Reviewer's report

Title: HNF1B polymorphism in endometrial cancer patients: effects on overall survival

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Reviewer: Jeremy Squire

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HNF1B is a member of the homeodomain-containing superfamily of transcription factors. The protein has been shown to function in nephron development, and regulates development of the embryonic pancreas. Mutations in the HNF1B gene are associated with a spectrum of human diseases including diabetes, renal cysts, and diseases of the pancreas, liver and genital tract. Thus it is likely that HNF1B has a role in the development and function of these respective organs. More recently, genome-wide association studies have linked DNA sequence variants of HNF1B to both an increased risk of prostate cancer, and a protective effect against type 2 diabetes. These recent reports further define the wide ranging role of HNF1B in human health and disease.

This study is the first to examine the prognostic impact of the rs4430796 germline DNA variants in endometrial cancer (EC). It is therefore important because of this and the recent GWAS studies in ovarian cancer drawing attention to HNF1B variants.

There are some major points that must be addressed before this study can be published:

1. There is virtually no consideration of the biology of the rs4430796 SNP on HNF1B transcription factor function and how the GG allele may be mechanistically involved in poor outcome. The authors should provide more background about how variations of this protein might be associated with poor outcome in EC.

2. The proposed interaction (page 10) of the genotypes in the post-surgical radio-chemotherapy subjects is confusingly presented and also lacks a biological mechanism. Presumably some role for DNA repair related to advantage of one isoform over the other is involved? The reader needs some guidance to understand what model is being proposed and whether it makes biological and clinical sense.

3. There is a real risk with such a small sample size that there is marked bias in the distribution of the GG genotypes that has led to false conclusions in this particular study group. The authors should better justify why this first study is representative and not going to cause others to embark on fruitless validation studies.
4. How would the biology of HNFIB likely relate to established pathways in EC such as AKT and ARID1A? If there are no established links there are likely informatics approaches that could be used to demonstrate a putative relationship. Such data may add to the argument that this protein could impact the molecular oncology of EC profoundly.

**Level of interest:** An article of limited interest

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

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests