Author's response to reviews

Title: Association between LRP5 polymorphism and bone mineral density: a Bayesian meta-analysis

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Author's response to reviews: see over
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Dr Ashleigh Manning
Assistant Editor
BMC-series journals

Re: Manuscript 1189420948185141

Dear Dr Manning,

Thank you for your email dated April 18, 2008, with the three Reviewers’ comments on our manuscript. We are pleased that all reviewers recognized the importance of our work in related research area. We also thank the reviewers for helpful comments, which we have addressed in the following attachment. Parts of the manuscript have been changed in response to the comments, and the changes are yellow high-lighted in the revised manuscript.

Since the submission of our manuscript, we have identified some new published papers on the association between LRP5 gene and BMD. We have now included these studies in our revised manuscript. We think that the present result is more reliable in terms of effect size.

We hope that our response is satisfactory to you and trust that the manuscript is now suitable for publication in the BMC Medical Genetics.

Yours sincerely,

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Response to Reviewer 1

1. “The number of studies in the meta-analysis is relatively small. As stated in Methods, authors did not include studies published after April-07. Therefore, I would suggest them to make an effort to include some other recent studies (ie, Brixen et al, and Grundberg et al)”

At the time we were completing this meta-analysis, the above studies were not published. However, in this revised manuscript, we have now included those studies in our analysis. As expected, the results have changed slightly but the general trend remained unchanged.

2. “Authors should explore if age or menopausal status have any influence on the relationship between genotypes and BMD”

We thank the Reviewer for the good suggestion. However, since we based our analysis on summary data, it was not possible to examine the effect of age and menopausal status. Moreover, most original studies have adjusted the result for age, menopausal status and other important covariates.

3. “Data synthesis and analysis. For the benefit of the non-expert reader, the meaning of the symbols (d, sigma,..) should be explained (page 6)”

We have now explained the symbols in text (page 6-7).

4. “The sentence in the last paragraph of Methods, is confusing, as the funnel plot is a method to look for publication bias, not to assess heterogeneity.”

The text has now modified to read “Funnel plots were performed to identify any possible evidence of publication bias” (page 8).

5. “Results. Please, give the inconsistency coefficient for the femoral neck analysis”.

We actually presented the inconsistency coefficient ($I^2$) for the femoral neck in the text (page 11). The $I^2$ for femoral neck was 46.8%.
6. “Results. How did authors calculate the “average” standard deviation that was used to estimate probabilities in the Bayesian analysis? How large was it?”

A standard deviation of 0.12 g/cm² was applied for femoral neck BMD and 0.17 g/cm² for lumbar spine BMD. These SDs reflect the average values across studies included in the analysis as well as in the general population. We have now added a note in the text and in the figure legend.

7. “Discussion. In order to put the results in context, authors should comment on the differences in BMD found in meta-analysis of other genes (ie, VDR, Col1A1, ER, MTHFR)”

We have now discussed this point in the manuscript (page 13).

8. “Discussion. The last sentence of the first paragraph in page 12 should be modified. Factors other than BMD influence fracture risk and fracture risk was not used as endpoint in the meta-analysis. Therefore, the study does not permit to determine the relationship of the LRP5 polymorphism, if any, with fractures”

We have now clarified this point in the conclusion (page 13).

9. “Figures 2 and 3. Please correct the year in the study by Ezura et al”

Thank you for pointing this out. We have now fixed the year to 2007.

Discretionary Revisions

1. “Did authors consider in some way the quality of studies (ie, genotyping methods, bias in the selection of cases and controls, etc.)?”

Most studies used the same protocol of genotyping, and genotyping error was not reported in primary studies. Only one study was case-control, the rest were either cross-sectional or cohort studies.

2. “Was the proportion of AA genotypes in the individual studies associated with the average BMD?”
The following figures show the correlation between the AA relative frequencies (x-axis) and BMD (y-axis) for individual studies. There appears to be a weak but positive correlation, in which studies with higher AA genotype frequencies reported greater BMD values. Furthermore, this way reflects the fact that Caucasian population has higher AA frequency and higher BMD than Asian population.
Response to Reviewer 2

1. “In Table 3, authors should provide p-values for WMD”
We have now provided the p-values for each analysis of WMD in BMD in Table 3.

2. “It is hard to understand Figure 4. Authors need to explain Figure 4 in detail for readers”.
We have provided a brief explanation in the Results section and footnotes of the figure.

3. “It is good to explain the difference between a Bayesian meta-analysis and a conventional meta-analysis”
We have now provided more information of Bayesian approach in Methods and Discussion sections.
Response to Reviewer 3

“However, a large-scale multicenter collaborative study (GENOMOS Study) has been recently published (JAMA. 2008 Mar 19; 299(11):1277-90). This study has already pooled the association between LRP5 polymorphism (including A1330V) and bone mineral density and fracture in both men and women based on individual level data on 37534 individuals. It seemed that there was no necessary to conduct another meta-analysis, because this issue was extensively addressed by the GENOMOS Study”

At the time of completing our analysis, the GENOMOS Study was not yet published. However, it is interesting to observe that the estimate of effect for the A1330V polymorphism on BMD in our analysis was very comparable to that of the GENOMOS Study’s. We have now incorporated the GENOMOS data in our analysis.

Even in the presence of the GENOMOS Study, we think our analysis is necessary in the field because the GENOMOS Study only focused on the Caucasian population. Our study has included data from Asian populations.

1. “Title: It would be better to omit the word of “Bayesian” because the main results were generated from usual meta-analysis rather than Bayesian meta-analysis”. We would like to keep the title because it is indeed the basis of our analysis

2. “They might miss a few important studies (e.g., E. Grundberg et al. Osteoporos Int. 2007 Nov 17 [Epub ahead of print] )”.
   As mentioned above, at the time of completing this meta-analysis, the above studies were not published. However, in this revised manuscript, we have now included the above studies in our analysis.