Author’s response to reviews

Title: Analysis of SNP-SNP interactions and bone quantitative ultrasound parameter in early adulthood

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Dear Jose A. Riancho,

Many thanks for your comments on our paper entitled "Analysis of SNP-SNP interactions and bone quantitative ultrasound parameter in early adulthood" (MGTC-D-17-00132). We have now revised the manuscript according to the useful comments of the reviewers. We would like to note that to meet the suggestions of the reviewer 1 the “Abstract, Discussion and Conclusion” sections have been modified significantly. We hope now you will find it suitable for publication in your prestigious journal.

Looking forward to hearing from you soon,

Warm regards
John Loughlin (Reviewer 1):

This is a clearly written manuscript with a very well defined aim. The sample size for SNP-SNP epistatic interaction analysis is modest, and the authors do acknowledge this. They also apply a p-value threshold to avoid false-positives. None of the p-values surpass this threshold, so the conclusion should be that they have not generated robust evidence to support any SNP-SNP epistatic interactions. But that is not the message given in the Abstract or the Discussion. Instead, a reader may leave with the impression that significant effects have been detected. The authors should be lauded for setting a threshold. After all, the large number of tests performed does mean that p-values <0.05 will be observed by chance; the p-values that they report fall within the range that one would expect when there are no actual genuine effects. But there is a sense that the authors have partly abandoned this objective approach and drawn subjective conclusions from the p-values that are <0.05. In reality, they failed to detect p-values that surpassed their threshold and as such, they should report that no significant SNP-SNP epistatic interactions were observed. For this manuscript to be publishable, the authors would therefore need to change much of the tone of their conclusions. The issue is that the failure to observe SNP-SNP epistatic interactions may be because none exist for the SNPs tested or that the effects are so weak that the sample size used is much too small to detect them. As such, reporting a negative finding in this regard doesn't really add anything to our current knowledge; does the manuscript therefore merit publication at all?

We would like to thank this reviewer for his comments. As the reviewer suggested, we have included the modest sample size as a limitation of this study in the “Discussion” section of the revised manuscript (page 9, lines 9-11). In addition, accordingly with reviewer suggestion and in order to leave a clear message for the readers, several novel sentences have been included in the “Abstract, Discussion and Conclusion” sections of the revised manuscript to highlight that
the detected SNP-SNP interactions did not remain significant after applying the highly conservative Bonferroni correction for multiple testing (p<0.0001) and therefore, our findings do not support a relevant genetic contribution of SNP-SNP epistatic interactions to heel ultrasound measurements in young adults (page 2, lines 21-22, 24-28; page 7, lines 24-29; page 9, lines 7-9, 19-23).

Finally, we would like to note that our study is the first aiming to investigate the possible role of SNP-SNP interactions in the genetic architecture of QUS. We believe, that although our results do not reach the stringent significance level required for multiple testing, we have contributed with novel genetic data and have opened a new line of research in this field. In fact, this study would lead to future international research collaboration to collect larger study cohorts in order to confirm our preliminary results. In addition, in the research area of genetic of complex traits, the literature is plenty of studies reporting no association results, that have contributed to the characterization of the genetic map of several traits such as cancer, autoimmunity, body mass index or obesity among others. Thus, we think our results deserve publication.

Javier del Pino (Reviewer 2)

This is an interesting study about the relationship between QUS and the interaction of several genetic variants related to bone density in a young Spanish population. Its results highlight the interaction between genetic variants of the ESR1 and LRP5 genes involved in the maintenance of bone mass.

We like to thank this reviewer his/her constructive comments.

Minor revision

The authors consider that their results may suggest an influence on early mineralization (page 6, lines 14-16). However, neither ESR1 nor LRP5 are involved in bone mineralization. In addition, BUA is a measure of bone density but not of bone mineralization.

Accordingly with reviewer suggestion and to be more accurate, the terms “mineralization" has been removed in the “Discussion” section of the revised manuscript (page 8, line 20).