Author's response to reviews

Title: Suggestive evidence of associations between liver X receptor beta polymorphisms with type 2 diabetes mellitus and obesity in three cohort studies: HUNT 2 (Norway), MONICA (France) and HELENA (Europe)

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

Thank you very much for giving us the opportunity to answer the reviewer’s comments for the second time.

We have revised our manuscript in light of the remaining comments from the reviewer. Below you will find our point-to-point response to his concerns. We performed all the corrections the reviewer had asked us.

You will find enclosed our revised manuscript entitled “Suggestive evidence for associations between liver X receptor β polymorphisms with type 2 diabetes mellitus and obesity in three cohort studies: HUNT2 (Norway), MONICA (France) and HELENA (Europe)”. Our changes are highlighted in blue throughout the revised manuscript.

We do hope the revised manuscript will now be acceptable for publication in *BMC Medical Genetics*.

Thank you again for your interest.

Sincerely yours,

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Reviewer's report
Title: Suggestive evidence of associations between liver X receptor beta polymorphisms with type 2 diabetes mellitus and obesity in three cohort studies: HUNT 2 (Norway), MONICA (France) and HELENA (Europe)
Version: 2 Date: 9 August 2010
Reviewer: Hans-Ulrich Häring

Reviewer's report: The revised manuscript by Solaas et al. is not significantly improved and the authors have not sufficiently responded to the reviewers’ comments.

Major comments:
1. Bonferroni correction for the number of tested single nucleotide polymorphisms (SNPs) is urgently warranted.

We now performed correction for multiple testing and used \( p \leq 0.01 \) (0.05/5 tested SNPs) as the new threshold for statistical significance. We added this element in the method section page 7. For the associations presenting a p value between 0.01 and 0.05, we now use the terms ‘suggestive evidence’ or ‘tended to be associated with’ throughout the manuscript (abstract, results and discussion) as a consequence.

2. It is surprising that NR1H2 variants and measures of obesity did not associate in the meta-analysis comprising the HUNT2 and MONICA studies, though separate analysis of these studies revealed an association between genetic variation in NR1H2 and obesity measures. This finding should be added to the manuscript and thoroughly discussed.

We included the meta-analysis for the 5 SNPs regarding BMI or waist-to-hip ratio in the manuscript.

   - We incorporated these results page 9:
     “When combining the two adult HUNT2 and MONICA studies (n=4304), the T allele of rs2303044 was marginally associated with higher waist-to-hip ratio (size effect: +0.0055±0.0028, \( p=0.05 \) (heterogeneity \( p=0.86 \)). Similar association was detected for the T allele of rs3219281 (size effect: +0.0051±0.0024, \( p=0.03 \) (heterogeneity \( p=0.55 \)).) When combining the three HUNT2, MONICA and HELENA studies (n=5448), the T allele of rs2303044 was significantly associated with higher BMI (size effect: +0.41±0.19 kg/m², \( p=0.0096 \) (heterogeneity \( p=0.39 \))).”

   - We discussed this point page 10:
     “We also showed that the G allele of rs17373080 was associated with higher risk of obesity or overweight in the MONICA and the HELENA studies, respectively. In line with our results, Dahlman et al. reported a marginal association (\( p=0.06 \)) between rs17373080 and the risk of obesity in a study of 559 obese and 438 non-obese individuals [33]. However, they detected no association between rs17373080 and BMI as a continuous trait in 1721 adults [32]. We confirmed this absence of association in a larger sample (n=5448). Only rs2303044 was significantly associated with BMI when combining the 2 adult and the adolescent studies. The presence of many confounding factors and compensation mechanisms may hide the impact of LXRβ on fat mass.”

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests: I declare that I have no competing interests.