Reviewer's report

Title: Liver X receptor beta polymorphisms in type 2 diabetes mellitus and obesity in three cohort studies: HUNT 2 (Norway), MONICA (France) and HELENA (Europe)

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Reviewer: Hélène Choquet

Reviewer's report:

Review of the paper “Liver X receptor β polymorphisms in type 2 diabetes mellitus and obesity in three cohort studies: HUNT 2 (Norway), MONICA (France) and HELENA (Europe).”

In this report, K. Solaas and colleagues estimated the associations between SNPs in the gene LKRβ and risk of type 2 diabetes (T2D), obesity and related traits using three independent cohorts. They also investigated the functional effects of one disease-associated SNP. The study appears comprehensive, however the genetic study design is not strong enough to convince the readers about effects of these LKRβ polymorphisms on T2D and obesity.

Minor points:

1. In the Background subsection, the authors said that “We then performed association studies in 3 independent cohorts to determine if the LXRβ SNPs were associated with T2DM, obesity …” but in fact only one case-control study (HUNT 2) was used to test association between the LXRβ SNPs and T2DM and only two case-control studies (MONICA and HELENA) were used to test association between the LXRβ SNPs and obesity. The authors should clarify this issue.

2. It may be worthwhile to present briefly the clinical characteristics (sex ratio, age, BMI) of the studied subjects in a single table for each population (96 Norwegian individuals and subjects selected from the HUNT 2, MONICA and HELENA studies).

3. The design used in gene sequencing is not clear enough. The authors started by “re-sequencing” the LXRβ gene in 96 Norwegian individuals to search variants, apparently already identified. How did the authors select the 96 individuals sequenced? Furthermore, it is difficult to understand why the term “re-sequenced” was used? The authors should more explain why they chose this strategy.

4. The authors gave the genotype success rates for the individual SNPs in each study but we do not know if the authors double genotyped a subfraction of the sample for the individual SNPs. The authors should provide a concordance rate (quality control procedure), especially for the rs2303044 in the MONICA study for
which the genotype population distribution deviated from the Hardy-Weinberg equilibrium (p=0.017).

5. It might be interesting to describe briefly the Breslow-Day tests in the Methods subsection.

6. In the Results subsection (“Identification of LXR# SNPs and haplotype blocks” part), the authors noted that “the three tag-SNPs and the two SNPs showing little LD with other SNPs were selected to cover the entire common genetic variability of the LXR# gene”. It would be interesting for the authors to assess the percent of genetic variability at the LXR# locus represented by these five SNPs.

7. In Tables 2, 3, and 4: rs26955121 should be rs2695121.

8. Concerning the “Association between the LXR# SNPs and T2DM-related quantitative phenotypes in HUNT 2”, do the authors have access to HOMA-IR index and HOMA-B cell index for the HUNT 2 cohort?

9. In the Results subsection, in the “Association between the LXR# SNPs and obesity- or T2DM-related quantitative phenotypes in HUNT 2” part, why only control individuals were selected for these analyses?

10. Depending on the study, p-values were adjusted for different confounding variables: age, gender and centre for HELENA study and age, gender, centre, smoking habit, alcohol consumption and physical activity level for MONICA study. These different adjustments make it difficult to compare results between the three studied populations.

11. An a posteriori statistical power calculation could be informative for association studies. It may be worthwhile to present these informations in the discussion.

12. Concerning the functional studies, the term “disease-associated SNPs” should be change since only one SNP (rs28514894, a perfect LD with rs17373080) has been tested using in vitro functionality studies.

Major points:

1. Generally in the manuscript, the authors consider that a p-value of 0.05 is sufficient to confirm that an association is correct. I think this should be discussed quite carefully in the context of multiple testing.

2. In Additional Tables 2, 3, and 4: the authors should provide ORs and 95% CI.

3. In the Results subsection, the authors should specify why they chose to present results under a dominant model. If the authors did not obtain better results and p-values under additive and recessive models, they should specify that and if not, they should present these informations and complete all the tables.

4. In the Discussion subsection, the authors suggest that “no LXR# SNPs have
been significantly associated with obesity or T2M in genome-wide association studies (GWAS) … nominal associations with LXR# SNPs may have gone unreported”. But in my view, it might be interesting to collaborate with consortium and to use data from genome-wide association studies to confirm effect of LXR# SNPs on T2D and obesity and why not to perform a meta-analysis. In fact, the current genetic design is not strong enough to convince the readers about effects of these polymorphisms on T2D and obesity in these populations, especially because the sample sizes of the three cohorts are too weak. Case-control studies with T2D and obesity in largest populations are therefore needed.

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

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interest's below.