disease.

Given that the hypothesis is that CPA4 may enhance progression of disease, it would be worthwhile to examine the associations with a polychotomous outcome. In other words, examine the genotype frequency in SNPs comparing each group (high-risk, intermediate-risk) to the control group. If the hypothesis holds true, we would expect to see a higher frequency of the “TT” genotype among high-risk cases. Despite sample size constraints, this would be worthwhile to explore.

SNP selection was based on a strategy of selected those with a MAF of > 5% in the HapMap database in the EA (Caucasian) sample. Was the expression of selected SNPs different in the African American sample? It would be worthwhile to comment given AA men comprise 18% of the study sample. Were any of the SNPs in LD with one another? Again, would be worthwhile to comment.

Table 4 should be included within the manuscript and not appended as a supplement as the major findings of the paper are reported in the table. If need be, Table 3 and Table 4 could be combined into a single table. It is unnecessary to report both CIs and p-values, so p-values can be omitted.

Minor note: ‘Carboxypeptidase’ is misspelled in the TITLE and the first sentence of the abstract as well as ‘metallocarboxypeptidase’ (attention to detail).
**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.