Reviewer's report

Title: Large effects on body mass index and insulin resistance of fat mass and obesity associated gene (FTO) variants in patients with polycystic ovary syndrome (PCOS): a case control study

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Reviewer: Thomas Barber

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The manuscript by Tan et al. is well-written and covers an important topic. The association between obesity and insulin resistance with PCOS and the genetic factors involved are very relevant to the aetiology of PCOS. This case-control study includes a respectable number of PCOS cases and controls and, as demonstrated by the authors, appears to be adequately powered. This reviewer has a few comments to make as detailed below:

- Major Compulsory Revisions

1. My main concern relates to the number of analyses performed in this study. The authors genotyped SNPs within four separate genes and performed numerous analyses on each one including correlations with various metabolic and endocrine phenotypes. Although there is mention of Bonferroni-adjustment in the methods, I feel that there could be more mention of this in the results section. Furthermore, the high number of analyses performed could be mentioned as a limitation of the study in the discussion section. It may be worth considering statistical review of the manuscript for this reason.

2. I do not fully agree with one of the conclusions that FTO variants may have a greater effect on BMI in women with PCOS than in the general population. I believe that there may be alternative explanations to this apparent finding that should be discussed further by the authors in their manuscript. The numbers of cases and controls in this study were disparate which would presumably have resulted in differences of power to detect effects on BMI between each of the groups. Furthermore, figure 1 demonstrates a larger distribution of BMI amongst the PCOS group than amongst the controls. These two factors may offer an alternative explanation to the apparent larger effect of FTO variants on BMI within the PCOS group than among controls. Only through studying a much larger population of PCOS cases would the true effect-size of FTO variants on BMI in this group become apparent.
3. In the methods section, it is stated that there are 386 PCOS cases, all of whom satisfied Rotterdam criteria. It would be useful to include the numbers of PCOS cases that satisfied all three criteria, and numbers of those that satisfied only two criteria. It is well-established that women who satisfy all three Rotterdam criteria are significantly more insulin-resistant than those women with polycystic ovaries who only have one of hyperandrogenism or oligo-amenorrhoea (see Barber et al. Clinical Endocrinology [2007], 66, 513-517). Therefore, in the context of a study that assesses the effects of gene variants on insulin resistance in PCOS, it would seem relevant to include details on Rotterdam phenotypic subgroups.

- Minor Essential Revisions

1. Abstract: it would be useful to give a mention of the control group.

2. Background, 1st paragraph, 3rd sentence: This sentence implies that the association of PCOS with obesity is secondary to the association of PCOS with insulin resistance, which is misleading. Rather, it should be made clear that there exists an association between PCOS and obesity, and between PCOS and insulin resistance. The relationships between these factors are not completely understood, but it is reasonable to postulate that insulin resistance in PCOS, at least in part results from the association of PCOS with obesity. There is also evidence that insulin resistance in PCOS plays an important role in its aetiology (through, for example effects of hyperinsulinaemia on ovarian steroidogenesis).

3. Results: From figure 1, it appears that data for BMI was available for the controls. Were any other phenotypic data available for the control group? It would be interesting to show analyses on the effects of genotype variants on BMI and other phenotypic variants. Results: I was surprised that the variant within TCF7L2 had an effect on BMI within the PCOS cases group. As the authors correctly state, the likely effect of variants within TCF7L2 on risk of T2D is through effects on the beta-cell. Would the authors like to speculate on a possible mechanism by which variants in TCF7L2 affect BMI in PCOS cases? Have any other previous studies demonstrated such an effect on BMI? Does a similar effect of TCF7L2 variants on BMI exist in the control group?

- Discretionary Revisions

None.

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

**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