Author's response to reviews

Title: Genome Wide Association Study Identifies KCNMA1 Contributing to Human Obesity

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Author's response to reviews: see over
Dear Editor,

We appreciate the valuable comments by the reviewers on our manuscript Genome Wide Association Study Identifies KCNMA1 Contributing to Human Obesity (MS: 1827245979493622). Below we have answered all comment by the reviewers. The manuscript has been changed accordingly. We hope that our updated and improved manuscript can be accepted for publication in your excellent journal.

Yours sincerely,

Peter Arner
Reviewer's report

Reviewer: Ge Zhang

In this revised version, the authors have made substantial modifications following the reviewers' comments. However, some improvements need to be made before the manuscript can be accepted for publication.

The language need to be improved.

A native English speaker has now read the manuscript and made improvements to the language.

“The fact that that HWE was respected support the global absence of relatedness” --- HWE does not necessarily rule out relatedness. The absence of apparent relatedness (in cohort 1) can be supported by the QQ plot.

We have updated this sentence which now reads: The absence of apparent relatedness in cohort 1 was supported by the strong overlap between expected and observed p-values in the Q-Q plot (Supplemantary Figure).

Reviewer: Zoltan Kutalik

The manuscript has been improved over its previous version, but could still profit from polishing the English.

A native English speaker has now read the manuscript and made improvements to the language.

- Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)
  Imputation of 32 BMI associated GIANT variants, power calculations, calculation of relatedness, ancestry principal components, etc. were ignored, but these revisions I deem not to be essential if acknowledged as weaknesses.

We know acknowledge these weaknesses in the discussion:
“One weakness in our analysis was that we, due to small sample size and different ethnicity, did not perform imputation of all BMI associated loci in published GWAs.”

“Besides small sample size there are other weaknesses in our GWA, e.g. we did not calculate power and ancestry principal components, nor did we formally test for relatedness between subjects.”

- Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

Ancestry principal components (calculated based on 406,177 SNPs of the discovery study) were not calculated and no convincing argument was presented how relatedness was assessed. Since only one of the presented studies had genome-wide data available for the authors, it is not that crucial, however these missing issues have to be mentioned in the discussion.

See reply to the above question.
- Minor Essential Revisions

1. It should be clearly stated which cohort is in silico-replication, which one is de novo.

   We have clarified de novo versus in silico replication in the methods section.

   “Thus all above cohorts were de novo genotyped in this project. By contrast for cohort 7 we performed in silico replication using available Affymetrix 6.0 GWA genotypes”

2. Ancestry principal component (e.g. as done in Novembre et al 2008, Nature) and relatedness was not convincingly assessed, this has to be stated in the discussion as a weakness of the study. Adjusting for relatedness is extremely important for studies with extreme phenotypes, hence at least some supporting arguments are needed why the authors claim there is no relatedness present.

   We now mention the weaknesses in the discussion.

   “Besides small sample size there are other weaknesses in our GWA., e.g. we did not calculate power and ancestry principal components, nor did we formally test for relatedness between subjects.”

   In addition as suggested by the other reviewer, we now use the QQ-plot to support the absence of relatedness.

3. English has to be checked, especially for the newly introduced bits, e.g. last but one paragraph of the Methods/Cohorts section on relatedness is confusing. What do they mean by “apparently no familiar link”? The sentence “If the relatedness has not been tested…” is very unclear to me, please rephrase.

   A native English speaker has now read the manuscript and made improvements to the language.