Reviewer's report

Title: Androgen-regulation of the protein tyrosine phosphatase PTPRR activates ERK1/2 signalling in prostate cancer cells

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Reviewer: Michael Ladomery

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Summary:

The role of androgens in driving prostate cancer is well established, but much still remains to be done in terms of understanding exactly how this occurs. This study starts with a genome-wide study aimed at identifying novel androgen-regulated genes. The study then wisely focuses on a single gene, PTPRR, which appears to be downregulated by androgen. Its regulation by AR is convincingly demonstrated in a range of appropriate PCa cell lines. PTPRR is also shown to be involved in the regulation of the RAS/ERK1/2 pathway - a highly significant finding.

Major Essential Revisions:

1. Ideally some transcription assays should have been included, for instance the dual luciferase/renilla assay using the PTPRR promoter, and with the putative AR binding sites mutated as well. I feel that this type of additional experiment would make it unequivocally clear that PTPRR is a direct (as opposed to indirect) AR target.

2. I am very persuaded by the cell line work - it is robust and several controls and derivative cell lines are used. What convinces me less is the analysis done on a very small patient cohort. N=7 is simply too small to be able to draw any conclusions. I totally appreciate the practicalities of looking at larger cohorts and the genetic heterogeneity and complexity of PCa cases, but as it stands Fig 4B really doesn't add enough to the paper. So it would be great if this aspect of the work could be enhanced significantly. Also pertinent to the focus of the paper, would it be possible to include some kind of AR status in the clinical samples. Alternatively, perhaps some mouse xenograft work could be carried out, eg orthotopic injection of cell lines in which PTPRR expression is manipulated.

Minor Essential Revisions:

1. A very minor point, but can the first results paragraph make it clear that the data presented in Figure 1 relates to LNCaP cells.

2. In regards to Sup Fig 2, p.5 "binding sites were identified close to the PTPRR gene" - the word close is not very clear (how close?). Could you also illustrate the exact sequences that could be bound by AR; and provide a scale on this Figure.
3. Fig3A, I note there is some baseline expression of PTPRR in the control. I wonder what might happen with siRNA mediated knockdown of PTPRR, might pERK1/2 levels rise? this simple assay could lend additional weight to the conclusions.

4. Space permitting, I wonder whether a figure that illustrates PTPRR structure (gene and protein) might be of interest to the readership (many of whom are likely to be unfamiliar with it).

5. Could the discussion include (if known) information about normal tissue expression and developmental roles (if known) of PTPRR, and also if it is alternatively spliced. (On the latter point, I notice a 2004 study on murine Ptprr that describes several splice variants: PMID: 15461663).

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

**Quality of written English:** Acceptable

**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 interest