Reviewer's report

Title: The 4q27 locus and familial prostate cancer risk

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Reviewer's comments

Title: The 4q27 locus and familial prostate cancer risk.

# It is not clear whether this study is focused on familial or sporadic prostate cancer (PCa). The subject recruitment part did not clearly state about this, but only mentioned that family history of PCa were collected. In addition, the authors stated that “relatively small number of men with a family history of PCa in our study”. So it looks like the study design was to assess the association between genetic variations and the risk of all PCa (sporadic and familial). That is, it is inappropriate to use familiar PCa in the title just because the only significant finding in this study was observed in men with family history.

# In Background, 2nd paragraph, the authors stated “Although the etiology of the inflammatory milieu is yet to be determined, …”, which is not true. There are abundant papers about inflammation responses in PCa recently. The authors should perform a through search before starting this work.

# In background and discussions, the authors stated “extensive linkage disequilibrium within 4q27 has hindered efforts to identify the true causal variants”, which is not true. The common disease/common variants hypothesis clearly tell us that the high LD is actually indirectly facilitate us to establish the association between genetic variations and the risk of PCa through LD between causal SNPs and non-causal SNPs.

# This study population included 23 Asians, to prevent population stratification, the authors should state how the difference the results were when they included only Caucasians and total population.

# The author should include whether this study has been approved by IRB in the Method part.

# The selection of the genetic variants was totally based on previous study, which could not represent sufficient genetic information of each gene. In addition, this has limited the ability of performing haplotype analysis in this study. For future study, it is better to perform a systematic selection of SNPs instead of merely replicate the significant SNPs from previous studies since different SNPs may be associated with the outcome of interest in different populations, even though the population are Caucasians.
# In Method part, the authors did not state why rs2069762 was genotyped by two different platforms, Sequenom and Taqman.

# Lack of a table illustrates the demographic information of the study population, which is important for the readers to understand the distribution of the study population in term of potential risk factors.

# In statistical analysis, it is not clear what the difference between the following statements. The authors should rewrite the sentences to clarify the purpose of each analysis to prevent confusion. “Polytomous logistic regression models were used to estimate odds ratios (OR) by tumor stage (stage I-II and stage III-IV tumors) and grade (moderate grade and high grade tumors). Tests for association between genotypes and case-control status were performed under dominant, recessive, co-dominant, and per allele models.” and “Heterogeneity in the ORs by tumor stage (stage I-II (0) and stage III-IV (1)) and grade (moderate-grade (0) and high-grade (1)) were tested using polytomous logistic regression models.”

# It is highly possible that the null findings in this study is a result of inappropriate selection of SNPs. For example, “In this study we selected variants that were most strongly associated with autoimmune disease susceptibility and are the first, to our knowledge to investigate variants within the IL-21 gene region for prostate cancer risk.” The SNP selected may be strongly associated with autoimmune disease but not with PCa, so the link of these two by merely inflammation response is too weak.

# It is not true that “Although prostate cancer GWAS have thus far failed to implicate the 4q27 region as a candidate risk locus, the complex and heterogeneous nature of prostate cancer may suggest that multiple, low to moderate risk alleles (possibly not identified by GWAS) will be implemented in the disease.” The SNPs identified by GWAS tend to have OR between 0.67 to 1.50, which are definitely not strongly associated with the outcome. The authors may need to update their genetic knowledge before performing this type of study.

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

**Quality of written English:** Needs some language corrections before being published

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

**Declaration of competing interests:**

I declare that I have no competing interests.