Author's response to reviews

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)

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Author's response to reviews: see over
Second revision of the manuscript 1721762553281595 by Tan et al.

Dear Editor,

please find enclosed our revised manuscript 1721762553281595 titled ‘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)’ by Tan et al. for BMC Med Genetic.

We would like to thank you and the reviewers for the constructive review of our manuscript, and we appreciate the opportunity to submit a revised version of the paper. On the following pages we responded to each criticism and indicated the changes that we have made.

We thank you for re-considering our manuscript for publication in BMC Med Genetic.

Sincerely,

PD Dr. Anke Hinney

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Reviewer 3 (Margit Urbanek)

1. In table 3 are the p-values the nominal P-values or the corrected p-values?
   Table 3 shows nominal p-values; corrected p-values are provided in the text.

2. Some aspects of the power analysis needs to be clarified.
   a. What is meant by standardized additive genetic risk. Does it refer to genotype relative risk or % of relative risk explained by locus?
   b. The authors should be more specific with regards to phenotype when stating that markers for FTO or TCF7L2 have a standardized effect size of 0.1. Is it with obesity, type 2 diabetes or a quantitative trait?
      This aspect has been addressed by modifying the sentence as follows: "For larger MAFs like 46.2%, smaller effect sizes of 0.2 will be detectable with a similar power. For comparison, standardized effect sizes like 0.1 have for example been reported for markers in FTO or TCF7L2 in unselected or control individuals for quantitative traits [9, 44]. A standardized effect size of e.g. 0.1 in the additive genetic model implies that the distributions for the three genotypes are shifted by 1/10 of as standard deviation for the respective quantitative trait" (page 7, line 26).
   c. If the standardized effect sizes that have been observed for FTO or TCF7L2 are 0.1 and even under the most informative conditions of MAF of 46.2% there is only sufficient power to detect and effect of 0.2, then the study is not “well-powered.” The authors need to indicate that. This is especially an issue for the variants where they did not detect an effect since these loci are even more underpowered.
      This issue has been addressed by modifying the sentence as follows: "Thus, except for rs2229616 with its low allele frequency (1.6%, Table 1), the study was well powered to detect strong to moderate genetic effects (in the range of a standardized effect of 0.2), which might be present in our highly selected sample of PCOS patients.” (page 8, line 3).

Thank you for your time and effort in evaluating our manuscript.

Yours sincerely,

PD Dr. Anke Hinney