Author's response to reviews

Title: The TCF7L2 rs7903146 (T) allele is associated with type 2 diabetes in urban Ghana: a hospital-based case-control study

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Response to reviewers

Reviewer Michelle Ramsay
The authors have appropriately taken into consideration the comments from the first round of reviews. I do have a few more comments and suggestions for consideration.

Major comment: The title remains misleading - suggesting that they have confirmed many variants previously associated (at least 60 loci detected in European and Asian populations) with T2D in Ghana. In fact no comment can be made about the other two loci that were tested since there was no power and other SNP variants within those genes may well be associated with T2D in Ghana, but have not been tested.
May I suggest the following?
"The TCF7L2 rs7903146 (T) allele is associated with type 2 diabetes in urban Ghana: a hospital-based case-control study"
The interest is then that it has been associated with T2D in all populations studied to date, including one from SSA.

Response: We have followed this suggestion and changed the title accordingly.

The discussion remains long and some of the interpretations are explanations are very sweeping and general, e.g. paragraph 3 and the out-of-Africa comment and selection (to make these statements you need more data on many loci in the vicinity to be able to test for and comment on selection etc.), and paragraph 4 and the "unthrifty allele". I suggest deleting these sentences of conjecture.

Response: As suggested, we have shortened the discussion, and in particular, we have removed the sections on out-of-Africa migration and unthrifty alleles.

Minor comments.
Methods section in "Data management and analysis". Please correct "by height squared in m" not cm.

Response: This error has been corrected.

Results section in "Genetic variants and type 2 diabetes". last sentence – In contrast, two haplotypes (not combinations) were nominally....
Response: Changed as suggested.

Discussion, paragraph 3. "....role of common polymorphisms for...." is misleading.
I think what you mean is "...role of polymorphisms previously associated with type 2 diabetes in other populations for association with type 2 diabetes in...."

Response: Changed as suggested.

Reviewer Per Medbøe Thorsby
The authors have tried to address my mayor concern on selection bias, especially in the control group: “To use unmatched controls may influence on the genetic risk observed. Since these controls were younger and may also differ from the cases in anthropometrics, ethnicity and SES background that may influence heavily on diabetes prevalence. Also to use only 50% of controls compared to cases may give rise to selection bias.” Still this is a mayor limitation in the present study even though they have corrected for age in their analysis, one would suspect that some of the persons in the control group actually will have increased FBG and probably diabetes when older and with higher weight.
As the study is designed, the control group represents “super controls”; younger, slimmer, less hypertension and higher SES. And the difference in allele frequencies between them and the patients may have been overestimated and may represent a type I statistical error.

**Response:** We explicitly highlight the limitations of the unmatched study design in the revised discussion: “A major limitation lies in the unmatched design of our case-control study. Controls were younger, leaner, and had less hypertension as well as a higher SES than patients. Some controls may consequently show increased FBG and possibly diabetes when they become older and/or gain weight.” This is followed by: “In multivariate analysis, we have accounted for the differences in age (and gender, obesity, and hypertension) between cases and controls. Nevertheless, we cannot rule out residual attenuation by an over-representation of young participants in the control group.”

Also, we now address the possibility of type I statistical errors in the revised discussion: “One study limitation is the comparatively small sample size […] which may also contribute to the possibility of type I statistical errors.”

Other comments of my first review are properly addressed. One minor concern to the present manuscript: the part in the discussion on technicalities on genotyping should be moved to the methods part

**Response:** Done as requested.